Corticosteroid nasal irrigations after endoscopic sinus surgery for recalcitrant chronic rhinosinusitis

A thesis submitted to fulfil the requirements for the degree of Doctor of Philosophy at the Australian School of Advanced Medicine, Faculty of Human Sciences, Macquarie University, Sydney, Australia

The institutes associated with the work include

Macquarie University Hospital,

Applied Medical Research Centre, University of New South Wales

and St Vincent Hospital.

Kornkiat Snidvongs, MD

May 2013

Table of Contents

Abstract

Chronic rhinosinusitis (CRS) is a heterogeneous disease with multiple pathogenic factors and various inflammatory mechanisms. Although high eosinophil content in the sinus tissue has been acknowledged as a marker of recalcitrant CRS, eosinophilic chronic rhinosinusitis (ECRS) is traditionally diagnosed by its phenotypes other than structured histopathology profiling. Osteitis is another marker associated with recalcitrant inflammation. However, the pathogenesis of osteitis in patients without previous sinus surgery is poorly understood. Patients with ECRS and patients with osteitis have higher disease severity and poorer treatment outcomes. Both observed changes are thought to be features of disordered inflammation. Currently, topical steroid is the first line drug recommended for treating CRS. Although having strong anti-inflammatory effects, topical steroid sprays provide poor sinus delivery. Published randomized controlled trials on the efficacy of topical steroids in CRS use either nasal delivery (nasal drop, nasal spray) or sinus delivery (sinus catheter, sinus irrigation) in patients with or without sinus surgery. This heterogeneity influences topical drug delivery and distribution. This thesis examines the basis of diagnosis, characterisation of the inflammatory process, influence of surgery and device in drug delivery and proposes a revised treatment of CRS with postoperative corticosteroid nasal irrigation which combines the therapeutic effects of sinus surgery and sinus delivery of corticosteroid for an inflammatory condition. In this treatment paradigm, the purpose of sinus surgery is to create access for topical therapies rather than a fundamental concept of relieving ostiomeatal obstruction. Even for the challenging subgroups of ECRS and patients with osteitis, had favourable outcomes and even greater improvement than the non ECRS subgroup.

When CRS is managed as an inflammatory condition with local mucosal inflammation controlled with effectively delivered pharmaceutical solutions, therapy is greatly optimized compared to traditional regimes.

Statement of originality

I hereby declare that the work presented in this thesis has not been submitted for a higher degree to any other university or institution. To the best of my knowledge this submission contains no material previously published or written by another person, and is my own work unless stated otherwise. Any contribution made to the research by others is explicitly acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

This study was approved by the Macquarie University Human Ethics Committee (5201200048) and HREC St Vincent's Hospital (HREC/10/ SVH/10), and performed in accordance with institutional ethics committee guidelines. The protocol is Mometasone/ Fluticasone/ Budesonide irrigation in the treatment of CRS.

Kornkiat Snidvongs

(MQ42045835)

May 2013

Acknowledgements

Firstly, I would like to acknowledge my supervisor and co-supervisor, Raymond Sacks and Richard Harvey who provide me great opportunities to further my knowledge both in research and clinical practice. You are more than supervisors. Actually, you've been good friends along the way. Thank you so much for your continual help, support and guidance.

I would like to thank Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand for supporting me with a scholarship. I am also truly grateful to Australian School of Advanced Medicine for providing me ASAM Top-Up Support throughout my candidature and providing me with Skipper Postgraduate Research Travel Award in order to present my work at The *24th Congress of the European Rhinologic Society*, in conjunction with the *31st International Symposium on Infection and Allergy of the Nose* 2012, in Toulouse, France. Additionally I am grateful to Macquarie University for providing me with Postgraduate Research Fund (PGRF) in order to present my work at the 2nd meeting of European Academy of ORL and Head & Neck Surgery 2013 in Nice, France. Lastly, I am grateful to Australasian Rhinologic Society for providing me The Inaugural PJ Wormald Prize to present my work at The 116th Combined Otolaryngological Spring Meeting (COSM), Orlando, USA 2013.

To Ellie Pratt, Susan Small, Seamus Phillips, David Chin, Dustin Dalgorf and the members of staff at Macquarie University Hospital, St Vincent's Hospital and Sydney Adventist Hospital, thanks for making work such an enjoyable place. Thanks to all

the past and present members of ASAM who have supported me along the way. Your help has been greatly appreciated.

In particular, I would like to thank Larry Kalish and George Marcells for their clinical advice and encouragement. I would also like to thank Mary Simons for her advice on the search and the endnote program.

To Miti and May Rungwaimanee, thank you for keeping me grounded and reminding me that life exists beyond a PhD. Your ongoing friendship means a lot to me.

Finally, I would like to dedicate this thesis to my family. To Mom-Sukanya Snidvongs, my wife-Apiradee Snidvongs, my daughter-Jidapa Snidvongs, my son-Jirayu Snidvongs, without whom my PhD experience would not have been so amusing. Thank you for always being the wind beneath my wings. I honestly couldn't have achieved this without you.

List of publications arising from this thesis

1. **Kornkiat Snidvongs**, Matthew Lam, Raymond Sacks, Peter Earls, Larry Kalish, Seamus Phillips, Elenor Pratt, Richard John Harvey.

Structured histopathology profiling of chronic rhinosinusitis in routine practice.

Int Forum Allergy Rhinol. 2012 Sep;2(5):376-85.

2. **Kornkiat Snidvongs**, David Chin, Raymond Sacks, Peter Earls, Richard John Harvey.

Eosinophilic rhinosinusitis is not a disease of ostiomeatal occlusion.

Laryngoscope. 2013 Apr 2. doi: 10.1002/lary.23721. [Epub ahead of print]

3. **Kornkiat Snidvongs**, Rohan McLachlan, David Chin, Elenor Pratt, Raymond Sacks, Peter Earls, Richard John Harvey.

Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis.

Rhinology. 2012 Sep;50(3):299-305.

4. **Kornkiat Snidvongs**, Rohan McLachlan, Raymond Sacks, Peter Earls, Richard John Harvey.

Correlation of the Kennedy Osteitis Score to clinico-histologic features of chronic rhinosinusitis.

Int Forum Allergy Rhinol. 2012 Nov 7. doi: 10.1002/alr.21113. [Epub ahead of print]

5. **Kornkiat Snidvongs**, Larry Kalish, Jonathan C Craig, Raymond Sacks, Richard John Harvey.

Topical steroid for chronic rhinosinusitis without polyps.

Cochrane Database Syst Rev. 2011 Aug 10;(8):CD009274.

6. Larry Kalish, **Kornkiat Snidvongs**, Rahuram Sivasubramaniam, Daron Cope, Richard John Harvey.

Topical steroid for nasal polyps.

Cochrane Database Syst Rev. 2012 Dec 12;12:CD006549. doi: 10.1002/14651858.CD006549

7. **Kornkiat Snidvongs**, Larry Kalish, Raymond Sacks, Rahuram Sivasubramaniam, Daron Cope, Richard John Harvey.

Sinus surgery and delivery method influence the effectiveness of topical corticosteroid for chronic rhinosinusitis; systematic review and meta-analysis.

Am J Rhinol Allergy. 2013, in press

8. **Kornkiat Snidvongs**, Elenor Pratt, David Chin, Raymond Sacks, Peter Earls, Richard John Harvey.

Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis.

Int Forum Allergy Rhinol. 2012 Sep;2(5):415-21.

List of conference proceedings and presentation at scientific meetings

1. **Kornkiat Snidvongs**, Mathew Lam, Raymond Sacks, George Marcells, Larry Kalish, Seamus Phillips, Richard Harvey.

Predicting Eosinophilic chronic rhinosinusitis: Relationship of phenotype to serum and tissue biomarkers. Poster presentation in The 22nd Annual Scientific Meeting of the Australasian Society of Clinical Immunology and Allergy (ASCIA), Sydney, Australia 2011.

2. **Kornkiat Snidvongs**, Rohan McLachlan, David Chin, Elenor Pratt, Raymond Sacks, Peter Earls, Richard John Harvey.

Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis. Oral presentation in The 62nd Annual Scientific Meeting of Australian Society of Otolaryngology Head & Neck Surgery (ASOHNS), Adelaide, Australia 2012.

3. **Kornkiat Snidvongs**, Larry Kalish, Raymond Sacks, Rahuram Sivasubramaniam, Daron Cope, Richard John Harvey.

Intranasal corticosteroid for chronic rhinosinusitis and the impact of sinus surgery. Oral presentation in The 24th Congress of the European Rhinologic Society, in conjunction with the 31st International Symposium on Infection and Allergy of the Nose, Toulouse, France 2012

4. **Kornkiat Snidvongs**, Elenor Pratt, David Chin, Raymond Sacks, Peter Earls, Richard John Harvey.

Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. Oral presentation in The 24th Congress of the European Rhinologic Society, in conjunction with the 31st International Symposium on Infection and Allergy of the Nose, Toulouse, France 2012

5. **Kornkiat Snidvongs**, David Chin, Raymond Sacks, Peter Earls, Richard John Harvey.

Eosinophilic rhinosinusitis is not a disease of ostiomeatal occlusion. Oral presentation in The 6th Annual Scientific Meeting of Australasian Rhinologic Society (ARS), Sunshine coast, Australia 2012.*

*Awarded The Inaugural PJ Wormald Prize

6. **Kornkiat Snidvongs**, David Chin, Raymond Sacks, Peter Earls, Richard John Harvey.

Eosinophilic rhinosinusitis is not a disease of ostiomeatal occlusion. Oral presentation in The 116th Combined Otolaryngological Spring Meeting (COSM), Orlando, USA 2013.

7. **Kornkiat Snidvongs**, Dustin Dalgorf, Raymond Sacks, Richard John Harvey.

Modified Lund Kennedy endoscopy score for defining inflammatory burden in chronic rhinosinusitis. Oral presentation in The 2nd Meeting of European Academy of Otorhinolaryngology and Head and Neck Surgery. Nice, France 2013.

Other publications arising from during the period of candidature

1. David Chin, **Kornkiat Snidvongs**, Larry Kalish, Raymond Sacks, Richard John Harvey

The outside-in approach to the modified endoscopic Lothrop procedure.

Laryngoscope. 2012 Aug;122(8):1661-9.

2. Matthew Lam, Laura Hull, Rohan McLachlan, **Kornkiat Snidvongs**, David Chin, Elenor Pratt, Larry Kalish, Raymond Sacks, Peter Earls, William Sewell, Richard John Harvey.

Clinical severity and epithelial endotypes in chronic rhinosinusitis.

Int Forum Allergy Rhinol. 2012 Oct 4. doi: 10.1002/alr.21082. (Epub ahead of print)

3. Leon T Lai, Michael K Morgan, David Chin, **Kornkiat Snidvongs**, June XZ Huang, Joanne Malek, Matthew Lam, Rohan McLachlan, Richard JohnHarvey.

A cadaveric study of the endoscopic endonasal transclival approach to the basilar artery.

J Clin Neurosci. 2013 Jan 10. doi:pii: S0967-5868(12)00446-8.

10.1016/j.jocn.2012.03.042. (Epub ahead of print)

4. David Chin, **Kornkiat Snidvongs**, Raymond Sacks, Richard John Harvey

Collateral thermal injury during endoscopic skull base surgery from endonasal CO2 laser and coblation.

J Laryngol Otol. 2013 Apr 10:1-4. [Epub ahead of print]

5. **Kornkiat Snidvongs**, Dustin Dalgorf, Raymond Sacks, Richard John Harvey.

Modified Lund Kennedy endoscopy score for defining inflammatory burden in chronic rhinosinusitis.

Otolaryngol Head Neck Surg (under submission)

Declaration of contribution to chapters

Chapter 1

Candidate was the major contributor to the manuscript.

Chapter 2

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 3

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 4

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 5

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 6

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 7

Candidate performed all data acquisition, analysis and interpretation of data. Candidate and the first author were the two major contributors to the manuscript.

Chapter 8

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 9

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript.

Chapter 10

Candidate was the major contributor to the manuscript.

List of tables

List of figures

Figure 7.2 Risk of bias graph

Figure 7.3 Risk of bias summary

Figure 7.4 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores

Figure 7.5 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by sinus surgery

Figure 7.6 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by topical delivery methods

Figure 7.7 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by polyp severity

Figure 7.8 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by steroid agent

Figure 7.9 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by quality of studies

Figure 7.10 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders

Figure 7.11 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score

Figure 7.12 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by sinus surgery status

Figure 7.13 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by topical delivery method

Figure 7.14 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by polyp severity

Figure 7.15 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by steroid agent

Figure 7.16 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by quality of studies

Figure 7.17 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders

Figure 7.18 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score

Figure 7.19 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score by sinus surgery

Figure 7.20 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score by topical delivery methods

Figure 7.21 Forest plot of comparison: Topical steroids versus placebo, outcome: change in polyp score

Figure 7.22 Forest plot of comparison: Topical steroids versus placebo, outcome: change in polyp score by sinus surgery status

Figure 7.23 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size)

Figure 7.24 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by sinus surgery status

Figure 7.25 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by topical delivery methods

Figure 7.26 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by polyp severity

Figure 7.27 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by steroid agent

Figure 7.28 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by quality of studies

Figure 7.29 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp recurrence after surgery

Figure 7.30 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp recurrence after surgery by quality of studies

Figure 7.31 Forest plot of comparison: Topical steroids versus placebo, outcome: peak nasal inspiratory flow

Figure 7.32 Forest plot of comparison: Topical steroids versus placebo, outcome: peak nasal inspiratory flow by sinus surgery status

Chapter 1

Background

Chronic rhinosinusitis (CRS) is a heterogeneous disease with various inflammatory and pathophysiology mechanisms.(Fokkens, Lund et al. 2012). One biomarker believed to be etiologically linked to recalcitrant CRS is high tissue eosinophilia(Fokkens, Lund et al. 2012). Patients with eosinophilic chronic rhinosinusitis (ECRS) associate with poor treatment outcomes(Soler, Sauer et al. 2010) and the need for revision surgery(Matsuwaki, Ookushi et al. 2008). The diagnostic criteria for ECRS are currently based on clinical features including asthma, polyps, aspirin sensitivity, high serum eosinophilia and IgE rather than sinus histopathology. However, many ECRS patients may not present with classic features and the subgroup of 'eosinophilia without polyps' has been demonstrated as the worst prognostic subgroup in one cohort study(Soler, Sauer et al. 2010). Thus the most significant finding may be the presence of eosinophilia when no other clinical features of traditional ECRS are present. The associations between tissue histopathology and other surrogate markers of ECRS are yet to be defined.

Osteitis is the other biomarker which associates with recalcitrant disease(Videler, Georgalas et al. 2011). The osteitic bones potentially serve as a nidus for inflammation and may explain failures from typical medical and surgical treatment. Osteitis is associated with previous surgery and the incidence increases with increasing number of previous operations(Georgalas, Videler et al. 2010). However non-operated patients also experience osteitis(Lee, Kennedy et al. 2006). The mechanism of osteitis in CRS is poorly understood and yet to be fully defined.

Inflammatory dysfunction is considered an important part of CRS. Topical steroid plays a significant role in the treatment of CRS. However patients with recalcitrant CRS

commonly have aggressive local mucosal inflammation, nasal polyposis and thick eosinophilic mucin which causes topical steroid inaccessible. Simply applying topical steroid through the nostrils does not imply delivery of the drug into the sinus. To deliver topical medicine into the sinuses, an appropriate access and delivery is required.

Prior to my candidature, one study by the candidate and colleagues demonstrates the inaccessibility of nasal irrigation to enter the paranasal sinus systems in non-operated CRS patients (Snidvongs, Chaowanapanja et al. 2008). This finding implies that sinus surgery greatly affects the amount of topical therapy, which comes into contact with paranasal sinus mucosa. Additional factors influencing mucosal drug delivery have been shown by other studies. The variety of extent of sinus surgery and ostial dimension brings about variable access and sinus penetration(Grobler, Weitzel et al. 2008; Singhal, Weitzel et al. 2010; Brenner, Abadie et al. 2011). High pressure and large volume devices offer a greatly enhanced ability to deliver solutions to the paranasal sinuses(Harvey, Goddard et al. 2008). In summary, delivery techniques, surgical state of the sinus cavity, delivery device, and fluid dynamics (volume, pressure, position) have a significant impact on the delivery of topical therapies to the sinus mucosa(Harvey and Schlosser 2009). Thus, a new treatment of postoperative corticosteroid nasal irrigation is proposed in this study in order to achieve favorable outcomes for treating patients with recalcitrant CRS. It provides a long term aggressive topical steroid therapy via a high pressure and large volume device administering through wide post sinus surgery cavities. The purpose of sinus surgery is to create the access for topical therapies rather than the fundamental concept of relieving ostiomeatal obstruction. The new therapy combines the actions of mechanical lavage (mechanical

removal of mucus, inflammatory products, and bacteria/biofilms) and pharmaceutical intervention.

This study aims to investigate the associations between ECRS and its phenotype, disease severity, the status of ostiomeatal complex occlusion and the presence of osteitis. Additionally, meta-analyses are performed to analyse the influence of sinus surgery and topical delivery method on the effectiveness of topical steroid. Lastly, the new treatment of postoperative corticosteroid nasal irrigation for CRS is proposed. Its effectiveness with subgroup analyses by tissue eosinophilia and osteitis are investigated.

References

Brenner, P. S., W. M. Abadie, E. K. Weitzel, R. F. Thomas and K. C. McMains. Unexpected consequences of transnasal balloon dilation of the maxillary ostium. *Int forum allergy rhinol* 2011;1(6): 466-470.

Fokkens, W. J., V. J. Lund, J. Mullol, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012;(23): 1-298.

Georgalas, C., W. Videler, N. Freling and W. Fokkens. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. *Clin Otolaryngol* 2010;35(6): 455-461.

Grobler, A., E. K. Weitzel, A. Buele, et al. Pre- and postoperative sinus penetration of nasal irrigation. *Laryngoscope* 2008;118(11): 2078-2081.

Harvey, R. J., J. C. Goddard, S. K. Wise and R. J. Schlosser. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008;139(1): 137-142.

Harvey, R. J. and R. J. Schlosser. Local drug delivery. *Otolaryngol Clin North Am* 2009;42(5): 829-845.

Lee, J. T., D. W. Kennedy, J. N. Palmer, M. Feldman and A. G. Chiu. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol* 2006;20(3): 278-282.

Matsuwaki, Y., T. Ookushi, D. Asaka, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. *Int Arch Allergy Immunol* 2008;146 Suppl 1: 77-81.

Singhal, D., E. K. Weitzel, E. Lin, et al. Effect of head position and surgical dissection on sinus irrigant penetration in cadavers. *Laryngoscope* 2010;120(12): 2528-2531.

Snidvongs, K., P. Chaowanapanja, S. Aeumjaturapat, S. Chusakul and P. Praweswararat. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol* 2008;22(5): 483-486.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

Videler, W. J., C. Georgalas, D. J. Menger, et al. Osteitic bone in recalcitrant chronic rhinosinusitis. *Rhinology* 2011;49(2): 139-147.

Chapter 2

Structured histopathology profiling of chronic rhinosinusitis in routine practice

ORIGINAL ARTICLE

Structured histopathology profiling of chronic rhinosinusitis in routine practice

Kornkiat Snidvongs, MD[1,2], Matthew Lam[3], Raymond Sacks, MBBCh, FCS(SA)ORL, FRACS[1,4,6], Peter Earls, MD[5], Larry Kalish, MBBS, MS, MMed(Clin Epi), FRACS[4,6], P. Seamus Phillips, BM, MSc, FRCS(ORL-HNS)[7], Eleanor Pratt, BA BSc[8] and Richard J. Harvey, MD[1,3]

Background: Tissue eosinophilia in chronic rhinosinusitis (CRS) is a marker of inflammatory disorders recalcitrant to surgical intervention. Eosinophilic chronic rhinosinusitis (ECRS) is traditionally associated with asthma, polyps, aspirin sensitivity, high serum eosinophilia, and elevated immunoglobulin E (IgE). However, patients with ECRS may not present with these associations and there is a need to establish other surrogate markers. The objective of the study was to determine the associations between the histopathology, serology, and clinical characteristics in CRS patients.

Methods: A cross-sectional study was undertaken of CRS patients undergoing surgery. Tissue eosinophilia and other pathological features were compared to traditional surrogate features of ECRS, as well as to symptoms, and to radiologic and endoscopic scores.

Results: A total of 51 patients were assessed (47% female, mean age 46.6 ± 4.1 years). High tissue eosinophilia (>10 per high-power field [HPF]) was more prominent in polyps (84%) ($\chi^2 = 25.76$; $p < 0.01$) but was also seen in non-polyp patients (19%). Asthma was not associated with high tissue eosinophilia ($p = 0.60$), with 43% of nonasthmatics demonstrating high tissue eosinophilia. Serum eosinophilia predicted high tissue eosinophilia at >0.30 × 10^9/L or 4.4% of leukocytes (sensitivity 52%, specificity 87%, receiver operating characteristic [ROC] $p = 0.001$), with low negative predictive value. Serum IgE was nonpredictive ($p = 0.08$).

Conclusion: The diagnosis of ECRS has unique prognostic implications. Traditional features of the ECRS phenotype are not necessarily reliable markers for the presence of tissue eosinophilia. Serum eosinophilia may be a good surrogate marker of tissue eosinophilia but of limited use. The routine use of structured histopathology reporting in CRS is suggested, to allow for the diagnosis of ECRS and to identify other prognostic markers.

Key Words:
chronic rhinosinusitis; eosinophil; eosinophilia; eosinophilic; histopathology; nasal polyps; asthma

How to Cite this Article:
Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol*, 2012; 2:376–385.

[1]*Australian School of Advanced Medicine, Macquarie University, Sydney, Australia;* [2]*Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Thailand;* [3]*Faculty of Medicine, University of New South Wales, Sydney, Australia;* [4]*Sydney Medical School, University of Sydney, Sydney, Australia;* [5]*Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia;* [6]*Department of Otolaryngology, Concord General Hospital, Sydney, Australia;* [7]*Department of Otorhinolaryngology, Guy's and St Thomas' NHS Trust, London, UK;* [8]*Sydney School of Public Health, University of Sydney, Sydney, Australia*

Correspondence to: Kornkiat Snidvongs, Australian School of Advanced Medicine, 2 Technology Place, Macquarie University, NSW2109, Sydney, Australia.; e-mail: drkornkiat@yahoo.com

Potential conflict of interest: R.J.H. has served on an advisory board for Schering Plough and Glaxo-Smith-Kline, was previously a consultant with Medtronic, speakers bureau for Merek Sharp Dolme and Arthrocare, and has received grant support from NeilMed. R.S. is a consultant for Medtronic and is on the speakers bureau for Merek Sharp Dolme.
Presented at the 57th Annual Meeting of the American Rhinologic Society, San Francisco, CA, September 10, 2011.

Chronic rhinosinusitis (CRS) is a heterogeneous disease with multiple pathogenic factors and various inflammatory mechanisms.[1] Two broad subtypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), have been proposed.[1] The addition of a third subtype, allergic fungal sinusitis (AFS), is also used.[2–4] Currently, the distinction between subtypes is clinically based, focusing on phenotype rather than underlying histopathology or serum markers. The underlying inflammatory profile is classified as predominantly eosinophilic, defined as eosinophilic chronic rhinosinusitis (ECRS)[2] or

Received: 14 August 2011; Revised: 6 October 2011; Accepted: 5 January 2012
DOI: 10.1002/alr.21032
View this article online at wileyonlinelibrary.com.

"This study aims to investigate the associations between ECRS and its phenotype and disease severity."

Abstract

Background:

Tissue eosinophilia in chronic rhinosinusitis (CRS) is a marker of inflammatory disorders recalcitrant to surgical intervention. Eosinophilic chronic rhinosinusitis (ECRS) is traditionally associated with asthma, polyps, aspirin sensitivity, high serum eosinophilia and elevated IgE. However patients with ECRS may not present with these associations and there is a need to establish other surrogate markers. The objective of the study was to determine the associations between the histopathology, serology and clinical characteristics in CRS patients.

Methods:

A cross-sectional study was undertaken of CRS patients undergoing surgery. Tissue eosinophilia and other pathological features were compared to traditional surrogate features of ECRS as well as to symptoms, radiologic and endoscopic scores.

Results:

51 patients were assessed (47% female, mean age 46.6±4.1yrs). High tissue eosinophilia (>10/HPF) was more prominent in polyps (84%) (x^2=25.76, p<0.01) but also seen in non-polyp patients (19%). Asthma was not associated with high tissue eosinophilia (p=0.60) with 43% of non-asthmatics demonstrating high tissue eosinophilia. Serum eosinophilia predicted high tissue eosinophilia at >0.30 $x10^9$/L or 4.4% of leukocytes (sensitivity 52%, specificity 87%, ROC p=0.001) with low negative predictive value. Serum IgE was non-predictive (p=0.08).

Conclusion:

The diagnosis of ECRS has unique prognostic implications. Traditional features of the ECRS phenotype are not necessarily reliable markers for the presence of tissue eosinophilia. Serum eosinophilia may be a good surrogate marker of tissue eosinophilia but of limited use. The routine use of structured histopathology reporting in CRS allow for the diagnosis of ECRS and identify other prognostic markers is suggested.

Key words: chronic rhinosinusitis, eosinophil, eosinophilia, eosinophilic, histopathology, nasal polyps, asthma

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disease with multiple pathogenic factors and various inflammatory mechanisms(Fokkens, Lund et al. 2007) Two broad subtypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), have been proposed(Fokkens, Lund et al. 2007). The addition of a third subtype, allergic fungal sinusitis, is also used (Lanza and Kennedy 1997 ; Meltzer, Hamilos et al. 2004; Chan and Kuhn 2009). Currently, the distinction between subtypes is clinically based, focusing on phenotype rather than underlying histopathology or serum markers. The underlying inflammatory profile is classified as predominantly eosinophilic, defined as eosinophilic chronic rhinosinusitis (ECRS) (Chan and Kuhn 2009) or non-eosinophilic. Neutrophilic and eosinophilic inflammation is relatively distinct pathologic processes. There is evidence that ECRS is associated with a greater symptom severity(Lee, Liang et al. 2009; Soler, Sauer et al. 2009; Sun, Joo et al. 2009), worse olfactory dysfunction(Soler, Sauer et al. 2010), comorbidities of asthma and bronchial hyperresponsiveness(Han, Kim et al. 2009; Amorim, Araruna et al. 2010) and overall poorer outcomes(Soler, Sauer et al. 2010; Tosun, Arslan et al. 2010). Superantigen-induced inflammation, allergic fungal rhinosinusitis, and aspirin exacerbated eosinophilic rhinosinusitis are known process in ECRS(Sok and Ferguson 2006). The diagnostic criteria for ECRS are currently based on clinical features rather than sinus histopathology.

Traditionally, biopsy reports following sinus surgery (ESS) gives limited information with a general diagnosis such as ‘chronic inflammation – no malignancy seen’ without any further useful detail other than excluding neoplasia. Considering our understanding of ECRS, a more detailed synoptic or standardized report of inflammation may allow easier differentiation of the ECRS and non-ECRS patient.

Treatment implications for histopathologic profiling include macrolide therapy for neutrophilic CRS to provide IL8-modifying antineutrophilic activities(Harvey, Wallwork et al. 2009) and the use of oral(Rupa, Jacob et al. 2010) or aggressive local(Steinke, Payne et al. 2009) corticosteroid therapy for those with significant eosinophilia.

The most significant finding may be the presence of eosinophilia when no other clinical features of traditional ECRS are present. Soler et al demonstrated that the worst prognostic group in their cohort post ESS was eosinophilia without polyps(Soler, Sauer et al. 2010). A strong corticosteroid approach is likely to be essential in any successful management of post-ESS ECRS. The use of systemic and topical (irrigation) steroid therapy can be directed well when significant eosinophilia has been demonstrated.

Traditional features of ECRS include asthma, polyps, aspirin sensitivity, high serum eosinophilia and IgE. However, many ECRS patients may not present with classic features and the associations between tissue histopathology and other surrogate markers of this disease are yet to be defined. The objective of this study was to determine the associations between histopathology, serology and clinical characteristics of the ECRS patient to assist post ESS management.

Material and Methods

Study design

A cross-sectional study of consecutive patients undergoing sinus surgery was undertaken. Data from histopathology, serum markers and clinical presentations was

pre-determined before the process of data collection and review. The study had ethical approval from the St Vincent's institutional review board.

Patient population

Adult patients (>18 years) with CRS with or without polyps who underwent ESS in a tertiary referral clinic were reviewed. CRS patients were defined according to EP3OS(Fokkens, Lund et al. 2007). All patients underwent ESS after failing previous medical therapy. No patients were using oral steroid for 4 weeks prior to surgery. Demographic data was recorded.

Histopathologic profiling

Histopathologic profiling used in our institution is as displayed in Figure 2.1. The report focuses on the status of tissue inflammation and mucin. The following components of the report are: Overall degree of inflammation (absent, mild, moderate severe), tissue eosinophilia (Figure 2.2a) (<5 per high power field (HPF), 5-10 per HPF, >10 per HPF), neutrophilic infiltrate (absent, focal, diffuse), inflammatory cell predominance (Lymphocytic, Lymphoplasmocytic, Eosinophilic, Lymphohistiocytic, Neutrophilic, Others), basement membrane thickening (absent, <7.5um, 7.5-15um, >15um)), sub-epithelial oedema (absent, mild, moderate, severe), hyperplastic/papillary change (absent, present), mucosal ulceration (absent, present), squamous metaplasia (absent, present), fibrosis (absent, present, extensive). Mucin was examined for the presence of fungal elements (absent, present), Charcot-Leyden Crystals (Figure 2.2b) (absent, present) and eosinophil aggregates (Figure 2.2c) (absent, present).

St Vincent's Hospital

Chronic Rhinosinusitis Histopathology report

Tissue			
	Tissue present	☐Respiratory mucosa ☐mucoserous glands ☐bone	
	Overall degree of inflammation	☐ absent ☐ mild	☐ moderate ☐ severe
	Eosinophil Count	☐ <5 per HPF ☐ 5-10 per HPF ☐ >10 per HPF	
	Neutrophillic Infiltrate	☐ absent ☐ focal ☐ diffuse	
	Inflammatory predominance	☐ Lymphocytic ☐ Lymphoplasmocytic ☐ Eosinophilic	☐ lymphohistiocytic ☐ Neutrophilic ☐Other_____
	Basement Membrane thickening	☐ absent ☐ <7.5µm ☐ 7.5 - 15µm ☐ >15 µm	
	Sub-epithelial oedema	☐ absent ☐ mild (focal or perivascular only) ☐ moderate (distortion of mucosal structure) ☐ severe (diffuse/polypoid change)	
	Hyperplastic/papillary change	☐ absent ☐ present	
	Mucosal ulceration	☐ absent ☐ present (with reactive changes)	
	Squamous metaplasia	☐ absent ☐ present	
	Fibrosis	☐ absent ☐ partial ☐ extensive	
Mucin			
	Fungal elements	☐ absent ☐ present	
	Charcot-Leyden Crystals	☐ absent ☐ present	
	Eosinophil aggregates	☐ absent ☐ present	
Conclusion			
	Site:		
	Diagnosis:		

Figure 2.1 Histopathologic profiling- as a structured inflammation report for routine clinical cases

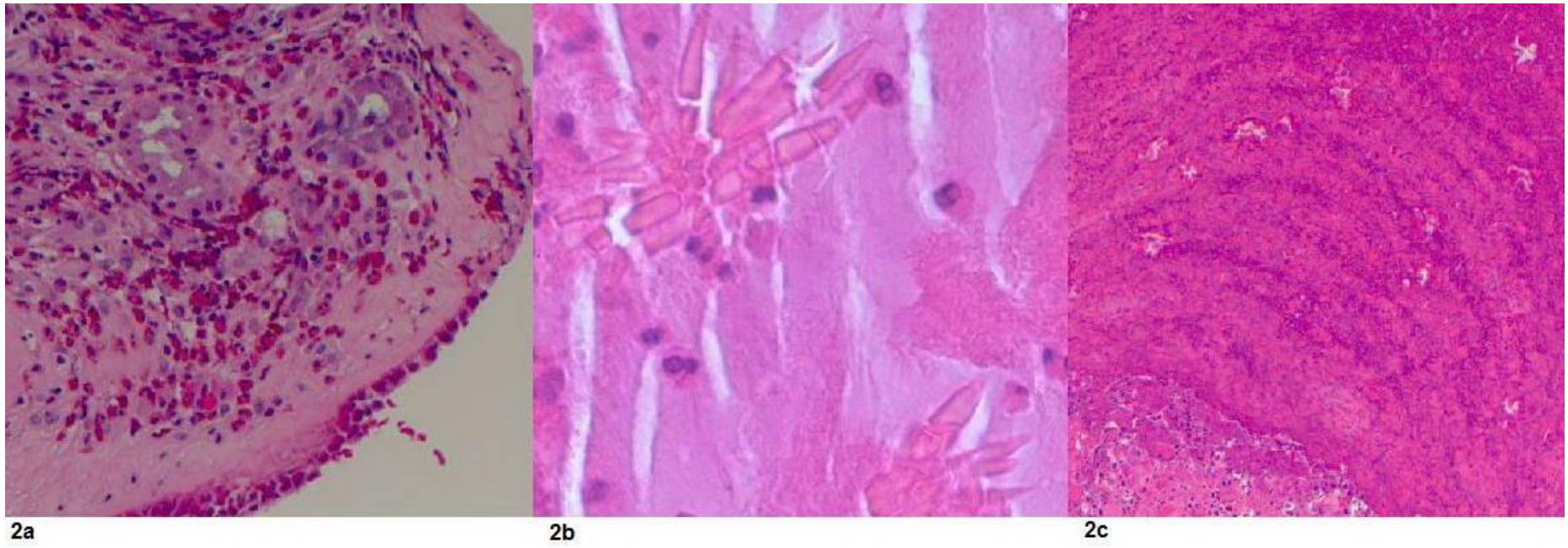


Figure2.2 Histopathology of ECRS: (2a) Tissue eosinophilia, (2b) Charcot-Leyden Crystals, (2c) Eosinophil aggregates

For the purpose of this study, the focus was primarily on histopathologic profiling of eosinophil-related findings. ECRS was histopathologically defined when tissue eosinophil was greater than 10/HPF(Soler, Sauer et al. 2010).

Serum markers

The seromarkers reported were: white blood cell count ($x10^9$/L), eosinophil count ($x10^9$/L), ESR (mm/hr), C-reactive protein (CRP)(mg/L), total IgE (kU/L) and radioallergosorbent tests (RAST) on a scale from 0 to 6 for grass mix, dust mite, moulds and epithelial dander.

Radiologic assessment

All pre-operative computed tomography (CT) scans were evaluated with Lund-Mackay scores and radiological osteitis scores. The maximum bone thickness of the anterior ethmoid, posterior ethmoid, maxillary and sphenoid sinuses was measured. Frontal sinus thickness was not evaluated. Osteoneogenesis was defined as bone thickness greater than 3 mm radiologically. as described by Lee et al(Lee, Kennedy et al. 2006). Osteitis was scored as 0 (<3mm), 1 (3-5mm) and 2 (>5mm). The maximum osteitis score for each individual was 16.

Clinical presentations

The Sino-Nasal Outcome Test 22(SNOT-22) was used for disease-specific quality of life assessment(Hopkins, Gillett et al. 2009). Pre-operative Lund-Kennedy endoscopy scores were recorded. Comorbidity of asthma was defined as clinically using an inhaled β-agonist or corticosteroid. Patients with suspected aspirin sensitivity on history were confirmed with a nasal lysine aspirin challenge as per the European Guidelines(Nizankowska-Mogilnicka, Bochenek et al. 2007).

Statistical analysis

Descriptive data was presented as percentage and mean±SD. Pearson correlation coefficients were performed for linear relationship of scale variables. Kendall's tau-B was used for ordinal values. Chi squared analysis was used for relationships of nominal variables. Student's T-test (two-tailed) was used for comparisons of parametric data. Mann-Whitney U Test (two-tailed) was used to compare non-parametric data. Statistical analyses were performed using SPSS v 17.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

Fifty-one patients with a mean age of 46.6 ±4.1 years were assessed. Twenty-four (47.1%) patients were female. Two (3.9%) patients were smokers and twelve (23.5%) had asthma. Two (3.9%) patients had aspirin hypersensitivity. Twenty-nine (56.9%) patients were diagnosed as CRSsNP, nineteen (37.3%) patients had CRSwNP and three (5.9%) had allergic fungal sinusitis.

The mean pre-operative Lund-Mackay CT score was 11.7 ±6.7 and the mean osteitis score was 1.0±1.6. The mean pre-operative SNOT-22 was 2.0 ±1.0 and the mean endoscopic score was 4.7±2.7

The mean serum total IgE was 137.8 ±165.6 kU/L. The mean white cell count was 7.1±2.4 $x10^3$/mL. The mean eosinophil count was 0.3 ±0.4 $x10^3$/mL. The mean ESR was 8.7±7.1mm/h. The mean CRP was 3.8±5.mg/L. RAST was negative for grass (57.6%), dust (63.6%), mould (75.8%) and epithelial (75.8%). Baseline histopathology by CRS subtypes and asthma status is displayed in Table 2.1.

Association between histopathology and clinical presentation

		Histopathology by CRS subtype: n (%)			Histopathology by asthma status: n (%)	
		CRSsNP	CRSwNP	AFS	No asthma	asthma
tissue eosinophilia (n=49)	<5 HPF	18 (66)	0 (0)	0 (0)	15 (41)	3 (25)
	5-10 HPF	4 (15)	3 (16)	1 (33)	6 (16)	2 (17)
	>10 HPF	5 (19)	16 (84)	2 (67)	16 (43)	7 (58)
Mucin Charcot-Leyden Crystals (n=43)	Absent	21 (91)	14 (82)	0 (0)	27 (79)	8 (89)
	Present	2 (9)	3 (18)	3 (100)	7 (21)	1 (11)
Mucin eosinophil aggregates (n=43)	Absent	20 (87)	12 (71)	0 (0)	26 (76)	6 (67)
	Present	3 (13)	5 (29)	3 (100)	8 (24)	3 (33)

Table2.1 Baseline histopathology

The clinical diagnosis (CRSsNP, CRSwNP or AFS) was significantly associated with 6 markers (Table 2.2): tissue eosinophilia (x^2=25.76,p<0.01), inflammatory cell predominance (x^2=22.17,p=0.01), sub-epithelial oedema(x^2=22.03,p<0.01), squamous metaplasia (x^2=7.02,p=0.03), Charcot-Leyden crystals (x^2=14.63,p<0.01) and mucin eosinophil aggregates (x^2=10.76,p=0.01). There was no significant association between any histopathololology markers and gender, asthma or smoking status. Twenty-three (46.9%) patients had strong tissue eosinophilia (>10/HPF). Tissue eosinophilia was prominent in patients with polyps (84%) (x^2=25.76, p<0.01), but still seen in a subgroup of non-polyp patients (19%), Asthma status did not predict high tissue eosinophilia (p=0.60) with 43% of non-asthmatics also showing high tissue eosinophilia. Five out of 24 (21%) patients with no asthma and no polyps (CRSsNP) still showed high tissue eosinophilia.

Association between histopathology and serological indices

There was an association demonstrated between tissue eosinophilia and serum eosinophilia (r=0.33, p=0.03) but not seen with serum total IgE. Serum eosinophilia only predicted tissue eosinophilia at >0.30 $x10^9$/L or 4.4% of white blood cells (sensitivity 52%, specificity 87%, positive predictive value 79%, negative predictive value 67%, ROC p=0.001). Considering the low negative predictive valve and the threshold of serum eosinophilia predicting high tissue eosinophilia, its utility may be limited unless obviously high. Serum IgE was non-predictive (ROC p=0.08). ROC curves by tissue eosinophilia of serum eosinophil count and the serum eosinophil percentage of white blood cells are shown in Figure 2.3.

	gender*	asthma*	aspirin sensitivity*	smoker*	diagnosis*	SNOT-22^	endoscopic score^	CT score^	osteitis@
tissue eosinophilia	NS	NS	NA	NS	<0.01	NS	0.004	0.001	NS
mucin Charcot-Leyden Crystals	NS	NS	NA	NS	<0.01	NS	0.03	NS	NS
mucin eosinophil aggregates	NS	NS	NA	NS	0.01	NS	0.03	NS	NS
tissue eosinophilia	0.03	NS	NS	NS	NS	NS	NS	NS	NS
mucin Charcot-Leyden Crystals	NS	0.03	NS	NS	NS	NS	NS	NS	NS
mucin eosinophil aggregates	NS	0.03	NS	NS	NS	NS	NS	NS	NS

Table 2.2: Statistical significance (p value) of the associations between histopathology, clinical presentations and seromarkers

* Chi squared ^ Student T-test @ Mann-Whitney U Test # Person correlation coefficients + Kendall's tau-B

NS- statistical non difference at the 0.05 α level NA- not available for analysis

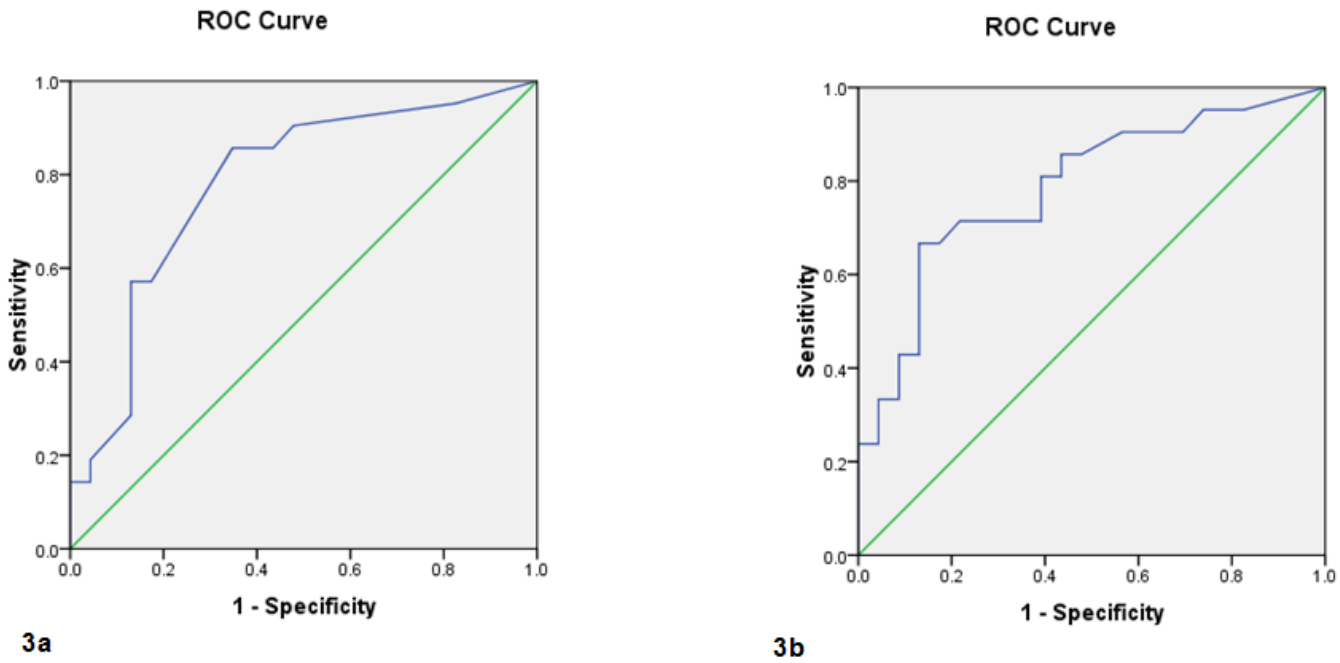


Figure 2.3 ROC curves for the diagnostic accuracy of serum eosinophil in predicting tissue eosinophilia (>10/HPF):

(3a) by total serum eosinophil count (x10^9/L), (3b) by serum eosinophil as a percentage of total white blood cells

Serum total IgE was associated with the presence of Charcot-Leyden Crystals in the mucin (r=0.35, p=0.03) and mucin eosinophil aggregates(r=0.36, p=0.03) (Table 2.2).

Comparison of clinical severity of ECRS and non ECRS by histopathology

Patients with high tissue eosinophilia of >10/HPF were defined as Eosinophilic Chronic rhinosinusitis (ECRS). Patients with ECRS and had significantly worse endoscopic scores (6.0±2.1) compared to non-ECRS (3.8±2.7), p=0.004. Similarly the mean CT scores of ECRS (15.1±6.2) were significantly more severe than non-ECRS (8.8±5.5), p=0.001. The mean SNOT-22 (1.92±1.1 and 1.99±1.0, p=0.84) and osteitis scores (1.24±2.1 and 0.80±1.3, p=0.38) of ECRS and non ECRS respectively were not significantly different.

Patients with eosinophil aggregates in their mucin had significantly worse endoscopic scores (6.6±2.7) than those without aggregates (4.6±2.3), p=0.03. The mean SNOT-22 (1.68±0.8 and 1.89±1.0, p=0.52), CT score (15.4±5.4 and 11.2±6.6, p=0.07) and osteitis scores (1.10±2.2 and 1.13±1.6, p=0.96) of ECRS and non ECRS respectively were not significantly different.

Charcot-Leyden Crystals were seen in patients with and without Polyps as well as in all AFS patients. Patients with Charcot-Leyden Crystals had a significantly more severe endoscopic score (6.6±2.7) than those without (4.6±2.3), p=0.03, however the mean SNOT-22 (1.83±0.8 and 1.84±0.9, p=0.99), CT score (15.3±5.4 and 11.6±6.6, p=0.16) and osteitis scores (1.38±2.4 and 1.06±1.6, p=0.65) of ECRS and non ECRS respectively were not significantly different.

Discussion

The number of eosinophils seen in sino-nasal tissue is increased in patients with CRSwNP(Scavuzzo, Fattori et al. 2005; Polzehl, Moeller et al. 2006; Van Zele, Claeys et al. 2006), allergic fungal rhinosinusitis(Carney, Tan et al. 2006), nonallergic fungal rhinosinusitis(Carney, Tan et al. 2006) and aspirin exacerbated eosinophilic rhinosinusitis(Soler, Sauer et al. 2009). There is currently no consensus on how to quantitatively define tissue eosinophilia. The overall mean percentage of tissue eosinophil (of inflammatory cells/HPF) is often 50% in CRSwNP, compared to 2% of CRSsNP (Fokkens, Lund et al. 2007). The current cut-offs proposed in the literature to define ECRS include tissue eosinophil >5% of all leukocytes in 5 visual field(Kim, Hong et al. 2007) or a tissue eosinophil count of greater than 5 cells /HPF (Kountakis, Arango et al. 2004; Soler, Sauer et al. 2009; Soler, Sauer et al. 2010). Recently, Soler et al proposed an optimal cut point of > 10 eosinophil/ HPF as this reflects the largest absolute difference in score changes on the Rhinosinusitis Disability Index (RSDI) after ESS(Soler, Sauer et al. 2010). The role of eosinophilia in defining CRS in the literature is summarized in Table 2.3 (See Appendix 2.1)

The presence of polyps predicts ECRS and this was well reported with other studies linking the number of eosinophil in CRSwNP subgroup (Scavuzzo, Fattori et al. 2005; Polzehl, Moeller et al. 2006; Van Zele, Claeys et al. 2006; Soler, Sauer et al. 2009) however it is not exclusively seen in polyp patients with 19% of CRSsNP patients having high tissue eosinophilia. This was an important group and potentially associated with the worst outcome(Soler, Sauer et al. 2010). Although serum eosinophilia predicts tissue eosinophilia, its utility is limited. The cut point at >0.30 $x10^9$/L or 4.4% of white blood cells as proposed is still within the normal range and has a negative predictive value of 67%. Han et al also proposed the same cut point of >0.30 $x10^9$/L for predicting bronchial hyperresponsiveness in CRSsNP with

sensitivity 70% and specificity 70%(Han, Kim et al. 2009). Sakuma, et al proposed the cut point of ≥ 6% eosinophil of total leukocytes for predicting ECRS with a sensitivity of 97.4% and a specificity of 70.7%. However, all their patients had abnormal serum eosinophilia as an inclusion criteria(Sakuma, Ishitoya et al. 2011). Lackner et al found that eosinophil as a percentage of leukocytes was not different between ECRS and controls, but they defined ECRS based purely on the phenotype of CRSwNP (Lackner, Raggam et al. 2007). In our study, three out of nineteen (16%) CRSwNP patients were non ECRS, so a subgroup of CRSwNP without high tissue eosinophilia may bring different results to the Lackner study. Serum IgE did not predict ECRS. Scavuzzo et al found a higher serum IgE level in CRSwNP compared to patients without CRS but they did not compare true eosinophilic inflammation (Scavuzzo, Fattori et al. 2005). Also considering a significant proportion of our CRSsNP had high eosinophilia (19%), this casts doubt on the conclusions of studies that only use the polyp phenotype to classify patients.

In our study, the diagnosis of asthma status was self-reported and based on current inhaled beta-agonist or corticosteroid use. Methacholine or beta-agonist challenge testing is not routinely performed in clinical practice. Without such tests, the prevalence of asthma in this study may be underreported. Our study, however, reflects clinical practice with asthma patients either self reporting symptoms or asthma medication used. This represents the real life dilemma of trying to establish the ECRS patient. In contrast to previous studies(Kountakis, Arango et al. 2004; Soler, Sauer et al. 2009), we found no association between tissue eosinophilia (defined as >10 cells/HPF) and asthma.

ECRS patients had more severe endoscopic and CT scores than non ECRS patients. In agreement with previous studies(Kountakis, Arango et al. 2004; Soler,

Sauer et al. 2009), the mean SNOT-22 and osteitis scores were not different from non ECRS. The literature on the association of eosinophilia with disease severity is summarized in Table 2.4 (See Appendix 2.2).

Tissue eosinophilia predicts significantly less improvement of symptoms(Baudoin, Cupic et al. 2006; Bonfils, Badoual et al. 2009; Myller, Toppila-Salmi et al. 2009), quality of life(Soler, Sauer et al. 2010) and relapse(Matsuwaki, Ookushi et al. 2008; Gelardi, Fiorella et al. 2009; Tosun, Arslan et al. 2010) after ESS. Although, some studies have not demonstrated a significant difference in the number of tissue eosinophil between groups of patients defined as successful or failed outcomes (Eweiss, Dogheim et al. 2009), there is a preponderance of studies which do demonstrate a link. The surgical biopsies in these patients may be altered by the use of preoperative systemic steroids and a confounding factor(Mullol, Obando et al. 2009). The relationship of eosinophilia to overall prognosis from the literature is summarized in Table 2.5 (See Appendix 2.3).

There are significant implications for treatment seen here, for example the efficacy of macrolides is greatest in neutrophilic diseases(Haruna, Shimada et al. 2009). This is due to the immunomodulatory response produced by macrolide therapy, which suppresses IL8 production and neutrophilic airway inflammation and thus likely to not be an effective treatment modality for ECRS (Harvey, Wallwork et al. 2009). Importantly, the presence of severe tissue eosinophilia in patients with CRSsNP, and who are without the other stigmata of disease, may explain the spectacular failure of some patients undergoing ESS with apparently limited disease. The possible injurious effects of surgery in patients with a developing eosinophilic inflammation may explain such phenomenon. Early postoperative commencement of either systemic or aggressive high dose topical steroid therapy in these patients may

greatly improve outcomes. It is highly likely that such a patient sub-group will go on to develop significant nasal polyps over time.

Conclusion

The identification of high eosinophilia in CRS is important. The diagnosis, severity and prognosis of ECRS differ greatly from other forms of CRS. Traditional clinical features of the ECRS phenotype are not necessarily good markers for the presence of eosinophilia in the sinus mucosa. Simple blood based measures have limited utility for assessing the degree of tissue eosinophilia in the upper airway. Tissue eosinophilia is strongly associated with ECRS and may be a good marker for ECRS regardless of CRS subtype. Considering the implications from published research on eosinophilia, assessment for tissue eosinophilia should be incorporated as part of a structured histology report in routine clinical practice.

References

Amorim, M. M., A. Araruna, L. B. Caetano, et al. Nasal eosinophilia: an indicator of eosinophilic inflammation in asthma. *Clin Exp Allergy* 2010;40(6): 867-874.

Ardehali, M. M., A. Amali, M. Bakhshaee, Z. Madani and M. Amiri. The comparison of histopathological characteristics of polyps in asthmatic and nonasthmatic patients. *Otolaryngology - Head & Neck Surgery* 2009;140(5): 748-751.

Armengot, M., L. Garin and C. Carda. Eosinophil degranulation patterns in nasal polyposis: an ultrastructural study. *American Journal of Rhinology & Allergy* 2009;23(5): 466-470.

Bachert, C., S. E. M. Claeys, P. Tomassen, T. van Zele and N. Zhang. Rhinosinusitis and asthma: a link for asthma severity. *Current Allergy & Asthma Reports* 2010;10(3): 194-201.

Bateman, N. D., A. Shahi, K. M. Feeley and T. J. Woolford. Activated eosinophils in nasal polyps: a comparison of asthmatic and non-asthmatic patients. *Clinical Otolaryngology* 2005;30(3): 221-225.

Baudoin, T., H. Cupic, G. Geber, et al. Histopathologic parameters as predictors of response to endoscopic sinus surgery in nonallergic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;134(5): 761-766.

Bhattacharyya, N. Cytological characterization of persistent paranasal sinus secretions after endoscopic sinus surgery. *American Journal of Rhinology* 2007;21(1): 1-4.

Bonfils, P., C. Badoual, N. A. Bonfils, D. Gallas and D. Malinvaud. Eosinophil infiltration of nasal polyps in patients with nasal polyposis: role in clinical evolution after medical and surgical treatment. *J Laryngol Otol* 2009;123(5): 509-516.

Carney, A. S., L.-W. Tan, D. Adams, et al. Th2 immunological inflammation in allergic fungal sinusitis, nonallergic eosinophilic fungal sinusitis, and chronic rhinosinusitis. *Am J Rhinol* 2006;20(2): 145-149.

Chan, Y. and F. A. Kuhn. An update on the classifications, diagnosis, and treatment of rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2009;17(3): 204-208.

Eweiss, A., Y. Dogheim, M. Hassab, H. Tayel and Z. Hammad. VCAM-1 and eosinophilia in diffuse sino-nasal polyps. *Eur Arch Otorhinolaryngol* 2009;266(3): 377-383.

Fokkens, W., V. Lund, J. Mullol and E. P. P. o. R. a. N. P. group. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007;(20): 1-136.

Gelardi, M., R. Fiorella, M. L. Fiorella, et al. Nasal-sinus polyposis: clinical-cytological grading and prognostic index of relapse. *J Biol Regul Homeost Agents* 2009;23(3): 181-188.

Han, D. H., S. W. Kim, S. H. Cho, et al. Predictors of bronchial hyperresponsiveness in chronic rhinosinusitis with nasal polyp. *Allergy* 2009;64(1): 118-122.

Haruna, S., C. Shimada, M. Ozawa, S. Fukami and H. Moriyama. A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis. *Rhinology* 2009;47(1): 66-71.

Harvey, R. J., B. D. Wallwork and V. J. Lund. Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2009;29(4): 689-703.

Hopkins, C., S. Gillett, R. Slack, V. J. Lund and J. P. Browne. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009;34(5): 447-454.

Kim, H. Y., H.-J. Dhong, S. K. Chung, Y.-J. Chung and J. Y. Min. Prognostic factors of pediatric endoscopic sinus surgery. *International Journal of Pediatric Otorhinolaryngology* 2005;69(11): 1535-1539.

Kim, J. W., S. L. Hong, Y. K. Kim, et al. Histological and immunological features of non-eosinophilic nasal polyps. *Otolaryngol Head Neck Surg* 2007;137(6): 925-930.

Kirtsreesakul, V. and V. Atchariyasathian. Nasal polyposis: role of allergy on therapeutic response of eosinophil- and noneosinophil-dominated inflammation. *American Journal of Rhinology* 2006;20(1): 95-100.

Kountakis, S. E., P. Arango, D. Bradley, Z. K. Wade and L. Borish. Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope* 2004;114(11): 1895-1905.

Lackner, A., R. B. Raggam, H. Stammberger, et al. The role of interleukin-16 in eosinophilic chronic rhinosinusitis. *European Archives of Oto-Rhino-Laryngology* 2007;264(8): 887-893.

Lanza, D. C. and D. W. Kennedy. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997 117(3 Pt 2): S1-7.

Lee, J. T., D. W. Kennedy, J. N. Palmer, M. Feldman and A. G. Chiu. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol* 2006;20(3): 278-282.

Lee, T. J., C. W. Liang, P. H. Chang and C. C. Huang. Risk factors for protracted sinusitis in pediatrics after endoscopic sinus surgery. *Auris Nasus Larynx* 2009;36(6): 655-660.

Matsuwaki, Y., T. Ookushi, D. Asaka, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. *Int Arch Allergy Immunol* 2008;146 Suppl 1: 77-81.

Meltzer, E. O., D. L. Hamilos, J. A. Hadley, et al. Rhinosinusitis: Establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004;131(6 Suppl): S1-62.

Mullol, J., A. Obando, L. Pujols and I. Alobid. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol Allergy Clin North Am* 2009;29(4): 657-668.

Myller, J. P., S. K. Toppila-Salmi, E. M. Toppila, et al. Mucosal eosinophils and l-selectin ligands are associated with invasive and noninvasive sinus surgery outcomes. *Am J Rhinol Allergy* 2009;23(1): 21-27.

Nizankowska-Mogilnicka, E., G. Bochenek, L. Mastalerz, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10): 1111-1118.

Polzehl, D., P. Moeller, H. Riechelmann and S. Perner. Distinct features of chronic rhinosinusitis with and without nasal polyps. *Allergy* 2006;61(11): 1275-1279.

Ponikau, J. U., D. A. Sherris, G. M. Kephart, et al. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitis. *Journal of Allergy & Clinical Immunology* 2005;116(2): 362-369.

Poznanovic, S. A. and T. T. Kingdom. Total IgE levels and peripheral eosinophilia: correlation with mucosal disease based on computed tomographic imaging of the paranasal sinus. *Archives of Otolaryngology -- Head & Neck Surgery* 2007;133(7): 701-704.

Ragab, A., P. Clement and W. Vincken. Correlation between the cytology of the nasal middle meatus and BAL in chronic rhinosinusitis. *Rhinology* 2005;43(1): 11-17.

Rupa, V., M. Jacob, M. S. Mathews and M. S. Seshadri. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. *Eur Arch Otorhinolaryngol* 2010;267(2): 233-238.

Sakuma, Y., J. Ishitoya, M. Komatsu, et al. New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. *Auris Nasus Larynx* 2011;38(5): 583-588.

Scavuzzo, M. C., B. Fattori, R. Ruffoli, et al. Inflammatory mediators and eosinophilia in atopic and non-atopic patients with nasal polyposis. *Biomedicine & Pharmacotherapy* 2005;59(6): 323-329.

Scavuzzo, M. C., B. Fattori, R. Ruffoli, et al. Inflammatory mediators and eosinophilia in atopic and non-atopic patients with nasal polyposis. *Biomed Pharmacother* 2005;59(6): 323-329.

Schmid, C., W. Habermann, H. Braun, et al. Released intranasal eosinophilic major basic protein as a diagnostic marker for polypoid chronic rhinosinusitis. *Otolaryngology - Head & Neck Surgery* 2010;143(3): 386-391.

Sok, J. C. and B. J. Ferguson. Differential diagnosis of eosinophilic chronic rhinosinusitis. *Current Allergy & Asthma Reports* 2006;6(3): 203-214.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

Soler, Z. M., D. A. Sauer, J. Mace and T. L. Smith. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2009;141(4): 454-461.

Soler, Z. M., D. A. Sauer, J. C. Mace and T. L. Smith. Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy* 2010;24(4): 281-285.

Steinke, J. W., S. C. Payne, M. E. Tessier, et al. Pilot study of budesonide inhalant suspension irrigations for chronic eosinophilic sinusitis. *J Allergy Clin Immunol* 2009;124(6): 1352-1354

Sun, D. I., Y. H. Joo, H. J. Auo and J. M. Kang. Clinical significance of eosinophilic cationic protein levels in nasal secretions of patients with nasal polyposis. *Eur Arch Otorhinolaryngol* 2009;266(7): 981-986.

ten Brinke, A., D. C. Grootendorst, J. T. Schmidt, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *Journal of Allergy & Clinical Immunology* 2002;109(4): 621-626.

Tosun, F., H. H. Arslan, Y. Karslioglu, M. S. Deveci and A. Durmaz. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol* 2010;119(7): 455-459.

Tosun, F., H. H. Arslan, Y. Karslioglu, M. S. Deveci and A. Durmaz. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Annals of Otology, Rhinology & Laryngology* 2010;119(7): 455-459.

Van Zele, T., S. Claeys, P. Gevaert, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* 2006;61(11): 1280-1289.

Yao, T., Y. Kojima, A. Koyanagi, et al. Eotaxin-1, -2, and -3 immunoreactivity and protein concentration in the nasal polyps of eosinophilic chronic rhinosinusitis patients. *Laryngoscope* 2009;119(6): 1053-1059.

Chapter2 Appendix

Appendix2.1

Table 2.3 Eosinophilia defining polypoid CRS

Appendix 2.2

Table 2.4 Eosinophilia with clinical severity

Appendix 2.3

Table 2.5 Eosinophilia with prognosis

Author	Year	n	Marker of eosinophilic inflammation	Association
Snidvongs(current study)	2011	51	tissue eosinophil (cells/HPF, scored as <5, 5-10, >10)	Tissue eosinophil (x^2=25.76, p<0.01), mucin Charcot-Leyden Crystals (x^2=14.63, p<0.01), mucin eosinophil aggregates (x^2=10.76, p=0.01) associated with the presence of polyps and AFS. None of these three markers associated with asthma status. ECRS was defined by having tissue eosinophil greater than 10cells/HPF.
Sakuma(Sakuma, Ishitoya et al. 2011)	2011	124	serum eosinophil (%per WBC)	Serum eosinophil percentage per WBC predicted ECRS (OR=1.49, p<0.001). The cut point of $\geq$ 6% had a sensitivity of 97.4% and a specificity of 70.7%.
Schmid(Schmid, Habermann et al. 2010)	2010	44	mucus eosinophil major basic protein levels	Mucus eosinophil major basic protein levels were elevated in CRSwNP (87%) compared to non CRS (5%), p<0.001.

Soler(Soler, Sauer et al. 2010)	2010	102	tissue eosinophil (cells/HPF)	The cut point of >10 cells/HPF associated less improvement in Rhinosinusitis Disability Index (RSDI) scores (p=0.04) in CRS patients.
Yao(Yao, Kojima et al. 2009)	2009	33	tissue eosinophil (cells/HPF)	Average number of tissue eosinophil (p<0.001) was higher in ECRS.
Kim(Kim, Hong et al. 2007)	2007	30	tissue eosinophil (% of the whole leukocytes /5 visual fields)	The average percentage out of the whole leukocytes of tissue eosinophil was greater in ECRS (26.1% + 8.2%) than nonECRS (3.1% + 2.1%) p=0.0001.
Lackner(Lackner, Raggam et al. 2007)	2007	20	tissue eosinophil(% of the whole leukocytes /HPF)	The percentage of tissue eosinophil was >50% in all ECRS and <30% in all healthy control.
Carney(Carney, Tan et al. 2006)	2006	58	tissue eosinophil (cells/HPF)	Mean tissue eosinophil (cells/HPF) was raised in patients with AFS (20; p<0.0001), nonallergic eosinophilic fungal sinusitis (14; p<0.0001), and CRS without polyps (8; p=0.001) when compared with healthy controls (0.2).

Polzehl(Polzehl, Moeller et al. 2006)	2006	20	tissue eosinophil (cells/HPF)	Median tissue eosinophil in patients with CRSwNP [51.7 (48.8–102.0)] was greater than CRSsNP [14.9(6.2–36.6)], p= 0.02.
Van Zele(Van Zele, Claeys et al. 2006)	2006	40	tissue eosinophil (cells/HPF)	CRSwNP had higher levels of tissue eosinophil (p=0.02) and eosinophil cationic protein(p=0.004) compared to CRSsNP.
Ponikau(Ponikau, Sherris et al. 2005)	2005	22	mucus toxic major basic protein (MBP) (microg/mL)	MBP concentrations in mucus reached 11.7 microg/mL in CRSwNP but were not detectable in healthy control subjects.
Scavuzzo(Scavuzzo, Fattori et al. 2005)	2005	44	tissue eosinophil (cells/ HPF)	Tissue eosinophilia (p<0.0001) and mucus ECP level (p<0.0001) were higher in patients with CRSwNP compared with non CRS.

Table2.3 Eosinophilia defining polypoid CRS

Author	Year	n	Marker of eosinophilic inflammation	Association
Snidvongs(current study)	2011	51	tissue eosinophil (cells/HPF, scored as <5, 5-10, >10)	ECRS had more severity in terms of endoscopic score (6.0±2.1) than non ECRS (3.8±2.7), p=0.004 and CT scores (15.1±6.2) than non ECRS (8.8±5.5), p=0.001. The mean SNOT-22 and osteitis score were not different between ECRS and non ECRS. ECRS was defined by having tissue eosinophil greater than 10cells/HPF.
Bachert(Bachert, Claeys et al. 2010)	2010	163	tissue eosinophil cationic protein (protein expression) (g/L)	Tissue eosinophil cationic protein at >17,109 g/L predicted asthma in patients with CRSwNP (odds ratio 8 [95% CI, 1.3-256]).
Soler(Soler, Sauer et al. 2010)	2010	101	tissue eosinophil (cells/HPF)	Mean tissue eosinophil count was higher in CRS patients with anosmia (140± 167.3) than normosmia (47.4± 88.2), p=0.001.

Ardehali(Ardehali, Amali et al. 2009)	2009	50	tissue eosinophil (scored as 0; 0-1; 3-10; 11-30 ;or >30 cells per HPF)	Eosinophilic infiltration was more prominent in the asthmatic CRSwNP compared with non-asthmatic CRSwNP (p=0.026).
Armengot(Armengot, Garin et al. 2009)	2009	36	tissue eosinophil (scored as <5, 5-19, 20-50 and >50 cells per HPF)	The mean number of tissue eosinophil was less when polyps not surpassing the middle turbinate compared to polyps with more polyp score (*p* =0.0342).
Han(Han, Kim et al. 2009)	2009	122	tissue eosinophil (cells/HPF)	The mean tissue eosinophil counts (p = 0.045) and serum eosinophil counts (p = 0.001) were higher in patients with CRSsNP with bronchial hyperresponsiveness (BHR) group than non-BHR.
Soler(Soler, Sauer et al. 2009)	2009	147	tissue eosinophil (≤5 or >5cells/HPF)	Tissue eosinophil greater than 5 cells/HPF correlated with the presence of nasal polyposis (r = -0.367; P < 0.001), asthma (r = 0.264; P = 0.001), aspirin intolerance (r = 0.279; P = 0.001), worse disease severity on CT (r = 0.414; P < 0.001), endoscopy (r = 0.376; P < 0.001), and smell identification test(r = -0.253; P = 0.002) without correlation with the Rhinosinusitis Disability Index [RSDI], the Chronic Sinusitis Survey [CSS] and Short Form Health Survey [SF-36].

Sun(Sun, Joo et al. 2009)	2009	78	tissue eosinophil (cells/HPF)	Tissue eosinophil was higher in CRSwNP with asthma (54±24) than non-asthma (21±15) and higher in aspirin intolerance (62±29) than tolerance (46±23). Significance was not provided.
Matsuwaki(Matsuwaki, Ookushi et al. 2008)	2008	56	tissue eosinophil (cells/HPF)	Tissue eosinophilia in CRS with asthma was greater when compared to CRS without asthma ($p<0.01$).
Poznanovic(Poznanovic and Kingdom 2007)	2007	303	serum eosinophil (cells/microL)	Eighty-nine percent of the abnormal eosinophil counts (>550 cells/microL) were associated with CT scores higher than 12($r=0.05$, $P>.05$).
Bateman(Bateman, Shahi et al. 2005)	2005	59	tissue eosinophil (scored from 0 to 100, based on counted cells/HPF)	Median tissue eosinophil count was higher in the asthma [73.5, (5.8-98)] over non-asthma [59, (15-94)] in CRSwNP ($p<0.05$).

Ragab(Ragab, Clement et al. 2005)	2005	25	mucus eosinophil (cells/mm^3)	Eosinophil count in middle meatal lavage of CRS were greater in asthma subgroup (7.3±3.8) than CRS with normal airway (2.4±7), p=0.045 and were correlated to FEVI (p=0.042) and Tiffineau index (p=0.037).
Kountakis(Kountakis, Arango et al. 2004)	2004	52	tissue eosinophil (≤5 or>5cells per HPF)	Patients with tissue eosinophil >5cells per HPF had more frequency of asthma (p=0.05), more severity in CT score (17.3±1.0 versus 9.5±1.2, p= .00002) and endoscopy score (7.2 ±0.7 versus 4.1± 0.8, p= .007) than ≤5 cells per HPF. There was no difference in symptom scores between the two groups.
Ten Brinke(ten Brinke, Grootendorst et al. 2002)	2002	89	serum eosinophil (x10/L^9) in asthmatic patients	Median serum eosinophil were higher in asthma with extensive sinus disease [0.44, (0.05-1.12)] than limited sinus disease [0.17, (0.01-1.29)], p<0.001. There was a significant positive correlation between serum eosinophil and CT scores (r = 0.46, p<0.001).

Table2.4. Eosinophilia with clinical severity

Author	Year	n	Marker of eosinophilic inflammation	Association
Soler(Soler, Sauer et al. 2010)	2010	102	tissue eosinophil(cells /HPF)	ECRS showed less improvement after ESS than non ECRS in the RSDI total (p = 0.044), RSDI functional (p = 0.018), CSS medication (p = 0.013), SF-36 general health (p = 0.008), SF-36 physical role (p = 0.036), and SF-36 vitality (p = 0.034) scales.
Soler(Soler, Sauer et al. 2010)	2010	101	tissue eosinophil (cells /HPF)	Tissue eosinophilia did not associate with olfactory recover after surgery, p=0.638.
Tosun(Tosun, Arslan et al. 2010)	2010	42	tissue eosinophil densities (<4 OR ≥4cells/ 1,000 microm^2) in CRSwNP	Tissue eosinophil densities ≥4 cells/ 1,000 microm^2 had a higher postoperative recurrence rate (81.8%) than <4 cells/ 1,000 microm^2 (25%),p<0.05.
Bonfils(Bonfils, Badoual et al. 2009)	2009	144	tissue eosinophil (%/WBC/HPF) in CRSwNP	Tissue eosinophil of ≤50 %/WBC/HPF had poorer control of posterior rhinorrhea after combined surgery and corticosteroid therapy (p=0.01).

Eweiss(Eweiss, Dogheim et al. 2009)	2009	50	tissue eosinophil (cells /HPF)	Tissue eosinophil was not different between CRSwNP who developed recurrent polyps after ESS and those who did not (p=1).
Gelardi(Gelardi, Fiorella et al. 2009)	2009	161	tissue eosinophil (cells/HPF)	Tissue eosinophilia, asthma and aspirin sensitivity collectively predicted a relapse of CRSwNP after ESS (Odd Ratio 4.5).
Haruna(Haruna, Shimada et al. 2009)	2009	68	tissue eosinophil (%/WBC/HPF)	Tissue eosinophil percentage was higher in non-responders after macrolides therapy ($p<0.05$).
Lee(Lee, Liang et al. 2009)	2009	53	serum eosinophil (cells/μl) in pediatric CRS	Serum eosinophil were not different between the protracted group and the resolved group after ESS, p=0.865.
Myller(Myller, Toppila-Salmi et al. 2009)	2009	23	tissue eosinophil (cells/mm^2)	Tissue eosinophil in postoperative maxillary sinus samples associated with postoperative symptom score, $p<0.05$(r- not provided).

Sun(Sun, Joo et al. 2009)	2009	78	tissue eosinophil (cells/HPF)	Tissue eosinophil ($p<0.001$) and mucus ECP levels ($p<0.001$) were higher in patients with recurrence polyps after ESS than non-recurrence.
Matsuwaki(Matsuwaki, Ookushi et al. 2008)	2008	56	tissue eosinophil (cells/HPF)	Tissue eosinophilia ($p<0.01$) and serum eosinophilia ($p<0.01$) were greater in recurrence subgroup than non-recurrence after surgery.
Bhattacharyya(Bhattacharyya 2007)	2007	43	mucus eosinophil count (graded on a 4-point Likert severity scale)	The cytological profile of persisting secretions after ESS was dominated by eosinophil in 59.9% of cases.
Baudoin(Baudoin, Cupic et al. 2006)	2006	100	tissue eosinophil (scored as <10, 10-20, >20 cells/HPF)	Tissue eosinophil predicted persistence nasal secretion after ESS ($p<0.05$).

Kirtsreesakul(Kirtsreesakul and Atchariyasathian 2006)	2006	68	tissue eosinophil (scored as no, slightly, moderate and grossly infiltration)	Non-eosinophil-dominated CRSwNP with positive skin test had the least therapeutic response to 6 weeks of budesonide nasal spray than non-eosinophil-dominated CRS with polyps with negative skin test and those with eosinophil-dominated ($p<0.05$).
Kim(Kim, Dhong et al. 2005)	2005	97	tissue eosinophil (graded as 1-2, 3-10, 11-30 and >30cells/HPF)	Tissue eosinophil ($p=0.24$) and serum eosinophil ($p=0.72$) were not different between the subgroups of good outcome and poor outcome after ESS.

Table2.5. Eosinophilia with prognosis

Chapter 3

Eosinophilic rhinosinusitis is not a disease of ostiomeatal occlusion

The Laryngoscope

Eosinophilic Rhinosinusitis is Not a Disease of Ostiomeatal Occlusion

Kornkiat Snidvongs, MD; David Chin, MD; Raymond Sacks, MD; Peter Earls, MD; Richard J. Harvey, MD

Objectives/Hypothesis: Ostiomeatal complex (OMC) occlusion may play a role in the pathogenesis of some chronic rhinosinusitis (CRS) subgroups, but its role in diffuse mucosal inflammation is strongly debated. The association between radiological OMC occlusion and its draining sinuses in patients with eosinophilic rhinosinusitis (ECRS) compared to non-ECRS is investigated.

Study Design: Case-control study.

Methods: Patients with CRS who underwent endoscopic sinus surgery were investigated. Preoperative computed tomography scans were evaluated. Structured histopathology reporting was performed. The study group was patients with high tissue eosinophil >10/high power fields (HPF), and the control group was patients with low tissue eosinophil ≤ 10/HPF. The radiological relationship of OMC occlusion to the draining sinuses was analyzed in each group.

Results: Seventy patients with a mean age of 49.7 ± 14.1 years were analyzed. Forty-one (48.2%) patients had high tissue eosinophil >10/HPF. All patients with ECRS had maxillary disease, and there were 36.2% without OMC occlusion. There was no association of OMC occlusion to either the anterior ethmoid (ECRS: odds ratio [OR], 1.84; 95% confidence interval [CI], 0.24-14.14; $P = .55$; non-ECRS: OR, 1.57; 95% CI, 0.34-7.33; $P = .56$) or frontal sinuses (ECRS: OR, 0.67; 95% CI, 0.12-3.82; $P = .65$; non-ECRS: OR, 1.58; 95% CI, 0.45-5.54; $P = .47$). For patients with non-ECRS, maxillary sinus disease was present in 96.2% of those with OMC occlusion and 50% of those without (OR, 25.0; 95% CI, 2.77-226.08; $P < .001$).

Conclusions: OMC occlusion is not associated with draining sinuses for patients with ECRS. Simple surgical interventions directed at the OMC are unlikely to be of benefit to this CRS subgroup.

Key Words: Ostiomeatal, chronic rhinosinusitis, eosinophilic, nasal polyps.

Level of Evidence: 3b.

Laryngoscope, 000:000–000, 2012

INTRODUCTION

The ostiomeatal complex (OMC) is well known for its potential influence on the pathogenesis of rhinosinusitis. It is a functional entity surrounding middle meatus and maxillary sinus ostium, which consists of ethmoid infundibulum, hiatus semilunaris, bulla ethmoidalis, uncinate process, and middle turbinate. Anatomically, it is a common pathway for ventilation and drainage of maxillary, anterior ethmoid, and frontal sinuses.[1] Anatomical obstruction of this unit, such as Haller cell, concha bullosa, paradoxical middle turbinate, or septal deviation, compromises ventilation and drainage of dependent sinuses and results in rhinosinusitis (Fig. 1A).[2] Functional endoscopic sinus surgery has been introduced to correct the OMC occlusion and restore normal physiology to paranasal sinuses.[1] There is a growing evidence base implicating inflammatory processes[3–7] over simple obstructive phenomenon as the pathophysiology of many chronic rhinosinusitis (CRS) patients (Fig. 1B).[8] There is substantial evidence from the literature that medical treatment for patients with CRS may initially be equally effective.[9,10]

Eosinophilic chronic rhinosinusitis (ECRS) is a subtype of recalcitrant CRS. Patients with ECRS and generally having a tissue eosinophil >10 cells per high power field (HPF), have worse disease severity[11] and poorer treatment outcomes compared to non-ECRS.[5] Superantigen-induced inflammation, allergic fungal rhinosinusitis, and aspirin-exacerbated eosinophilic rhinosinusitis are known processes in this subtype. Thus, OMC occlusion may not be the fundamental predisposing factor for the development of eosinophilic inflammation. Any interventions focused on correcting the OMC occlusion may not provide a significant modification of chronic mucosal inflammation and for long-term management do not alter the ability to provide enhanced topical corticosteroid therapy.[12,13] The recent work of Leung and colleagues revealed that OMC obstruction was correlated with sinus disease only for

From the Macquarie University (K.S., R.S., P.E.), Sydney, Australia; Department of Otolaryngology (K.S.), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, Department of Otolaryngology-Head and Neck, Skull Base Surgery (D.C., R.S.), and Department of Anatomical Pathology (P.E.), St. Vincent's Hospital, Sydney, Australia, University of Sydney (R.S.), Sydney, Australia, Department of Otolaryngology (R.S., R.J.H.), Concord General Hospital, Sydney, Australia, and University of New South Wales (R.J.H.), Sydney, Australia.

Editor's Note: This Manuscript was accepted for publication August 13, 2012.

This work was performed at Macquarie University Hospital, St. Vincent's Hospital, Sydney, Australia.

Richard J. Harvey, MD, has served on an advisory board for Schering Plough and Glaxo-Smith-Kline and on the speakers bureau for Merck Sharp Dohme and Arthrocare, was a previous consultant with Medtronic and Olympus, and has received grant support from NeilMed. Raymond Sacks, MD, is a consultant for Medtronic and Nyamed and is on the speakers bureau for Merck Sharp Dohme and Arthrocare.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Kornkiat Snidvongs, MD, 2 Technology Place, Macquarie University, Sydney, NSW 2109 Australia. E-mail: dhornkiat@yahoo.com

DOI: 10.1002/lary.23721

"This study aims to investigate the associations between ECRS and the ostiomeatal complex occlusion. Surgical interventions directed at the OMC are unlikely to be beneficial if ECRS is not a disease of OMC occlusion."

Abstract

Background:

Ostiomeatal complex (OMC) occlusion may play a role in the pathogenesis of some chronic rhinosinusitis (CRS) subgroups but its role in diffuse mucosal inflammation is strongly debated. The association between radiological OMC occlusion and its draining sinuses in patients with eosinophilic rhinosinusitis (ECRS) compared to non ECRS is investigated.

Methods:

Patients with CRS who underwent endoscopic sinus surgery were investigated. Pre-operative computed tomography scans were evaluated. Structured histopathology reporting was performed. The study group was patients with high tissue eosinophil >10/high power fields (HPF) and the control group were patients with low tissue eosinophil ≤10/HPF. The radiological relationship of OMC occlusion to the draining sinuses was analyzed in each group.

Results:

Seventy patients with a mean age of 49.7 ±14.1 years were analyzed. Forty-one (48.7%) patients had high tissue eosinophil >10/ HPF. All patients with ECRS had maxillary disease and there were 36.2% without OMC occlusion. There was no association of OMC occlusion to the either anterior ethmoid (ECRS; OR=1.84 (0.24, 14.14), p=0.55, non ECRS; OR=1.57 (0.34, 7.33), p=0.56) or frontal sinuses (ECRS; OR=0.67 (0.12, 3.82), p=0.65, non ECRS; OR=1.58 (0.45, 5.54), p=0.47). For patients

with non-ECRS, maxillary sinus diseases was present in 96.2% of those with OMC occlusion and 50% of those without (odd ratio (OR) =25.0 (2.77, 226.08); p<0.001).

Conclusion:

OMC occlusion is not associated with draining sinuses for patients with ECRS. Simple surgical interventions directed at the OMC are unlikely to be of benefit to this CRS subgroup.

Key words:

ostiomeatal, chronic rhinosinusitis, eosinophilic, eosinophilia, nasal polyps

Introduction

The ostiomeatal complex (OMC) is well known for its potential influence on the pathogenesis of rhinosinusitis. It is a functional entity surrounding middle meatus and maxillary sinus ostium which consists of ethmoid infundibulum, hiatus semilunaris, bulla ethmoidalis, uncinate process and middle turbinate. Anatomically, it is a common pathway for ventilation and drainage of maxillary, anterior ethmoid and frontal sinuses(Stammberger and Posawetz 1990). Anatomical obstruction of this unit such as Haller cell, concha bullosa, paradoxical middle turbinate or septal deviation compromises ventilation and drainage of dependent sinuses and results in rhinosinusitis(Messerklinger 1967) (Figure 3.1A). Functional endoscopic sinus surgery has been introduced to correct the OMC occlusion and restore normal physiology to paranasal sinuses(Stammberger and Posawetz 1990). There is a growing evidence base implicating inflammatory processes(Ferguson 2004; Reh, Wang et al. 2010; Sheahan, Ahn et al. 2010; Soler, Sauer et al. 2010; Tosun, Arslan et al. 2010) over simple obstructive phenomenon as the pathophysiology of many CRS patients(Timperley, Schlosser et al. 2010)(Figure3.1B). There is substantial evidence that medical treatment for patients with chronic rhinosinusitis (CRS) may initially be equally effective from the literature(Ragab, Lund et al. 2004; Khalil and Nunez 2006). Eosinophilic chronic rhinosinusitis (ECRS) is a subtype of recalcitrant CRS. Patients with ECRS generally having a tissue eosinophil greater than 10 cells per high power field (HPF), have worse disease severity(Snidvongs, Lam et al. 2012) and poorer

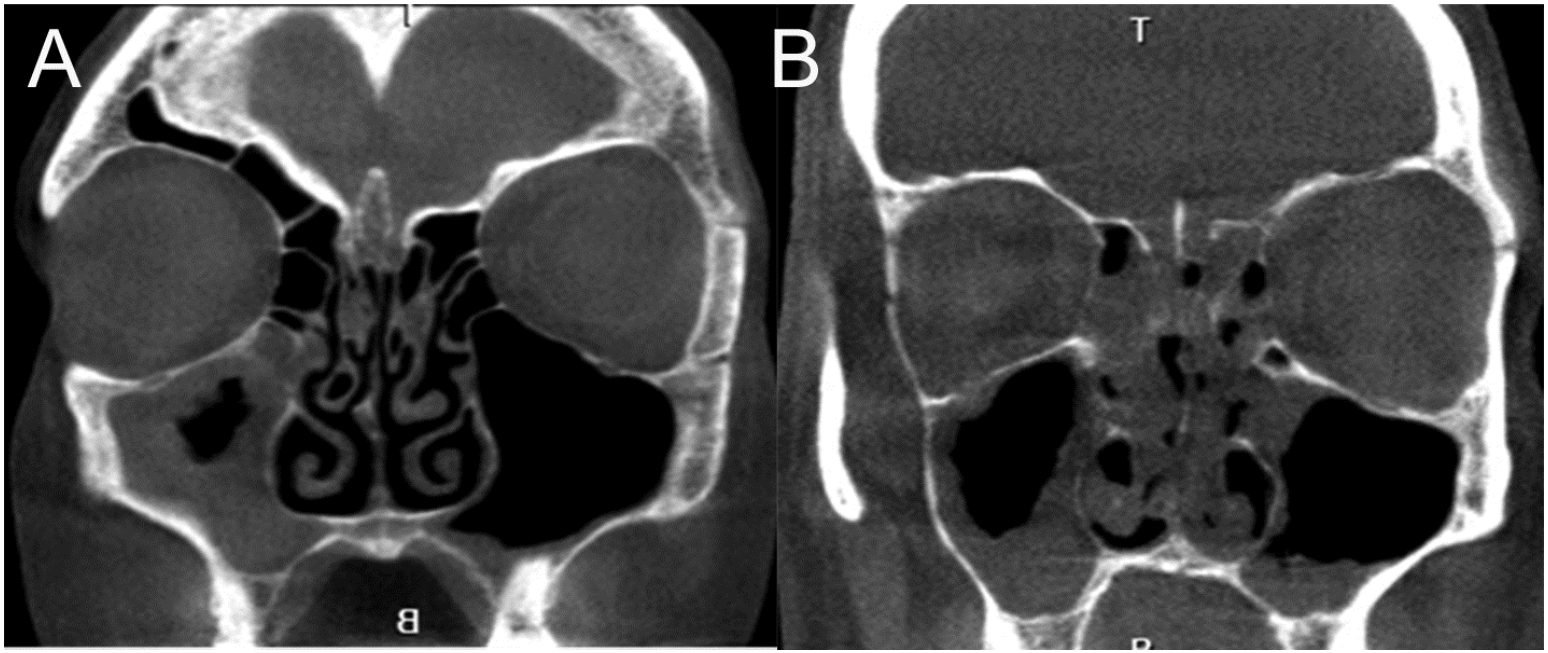


Figure3.1 Examples of two CRS subtypes: (A) Patients with non ECRS having anatomical OMC occlusion which compromises the ventilation and drainage of right maxillary sinus and (B) Patients with ECRS having diffuse mucosal inflammation in paranasal sinuses

treatment outcomes compared to non ECRS(Soler, Sauer et al. 2010). Superantigen-induced inflammation, allergic fungal rhinosinusitis, and aspirin exacerbated eosinophilic rhinosinusitis are known process in this subtype. Thus OMC occlusion may not be the fundamental predisposing factor for the development of eosinophilic inflammation. Any interventions focused on correcting the OMC occlusion may not provide a significant modification of chronic mucosal inflammation and, for the long term management, do not alter the ability to provide enhanced topical corticosteroid therapy(Grobler, Weitzel et al. 2008; Brenner, Abadie et al. 2011). The recent work of Leung and colleagues revealed that OMC obstruction was correlated with sinus disease only for patients with chronic rhinosinusitis without polyps (CRSsNP), but not chronic rhinosinusitis with polyps (CRSwNP) (Leung, Kern et al. 2011). As CRSwNP is one phenotype of ECRS, these findings suggest that ECRS may not be associated with OMC occlusion(Snidvongs, Lam et al. 2012).

As many as 19% of patients with CRSsNP have high tissue eosinophilia(Snidvongs, Lam et al. 2012) and ECRS without obvious polyps is a poor prognosis subgroup(Soler, Sauer et al. 2010). Thus the use of sinus histopathology as a criteria for comparison may be more accurate than the use of clinical phenotype. We aimed to investigate the association between OMC occlusion and its draining or dependent sinuses in patients with ECRS, compared to non ECRS.

Materials and Methods

A case-control study of consecutive patients undergoing endoscopic sinus surgery (ESS) was undertaken. The study had ethical approval from the St Vincent's institutional ethics review board.

Adult patients (>18 years) with CRS who underwent ESS in a tertiary referral clinic were investigated. CRS patients were defined according to EP3OS(Fokkens, Lund et al. 2007). All patients underwent ESS after failing previous medical therapy. Pre-operative medical therapy included a twenty-day course of cultured-directed antibiotics, a three-week course of oral steroid (unless contraindicated), a four-week course of simple topical nasal spray and nasal saline irrigation. No patients had oral steroid for at least 4 weeks prior to ESS. Pre-operative computed tomography (CT) scans were evaluated with Lund-Mackay scores. Most CTs were performed at the end of maximal medical therapy. Structured histopathology reporting was performed(Snidvongs, Lam et al. 2012). Attempt was made to collect the sinus tissue in every case. The approach was standardized by collecting the ethmoid mucosa from the same location, usually ethmoid bulla.

The study group was patients with high tissue eosinophil greater than 10/high power fields (HPF) and the control group was patients with low tissue eosinophil ≤ 10/HPF. The relationship of radiological OMC occlusion to the degree of mucosal disease in the dependent or draining sinuses; maxillary, anterior ethmoid and frontal sinuses, based on computed tomography (CT), was analyzed in each group. Additionally, we also investigated the relationship of radiological OMC occlusion to mucosal disease of associated sinuses in patients based on the phenotype of CRSwNP and CRSsNP as previously reported by Leung et al(Leung, Kern et al. 2011). ‘Mucosal disease’ was defined as a dichotomous outcome when evidence of mucosal thickening and inflammation was shown. The authors excluded mucous retention cyst and minor inflammation of dental root.

Statistical analysis

Each side of the paranasal sinuses were analyzed separately. Descriptive data was presented as percentage and mean±SD. Chi squared analysis and odd ratio with 95%CI was used for the risk of OMC occlusion to result in mucosal diseases of each and any draining sinuses. Statistical significance was determined when the significance level of less than 0.05. Statistical analyses were performed using SPSS v 20.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

Patient population

Seventy patients with a mean age of 49.7 ±14.1 years were assessed. Thirty (42.9%) patients were female. Sixty-four (45.7%) were revision surgical patients. The timing of the CT relative to surgery date is 18.45 ± 2.2 weeks. Fort-one (48.7%) patients had high tissue eosinophil >10/ HPF. Forty (57.1%) patients were diagnosed as CRSsNP and remaining classified as CRSwNP. High tissue eosinophil >10/ HPF was seen in 27.5% of CRSsNP patients. The mean baseline Lund-Mackay CT score was 13.4±6.2 and 62.5% of OMCs were occluded (Figure3.2). The frequency of nasal polyps ($p<0.001$), asthma ($p=0.002$) and ASA sensitivity ($p=0.01$) was greater in patients with ECRS than non ECRS. There was no difference in mean age, gender and history of previous surgery and smoking between the two groups. Demographic data was displayed in Table3.1.

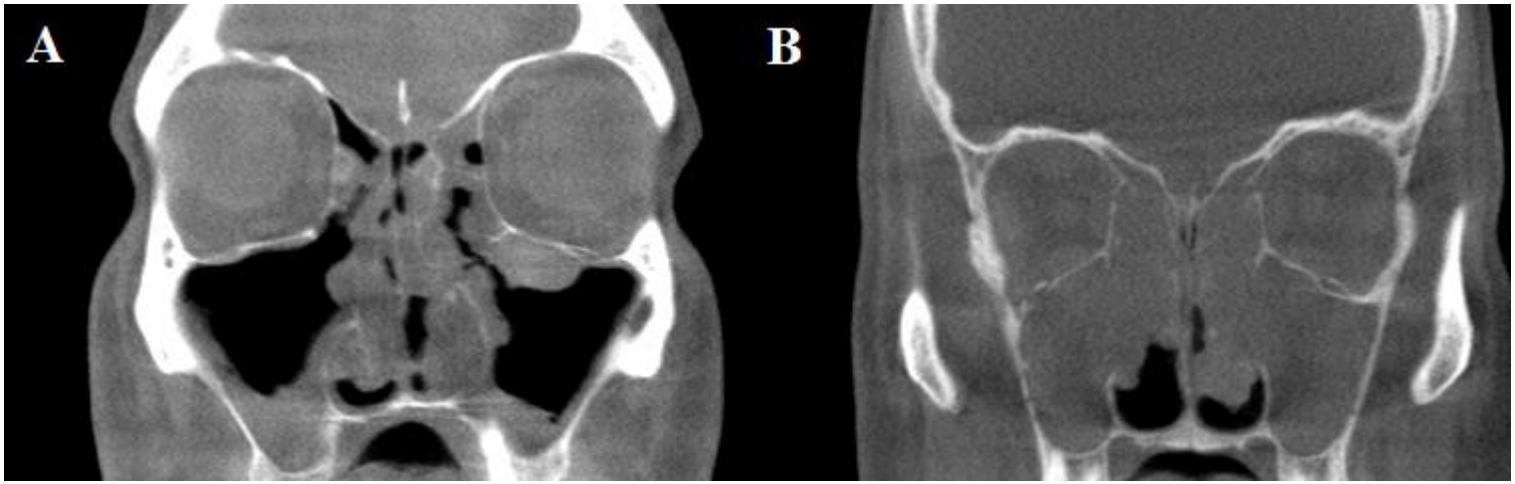


Figure3.2 Examples of (A) the non-occlusion and (B) the occlusion of the ostiomeatal complex

	ECRS (n=41)	**Non ECRS** (n=29)	p-value
age (mean±SD)	48.3±13.2	50.2±15.4	0.71
female (%)	39.0	48.3	0.40
CRSwNP(%)	73.2	34.5	<0.001
asthma(%)	39.0	17.2	0.002
ASAsensitivity(%)	9.8	0	0.01
smoker(%)	4.9	3.4	0.63
revision surgery(%)	48.8	41.4	0.38

Table3.1 Demographic data of patients with ECRS and non ECRS

The relationship of OMC occlusion to draining sinuses; patients with non-ECRS versus ECRS

Data is displayed in Table 3.2 and 3.3. In non-ECRS patients, maxillary sinus disease was present in 96.2% of those with OMC occlusion and 50% of those without OMC occlusion ($p<0.001$). The odd ratio for risk for maxillary sinus disease from OMC occlusion was 25.0 (2.77, 226.08). In contrast for ECRS patients, all (100%) had mucosal disease in maxillary sinus regardless of the presence or absence of OMC occlusion. OMC occlusion was present in 63.8% of those with ECRS. The odd ratio could not be determined when there were no patients having disease free despite 36.2% having an open OMC. The risk of having disease, from OMC occlusion, in the anterior ethmoid (ECRS; OR=1.84 (0.24, 14.14), p=0.55, non ECRS; OR=1.57 (0.34, 7.33), p=0.56) and frontal sinus (ECRS; OR=0.67 (0.12, 3.82), p=0.65, non ECRS; OR=1.58 (0.45, 5.54), p=0.47) were similar for patients with ECRS and non ECRS.

The relationship of OMC occlusion to draining sinuses; patients with CRSsNP versus CRSwNP

For patients with CRSsNP, maxillary sinus disease was present in all (100%) patients having OMC occlusion and 52.6% of those with non-occlusion, $p<0.001$. The odd ratio could not be determined when there were no patients with OMC occlusion and maxillary sinus disease free. In patients with CRSwNP, there was no relationship of maxillary sinus disease to OMC status, (p=0.39). The odd ratio for risk of OMC occlusion to result in maxillary sinus diseases was as low as 0. The risk of having diseases in anterior ethmoid and frontal sinuses OMC occlusion and non-occlusion were similar to result in.

Mucosal disease in each anterior sinus	**ECRS**			**Non ECRS**			**CRSwNP**			**CRSsNP**		
	OMC occlusion		p-value	OMC occlusion		p-value	OMC occlusion		p-value	OMC occlusion		p-value
	Present	Absent		Present	Absent		Present	Absent		Present	Absent	
Maxillary (%)	100	100	NA	96.2	50	<0.001	96.4	100	0.39	100	52.6	<0.001
Anterior ethmoid (%)	94.6	90.5	0.55	84.6	77.8	0.56	89.3	90.0	0.94	91.4	78.9	0.19
Frontal (%)	86.5	90.5	0.65	84.0	52.9	0.47	92.9	90.0	0.72	64.7	55.6	0.51

Table3.2 Percentage of mucosal disease in draining sinuses in each CRS subtypes when the OMC occlusion was present and absent

NA: not applicable; Statistical significance cannot be assessed when the event of mucosal disease is constant for OMC status

This was true for both patients with CRSsNP and CRSwNP. Data is displayed in Table 3.2 and 3.3.

Discussion

While OMC occlusion is associated with maxillary sinus disease with an odds ratio of 25 (2.8, 266.1), p<0.001 for patients with non ECRS, it is not true for patients with ECRS or for CRSwNP. These findings are complimentary to those reported by Leung et al(Leung, Kern et al. 2011) who reported an association of OMC occlusion with CRSsNP but not with CRSwNP. Disease of anterior ethmoid and frontal sinuses failed to show an association with the OMC occlusion for all CRS subtypes; ECRS, non ECRS, CRSwNP or CRSsNP. While the authors concede that the traditional concept of OMC blockage is a fundamental predisposing factor for CRS, it is true for only some subgroups of CRS. Patients with anatomical OMC occlusion may compromise the ventilation and drainage of adjacent sinuses and result in acute rhinosinusitis, recurrent acute rhinosinusitis, non ECRS or CRSsNP. Such simple forms of CRS do occur (Figure 3.1A). In contrast to those subgroups, patients with ECRS have diffused mucosal inflammation in paranasal sinuses and often a broader airway wide inflammatory condition (Figure 3.1B). Such diffuse disease is unlikely to be caused by anatomical OMC obstruction. Superantigen-induced inflammation, allergic fungal rhinosinusitis, and aspirin exacerbated eosinophilic rhinosinusitis have been shown in literature as processes in the development of eosinophilic inflammation(Sok and Ferguson 2006). Simple surgical interventions which aim to manipulate OMC occlusion such as minimally invasive sinus technique (MIST), balloon sinuplasty and simple antral

OMC	ECRS				Non ECRS				CRSwNP				CRSsNP			
	Dis	Non-dis	n	OR	Dis	Non-dis	n	OR	Dis	Non-dis	n	OR	Dis	Non-dis	n	OR
Maxillary sinus																
Occ	37	0	37	NA	25	1	26	25.0 (2.77, 226.08)	27	1	28	0	35	0	35	NA
Non-occ	21	0	21		9	9	18		20	0	20		10	9	10	
n	58	0	58		34	10	44		47	1	48		45	9	45	
Anterior ethmoid sinus																
Occ	35	2	37	1.84 (0.24,14.14)	22	4	26	1.57 (0.34, 7.33)	25	3	28	0.93 (0.14, 6.12)	32	3	35	2.84 (0.56, 14.34)
Non-occ	19	2	21		14	4	18		18	2	20		15	4	19	
n	54	4	58		36	8	44		43	5	48		47	7	54	

Frontal sinus																
Occ	32	5	37	0.67 (0.12, 3.82)	16	9	25	1.58 (0.45, 5.54)	26	2	26	1.44 (0.19, 11.22)	22	12	34	1.47 (0.46, 4.71)
Non-occ	19	2	21		9	8	17		18	2	18		10	8	18	
n	51	7	58		25	17	42		44	4	44		32	20	52	

Table3.3 The risks of OMC occlusion to result in mucosal disease in draining sinuses in each CRS subtype

OMC: ostiomeatal complex occlusion; ECRS: eosinophilic chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with polyps; CRSsNP: chronic rhinosinusitis without polyps; Dis: diseased; Non-dis: non-diseased; n: total number OR: odd ratio (95%CI); Occ: occluded; Non-occ: non-occluded; NA: not applicable; Odd ratio cannot be calculated when the number of subject with OMC occlusion having non-events is 0.

washouts are unlikely to provide a long term modulation on the pathophysiology of patients with ECRS or alter the dynamics of postsurgical topical therapy. Diffuse eosinophilic inflammation often requires corticosteroid therapy (whether delivered systemically or locally) rather than the promotion of sinus ventilation and drainage.

The authors still perform sinus surgery regularly for CRS patients but the focus of the surgery as significantly evolved. The philosophy is to provide a single sinus cavity in which all frontal, ethmoid, maxillary and sphenoid sinuses are in communication. Obstructive phenomena are eliminated with this approach and fundamentally a simple "neo-sinus" is created in which eosinophilic hypersecretion can be removed and topical steroid effectively delivered throughout the entire cavity. The surgical endpoint is a single cavity with complete partition removal. The recent study revealed that local mucosal inflammation can be well controlled when steroid solution is delivered in this manner(Snidvongs, Pratt et al. 2012). Corticosteroid nasal irrigations after endoscopic sinus surgery are beneficial for the management of chronic rhinosinusitis(Snidvongs, Kalish et al. 2011). When subgroup analysis was performed, even the most challenging eosinophilic patients (>10/HPF) had as good or better performance compared to those with low tissue eosinophilia (≤10/HPF) in symptom, SNOT-22 and endoscopy scores.

Conclusion

OMC occlusion is not associated with draining sinuses for patients with ECRS or CRSwNP. Diffuse eosinophilic inflammation is unlikely to be predisposed by anatomical OMC blockage. Simple interventions manipulating the OMC are unlikely to be beneficial to this common subgroup. Aggressive topical corticosteroid therapy after surgical technique to provide access may bring about more favorable outcomes.

References

Brenner, P. S., W. M. Abadie, E. K. Weitzel, R. F. Thomas and K. C. McMains. Unexpected consequences of transnasal balloon dilation of the maxillary ostium. *Int forum allergy rhinol* 2011;1(6): 466-470.

Ferguson, B. J. Categorization of eosinophilic chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2004;12(3): 237-242.

Fokkens, W., V. Lund and J. Mullol. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology. Suppl* 2007;(20): 1-136.

Grobler, A., E. K. Weitzel, A. Buele, et al. Pre- and postoperative sinus penetration of nasal irrigation. *Laryngoscope* 2008;118(11): 2078-2081.

Khalil, H. S. and D. A. Nunez. Functional endoscopic sinus surgery for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2006;(3): CD004458.

Leung, R. M., R. C. Kern, D. B. Conley, B. K. Tan and R. K. Chandra. Osteomeatal complex obstruction is not associated with adjacent sinus disease in chronic rhinosinusitis with polyps. *Am J Rhinol Allergy* 2011;25(6): 401-403.

Messerklinger, W. On the drainage of the normal frontal sinus of man. *Acta Otolaryngol* 1967;63(2): 176-181.

Ragab, S. M., V. J. Lund and G. Scadding. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope* 2004;114(5): 923-930.

Reh, D. D., Y. Wang, M. Ramanathan, Jr. and A. P. Lane. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. *Am J Rhinol Allergy* 2010;24(2): 105-109.

Sheahan, P., C. N. Ahn, R. J. Harvey, et al. Local IgE production in nonatopic nasal polyposis. *J Otolaryngol Head Neck Surg* 2010;39(1): 45-51.

Snidvongs, K., L. Kalish, R. Sacks, J. C. Craig and R. J. Harvey. Topical steroid for chronic rhinosinusitis without polyps. *Cochrane Database Syst Rev* 2011;(8): CD009274.

Snidvongs, K., M. Lam, R. Sacks, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int forum allergy rhinol* 2012;in press.

Snidvongs, K., E. Pratt, D. Chin, et al. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2012;in press.

Sok, J. C. and B. J. Ferguson. Differential diagnosis of eosinophilic chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2006;6(3): 203-214.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

Stammberger, H. and W. Posawetz. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. *Eur Arch Otorhinolaryngol* 1990;247(2): 63-76.

Timperley, D., R. J. Schlosser and R. J. Harvey. Chronic rhinosinusitis: an education and treatment model. *Otolaryngol Head Neck Surg* 2010;143(5 Suppl 3): S3-8.

Tosun, F., H. H. Arslan, Y. Karslioglu, M. S. Deveci and A. Durmaz. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol* 2010;119(7): 455-459.

Chapter 4

Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis

ORIGINAL CONTRIBUTION

Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis*

Kornkiat Snidvongs[1], Rohan McLachlan[2], David Chin[3], Eleanor Pratt[4], Raymond Sacks[5], Peter Earls[6], Richard J. Harvey[7]

* Macquarie University, Australia and Faculty of Medicine, Chulalongkorn University, Thailand
* University of New South Wales, Australia
* St Vincent's Hospital, Australia
* University of Sydney, Australia
* Macquarie University, University of Sydney, Australia
* Department of anatomical pathology, St Vincent's Hospital, Australia
* St Vincent's Hospital, Macquarie University and University of New South Wales, Australia

Rhinology 50: 299-305, 2012
DOI: 10.4193/Rhino12.032

*Received for publication:
January 27, 2012
Accepted: March 7, 2012

Summary

Background: Causes of osteitis in chronic rhinosinusitis (CRS) other than previous surgery are poorly defined. Patients with eosinophilic CRS (ECRS) have more severe disease and poorer outcomes despite repeated surgery. Associations between osteitis and markers of ECRS are not well described.

Methods: A cross-sectional study of CRS patients undergoing sinus surgery was conducted. Osteitis was scored radiologically using previously published measures. Associations between osteitis and histopathology, symptoms, endoscopy, CT mucosal score and seromarkers were analyzed.

Results: Eighty-eight patients were assessed of whom forty-five had osteitis. Patients undergoing revision surgery recorded higher osteitis scores. Patients with mucosal eosinophilia had higher osteitis score than those without. Patients with osteitis had higher serum eosinophil. Similar relationships were also found in primary surgery. Osteitis was associated with endoscopic and radiologic, but not symptomatic disease severity.

Conclusions: Osteitis is associated with tissue and serum eosinophilia in both patients with and without prior surgery. Patients with these features may benefit from post-operative corticosteroid therapy to prevent osteitis.

Key words: osteitis, eosinophilia, eosinophils, sinusitis, polyps

Introduction

Osteitic bone is a feature of chronic rhinosinusitis (CRS) and often associated with recalcitrant disease[1-5]. The osteitic bones potentially serve as a nidus for inflammation and may explain failures from typical medical and surgical treatment. Osteitis is associated with previous surgery and the incidence increases with increasing number of previous operations [2,3]. However, non-operated patients also experience osteitis with an incidence of 5 [3] to 33% [2] and thus mucosal loss from surgery is not a simple answer to the origins and implication of osteitis [4]. The mechanism of osteitis in CRS is poorly understood and yet to be fully defined. Although, bacteria may play a role in

299

"This study aims to investigate the associations between osteitis and markers of ECRS."

Abstract

Background:

Causes of osteitis in chronic rhinosinusitis (CRS) other than previous surgery are poorly defined**.** Patients with eosinophilic CRS (ECRS) have more severe disease and poorer outcomes despite repeated surgery. Associations between osteitis and markers of ECRS are not well described.

Methods:

A cross-sectional study of CRS patients undergoing sinus surgery was conducted. Osteitis was scored radiologically using previously published measures. Associations between osteitis and histopathology, symptoms, endoscopy, CT mucosal score and seromarkers were analyzed.

Results:

88 patients were assessed (45.5% female, age 50.3±13.6 years). 45 (51.1%) patients had osteitis. Patients undergoing revision surgery recorded higher osteitis scores (6.0(3.8-10.3) versus 0.0(0.0-3.0), $p<0.01$). Patients with mucosal eosinophilia (>10/HPF) had higher osteitis score (4.0(1.0-6.0)) than those without (1.0(0.0-5.8), $p=0.04$). Patients with osteitis had higher serum eosinophil (x109/L) (0.3(0.2-0.5) versus 0.1(0.1-0.2), $p<0.001$). Similar relationships were also found in primary surgery: (3.0(0.0-4.0) versus 0.0(0.0-0.0), $p=0.001$ and 0.3(0.1-0.6) versus 0.1(0.1-0.2), $p=0.01$ respectively). Osteitis was associated with endoscopic (6.1±2.9

versus 4.4±3.6, p=0.03) and radiologic (14.0±6.0 versus 10.1±5.7, p=0.005), but not symptomatic disease severity (p=0.56).

Conclusions:

Osteitis is associated with tissue and serum eosinophilia in both patients with and without prior surgery. Patients with these features may benefit from post-operative corticosteroid therapy to prevent osteitis.

Key words

osteitis, eosinophilia, eosinophils, sinusitis, polyp

Introduction

Osteitic bone is a feature of chronic rhinosinusitis (CRS) and often associated with recalcitrant disease(Videler, Georgalas et al. 2011). The osteitic bones potentially serve as a nidus for inflammation and may explain failures from typical medical and surgical treatment. Osteitis is associated with previous surgery and the incidence increases with increasing number of previous operations(Georgalas, Videler et al. 2010). However non-operated patients also experience osteitis with the incidence of 5(Lee, Kennedy et al. 2006) to 33%(Georgalas, Videler et al. 2010) and thus mucosal loss from surgery is not a simple answer to the origins and implication of osteitis(Kennedy, Senior et al. 1998). The mechanism of osteitis in CRS is poorly understood and yet to be fully defined. Although, bacteria may play a role in the pathogenesis by infecting sinus walls or producing biofilm which results in the release of mediators, to date bacteria have not been demonstrated in bone of the paranasal sinuses(Videler, Georgalas et al. 2011). Osteitis is thought to be a disordered inflammatory process rather than chronic bone infection or osteomyelitis, similar to recent research into the mucosal inflammation of CRS(Kern, Conley et al. 2008).

Eosinophilic chronic rhinosinusitis (ECRS) is a subtype of recalcitrant CRS. Patients with ECRS having tissue eosinophil greater than 10 cells per high power field (HPF) have worse disease severity(Snidvongs, Lam et al. 2012) and poorer treatment outcomes compared to non-eosinophilic CRS(Soler, Sauer et al. 2010). A recent study by Mehta, et al.(Mehta, Campeau et al. 2008)found a correlation between

osteitis of the paranasal sinuses, based on radiology, with serum and sputum eosinophil levels in asthmatic patients. Additionally, Tran et al(Tran, Beule et al. 2007) found that patients with CRS with eosinophilic mucin had an increased rate of restenosis and revision surgery after endoscopic modified Lothrop procedure. These findings suggest that tissue eosinophila and a systemic response with serum eosinophilia may predispose or be associated to the osteitic bone seen in recalcitrant CRS. The objective of this study is to investigate an association between osteitis and eosinophilic markers of ECRS.

Material and Methods

Study design

A cross-sectional study of consecutive patients undergoing sinus surgery was undertaken. The study had ethical approval from the St Vincent's Hospital institutional review board.

Patient population

Adult patients (>18 years) with CRS with or without polyps who underwent ESS in a tertiary referral clinic were reviewed. CRS patients were defined according to EP3OS(Fokkens, Lund et al. 2007). All patients underwent ESS after failing previous medical therapy. No patients used oral steroid for 4 weeks prior to surgery.

Demographic data was recorded. Comorbidity of asthma was defined as clinically using an inhaled β-agonist or corticosteroid. Patients with suspected aspirin sensitivity on history were confirmed with a nasal lysine aspirin challenge as per the

European Guidelines(Nizankowska-Mogilnicka, Bochenek et al. 2007). The Sino-Nasal Outcome Test 22(SNOT-22) was used for disease-specific quality of life assessment(Hopkins, Gillett et al. 2009). Preoperative Lund-Kennedy endoscopy scores were recorded. A structured histopathology report was used to define inflammatory features of the disease(Snidvongs, Lam et al. 2012). Histopathology reported tissue eosinophilia (<5 per high power field (HPF), 5-10 per HPF, >10 per HPF), Charcot-Leyden Crystals (absent, present), eosinophil aggregates (absent, present) and severity of inflammation (absent, mild, moderate and severe). Three high power fields were analyzed to reach a consensus as the density of eosinophilia. The seromarkers reported were: eosinophil count (x109/L), total IgE (kU/L), C-reactive protein (CRP) (mg/L) and erythrocyte sedimentation rate (ESR) (mm/hour). All preoperative computed tomography (CT) scans were evaluated with Lund-Mackay scores.

Global Osteitis Scoring Scale

Osteitis was defined as the process of bone thickening in patients with CRS was presented(Videler, Georgalas et al. 2011). No distinction is made between osteitis and neo-osteogenesis nor an assumption of the origins. Bony walls of the paranasal sinuses were assessed for presence, severity and extent of osteitis by using Global Osteitis Score(Georgalas, Videler et al. 2010). All ten sinuses (Right and left frontal, anterior ethmoid, posterior ethmoid, maxillary and sphenoid) were scored ranging from 0 to 4 as follows:

0: Less than 50% of the sinus involved and <3 mm wide. (Figure 4.1A)

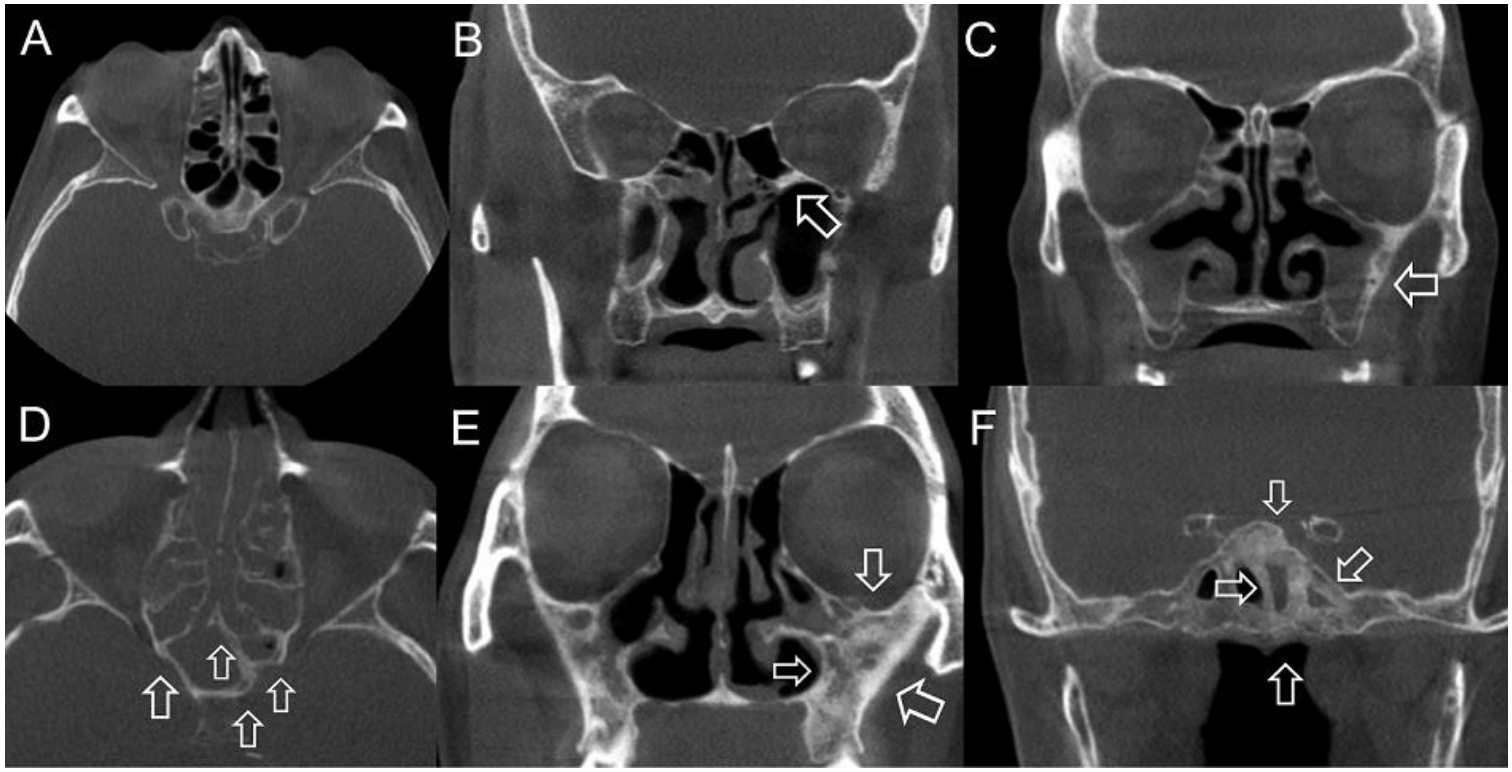


Figure 4.1 Examples of osteitis (arrow) and Global Osteitis Scoring Scale in CRS patients:(A) score 0 (B) score 1 (C) score 2 (D) score 3 (E) score 4 of maxillary sinus (F) score 4 of sphenoid sinus

1: Less than 50% of the sinus involved and 3–5 mm width. (Figure 4.1B)

2: Less than 50% of the sinus involved and wider than 5 mm or greater than 50% of the sinus involved and <3 mm wide.(Figure 4.1C)

3: Greater than 50% of the sinus involved and 3–5 mm wide. (Figure 4.1D)

4: Greater than 50% of the sinus involved and thicker than 5 mm. (Figure 4.1E, 4.1F)

The Global Osteitis Score ranges from 0 to 40. Woven bone with thickened, irregular, heterogeneous lining of the sinus walls was measured other than normal lamellar bony wall.

Statistical analysis

Descriptive data was presented as percentage, mean and standard deviation (SD) for parametric data, median and interquartile range (IQR) for non-parametric data. Student's T-test and Mann-Whitney U test (two-tailed) were used for comparisons of unrelated groups of parametric and non-parametric data respectively. Kruskal-Wallis was used for comparisons of non-parametric data of more than two groups. Chi squared analysis was used for relationships of nominal variables. Pearson correlation coefficients were performed for linear relationship of scale variables. Spearman's correlation coefficients were used for ordinal values. Statistical analyses were performed using SPSS v 17.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

Patient population

Eighty-eight patients with a mean age of 50.3 ±13.6 years were assessed. Forty (45.5%) patients were female. Nine (10.2%) patients were smokers and twenty (22.7%) had asthma. Three (3.4%) patients had aspirin hypersensitivity. Forty-two (47.7%) patients were diagnosed as CRSsNP. Thirty-three (37.5%) had revision surgery. The number of previous surgery ranged from 1 to 12. Forty-five (51.1%) of total patients had some form of osteitis. The prevalence of osteitis was 75.8% (25/33) for patients with revision surgery and 36.4% (20/55) for patients with primary surgery. It is acknowledged that the patient population is from a tertiary hospital clinic.

Association between osteitis and clinical presentation

The mean age of patients with osteitis (51.6±14.5) was similar to those without (47.5±12.0), p=0.18. The Global Osteitis Score of patients increased with the increase of age (r=0.23, p=0.04), (Figure4.2) but was not correlated to age in the primary surgery group (r=0.01, p=0.94). The presence of osteitis was not associated with gender (p=0.66), smoking (p=0.48), the comorbidities of asthma (p=0.40) nor aspirin hypersensitivity (p=1.0). Osteitis was associated with the presence of polyps (x2=4.6, p=0.05) and previous surgery (x2=12.8, p<0.001). The median Global Osteitis Score was greater in patients with CRSwNP (4.0(2.0-6.0)) than patients with CRSsNP (0.0(0.0-5.3), p=0.03) (Figure4.3) and greater in patients undergoing revision surgery (6.0(3.8-10.3)) than primary surgery (0.0(0.0-3.0), p<0.001) (Figure4.4). The median of number of previous surgeries were higher in patients with osteitis (1.0(0.0-2.0)) than those without (0.0(0.0-0.0), p=0.001).

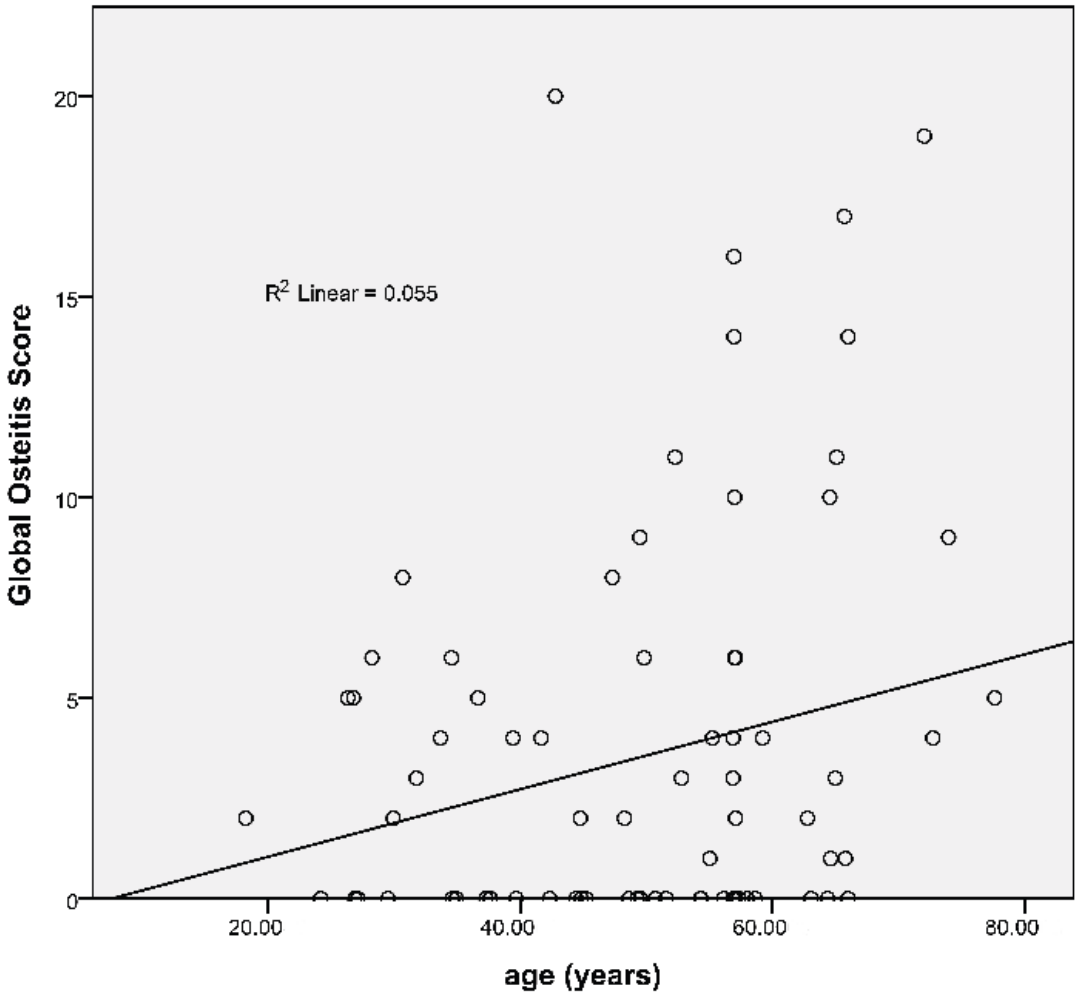


Figure 4.2 Global Osteitis Score by age

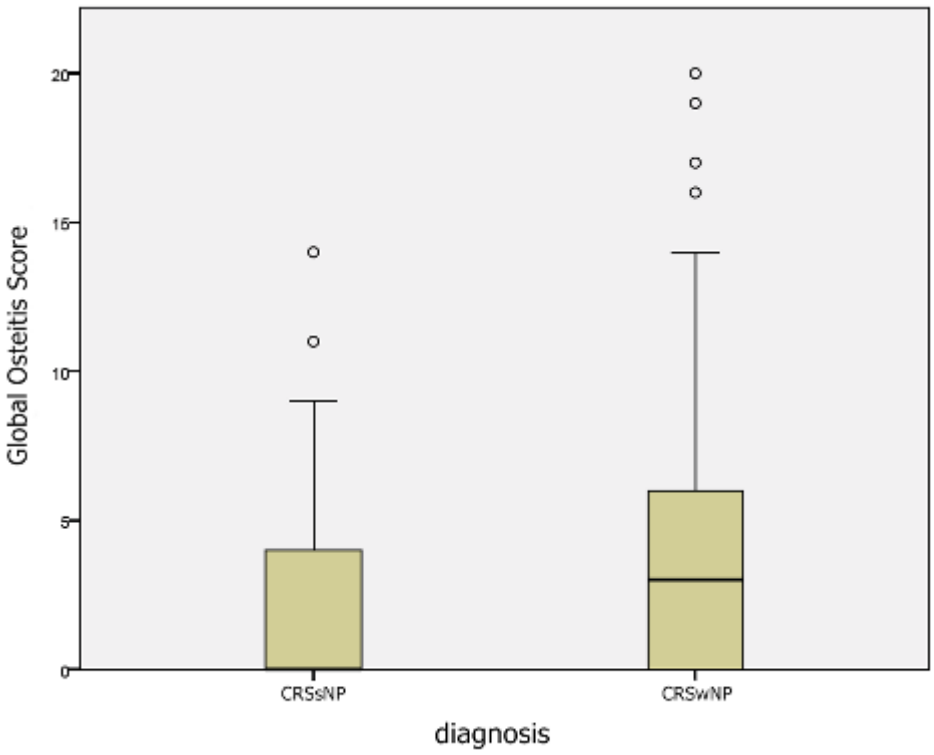


Figure 4.3 Global Osteitis Score by diagnosis

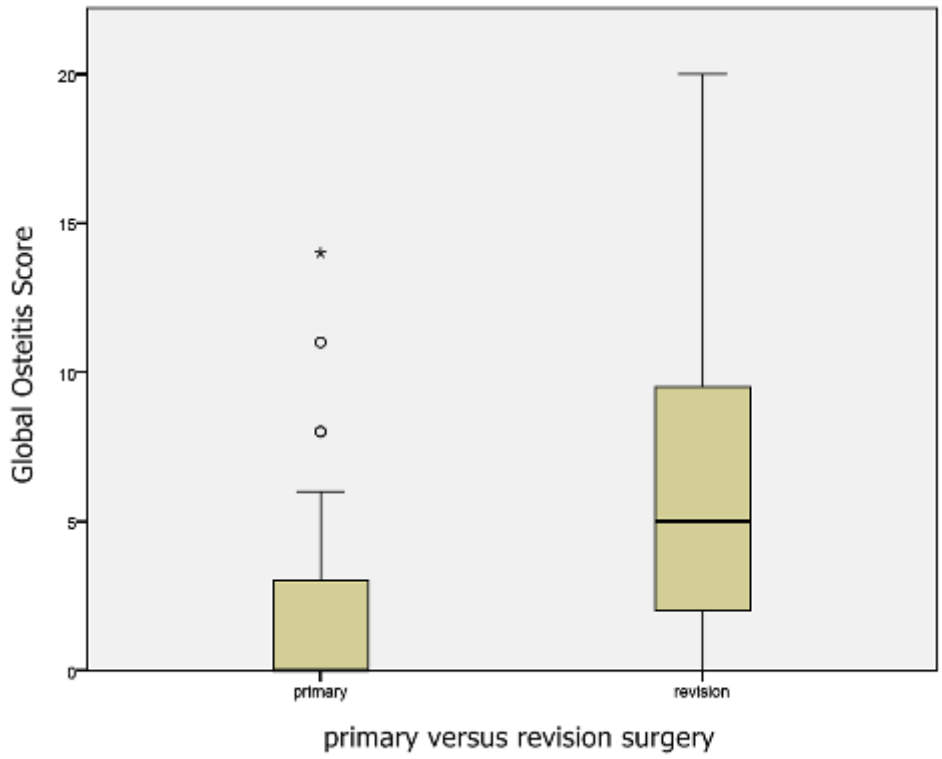


Figure 4.4 Global Osteitis Score by primary versus revision surgery

When un-operated CRS patients (primary surgery subgroup) were assessed independently, the Global Osteitis Score of patients with osteitis was neither correlated with age (p=0.94) nor the presence of polyps (p=0.15). The median Global Osteitis Score in patients with CRSwNP (2.5(1.3-4.0)) was not different from patients with CRSsNP (0.0(0.0-0.0), p=0.23). The presence of osteitis was not associated with gender (p=0.77), smoking (p=1.0), the comorbidities of asthma (p=0.68) and aspirin hypersensitivity (p=0.43).

Association between osteitis and disease severity

The mean SNOT-22 in patients with osteitis (2.0±1.0) was not different from those without (1.9±1.1), p=0.56. Patients with osteitis had greater endoscopy score (6.1±2.9 versus 4.4±3.6, p=0.03) and CT score (14.0±6.0 versus 10.1±5.7, p=0.005) than those without. Data was displayed in Table4.1.

Similar findings were found in the primary surgery subgroup. The mean SNOT-22 in patients with osteitis (1.8±0.8) was not different from those without (1.7±1.0), p=0.75. Patients with osteitis had greater endoscopy score (6.6±2.9 versus 4.5±3.6, p=0.03) and CT score (15.6±5.5 versus 10.4±5.2, p=0.002) than those without.

Association between osteitis and histopathology

The median Global Osteitis Score was greater in patients with tissue eosinophilia (≥10/HPF) (4.0(1.0-6.0)) than those with less tissue eosinophil (1.0(0.0-5.8), p=0.04) (Figure 4.5). No association with Charcot-Leyden crystals (4.0(0.0-6.0) versus

		Total population			Primary surgery subgroup		
		Non-osteitis	Osteitis	p-value	Non-osteitis	Osteitis	p-value
Disease severity (mean±SD)	SNOT-22	1.85±1.1	2.03±1.0	0.56	1.7±1.0	1.8±0.8	0.75
	Endoscopy score	4.38±3.6	6.07±2.9	0.03	4.5±3.6	6.6±2.9	0.03
	CT score	10.14±5.7	13.95±6.0	0.005	10.4±5.2	15.6±5.5	0.002
Seromarkers (median(IQR))	Serum eosinophil(x109/L)	0.1(0.1-0.2)	0.3(0.2-0.5)	<0.001	0.1(0.1-0.2)	0.3(0.1-0.6)	0.01
	Serum IgE(kU/L)	29.0(18.8-69.3)	78.0(29.5-252.0)	0.01	31.0(19.0-73.0)	41.0(25.0-63.0)	0.46
	CRP(mg/L)	2.5(0.9-7.0)	1.9(0.8-2.5)	0.20	2.1(0.6-5.2)	1.4(0.8-2.2)	0.45
	ESR(mm/hour)	5.5(2.0-10.0)	6.0(3.0-12.5)	0.40	5.0(2.0-10.0)	5.0(2.0-12.3)	0.73

Table 4.1 Disease severity and seromarkers by the presence of osteitis in total population and primary surgery subgroup

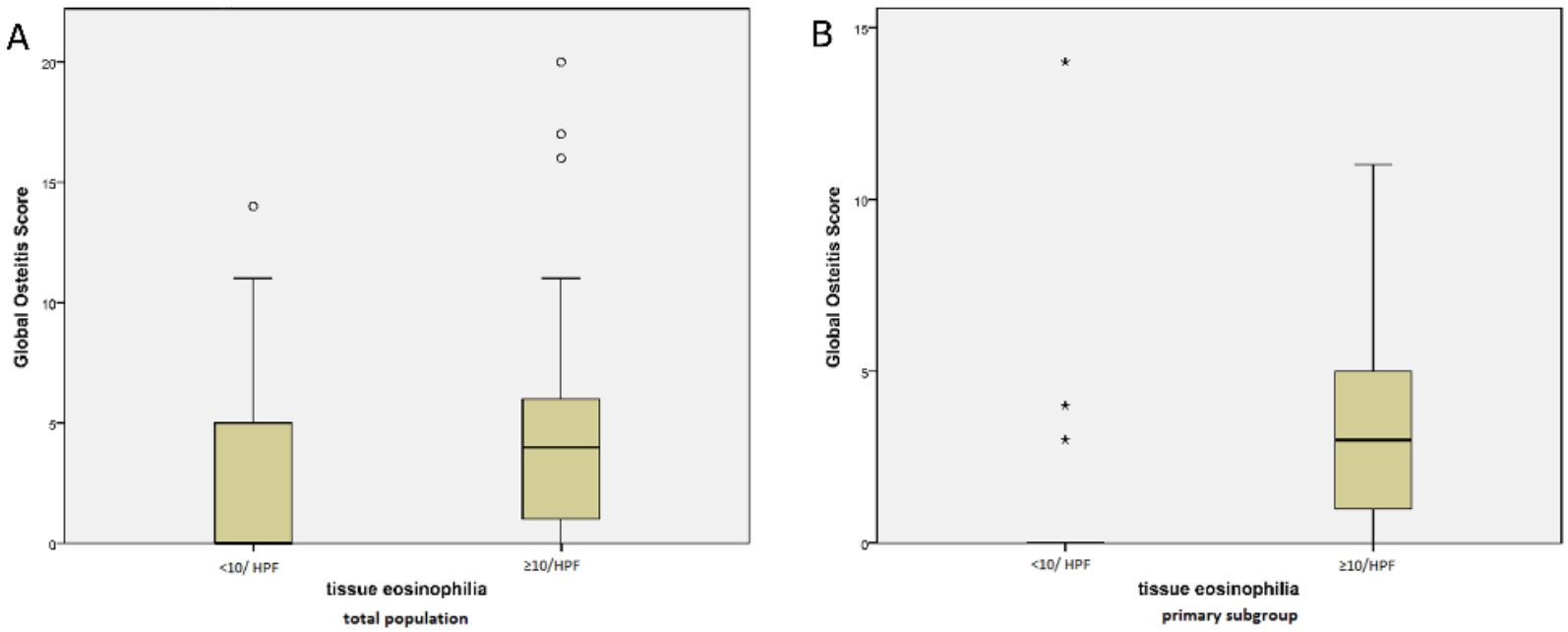


Figure 4.5 Global Osteitis Score by tissue eosinophilia (≥10/HPF) (A) total population (B) primary subgroup

2.0(0.0-6.0), p=0.65) and eosinophil aggregates (4.0(0.0-6.0) versus 2.0(0.0-7.0), p=1.0) were found. Data was displayed in Table4.2.

Similar findings were found in the primary surgery subgroup. The median Global Osteitis Score was greater in patients with tissue eosinophilia (≥10/HPF) (3.0(0.0-4.0)) than those with less tissue eosinophil (0.0(0.0-0.0), p=0.001) (Figure 4.5). There was no significant difference (p=0.27) between the median Global Osteitis Score for primary group and the severity of tissue inflammation (Kruskal Wallis). The Global Osteitis Score was not correlated to age in the primary surgery group (r=0.01, p=0.94).

Association between osteitis and seromarkers

Data was displayed in Table4.1. Patients with osteitis had higher median serum eosinophil count (0.3(0.2-0.5) x109/L versus 0.1(0.1-0.2) x109/L, p<0.001) and median serum IgE level (78.0(29.5-252.0) versus 29.0(18.8-69.3), p=0.01) than those without. Median of CRP (1.9(0.8-2.5) versus 2.5(0.9-7.0), p=0.20) and ESR (6.0(3.0-12.5) versus 5.5(2.0-10.0), p=0.40) were not different between patients with osteitis and without. The median Global Osteitis Score was greater in patients with high serum eosinophilia (≥0.3 x109/L) (5.0(1.8-11.0) versus 0.0(0.0-4.0), p=0.004) (Figure 4.6).

In the primary surgery subgroup, patients with osteitis had higher median serum eosinophil count (0.3(0.1-0.6) x109/L versus 0.1(0.1-0.2) x109/L, p=0.01) compared

Factors		Global Osteitis Score in total population		Global Osteitis Score in primary surgery subgroup	
		median(IQR)	p-value	median(IQR)	p-value
Tissue eosinophilia	<10/HPF	1.0(0.0-5.8)	0.04	0.0(0.0-0.0)	0.001
	≥10/HPF	4.0(1.0-6.0)		3.0(0.0-4.0)	
Charcot-Leyden	absent	2.0(0.0-6.0)	0.65	0.0(0.0-2.0)	0.98
	present	4.0(0.0-6.0)		2.0(0.0-5.5)	
Eosinophil aggregates	absent	2.0(0.0-7.0)	1.0	0.0(0.0-2.3)	0.68
	present	4.0(0.0-6.0)		0.0(0.0-5.0)	
Severity of inflammation	absent	NA	0.03	NA	0.27
	mild	0.0(0.0-4.0)		0.0(0.0-2.8)	
	moderate	3.0(0.0-5.8)		1.0(0.0-4.0)	
	severe	6.0(3.5-13.5)		4.5(0.8-9.8)	

Table 4.2 Global Osteitis Score by histopathology in total population and primary surgery subgroup

NA: There were no patients with absent inflammation.

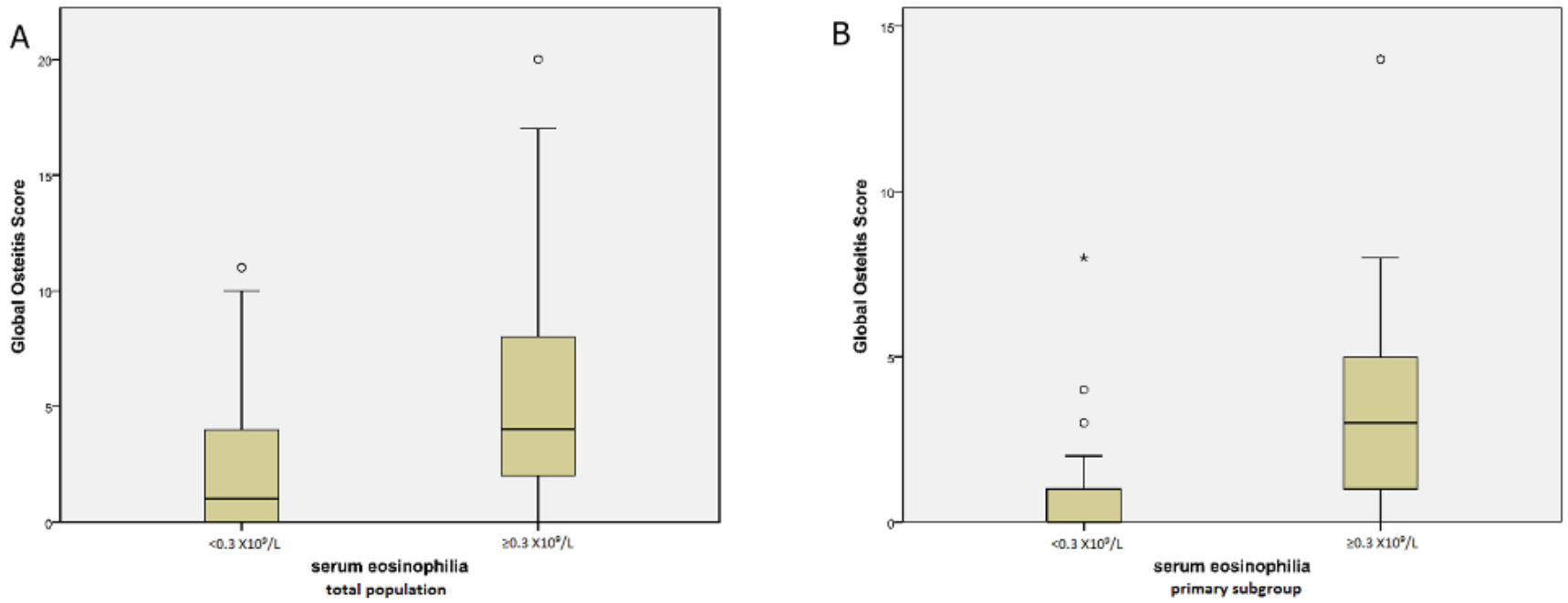


Figure 4.6 Global Osteitis Score by serum eosinophilia (≥0.3 x109/L) (A) total population (B) primary subgroup

to patients without osteitis but similar median serum IgE level (41.0(25.0-63.0) versus 31.0(19.0-73.0), p=0.46). The CRP (1.4(0.8-2.2) versus 2.1(0.6-5.2), p=0.45) and ESR (5.0(2.0-12.3) versus 5.0(2.0-10.0),p=0.73) were not different between groups. The median Global Osteitis Score was greater in patients whose serum eosinophilia was beyond previously reported threshold(Han, Kim et al. 2009; Snidvongs, Lam et al. 2012) (≥0.3 x109/L) (3.0(0.8-6.5) versus 0.0(0.0-0.0), p=0.002) (Figure 4.6).

Discussion

The prevalence of osteitis in this study was similar to Georgalas, et al(Georgalas, Videler et al. 2010) and Lee, et al(Lee, Kennedy et al. 2006). The presence of osteitic bones is widely accepted to be associated with previous surgery and it is also shown by this study. However, osteitis is multifactorial which can be found in non-operated patients. It is associated with other features of ECRS such as the presence of polyps, high tissue eosinophil ≥10/HPF, high serum eosinophil ≥0.3 x109/L and high serum IgE. Importantly, in a primary surgery subgroup, only true eosinophilic states which are tissue and serum eosinophilia show significant correlations. Although nasal polyps is a clinical feature of ECRS, the phenotype and the endotype are different in many patients, as tissue eosinophilia is also present in up to 19% of patients with CRSsNP(Snidvongs, Lam et al. 2012).

The relationship between osteitis of paranasal sinuses and high eosinophil level in serum and sputum was also reported by Metha, et al(Mehta, Campeau et al. 2008). The pathogenesis of this relationship is not known. To date bacteria have not been

demonstrated as common feature in the bone of CRS patients(Videler, Georgalas et al. 2011). The pathogenesis of osteitis may be either infection as shown from animal models studies(Perloff, Gannon et al. 2000) and/or inflammation. A chronic process of eosinophilic mucosal inflammation of ECRS may initiate bone remodeling including periosteal reaction, osteoclast proliferation, bone resorption, new bone formation, fibrosis and cellular infiltration. This response is similar to the reaction to other stimuli such as mechanical stress and post-traumatic repair(Videler, Georgalas et al. 2011). We do not have sufficient information to determine the length of symptoms (beyond 3mths) for our patient population. The osteitis may be related to duration of inflammation. To explore this further we looked at the relationship of age and osteitis score. There was no correlation between the age of the patients and osteitis in the non-operated subgroup (r =0.01, p=0.94). There is an association with age and the total group but this is confounded by prior surgery in the total population. Although eosinophilia is associated with clinical severity, the histological severity of inflammation was not associated with and global osteitis score was found in the primary surgery subgroup ((p=0.27). Possible alternative explanations of this association with eosinophilia could include a chronic inflammation dominated by a cytokine milieu of Th2 inflammation affecting not only sinus mucosa but also the bony walls. The systemic release of pro-inflammatory cytokines, such as IL-4 a known inducer of neo-osteogenesis(Lorenzo 1991), may trigger bone neo-osteogenesis in significant ECRS cases. However eosinophil infiltration is not common in bony histopathology of CRS patient and a systemic response may be required to initiate the osteitis. The majority of current animal models of CRS are

based on ostial obstruction and bacterial inoculation(Perloff, Gannon et al. 2000) and not an eosinophilic airway process and thus may be unreliable surrogates for research on bone changes.

Patients with osteitis have greater disease severity in endoscopy and CT score but similar symptoms compared to those without. These were similarly reported by other studies(Giacchi, Lebowitz et al. 2001; Cho, Min et al. 2006; Lee, Kennedy et al. 2006; Bhandarkar, Mace et al. 2011). The greater disease severity in patients with ECRS shown in our previous study is analogous to these findings(Snidvongs, Lam et al. 2012). It is also shown in the literature that CRS patients with osteitis have poorer treatment outcomes(Kim, Dhong et al. 2006). The ECRS subgroup is also related to an increased rate of restenosis and revision surgery after endoscopic sinus surgery(Soler, Sauer et al. 2010) and modified Lothrop procedure (Tran, Beule et al. 2007). If there is a causal link between osteitis, strong tissue eosinophilia and serum eosinophilia then structured histopathology(Snidvongs, Lam et al. 2012) reporting and serum analysis may be helpful to define a subgroup at risk for osteitis . The simple concept of endoscopic sinus surgery to create ventilation and drainage may be an inappropriate philosophy for patients with osteitis. Remnants of diseased bone may serve as a constant nidus for inflammation, inducing recurrent edema and hypertrophy of the overlying mucosa(Videler, Georgalas et al. 2011) and complete removal may be required. Additionally, a strong post-operative corticosteroid therapy regime may be appropriate for the patients with serum eosinophilia >0.3 $x10^9$/L and high tissue eosinophilia (>10/HPF) to prevent post-surgery osteitis if systemic mediators are involved in osteitis formation.

Conclusion

Osteitis is associated with tissue and serum eosinophilia in both patients with and without prior surgery. Potentially, patients with these features may benefit the most from post- operative corticosteroid therapy to prevent further osteitis and should be an area of future research.

References

Bhandarkar, N. D., J. C. Mace and T. L. Smith. The Impact of Osteitis on Disease Severity Measures and Quality of Life Outcomes in Chronic Rhinosinusitis. *Int Forum Allergy Rhinol* 2011;1(5): 372-378.

Cho, S. H., H. J. Min, H. X. Han, S. S. Paik and K. R. Kim. CT analysis and histopathology of bone remodeling in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;135(3): 404-408.

Fokkens, W., V. Lund and J. Mullol. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007;(20): 1-136.

Georgalas, C., W. Videler, N. Freling and W. Fokkens. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. *Clin Otolaryngol* 2010;35(6): 455-461.

Giacchi, R. J., R. A. Lebowitz, H. T. Yee, J. P. Light and J. B. Jacobs. Histopathologic evaluation of the ethmoid bone in chronic sinusitis. *Am J Rhinol* 2001;15(3): 193-197.

Han, D. H., S. W. Kim, S. H. Cho, et al. Predictors of bronchial hyperresponsiveness in chronic rhinosinusitis with nasal polyp. *Allergy* 2009;64(1): 118-122.

Hopkins, C., S. Gillett, R. Slack, V. J. Lund and J. P. Browne. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009;34(5): 447-454.

Kennedy, D. W., B. A. Senior, F. H. Gannon, et al. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. *Laryngoscope* 1998;108(4 Pt 1): 502-507.

Kern, R. C., D. B. Conley, W. Walsh, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. *Am J Rhinol* 2008;22(6): 549-559.

Kim, H. Y., H. J. Dhong, H. J. Lee, et al. Hyperostosis may affect prognosis after primary endoscopic sinus surgery for chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;135(1): 94-99.

Lee, J. T., D. W. Kennedy, J. N. Palmer, M. Feldman and A. G. Chiu. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol* 2006;20(3): 278-282.

Lorenzo, J. A. The role of cytokines in the regulation of local bone resorption. *Crit Rev Immunol* 1991;11(3-4): 195-213.

Mehta, V., N. G. Campeau, H. Kita and J. B. Hagan. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. *Mayo Clin Proc* 2008;83(6): 671-678.

Nizankowska-Mogilnicka, E., G. Bochenek, L. Mastalerz, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10): 1111-1118.

Perloff, J. R., F. H. Gannon, W. E. Bolger, et al. Bone involvement in sinusitis: an apparent pathway for the spread of disease. *Laryngoscope* 2000;110(12): 2095-2099.

Snidvongs, K., M. Lam, R. Sacks, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol* 2012;In press.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

Tran, K. N., A. G. Beule, D. Singal and P. J. Wormald. Frontal ostium restenosis after the endoscopic modified Lothrop procedure. *Laryngoscope* 2007;117(8): 1457-1462.

Videler, W. J., C. Georgalas, D. J. Menger, et al. Osteitic bone in recalcitrant chronic rhinosinusitis. *Rhinology* 2011;49(2): 139-147.

Chapter 5

Correlation of the Kennedy Osteitis Score to clinico-histologic features of chronic rhinosinusitis

ORIGINAL ARTICLE

Correlation of the Kennedy Osteitis Score to clinico-histologic features of chronic rhinosinusitis

Komkiat Snidvongs, MD[1,2], Rohan McLachlan[3], Raymond Sacks, MD[1,4], Peter Earls, MD[5] and Richard J. Harvey, MD[1,3]

Background: Osteitis is a feature of chronic rhinosinusitis (CRS) and often associated with recalcitrant disease. Radiological characteristics of osteitic sinus changes are commonly reported in practice but the clinical and pathologic significance is poorly defined. The objective of this study was to correlate the Kennedy Osteitis Score (KOS) to clinico-histologic features of CRS.

Methods: A cross-sectional study of CRS patients undergoing sinus surgery was conducted. Osteitis was scored radiologically using the KOS. Associations between osteitis and histopathology, symptoms, 22-item Sino-Nasal Outcomes Test (SNOT-22), endoscopy, computed tomography (CT) mucosal score, and serumarkers were assessed. Interobserver correlation coefficient was performed. Additionally, the KOS was correlated to an alternate Global Osteitis Score.

Results: A total of 88 patients were assessed (45.5% female, age 50.3 ± 13.6 years); 45 (51.1%) patients had osteitis. Patients with KOS >0, had greater endoscopy score (6.1 ± 2.9 vs 4.4 ± 3.6, $p = 0.03$) and CT score (14.0 ± 6.0 vs 10.1 ± 5.7, $p < 0.01$) than those without osteitis. There was no difference in symptom score (2.4 ± 1.3 vs 2.4 ± 1.1, $p = 0.89$) and SNOT-22 (2.0 ± 1.0 vs 1.9 ± 1.1, $p = 0.56$) in patients with and without osteitis. KOS was higher in patients with tissue eosinophilia >10/high-power field (HPF) (median 3.0 [IQR, 1.0–5.3] vs 0.0 [0.0–4.0], $p = 0.03$) and serum eosinophilia >0.3 × 10^9/L (4.0 [2.0–7.0] vs 1.0 [0.0–4.0], $p < 0.01$). Importantly, this was also true for those without prior surgery. The interobserver correlation coefficient was good ($R = 0.86$, $p < 0.001$). There was a significant correlation between the KOS and the Global Osteitis Score ($R = 0.93$, $p < 0.001$).

Conclusion: The KOS is a simple, easy, and reproducible scale in assessing osteitic bones in patients with CRS and can predict measures of severity in eosinophilic rhinosinusitis. © 2012 ARS-AAOA, LLC.

Key Words:
rhinosinusitis; osteitis; chronic rhinosinusitis; eosinophilic; nasal polyps

How to Cite this Article:
Snidvongs K, McLachlan R, Sacks R, Earls P, Harvey RJ. Correlation of the Kennedy Osteitis Score to clinico-histologic features of chronic rhinosinusitis. *Int Forum Allergy Rhinol*, 2012; 00:X-XX.

[1]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia; [2]Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Thailand; [3]University of New South Wales, Sydney, Australia; [4]University of Sydney, Sydney, Australia; [5]Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia

Correspondence to: Komkiat Snidvongs, MD, The Australian School of Advanced Medicine, 2 Technology Place, Macquarie University, Sydney, NSW 2109, Australia; e-mail: drkomkia@yahoo.com, komkiat.snidvongs@students.mq.edu.au

Potential conflict of interest: R.J.H. has served on an advisory board for Schering Plough and Glaxo-Smith-Kline, was a consultant with Medtronic, was on the speakers bureau for Merek Sharp Dolme and Arthrocare, and has received grant support from NeilMed. R.S. is a consultant for Medtronic and on the speakers bureau for Merek Sharp Dolme.
Presented orally at the Annual ARS Meeting on September 8, 2012, Washington, DC.

Evidence of bone resorption, new bone formation, fibrosis, and inflammation have been shown in underlying bone in chronic rhinosinusitis (CRS).[1,2] The term "osteitis" is used in defining the process of bony paranasal sinus involvement in patients with CRS where neo-osteogenesis occurs.[3] The prevalence of osteitis in CRS is around 40% to 50%,[4–6] and increases to as much 76% in patients having previous sinus surgery.[4,6] Patients with osteitis have more disease severity endoscopically and radiographically,[4] which is associated with recalcitrant disease.[3]

Received: 30 April 2012; Revised: 17 August 2012; Accepted: 13 September 2012
DOI: 10.1002/alr.21113
View this article online at wileyonlinelibrary.com.

"The associations between osteitis and markers of ECRS has been demonstrated. This study aims to correlate the Kennedy Osteitis Score (KOS) to clinico-histologic features of CRS."

Abstract

Background:

Osteitis is a feature of chronic rhinosinusitis (CRS) and often associated with recalcitrant disease. Radiological characteristics of osteitic sinus changes are commonly reported in practice but the clinical and pathologic significance is poorly defined. The objective of this study was to correlate the Kennedy Osteitis Score (KOS) to clinico-histologic features of CRS.

Methods:

A cross-sectional study of CRS patients undergoing sinus surgery was conducted. Osteitis was scored radiologically using KOS. Associations between osteitis and histopathology, symptoms, SNOT-22, endoscopy, CT mucosal score and seromarkers were assessed. Interobserver correlation coefficient was performed. Additionally, the KOS was correlated to an alternate Global Osteitis Score.

Results:

88 patients were assessed (45.5% female, age 50.3±13.6 years). 45 (51.1%) patients had osteitis. Patients with KOS greater than 0, had greater endoscopy score (6.1±2.9 versus 4.4±3.6, p=0.03) and CT score (14.0±6.0 versus 10.1±5.7, p<0.01) than those without osteitis. There was no difference in symptom score (2.4±1.3 versus 2.4±1.1, p=0.89) and SNOT-22 (2.0±1.0 versus 1.9±1.1, p=0.56) in patients with and without osteitis. KOS was higher in patients with tissue eosinophilia > 10/HPF (3.0(1.0-5.3) v 0.0(0.0-4.0), p=0.03) and serum eosinophilia >0.3 $x10^9$/L

(4.0(2.0-7.0) versus 1.0(0.0-4.0), p<0.01). Importantly, this was also true for those without prior surgery.The interobserver correlation coefficient was good (R=0.86, p<0.001). There is a significant correlation between KOS and Global Osteitis Score (R=0.93, p<0.001).

Conclusions:

KOS is a simple, easy and reproducible scale in assessing osteitic bones in patients with CRS and can predict measures of severity in eosinophilic rhinosinusitis.

Key words:

rhinosinusitis, osteitis, chronic rhinosinusitis, eosinophilic, nasal polyps

Introduction

Evidence of bone resorption, new bone formation, fibrosis and inflammation have been shown in underlying bone in chronic rhinosinusitis (CRS)(Kennedy, Senior et al. 1998)'(Khalid, Hunt et al. 2002). The term “osteitis” is used defining the process of bony paranasal sinus involvement in patients with CRS where neo-osteogenesis occurs(Videler, Georgalas et al. 2011). The prevalence of osteitis in CRS is around 40-50%(Lee, Kennedy et al. 2006; Georgalas, Videler et al. 2010; Snidvongs, McLachlan et al. 2012) and increases to as much 76% in patients having previous sinus surgery(Georgalas, Videler et al. 2010; Snidvongs, McLachlan et al. 2012). Patients with osteitis have more disease severity endoscopically and radiographically(Snidvongs, McLachlan et al. 2012) and is associated with recalcitrant disease(Videler, Georgalas et al. 2011).

The pathological criteria of osteitis are the presence of bony remodeling with new immature woven bone formation seen overlying organized lamellar bone(Lee, Kennedy et al. 2006) (Figure 5.1). These bone changes are not routinely reported in histological sections due to the under recognition by pathologists of both the process and its significance. In practice, computed tomography (CT) is the practical diagnostic tool for both determining the presence of osteitis and for grading severity and extent. The Kennedy Osteitis Score is proposed, based on a previously described grading system for radiographic measures of ethmoid bone partitions, maxillary and sphenoid sinus walls (Lee, Kennedy et al. 2006). Georgalas and colleagues proposed Global Osteitis

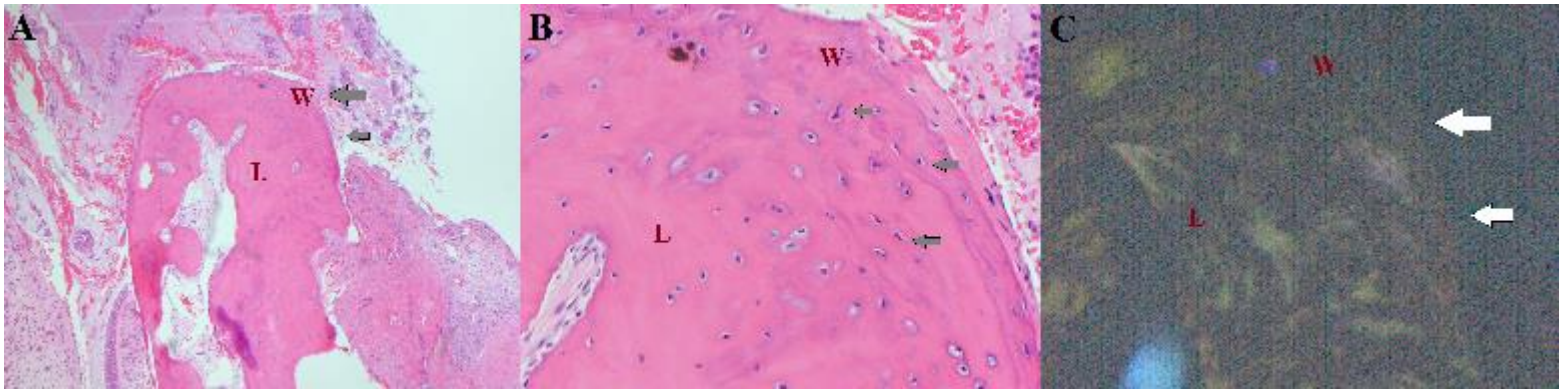


Figure 5.1 Histopathology of osteitis showing newly formed woven bone (W), lamella bone (L) and osteoblastic activity (arrow) (A) Hematoxylin and Eosin (H&E) stain, low power (B) H&E stain, high power (C) H&E stain, high power under polarized light

Score(Georgalas, Videler et al. 2010) based on the similar principle to the Kennedy grading system. The Global Osteitis Score gives a higher score when osteitic bones are with greater than 50% of the sinus walls involved.

The objectives of this study were to propose the Kennedy osteitis score and determine its correlation with the clinico-histologic features of CRS, to investigate its reproducibility and compare the two osteitis scoring systems.

Material and methods

Study design

A cross-sectional study of consecutive patients undergoing sinus surgery was undertaken. The study had ethical approval from the St Vincent's Hospital institutional review board.

Patient population

Adult patients (>18 years) with CRS with polyps (CRSwNP) or without polyps (CRSsNP) who underwent endoscopic sinus surgery (ESS) in a tertiary referral clinic were reviewed. CRS patients were defined according to EP3OS(Fokkens, Lund et al. 2007). All patients underwent ESS after failing previous medical therapy. No patients used oral steroid for 4 weeks prior to surgery.

Demographic data was recorded. Comorbidity of asthma was defined as clinically using an inhaled β-agonist or corticosteroid. Patients with suspected aspirin sensitivity on history were confirmed with a nasal lysine aspirin challenge as per the European Guidelines(Nizankowska-Mogilnicka, Bochenek et al. 2007). Five item symptom score of the following was used: nasal obstruction, post nasal discharge, thick nasal discharge, loss of smell and taste, facial pain and pressure. These were recorded on a Likert scale from 0 (no symptom) to 5 (very severe). The Sino-Nasal Outcome Test 22(SNOT-22) was used for disease-specific quality of life assessment. Preoperative Lund-Kennedy endoscopy scores were recorded. A structured histopathology report(Snidvongs, Lam et al. 2012) was used to define inflammatory features of the disease. Histopathology reported tissue eosinophilia (<5 per high power field (HPF), 5-10 per HPF, >10 per HPF), Charcot-Leyden Crystals (absent, present), eosinophil aggregates (absent, present) and severe of inflammation (absent, mild, moderate, severe). Three high power fields were analyzed to reach a consensus as the density of eosinophilia. The seromarkers reported were: eosinophil count ($x10^9$/L) and total IgE (kU/L). All preoperative computed tomography (CT) scans were evaluated with Lund-Mackay scores.

Kennedy Osteitis Scoring System

The original description of the Kennedy Osteitis grade was mild (<3 mm), moderate (4–5 mm), or severe (>5 mm). This was been modified to create a summary score so that comparable assessments to the Global Osteitis Score. Two assessors (KS, RM) gave

radiographical osteitis score independently. One scored all patients and the other scored a random sample of half the population. The slice having maximum thickness of paranasal sinuses bony walls was defined. The perpendicular plane to the sinus wall was drawn and measured to determine the degree of osteitis by using Kennedy Osteitis Scoring System. All ten sinuses (Right and left frontal, anterior ethmoid, posterior ethmoid, maxillary and sphenoid) were scored as being 0 (lesser than 3 mm) (Figure 5.2A), 1 (3–5 mm) (Figure 5.2B), or 2 (greater than 5 mm) (Figure 5.2C). The total osteitis score ranges from 0 to 20. Woven bone with thickened, irregular, heterogeneous lining of the sinus walls was measured other than normal lamellar/cortical bony wall.

Global Osteitis Scoring Scale

The presence, severity and extent of osteitis was also scored by using Global Osteitis Score, proposed by Georgalas and colleagues(Georgalas, Videler et al. 2010). Bony walls of paranasal sinuses were scored ranging from 0 to 4 making the total score of 0 to 40 as follows:

0: Less than 50% of the sinus walls involved and osteitis <3 mm wide.

1: Less than 50% of the sinus was involved and 3–5 mm width.

2: Less than 50% of the sinus involved and wider than 5 mm or greater than 50% of the sinus wall involved and <3 mm wide osteitic changes.

3: Greater than 50% of the sinus wall involved and 3–5 mm.

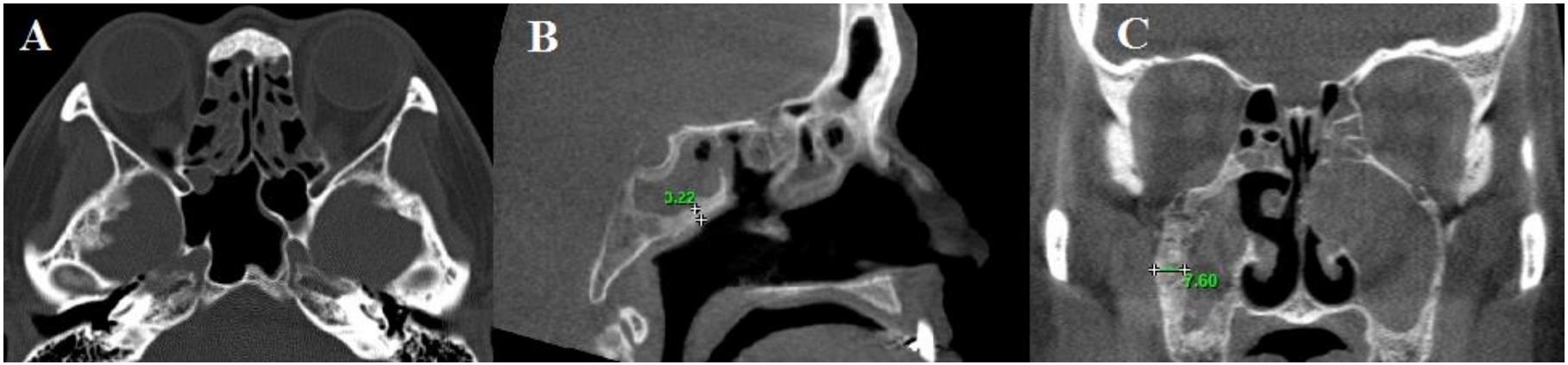


Figure 5.2 Examples of Kennedy Osteitis Score in CRS patients. The perpendicular plane to the sinus wall was drawn and the maximum bony thickness of osteitic bones was measured: (**A**) score 0 (**B**) score 1 (**C**) score 2

4: Greater than 50% of the sinus wall and thicker than 5 mm.

Statistical analysis

Descriptive data was presented as percentage, mean and standard deviation (SD) for parametric data, median and interquartile range (IQR) for non-parametric data. Student's T-test and Mann-Whitney U test (two-tailed) were used for comparisons of unrelated groups of parametric and non-parametric data respectively. Kruskal-Wallis was used for comparisons of non-parametric data of more than two groups. Intraclass correlation coefficient (single measures, two-way mixed effects model) was used to assess the consistency of measurements performed by two observers. Spearman's correlation coefficients were used for ordinal values. Pearson correlation coefficients were performed for linear relationship of two sets of scale variables measured by using two scoring systems. Statistical analyses were performed using SPSS v 20.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

Patient population

Eighty-eight patients with a mean age of 50.3 ±13.6 years were assessed. Forty (45.5%) patients were female. Nine (10.2%) patients were smokers and twenty (22.7%) had asthma. Three (3.4%) patients had aspirin hypersensitivity. Forty-two (47.7%) patients were diagnosed as CRSsNP. Thirty-three (37.5%) had revision surgery. The

number of previous surgery ranged from 1 to 12. Forty-five (51.1%) of total patients had some form of osteitis. The prevalence of osteitis was 75.8% (25/33) for patients with revision surgery and 36.4% (20/55) for patients with primary surgery. It is acknowledged that the patient population is from a tertiary hospital clinic.

Correlation of Kennedy Osteitis Score to CRS phenotypes and co-morbidity

Kennedy Osteitis Score was significant greater in patients with revision surgery (4.0(2.0-5.0) versus 0.0(0.0-3.3), $p<0.001$) (Figure5.3A) and CRSwNP (2.5(0.0-5.0) versus 0.0(0.0-4.0), $p=0.04$). However, in un-operated subgroup, the score was not different between CRSwNP (1.0(0.0-4.0)) and CRSsNP (0.0(0.0-2.5)), $p=0.24$. It was similar regarding gender ($p=0.27$), asthmatic status ($p=0.28$), aspirin sensitivity ($p=0.87$), and smoking ($p=0.40$).

Correlation of Kennedy Osteitis Score to clinical severity

Patients with Kennedy Osteitis Score greater than 0, had greater endoscopy score (6.1±2.9 versus 4.4±3.6, $p=0.03$) and CT score (14.0±6.0 versus 10.1±5.7, $p=0.005$) than those with negative score. The mean symptom score (2.4±1.3 versus 2.4±1.1, $p=0.89$) and SNOT-22 score (2.0±1.0 versus 1.9±1.1, $p=0.56$) in patients with osteitis were not different from those without. Kennedy Osteitis Score was well correlated with endoscopy score ($R=0.25$, $p=0.03$) and CT score ($R=0.35$, $p=0.001$) but not symptom score ($R=0.10$, $p=0.56$) and SNOT-22 ($R=0.23$, $p=0.12$).When the primary surgery subgroup was investigated, similar findings were found (Table5.1).

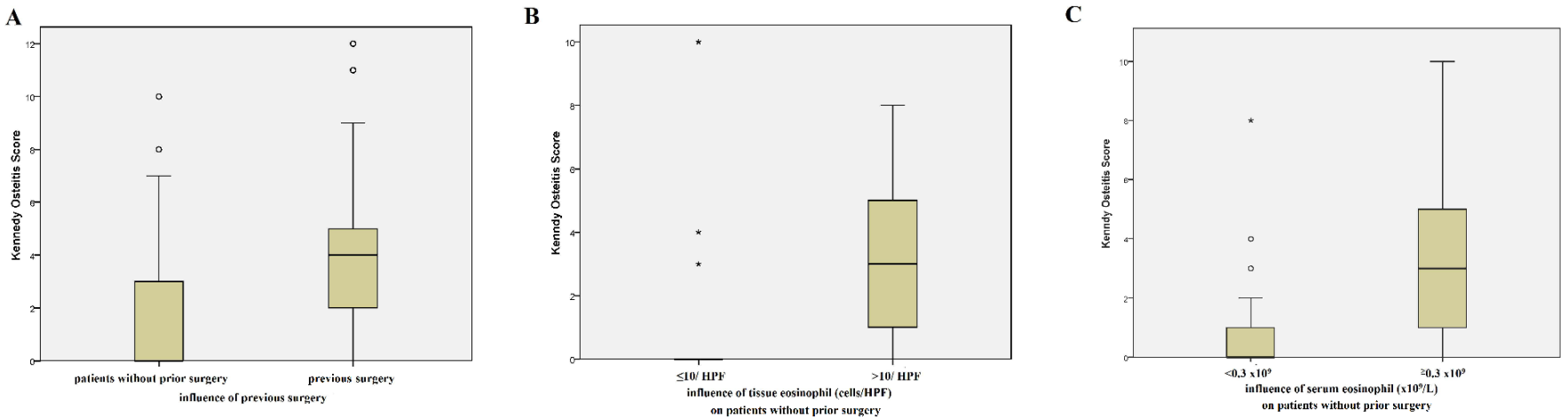


Figure 5.3 Kennedy Osteitis Score (median with interquartile range) is (A) significantly greater in patients with previous surgery. In patients without prior surgery, it is (B) significantly greater in patients with high tissue eosinophilia (>10/HPF) and (C) high serum eosinophilia (≥0.3 x10^9/L)

		Total population			Primary surgery subgroup		
		Non-osteitis	Osteitis (score>0)	p-value	Non-osteitis	Osteitis (score>0)	p-value
Disease severity (mean±SD)	Symptom score	2.4±1.0	2.4±1.3	0.97	2.4±1.1	2.5±1.4	0.84
	SNOT-22	1.9±1.1	2.0±1.0	0.56	1.7±1.0	1.8±0.8	0.75
	Endoscopy score	4.4±3.6	6.1±2.9	0.03	4.5±3.6	6.6±2.9	0.03
	CT mucosal score	10.1±5.7	14.0±6.0	0.005	10.4±5.2	15.6±5.5	0.002
Disease severity to Kennedy Osteitis Score		Spearman correlation		p-value	Spearman correlation		p-value
	Symptom score	0.10		0.56	0.03		0.85
	SNOT-22	0.23		0.12	0.16		0.44
	Endoscopy score	0.25		0.03	0.31		0.03
	CT mucosal score	0.35		0.001	0.49		<0.001
	Serum Eosinophilia	0.45		<0.001	0.43		0.01

Table 5.1 Disease severity by the presence of osteitis in total population and primary surgery subgroup

Correlation Kennedy Osteitis Score to CRS histopathology

Kennedy Osteitis Score was significant greater in patients with tissue eosinophilia greater than 10/HPF (3.0(1.0-5.3) versus 0.0(0.0-4.0), p=0.03 and serum eosinophilia greater than 0.3 $x10^9$/L (4.0(2.0-7.0) versus 1.0(0.0-4.0), p=0.003. It was similar regarding the severity of inflammation (p=0.10), the presence of Charcot-Leyden (p=0.78) and Eosinophil aggregates (p=0.64). Data was displayed in Table 5.2. When the primary surgery subgroup was investigated, similar findings were found (Figure5.3B).

Patients with Kennedy Osteitis Score greater than 0, had higher level of serum eosinophil ($x10^9$/L) (0.3(0.2-0.5) versus 0.1(0.1-0.2), p<0.001) (Figure 5.3C). and serum IgE (kU/L) (78.0(29.5-252.0) versus 29.0(18.8-69.3), p=0.01) than those with negative score. However, in un-operated subgroup, the serum IgE level was not different (41.0(25.0-63.0) versus 31.0(19.0-73.0), p=0.46.)

Interobserver reliability

Two scorers performed 44 of independent CT assessments. The intraclass correlation coefficient showed a significant correlation (R=0.86, p<0.001) (Figure5.4). Reliability statistics of 0.81-1.00 usually are interpreted as “almost perfect”(Landis and Koch 1977).

Correlation Kennedy Osteitis Score and Global Osteitis Score

Factors		Kennedy Osteitis Score in total population		Kennedy Osteitis Score in primary surgery subgroup	
		median(IQR)	p-value	median(IQR)	p-value
Tissue eosinophilia	≤10/HPF	0.0(0.0-4.0)	0.03	0.0(0.0-0.0)	0.001
	>10/HPF	3.0(1.0-5.3)		3.0(1.0-5.0)	
Charcot-Leyden	absent	2.0(0.0-4.5)	0.78	0.0(0.0-3.8)	0.98
	present	3.0(0.0-4.8)		0.0(0.0-5.0)	
Eosinophil aggregates	absent	2.5(0.0-5.0)	0.64	0.0(0.0-4.0)	0.68
	present	2.0(0.0-4.0)		0.0(0.0-4.5)	
Severity of inflammation	absent	NA	0.10	NA	0.30
	mild	0.0(0.0-4.0)		0.0(0.0-2.8)	
	moderate	3.0(0.0-4.8)		1.0(0.0-4.0)	
	severe	4.0(2.0-7.5)		4.5(0.8-6.8)	

Table 5.2 Kennedy Osteitis Score by histopathology in total population and primary surgery subgroup

NA: not applicable. There are no patients with absent inflammation

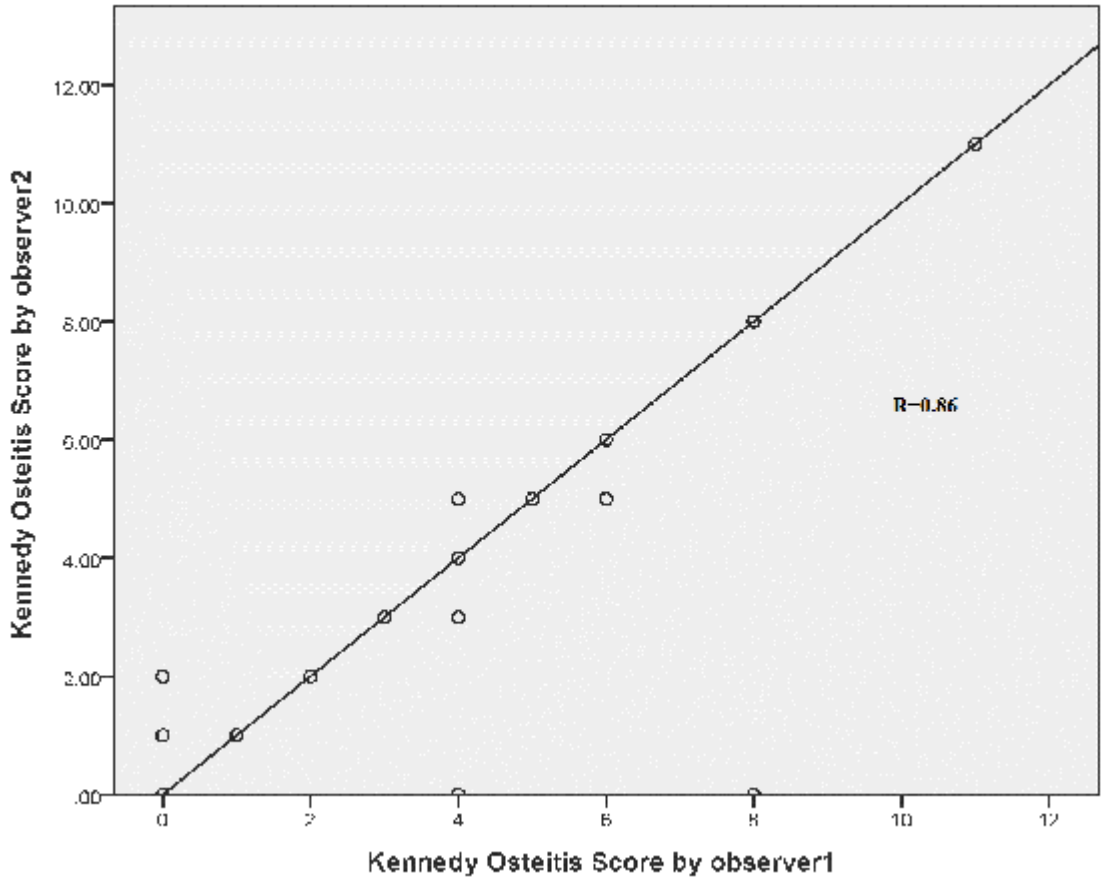


Figure 5.4 Interobserver correlation coefficient; scatter dots represent more than one data set

Both the Global Osteitis Score and Kennedy Osteitis Score are able to define patient subgroups. For primary versus revision surgery, the Global Osteitis Score was 6.0(3.8-10.3) versus 0.0(0.0-3.0), $p<0.001$ and for the KOS was 4.0(2.0-5.0) versus 0.0(0.0-3.3), $p<0.001$. Similarly, for the high tissue eosinophilic CRS (>10/HPF) the Global Osteitis Score was 4.0(1.0-6.0) versus 1.0(0.0-5.8), $p=0.04$ and the Kennedy Osteitis Score was (3.0(1.0-5.3) versus 0.0(0.0-4.0), $p=0.03$. When the two scoring systems were compared to each other, there was a significant correlation between Kennedy Osteitis Score and Global Osteitis Score ($R=0.93$, $p<0.001$) (Figure5.5).

Discussion

In the original Kennedy Osteitis Score, osteitis was classified as being mild (3 mm), moderate (4–5 mm), or severe (>5 mm), depending on the extent of bony thickness, and frontal sinus was not evaluated. In this study, the figures were minimally modified to mild (<3 mm), moderate (3–5 mm), or severe (>5 mm). Frontal sinus scoring was originally not included as the thickness of normal lamellar bony wall of frontal sinuses is often greater than 3mm, and there is a possibility of hypopneumatized or non-pneumatized frontal sinus. In this study, we also scored frontal sinuses therefore the correlation between the two scoring systems could be analyzed. Only the thickness of irregular woven bone of frontal sinuses was measured and, in particular, the frontal sinus septum.

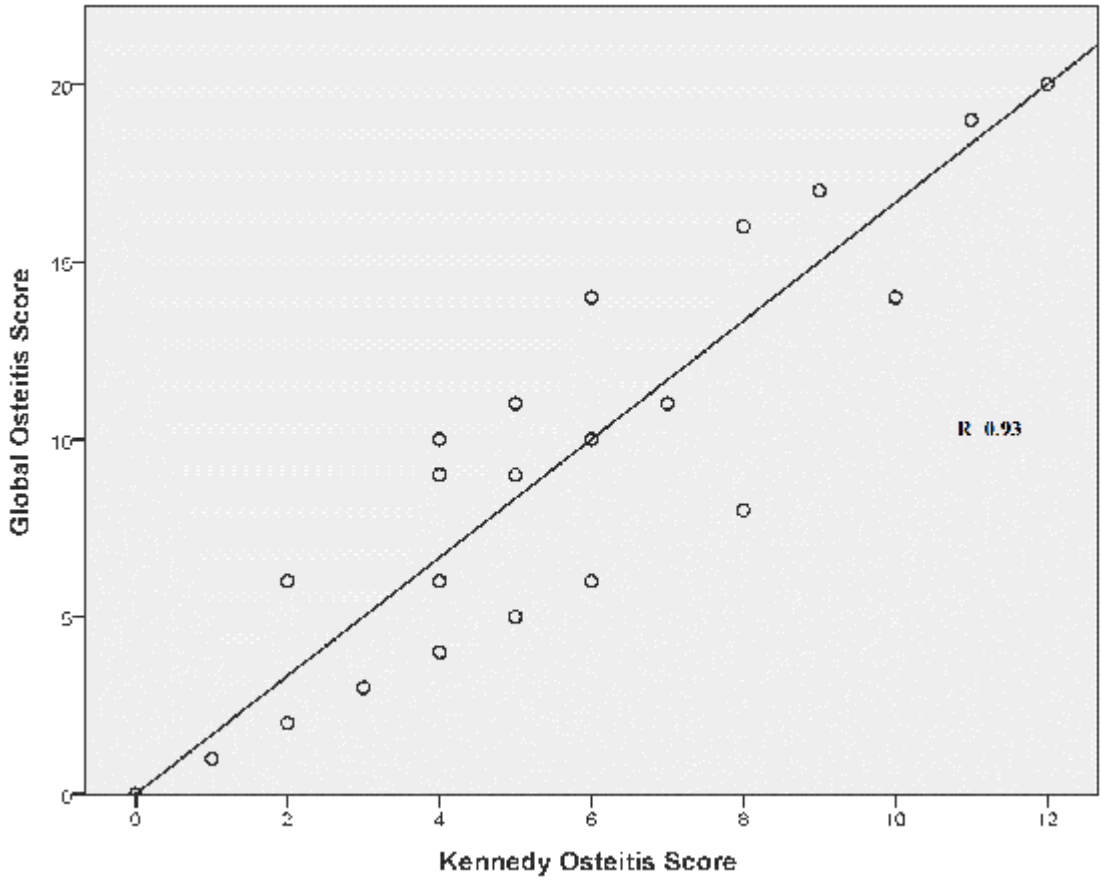


Figure 5.5 Association between Kennedy Osteitis Score and Global Osteitis Score; scatter dots represent more than one data set.

The Kennedy Osteitis Score is a useful tool to predict some measures of clinical severity. In agreement with previous studies(Lee, Kennedy et al. 2006; Georgalas, Videler et al. 2010; Bhandarkar, Mace et al. 2011), it is associated with revision surgery. Patients with Kennedy Osteitis Score >0 had greater endoscopy scores and CT scores than those with no evidence of osteitis. It failed to predict symptom severity as there was no difference in symptom score and SNOT-22 score between patients with osteitis and without. However no correlation of the SNOT symptom score with other CRS markers including CT score(Bradley and Kountakis 2005) and tissue eosinophilia(Snidvongs, Lam et al. 2012) was also shown in previous studies. Bhandarkar and colleagues investigated the impact of osteitis on quality of life outcomes after ESS. They mentioned patients with osteitis having greater baseline disease severity and less improvements in Rhinosinusitis Disability Index functional subscale. However osteitis is correlated with revision surgery which portends recalcitrant disease and the study did not analyse the subgroup of patients without prior surgery.

The histological features of osteitis in human studies and animal studies are summarized in Table5.3. The characteristic of osteitis are periosteal thickening, new woven bone formation and bone resorption. Fibrosis is presented in severe cases.Inflammatory involvement of the underlying bone matrix and/or in the Haversian system was described in animal studies but yet to be described in human studies.

Study	Type	Histopathology findings				
		periosteal thickening	new woven bone formation	bone resorption	fibrosis	inflammatory bony involvement
Lee2006(Lee, Kennedy et al. 2006)	human	present	present	not mentioned	not mentioned	not mentioned
Cho2006(Cho, Min et al. 2006)	human	present	present	present	not mentioned	not mentioned
Giachhi2001(Giacchi, Lebowitz et al. 2001)	human	present	present	present	present*	not mentioned
Kennedy1998(Kennedy, Senior et al. 1998)	human	not mentioned	present	present	present*	not mentioned
Tovi1992(Tovi, Benharroch et al. 1992)	human	present	present	not mentioned	present	not mentioned
Antunes2007(Antunes, Feldman et al. 2007)	animal	present	present	present	not mentioned	present
Khalid2002(Khalid, Hunt et al. 2002)	animal	not mentioned	present	present	present	present
Perloff2000(Perloff, Gannon et al. 2000)	animal	not mentioned	not mentioned	present	present	present
Norlander1992(Norlander, Westrin et al. 1994)	animal	present	present	present	not mentioned	not mentioned
Westrin1992(Westrin, Norlander et al. 1992)	animal	present	present	present	present	not mentioned

Table 5.3 Histopathology findings of osteitis from human and animal studies

*present in severe cases

In this study, tissue eosinophilia was defined as having tissue eosinophil >10/HPF because this cut-off point associated with less improvement after treatment(Soler, Sauer et al. 2010). Serum eosinophilia was defined as having serum eosinophil greater than 0.3 $x10^9$/L according to the ROC curve for the diagnostic accuracy of serum eosinophil in predicting tissue eosinophilia(Snidvongs, Lam et al. 2012). Kennedy Osteitis Score was shown useful to predict eosinophilic CRS which has been recognized as a challenging subgroup of CRS. It was significant greater in patients with tissue eosinophilia greater than 10/HPF and patients with serum eosinophilia greater than 0.3 $x10^9$/L. This is in agreement with the previous study by Mehta and colleagues(Mehta, Campeau et al. 2008). Additionally, Bhandarkar, et al also reported an association between the presence of osteitis and CRSwNP(Bhandarkar, Mace et al. 2011) while the correlation between CRSwNP and eosinophilic CRS has been revealed(Snidvongs, Lam et al. 2012). Eosinophilic CRS is recognized as a challenging subgroup of CRS. Patients with eosinophilic CRS have higher disease severity(Snidvongs, Lam et al. 2012) and worse outcome after ESS(Soler, Sauer et al. 2010) when compared to patients with non-eosinophilic CRS. Potentially, this subgroup may benefit the most from post- operative corticosteroid therapy to prevent further osteitis(Snidvongs, McLachlan et al. 2012). The high interobserver correlation coefficient of 0.86 indicates high reproducibility of Kennedy Osteitis Score. The methodology of this scoring by measurement of the maximum thickness of woven bony walls is simple and easy. Global Osteitis Score may be more complex assessing for

both severity (bony thickness) and extension (percentage of bony walls involvement) but it may potentially better describe extensive changes. A significant correlation was shown between the two scoring systems in this study. Prospective trial is required to see if this scoring system is prognostic for treatment outcome.

Conclusions

Kennedy Osteitis Score is correlated well with clinico-histologic features of CRS and predicts disease severity in a challenging subgroup of patients, with eosinophilic rhinosinusitis.

This scoring system is simple, easy and reproducible in assessing osteitic bones in patients with CRS. However, its influence on outcomes from interventions needs to be determined and thus its clinical utility remains in question.

References

Antunes, M. B., M. D. Feldman, N. A. Cohen and A. G. Chiu. Dose-dependent effects of topical tobramycin in an animal model of Pseudomonas sinusitis. *Am J Rhinol* 2007;21(4): 423-427.

Bhandarkar, N. D., J. C. Mace and T. L. Smith. The Impact of Osteitis on Disease Severity Measures and Quality of Life Outcomes in Chronic Rhinosinusitis. *Int Forum Allergy Rhinol* 2011;1(5): 372-378.

Bradley, D. T. and S. E. Kountakis. Correlation between computed tomography scores and symptomatic improvement after endoscopic sinus surgery. *Laryngoscope* 2005;115(3): 466-469.

Cho, S. H., H. J. Min, H. X. Han, S. S. Paik and K. R. Kim. CT analysis and histopathology of bone remodeling in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;135(3): 404-408.

Fokkens, W., V. Lund and J. Mullol. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007;(20): 1-136.

Georgalas, C., W. Videler, N. Freling and W. Fokkens. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. *Clin Otolaryngol* 2010;35(6): 455-461.

Giacchi, R. J., R. A. Lebowitz, H. T. Yee, J. P. Light and J. B. Jacobs. Histopathologic evaluation of the ethmoid bone in chronic sinusitis. *Am J Rhinol* 2001;15(3): 193-197.

Kennedy, D. W., B. A. Senior, F. H. Gannon, et al. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. *Laryngoscope* 1998;108(4 Pt 1): 502-507.

Khalid, A. N., J. Hunt, J. R. Perloff and D. W. Kennedy. The role of bone in chronic rhinosinusitis. *Laryngoscope* 2002;112(11): 1951-1957.

Landis, J. R. and G. G. Koch. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1): 159-174.

Lee, J. T., D. W. Kennedy, J. N. Palmer, M. Feldman and A. G. Chiu. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol* 2006;20(3): 278-282.

Mehta, V., N. G. Campeau, H. Kita and J. B. Hagan. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. *Mayo Clin Proc* 2008;83(6): 671-678.

Nizankowska-Mogilnicka, E., G. Bochenek, L. Mastalerz, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10): 1111-1118.

Norlander, T., K. M. Westrin and P. Stierna. The inflammatory response of the sinus and nasal mucosa during sinusitis: implications for research and therapy. *Acta Otolaryngol Suppl* 1994;515: 38-44.

Perloff, J. R., F. H. Gannon, W. E. Bolger, et al. Bone involvement in sinusitis: an apparent pathway for the spread of disease. *Laryngoscope* 2000;110(12): 2095-2099.

Snidvongs, K., M. Lam, R. Sacks, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol* 2012;In press.

Snidvongs, K., R. McLachlan, D. Chin, et al. Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis. *Rhinology* 2012;in press.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

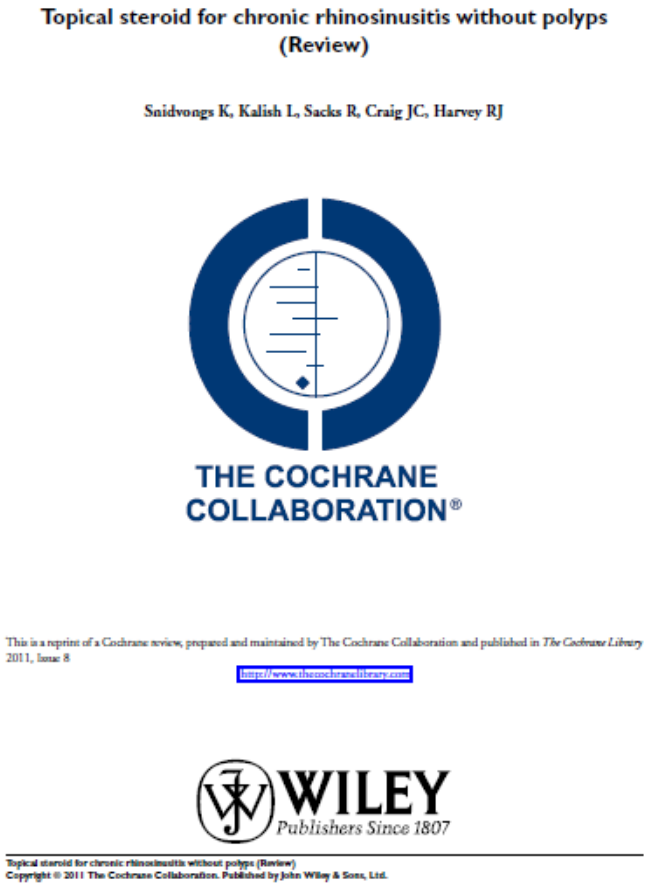
Tovi, F., D. Benharroch, A. Gatot and Y. Hertzanu. Osteoblastic osteitis of the maxillary sinus. *Laryngoscope* 1992;102(4): 426-430.

Videler, W. J., C. Georgalas, D. J. Menger, et al. Osteitic bone in recalcitrant chronic rhinosinusitis. *Rhinology* 2011;49(2): 139-147.

Westrin, K. M., T. Norlander, P. Stierna, B. Carlsoo and C. E. Nord. Experimental maxillary sinusitis induced by Bacteroides fragilis. A bacteriological and histological study in rabbits. *Acta Otolaryngol* 1992;112(1): 107-114.

Chapter 6

Topical steroid for chronic rhinosinusitis without polyps



Topical steroid for chronic rhinosinusitis without polyps
(Review)

Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 8

http://www.thecochranelibrary.com

WILEY
Publishers Since 1807

"This study aims to assess the effects of topical steroid for CRS without polyps and how sinus surgery and topical delivery method influence the impact of topical steroid."

Abstract

Background:

Topical corticosteroid is used as part of a comprehensivemedical treatment for chronic rhinosinusitis (CRS)without polyps.Nevertheless, there is insufficient evidence to show a clear overall benefit. Trials studying the efficacy of topical corticosteroid use various delivery methods in patients who have or have not had sinus surgery, which directly impacts on topical delivery and distribution.We aim to assess the effects of topical steroid in patients with CRS without nasal polyps and perform ameta-analysis of symptom improvement data, including subgroup analysis by sinus surgery status and topical delivery methods.

Methods:

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ISRCTN and additional sources for published and unpublished trials. The date of the most recent search was 9 July 2010. All randomised trials in which a topically administered corticosteroid was compared with either a placebo, no treatment or alternative topically administered corticosteroid for the treatment of CRS without polyps in patients of any age. Two authors reviewed the search results and selected trials meeting the eligibility criteria, obtaining full texts and contacting authors where necessary. We documented our justification for the exclusion of studies. Two authors extracted data using a pre-determined standardised data form.

Results:

Ten studies (590 patients) met the inclusion criteria. The trials were of low (six trials) and medium (four trials) risk of bias. The primary outcome was sino-nasal symptoms. When compared to placebo, topical steroid improved symptom scores (standardised mean difference -0.37; 95%confidence interval (CI) -0.60 to -0.13, P = 0.002; five trials, n = 286) and had a greater proportion of responders (risk ratio 1.69; 95% CI 1.21 to 2.37, P = 0.002; four trials, n = 263). With a limited number of studies, the subgroup analyses of patients who had received sinus surgery versus those who had not was not significant (P = 0.35). Subgroup analyses by topical delivery method revealed more benefit when steroid was administered directly to the sinuses than with simple nasal delivery (P = 0.04). There were no differences between groups for quality of life and adverse events.

Conclusions:

Topical steroid is a beneficial treatment for CRS without polyps and the adverse effects areminor. It may be included in a comprehensive treatment of CRS without polyps. Direct delivery of steroid to the sinuses may bring more beneficial effect. Further studies comparing different topical drug delivery methods to the sinuses, with appropriate treatment duration (longer than 12 weeks), are required.

Introduction

Description of the condition

Definition

There is currently no universally accept definition of chronic rhinosinusitis (CRS). However, the current definition of CRS, proposed by European position paper on rhinosinusitis and nasal polyps in 2007 (Fokkens, Lund et al 2007) is commonly used. This states that CRS is a group of disorders characterised by chronic inflammation of the mucosa of the nose and paranasal sinuses, with symptoms that have persisted for more than 12 weeks without complete resolution of symptoms, plus either positive endoscopic signs and/ or positive computed tomography (CT) findings. The differentiation between CRS with and without polyps is based on nasal endoscopy but some underlying pathophysiological differences may exist. CRS without polyps is defined when there are no visible polyps (only discharge or oedema) in the middle meatus following decongestant (Fokkens, Lund et al 2007). Presenting symptoms are two or more of nasal obstruction, nasal discharge, facial pain/pressure and reduction or loss of smell. One of these should be either nasal obstruction or nasal discharge. The definition of CRS has evolved. Earlier definitions proposed, such as that of the Rhinosinusitis Task Force (Benninger, Ferguson, et al 2003; Lanza and Kennedy 1997), all described persistent inflammatory changes defined by symptoms, endoscopy, radiology or combination of the three. Definitions of duration have also evolved, with 12 weeks now representing a time in which a simple infective process would have resolved.

Pathophysiology

There is heterogeneity in the aetiological factors reported in the literature, which describe various inflammatory and pathophysiologymechanisms. The predominant inflammatory cells observed in CRS can be either neutrophils or eosinophils. Eosinophilic CRS, dominated by the associated cytokine milieu of Th2 inflammation, includes superantigen-induced, allergic fungal rhinosinusitis, non-allergic fungal eosinophilic rhinosinusitis and aspirin-exacerbated eosinophilic rhinosinusitis (Sok and Ferguson 2006). Factors believed to be aetiologically linked to CRS include both host factors, such as ciliary impairment, allergy, aspirin sensitivity, laryngopharyngeal reflux, immunodeficiency and genetic factors, and non-host factors such as environmental factors, pollution, smoking, *Staphylococcus aureus* enterotoxins, biofilm formation and micro-organisms. Osteitis of underlying bones in the ostiomeatal complex is significantly involved in the process (Kennedy 2004). Micro-organisms are recognised as disease-modifiers, rather than causative agents (Harvey and Schlosser 2009; Kern, Conley, et al 2008). The fundamental theory of ostiomeatal complex blockage causing sinonasal inflammation may explain acute rhinosinusitis and a small subgroup of CRS but is not the major pathogenic process. Treatment of infection and functional endoscopic sinus surgery to correct the anatomical obstruction of CRS do not always resolve the disease. A growing body of evidence is evolving, which involves a shift from recognising the disease as chronic infection to chronic inflammation.

Prevalence

As there is currently no universally accepted definition of CRS and it includes a spectrum of diseases, the prevalence remains speculative. Either nasal endoscopy or a CT scan is required for a definitive diagnosis, therefore it is usually overestimated when reported by general practitioners without endoscopy or radiology, or by survey/ symptom-based studies. In the United States, a prevalence of 15.5% was estimated by population survey which used the criterionof having more than threemonths of sinus trouble (Blackwell and Coles 2002), but a prevalence of 2% was found using ICD-9 coding by doctors (Shashy, Moore, et al 2004). Prevalence has been shown to increase with age and to be higher in females (Fokkens, Lund et al 2007). CRS significantly impacts on patient quality of life (Linder 2004). In comparison to other common chronic debilitating diseases, such as congestive heart failure, angina, chronic obstructive pulmonary disease and back pain, CRS has been shown to have an equivalent or lower score, representing greater disease burden, using themedical outcome study short-form 36-item health survey (Gliklich and Metson1995; Metson and Gliklich 2000).

Description of the intervention

Anti-inflammatory therapy, including corticosteroid and low-dose macrolides, plays a significant role in the treatment of CRS. Topical corticosteroid is more widely used than oral steroid because treatment can be given for longer without significant side effects. Intranasal corticosteroid therapy is often prescribed for patients with CRS, but with considerable variability in timing, frequency, dose, topical delivery method and specific agent used, and whether with or without sinus surgery (Benninger,

Ferguson, et al 2003; Spector, Bernstein, et al 1998). The topical delivery method significantly affects the amount of steroid that comes into contact with the paranasal sinus mucosa (Grobler, Weitzel, et al 2008; Harvey, Debnath, et al 2009). Simple nasal delivery methods are drops, sprays, aerosols, nebulisers and atomisers. Direct sinus cannulation and nasal irrigation with squeeze bottles and neti pots are likely to provide better delivery to the sinuses, especially in the post-sinus surgery setting (Grobler, Weitzel, et al 2008; Harvey, Debnath, et al 2009). Classes of topical corticosteroid include first-generation intranasal steroids (beclomethasone dipropionate, triamcinolone acetonide, flunisolide and budesonide) and newer preparations (fluticasone propionate, mometasone furoate, ciclesonide and fluticasone furoate). The use of topical corticosteroid has been widely advocated for the treatment of CRS as inflammation is considered a major component of this condition (Fokkens, Lund et al 2007; Hamilos 2000; McNally, White, et al 1997). The mechanism of action is a combination of anti-inflammatory effects, such as reducing pro-inflammatory and increasing anti-inflammatory gene transcription, reducing airway inflammatory cell infiltration, and suppression of the production of pro-inflammatory mediators, cell chemotactic factors and adhesion molecules (Mullol 2009).

Why it is important to do this review

A previous systematic review (Kalish, Arendts, et al 2009) found insufficient evidence to show a clear overall benefit for topical steroid in CRS without polyps. Trials studying the efficacy of topical corticosteroid used various topical delivery methods

including nasal spray and direct application into the sinus cavities. Patient status varied from non-surgical to post-sinus surgery. These differences have been shown to greatly affect topical delivery and distribution (Harvey, Debnath, et al 2009).

To deliver medicine into the sinuses, an appropriate technique and device of administration is required. Devices that deliver a greater volume with higher positive pressure, such as squeeze bottles, are likely to give better distribution for local drug delivery (Harvey and Schlosser 2009). It is important to consider whether patients have had paranasal sinus surgery because this affects drug delivery (Grobler, Weitzel, et al 2008; Harvey and Schlosser 2009).The oedematous inflammatory mucosa and ostiomeatal blockage of non-surgical CRS allows less than 1% of solution volume to enter the sinus cavities (Snidvongs, Chaowanapanja, et al 2008). Sinus surgery, with an adequate ostia dimension, is necessary for appropriate topical drug distribution (Harvey and Schlosser 2009). An ostial diameter of around 4.7mm is the minimum to ensure adequate delivery (Singhal, Weitzel, et al 2010), although various techniques of endoscopic sinus surgery with various ostial size may allow different distribution (Grobler, Weitzel, et al 2008; Harvey and Schlosser 2009).

An up to date Cochrane assessment of randomised controlled trials, evaluating the effects of topical steroids forCRSwithout polyps is required. It is also important to examine how administration with or without sinus surgery and topical delivery method con tribute to the effectiveness of the treatment. We plan to explore these factors in subgroup analysis.

Objectives

To assess the effects of topical steroid in CRS without nasal polyps, including a meta-analysis of symptomimprovement and subgroup analysis by sinus surgery status and topical delivery method.

Material and methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Inclusion criteria

• Participants in the trials have to be defined as having chronic rhinosinusitis (CRS) by either European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (Fokkens, Lund et al 2007); or Rhinosinusitis Task Force Report (Lanza and Kennedy 1997) and its revision (Benninger, Ferguson, et al 2003); or having chronic sino-nasal symptoms for longer than 12 weeks.

• Trials which included participants of any age, who had any co-morbidity including asthma and aspirin sensitivity, were either allergic or non-allergic, and were followed for any duration.

• Trials which included participants with CRS both with and without polyps if the majority of participants were without polyps. If possible, we only extracted data for participants with CRS without polyps.

Exclusion criteria

• Patients defined by the study authors as having acute or recurrent-acute sinusitis.

• Patients defined by the study authors as having CRS with polyps or nasal polyposis.

• Patients had CRS both with and without polyps and the majority of participants had polyps.

Types of interventions

• Any dose of topical steroid versus placebo.

• Any dose of topical steroid versus no treatment.

• Any dose of topical steroid versus alternative topical steroid.

We included trials which used any co-interventions including oral steroid, antihistamines, decongestants, antibiotics (topical or intravenous) when the co-interventions were equally applied in both groups.

Types of outcome measures

Primary outcomes

• Sino-nasal symptoms. These could be measured by symptom scores, proportion of patients showing improvement of symptoms or quality of life measures.

Secondary outcomes

• Endoscopic findings

• Radiological findings

• Adverse effects

Exclusion criteria of outcome measures

Studies reporting neither symptoms nor quality of life outcomes.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 9 July 2010.

Electronic searches

We searched the following databases fromtheir inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; ISRCTN; ClinicalTrials.gov; ICTRP and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2, Box 6.4.b. (Higgins and Green 2011)). Search strategies for major databases including CENTRAL are provided in Table 6.1

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, we searched PubMed, TRIPdatabase, NHS Evidence - ENT & Audiology and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

Two review authors performed data selection and extraction based on predetermined criteria and this was rechecked by the others. We resolved any disagreements by discussion until a consensus was reached.We reviewed the titles and abstracts of all studies obtained by the search and selected trials meeting the eligibility criteria. We obtained the full texts of the articles if there was insufficient

information to make a decision.We documented our justification for the exclusion of studies.

Data extraction and management

Two review authors independently extracted data using a pre-determined standardised data form structured to allow an intention to treat analysis. We extracted the following data:

• characteristics of trials - publication status, year, country of study, setting, design, inclusion and exclusion criteria, recruitment, methods, analysis and results;

• study methods - method of allocation, blinding and losses after randomisation (follow up losses and drop-outs);

• characteristics of participants - study population, number of participants in each arm, age, gender, nationality and diagnostic criteria, prior surgery (extent);

• characteristics of interventions - preparation used, dose, delivery method, length of treatment and follow up, compliance, co-interventions and intervention used in control group;

• outcomes - symptom score, number of responding patients, endoscopy, radiological findings, complications and adverse events, and drop-outs.

Assessment of risk of bias in included studies

1	rhinosinusitis/
2	(sinusiti* or rhinosinusiti* or rhiniti* or nasosinusiti* or pansinusiti* or ethmoiditis or antritis or sphenoiditis or ((sinus* or sinonasal or endonasal or paranasal or nose or nasal or rhinosinus*) and (inflammation or inflamed or pain* or ache or aching or infect* or pressure or purulen* or obstruct* or block* or drainage or discharge* or symptom* or disease*))).ti
3	chronic disease/
4	recurrent disease/
5	(chronic* or persist* or recur* or reoccur*).tw.
6	1 or 2
7	3 or 4 or 5
8	6 and 7
9	exp steroid/
10	exp antiinflammatory agent/
11	exp nonsteroid antiinflammatory agent/
12	10 not 11

13	(steroid* or corticosteroid* or glucocorticoid* or corticoid* or beclomethason* or beclamet or beclocort or beclometasone or becotide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or dexamethason* or dexamethason* or hexadecadrol or decadron or dexasone or hexadrol or budesonid* or horacort or pulmicort or rhinocort or methylfluorprednisolone or flunisolid* or nasalide or millicorten or oradexon or fluticason* or flonase or flounce or mometason* or nasonex or triamclinolon* or nasacort or tri next nasal or aristocort or volon).tw.
14	9 or 12 or 13
15	8 and 14
16	exp topical drug administration/ or exp topical treatment/
17	exp inhalational drug administration/ or exp inhaler/
18	exp intranasal drug administration/
19	nebulization/ or nebulizer/
20	(spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical*).tw.
21	16 or 17 or 18 or 19 or 20
22	15 and 21

Table6.1 Search strategy

We carried out the assessment of risk of bias in the included studies as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green 2011), taking the following into consideration:

• sequence generation;

• allocation concealment;

• blinding;

• incomplete outcome data;

• selective outcome reporting; and

• other sources of bias.

We used the Cochrane 'Risk of bias' tool in RevMan 5.1 (Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry. This involved making a judgement of low, high or unclear (or unknown) risk of bias. We have presented our assessments in Appendix6.2 and graphically in a 'Risk of bias' graph and summary (Figure 6.1and Figure 6.2).

Dealing with missing data

We contacted the authors via email to get raw data in cases of missing data or mixed populations. We only extracted data from CRS without polyps populations in case of

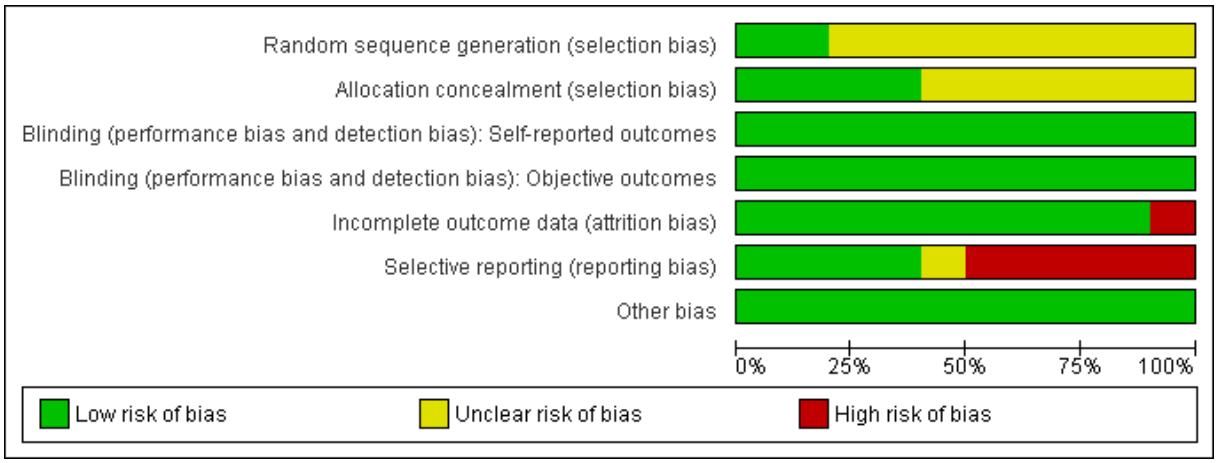


Figure 6.1. 'Risk of bias' graph: each risk of bias item presented as percentages across all included studies.

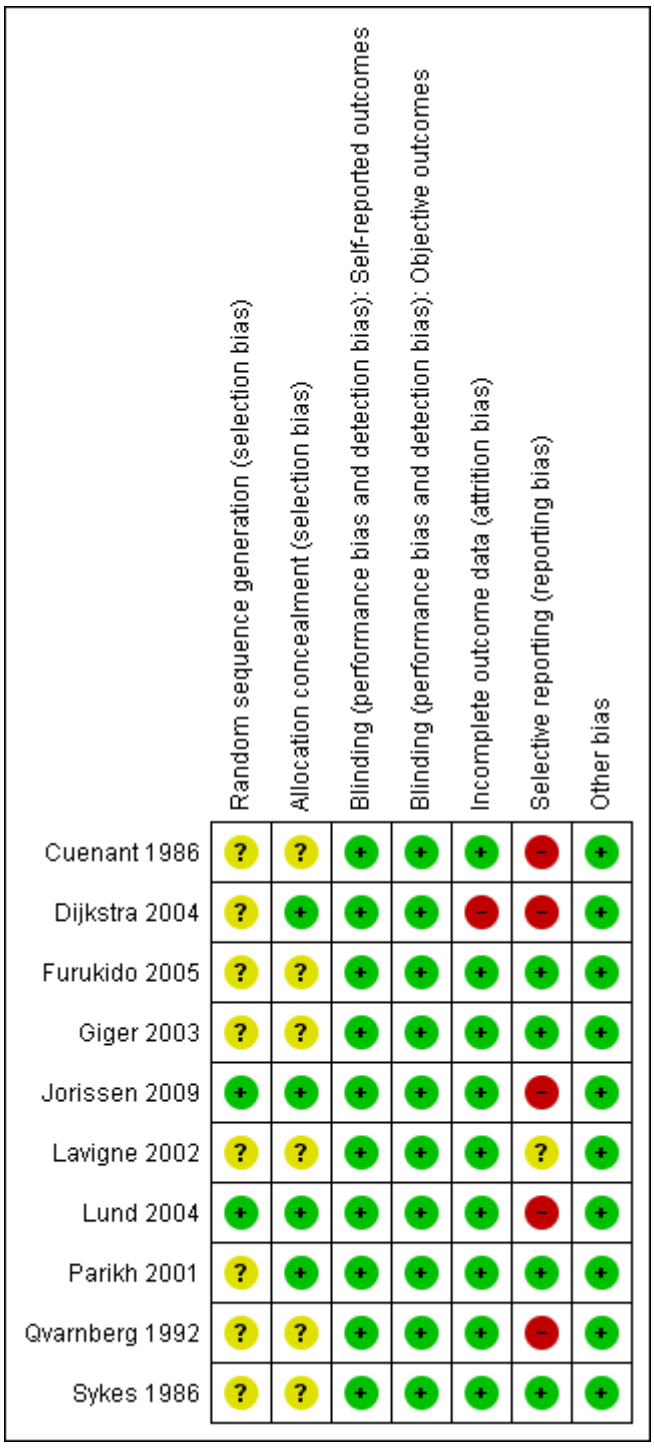


Figure 6.2 'Risk of bias' summary: each risk of bias item for each included study.

mixed populations of CRS with polyps and without polyps. Where original patient data were obtained, we based the analyses on intention-to-treat. We performed statistical assessments primarily with descriptive data via SPSS software (Statistical Software for Social Sciences, SPSS Inc., Chicago, IL). For missing standard deviations, we used either 95% confidence intervals (CIs), standard error or interquartile ranges for estimation to impute standard deviations. For missing means, we converted medians.

Assessment of heterogeneity

We assessed the significance of any discrepancies in the estimates of the treatment effects fromthe different trials bymeans ofCochran's Q test for heterogeneity and by a measure of the I2 statistic. We considered a value greater than 50% to represent substantial heterogeneity. We also used forest plots to assess heterogeneity visually.

Assessment of reporting biases

We assessed publication bias by means of a funnel plot when there was a sufficient number (greater than 10) of trials.

Data synthesis

We followed theCochrane Ear,Nose and ThroatDisordersGroup statistical guidelines and combined comparable and sufficient quality data to give a summary measure of effect. We used the standardised mean difference (SMD) and 95%CIs for continuous data such as postintervention scores or change in symptom scores. We used the risk ratio (RR) and 95%CI of responsiveness at a specific time point for dichotomous

data such as number of patients responding to treatment or number of patients having positive radiographs. We pooled the intervention effects when trials were sufficiently homogeneous. We used a fixed-effect model and assumed that each study was estimating the same quantity.We used subgroup analysis to explore possible sources of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis as follows.

• Surgical status

◦ Patients with sinus surgery versus those without sinus surgery.

• Topical delivery method

◦ Nasal (drops, sprays, nebulisers) versus sinus (direct cannulation, irrigation post-surgery) delivery method.

◦ Low volume (defined as any simple spray volume approximating < 1 ml) versus large volume (defined as any significant volume > 60 ml - representing a simple irrigation syringe or smallest commercial irrigation device. We pre-defined low and large volume based on previous studies showing how the volume applied affects sinus delivery (Beule , Athanasiadis, et al 2009).

◦ Low pressure (including spray, nebulisers, instilled solution through a tube and non-pressure irrigation) versus high pressure (including positive pressure irrigation). We investigated differences between the two subgroups for fixedeffect analyses

based on the inverse-variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

Results

Description of studies

Characteristics of included studies are displayed in Table 6.2 (Appendix6.1).

Results of the search

We retrieved a total of 666 references from the searches: 541 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 125 references for further consideration.We subsequently found one additional trial from a manual search guided by the identified references. A flow chart of study retrieval and selection is provided in Figure 6.3. Ten studies with a total of 590 patients met the inclusion criteria.

Included studies

There were 10 included studies with 13 included papers. Three papers were abstracts of presentations at academic meetings of three included studies (Dijkstra, Ebbens, et al 2004; Jorissen and Bachert 2009; Lund, Black, et al 2004). Eight trials (80%) (Dijkstra, Ebbens, et al 2004; Furukido, Takeno, et al 2005; Jorissen and Bachert 2009; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986) compared topical steroid against placebo. One trial (10%) (Giger, Pasche, et al

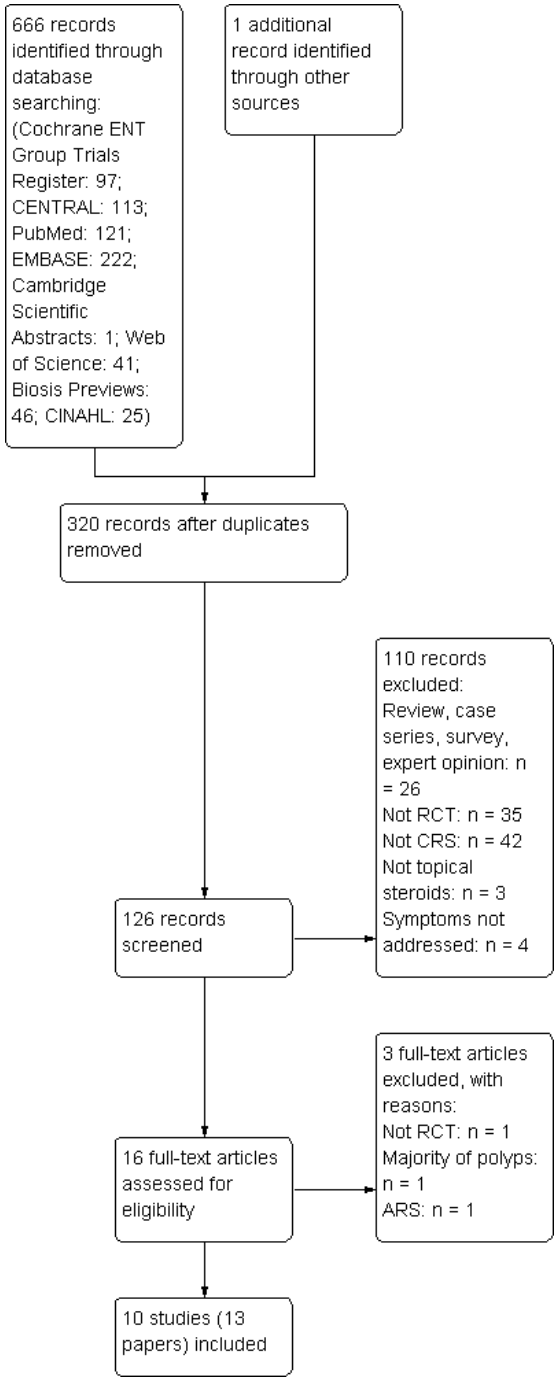


Figure 6.3 Identification of reports of randomised trials for inclusion in review

2003) with 112 patients compared two treatment regimes of steroid administration without comparing to placebo. One (10%) trial (Cuenant, Stipon, et al 1986) with 60 patients compared topical steroid with antibiotic against antibiotic alone. We found no trials comparing topical steroid versus alternative topical steroid. Four included studies were sponsored by pharmaceutical companies. Two were fully and two were partly supported as follows: Dijkstra,Ebbens, et al 2004 (GlaxoSmithKline (GSK)), Jorissen and Bachert 2009 (Schering- Plough Corp) Lund, Black, et al 2004 (AstraZeneca and R&D Lund), Lavigne, Cameron, et al 2002 (AstraZeneca Canada Inc and Fon de Recherche en Sante du Quebec). Medications were supplied by pharmaceutical companies in three studies: Parikh, Scadding, et al 2001 (Glaxo Wellcome Research), Sykes, Wilson, et al 1986 (Boehringer Ingelheim), Qvarnberg, Kantola, et al 1992 (Suomen Astra OY). Furukido, Takeno, et al 2005 was not funded by pharmaceutical companies. Two studies did not state how they were funded (Cuenant, Stipon, et al 1986; Giger, Pasche, et al 2003).

Dealing with missing data

We asked the trial authors to provide raw data where missing (Furukido, Takeno, et al 2005) and for mixed populations of polyps and non-polyps patients (Jorissen and Bachert 2009). For missing standard deviations, we used 95% confidence intervals (CIs) (Lund, Black, et al 2004) and interquartile ranges (Furukido, Takeno, et al 2005) for estimation to impute standard deviations. For missing means, we converted medians (Furukido, Takeno, et al 2005). We used data from another study (Lavigne, Cameron, et al 2002) to calculate the correlation coefficient in the

experimental and control group for the imputation of standard deviation of change in symptom scores (Furukido, Takeno, et al 2005).

Settings

Nine studies (90%) recruited patients from tertiary care, except Cuenant, Stipon, et al 1986 who did not state the enrolment setting. Patients were recruited from primary care in one trial (10%) (Lund, Black, et al 2004). This was a multicentre study recruiting patients from both primary care and tertiary care. Patients were recruited from 10 countries including the United Kingdom (Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Sykes, Wilson, et al 1986), the Netherlands (Dijkstra, Ebbens, et al 2004), Japan (Furukido, Takeno, et al 2005), Belgium (Jorissen and Bachert 2009), Canada (Lavigne, Cameron, et al 2002), South Africa (Lund, Black, et al 2004), Hungary (Lund, Black, et al 2004), Finland (Qvarnberg, Kantola, et al 1992), Switzerland (Giger, Pasche, et al 2003) and France (Cuenant, Stipon, et al 1986).

Participants

The mean age of patients was 38.55 (29.80) and ranged from 15 to 79. The percentage of men was 51.32.

Surgical status: patients with versus those without sinus surgery

Three trials (30%) administered steroid after sinus surgery (Dijkstra, Ebbens, et al 2004; Jorissen and Bachert 2009; Lavigne, Cameron, et al 2002). One trial (10%) administered steroid without sinus surgery (Furukido, Takeno, et al 2005) and one trial (10%) had a mixed population both with and without sinus surgery (Parikh,

Scadding, et al 2001). Patients' sinus surgery status was not stated in five trials (50%) (Cuenant, Stipon, et al 1986; Giger, Pasche, et al 2003; Lund, Black, et al 2004; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986).

Interventions

The steroid agents used differed across the studies. They were tixocortol pivalate (Cuenant, Stipon, et al 1986), fluticasone propionate (Dijkstra,Ebbens, et al 2004; Parikh, Scadding, et al 2001), betamethasone (Furukido, Takeno, et al 2005), beclomethasone dipropionate (Giger, Pasche, et al 2003), mometasone furoate (Jorissen and Bachert 2009), budesonide (Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Qvarnberg, Kantola, et al 1992) and dexamethasone (Sykes, Wilson, et al 1986).

Topical delivery method: nasal (drops, sprays, nebulisers) versus sinus (direct cannulation, irrigation post-surgery) delivery methods

Two trials (20%) used a sinus delivery technique whereby the drug was instilled through an intrasinus tube (Cuenant, Stipon, et al 1986; Lavigne, Cameron, et al 2002). Eight trials (80%) used nasal delivery by spray (Dijkstra, Ebbens, et al 2004; Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Sykes, Wilson, et al 1986), aerosol (Qvarnberg, Kantola, et al 1992) and drug instilled through an intranasal tube (Furukido, Takeno, et al 2005). No trials used nasal drops.

Pressure

All trials (100%) used low-pressure delivery, including sprays (Dijkstra, Ebbens, et al 2004; Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Sykes, Wilson, et al 1986), drug instilled through an intrasinus tube (Cuenant, Stipon, et al 1986; Lavigne, Cameron, et al 2002), drug instilled through an intranasal tube (Furukido, Takeno, et al 2005) and aerosol (Qvarnberg, Kantola, et al 1992). There were no studies using high-pressure delivery, e.g. nasal wash or sinus irrigation.

Volume

Seven trials (70%) used low-volume delivery (approximately <1 ml) (Dijkstra, Ebbens, et al 2004; Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986).Therewere no studies that used large-volume delivery. Three trials (30%) used 2 ml (Furukido, Takeno, et al 2005), 3 ml (Lavigne, Cameron, et al 2002) and 5 ml (Cuenant, Stipon, et al 1986).

Outcomes

Primary outcomes

Symptom scores

Nine trials (90%) reported symptom scores (Cuenant, Stipon, et al 1986; Dijkstra, Ebbens, et al 2004; Furukido, Takeno, et al 2005; Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Parikh, Scadding, et al 2001; Qvarnberg, Kantola, et al 1992). All studies (100%)

reported symptoms as an outcome. This was as a change score in four studies (40%) (Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lund, Black, et al 2004; Parikh, Scadding, et al 2001), baseline and postintervention scores in four studies (40%) (Dijkstra, Ebbens, et al 2004; Furukido, Takeno, et al 2005; Giger, Pasche, et al 2003; Lavigne, Cameron, et al 2002) and proportion of patients having improved symptoms in six studies (60%) (Cuenant, Stipon, et al 1986; Dijkstra, Ebbens, et al 2004; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986).

Proportion of patients showing improvement of symptoms (responders)

Five trials (50%) reported proportion of responders (Dijkstra, Ebbens, et al 2004; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986).

Quality of life measures

One trial (10%) reported a disease-specific quality of life scale and a general health quality of life scale (Lund, Black, et al 2004).

Secondary outcomes

Endoscopic findings

Two trials (20%) reported endoscopic scores (Jorissen and Bachert 2009; Parikh, Scadding, et al 2001).

Radiological findings

Three trials (30%) reported radiographs (Furukido, Takeno, et al 2005; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986).

Adverse effects

Adverse events were reported in five (50%) trials (Dijkstra, Ebbens, et al 2004; Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004).

Excluded studies

The majority of the 667 abstracts retrieved from the searches did not focus on the use of topical steroid in CRS without polyps. Of the 126 studies initially identified, 26 studies were reviews, case series, surveys or expert opinion. Among the 87 excluded studies, 36 were not randomised nor controlled. The study populations of 44 studies did not have CRS without polyps. The interventions (three) or primary outcomes (four) criteria were not met in a further seven studies.

Risk of bias in included studies

See Table 6.2 (Appendix 6.1). Our judgements about each risk of bias item presented as percentages across all the included studies are shown in Figure 6.1 and for each risk of bias item for each included study in Figure 6.2.Generally, the included studies had low risk of bias for blinding and incomplete outcome data, medium risk of bias for selective reporting and high risk of bias for allocation.

Allocation

Most studies provided insufficient information about the sequence generation process and how investigators could not foresee assignment.

Blinding

All studies blinded both patients and investigators. Most studies described study medications as being identical in appearance.

Incomplete outcome data

Most studies had a low risk of bias due to either intention-to-treat analysis or the number of missing patients not being large enough to change the effects.

Selective reporting

About half of the studies were free of selective reporting. Some pre-specified outcomes were incompletely reported.

Other potential sources of bias

All studies appear to be free of other sources of bias.

Effects of interventions

Topical steroid versus placebo (eight trials)

Symptom scores

Data addressing this comparison were available from five out of eight studies (Furukido, Takeno, et al 2005; Jorissen and Bachert 2009; Lavigne, Cameron, et al

2002; Lund, Black, et al 2004; Parikh, Scadding, et al 2001) and could be combined in the meta-analysis below. In the following studies the data could not be combined with the others because of symptoms being reported as proportion of responders without numeric scores (Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986) and symptoms being reported at two weeks, not at the endpoint of one year (Dijkstra, Ebbens, et al 2004).

The pooled results significantly favoured the topical steroid group (combined standardised mean difference (SMD) -0.37; 95%confidence interval (CI) -0.60 to -0.13, P = 0.002; five trials, 286 patients) (Figure 6.4). The I2 was 12%, suggesting no heterogeneity (x2 = 4.57, degrees of freedom (df) = 4, P = 0.33).

Subgroup analysis: patients with versus those without sinus surgery

We found no significant difference when we compared patients with and without sinus surgery (P = 0.35) (Figure 6.5).

Subgroup analysis: nasal (drops, sprays, nebuliser) versus sinus (direct cannulation, irrigation post-surgery) delivery methods

When we performed subgroup analyses we found significance when sinus deliverymethods (SMD-1.32; 95%CI -2.26 to -0.38) were compared to nasal deliverymethods (SMD-0.30; 95%-0.55 to -0.06) (P = 0.04) (Figure6.6).

Subgroup analysis: low versus high pressure/low versus large volume

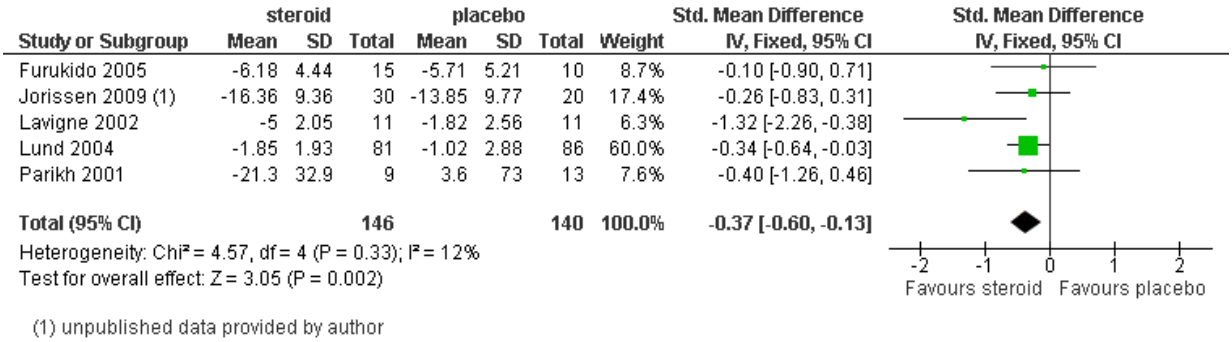


Figure 6.4 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Symptom scores

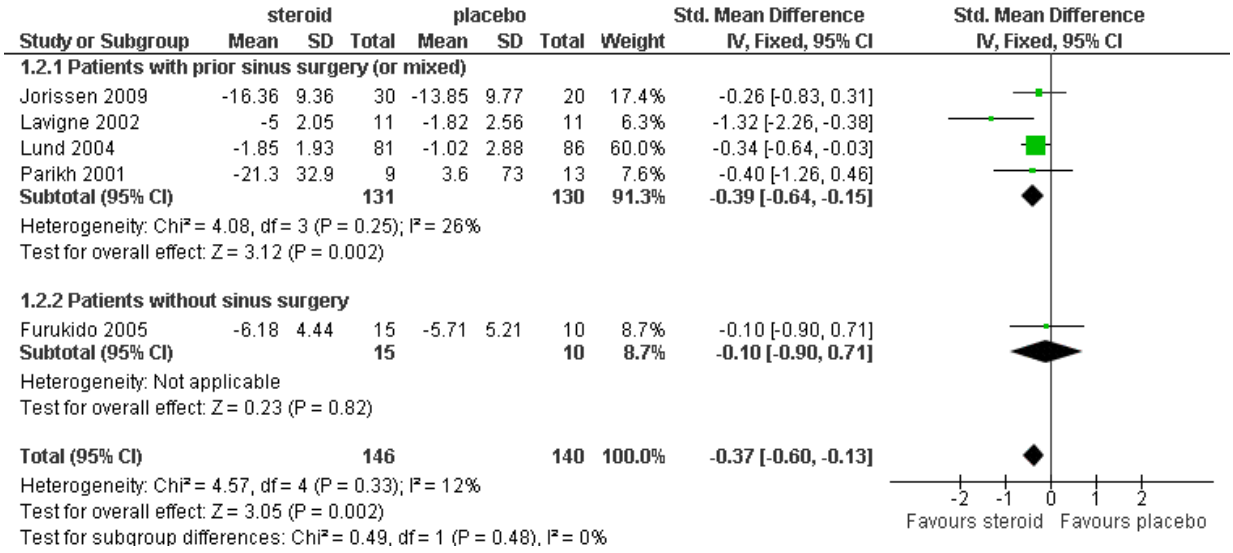


Figure 6.5 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Symptom scores by sinus surgery status

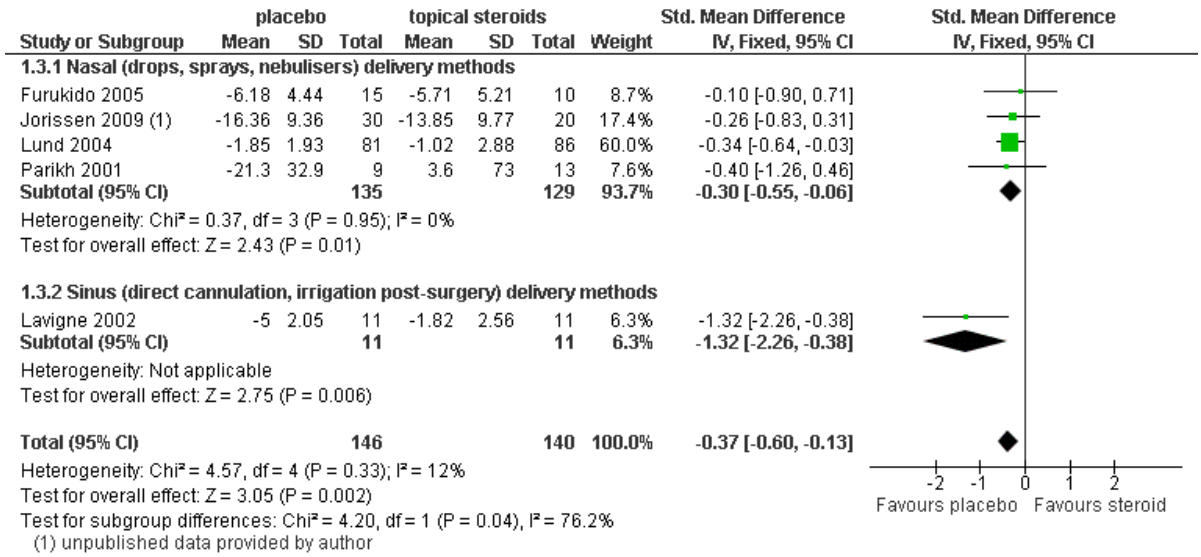


Figure 6.6 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Symptom scores by topical delivery methods

We could not performsubgroup analysis for low and high pressure as there were no trials delivering high pressure. Similarly we could not perform subgroup analysis for low and large volume as there were no trials delivering large volume. We could not create funnel plots or perform meta-regression as there were too few studies (< 10) in the meta-analysis.

Proportion of patients responding to treatment

We pooled data from four trials on the proportion of patients responding to treatment (Lavigne, Cameron, et al 2002; Lund, Black, et al 2004; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986). The pooled results significantly favoured the topical steroid group (RR 1.69; 95% CI 1.21 to 2.37, P = 0.002) (Figure 6.7). The I2 of 24%suggested no heterogeneity (x2 = 3.93, degrees of freedom (df) = 3, P = 0.27).

Subgroup analysis: patients with versus those without sinus surgery

We found no significant difference when we compared patients with and without sinus surgery (P = 0.27) (Figure 6.8).

Subgroup analysis: nasal (drops, sprays, nebuliser) versus sinus (direct

cannulation, irrigation post-surgery) delivery methods

We found no significant difference when we compared nasal and sinus delivery methods (P = 0.23) (Figure 6.9).

Subgroup analysis: low versus high pressure/low versus large volume

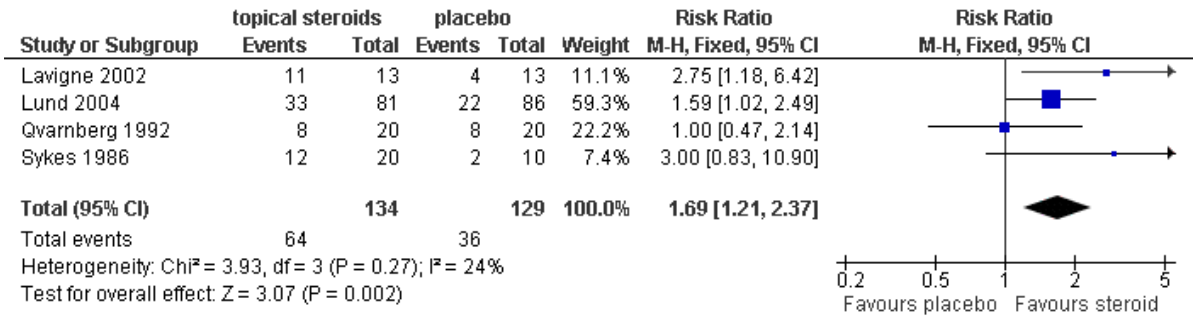


Figure 6.7 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Proportion of patients responding to treatment

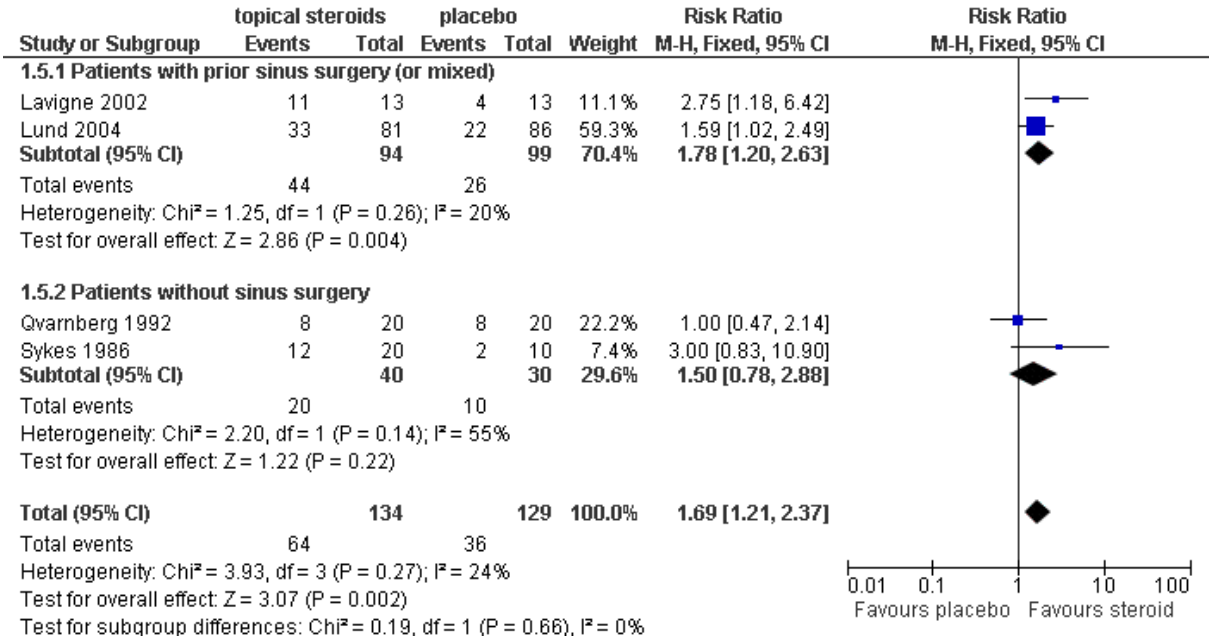


Figure 6.8 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Proportion of patients responding to treatment by sinus surgery

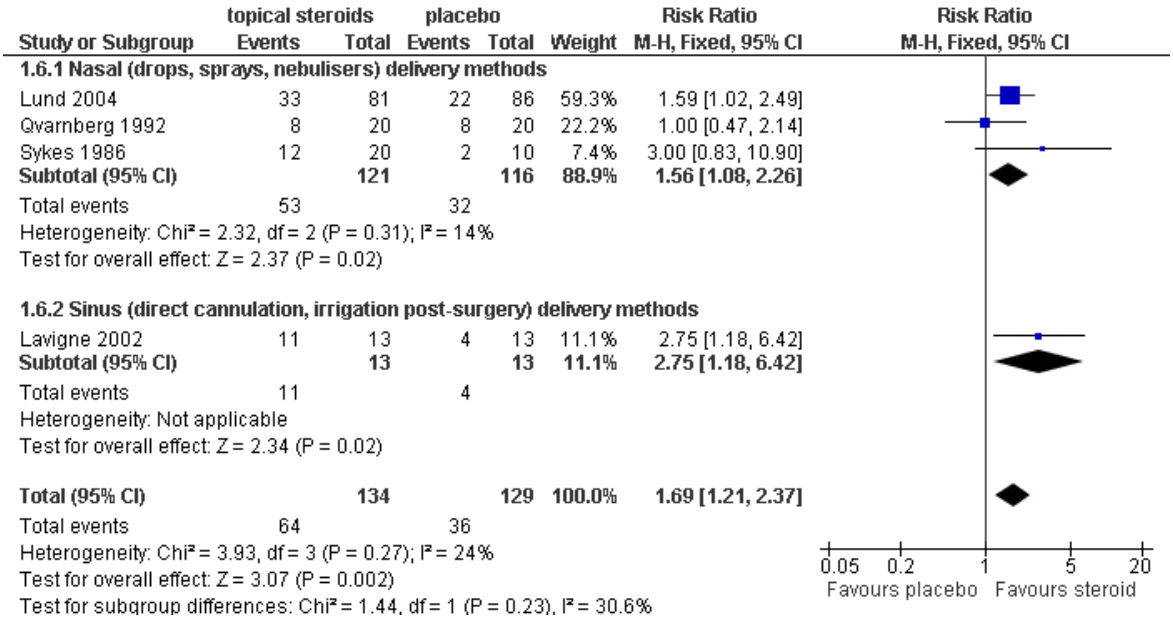


Figure 6.9 Forest plot of comparison: Topical steroids versus placebo in CRS, outcome: Proportion of patients responding to treatment by topical delivery methods

We could not performsubgroup analysis for low and high pressure as there were no trials delivering high pressure. We could also not perform subgroup analysis for low and large volume as there were no trials delivering large volume. We could not produce funnel plots or perform meta-regression as there were too few studies (<10) in the meta-analysis.

Quality of life

Only one trial (10%) reported a disease-specific quality of life scale and general health quality of life scale (Lund, Black, et al 2004). There was no difference between the two groups on either quality of life questionnaire. Only data for the disease-specific quality of life scale were provided and the mean difference was 0.11 (95% CI - 0.19 to 0.42, P = 0.46).

Endoscopic scores

Two trials (20%) reported endoscopic scores (Jorissen and Bachert 2009; Parikh, Scadding, et al 2001). The pooled results showed no difference between the two treatments (combined SMD -0.37; 95% CI -0.84 to 0.11, P = 0.13).

Radiographs

Three trials (30%) reported radiological changes (Furukido, Takeno, et al 2005; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986). We could not perform meta-analysis as the data were heterogeneous and included continuous (Furukido, Takeno, et al 2005), ordinal (Qvarnberg, Kantola, et al 1992) and dichotomous (Sykes, Wilson, et al 1986) data. The outcome in Furukido, Takeno, et al 2005 was

median total X-ray scores. They found no difference between groups with scores of 2 and 1.5 for steroids and placebo, respectively, decreased from a baseline of 3. The mean difference in final valuewas 0.50 (95%CI -0.75 to 1.75).The outcome in Qvarnberg, Kantola, et al 1992 was number of sinuses having four different degrees of mucosal thickening and they reported a non-significant higher number of improved sinuses in the steroid group, with a risk ratio of 0.74 (95% CI 0.40 to 1.36). In the steroid group, 11 (36%) had more than 50% mucosal thickening at the endpoint compared to 20 (65%) at baseline. In the placebo group, this was 16 sinuses (59%) at endpoint compared to 13 sinuses (48%) at baseline. The outcome of Sykes, Wilson, et al was the number of patients with improved sinus radiographs.They reported four (36%) having improvement in the steroid group but none (0%) in the placebo group. This was not significant, with a risk ratio of 0.67 (95% CI 0.41 to 1.09).

Adverse events

Adverse events were reported in four trials (40%) (Dijkstra, Ebbens, et al 2004; Jorissen and Bachert 2009; Lavigne, Cameron, et al 2002; Lund, Black, et al 2004) (Table 6.3). There was no difference between the study group and control in any trial. Most adverse events were mild and moderate (Jorissen and Bachert 2009; Lund, Black, et al 2004). Few were considered to be due to study medication (Jorissen and Bachert 2009; Lund, Black, et al 2004). The most common event was headache (Jorissen and Bachert 2009).

Topical steroid versus no treatment (one trial)

Study ID	Steroid group n(%)	Placebo group n(%)	Description of events reported	Remarks
Dijkstra 2004				Epistaxis: not higher in steroids group
Giger 2003	26* (47) 32** (56)		Epistaxis, dry nose, nasal burning, nasal itching, sinusitis, pharyngitis, otitis, change of taste, eczema, nausea/diarrhoea, nasal irritation, common cold	1. Mild 61.6%; moderate 4%; severe; 3.8% 2. Most common epistaxis 3. No candidiasis 4. No difference between od and bid 5. No change in morning serum cortisol level
Jorissen 2009	29 (63)	28 (62)	Headache, sinusitis, cold	1. Most common headache 2. Few drug-related events 3. Rare serious events
Lavigne 2002			Tube fell out, epistaxis, diabetes with glycaemia, tube infection, asthma	No sinus irritation from steroid instillation
Lund 2004	39 (48)	46 (53)	Respiratory infection, headache, blood-tinged secretion, viral infection, pharyngitis, sinusitis, flu-like, pain, rhinitis, external ear infection	1. Most events are mild or moderate 2. No serious events were due to study medication 3. No difference of steroids with placebo 4. No increased incidence of infection

Table 6.3 Topical steroids versus placebo in CRS, outcome: adverse events

*****receiving steroid twice daily; ** receiving steroid once daily

Symptom scores

Cuenant, Stipon, et al 1986 reported symptoms as all groups' symptoms without separate data. All patients improved their symptoms frombaseline for all parameters.

Comparison of two treatment regimes of steroid administration without comparing to placebo (one trial)

Symptom scores

Giger, Pasche, et al 2003 found no difference between administering topical steroid once and twice daily.

Adverse events

Giger, Pasche, et al 2003 found no difference between the study groups and control. Most adverse events were mild and moderate. The most common event was epistaxis. Morning cortisol was unchanged

Discussion

Summary of main results

Pooled data analyses of symptom scores and proportion of responding patients demonstrated significant benefit in the topical steroid group.The 10 included studieswere diverse, both clinically and methodologically. Variability included definitions of chronic rhinosinusitis, type of delivery, volume of delivery and surgical state. The majority of patients were defined as having chronic rhinosinusitis, but in

three trials (Dijkstra, Ebbens, et al 2004; Giger, Pasche, et al 2003; Jorissen and Bachert 2009) the populations were mixed. Sinus surgery status and topical delivery methods were also diverse. The outcome measures were scored using various validated and non-validated tools. Allocation, blinding and intention-to-treat analysis were different across studies. Although allocation details were unclear in some studies, we assumed that each trial conducted a randomised controlled study as stated. Five out of eight studies comparing topical steroid with placebo could be pooled for meta-analysis of symptom scores. There were three studies which were not pooled (Dijkstra, Ebbens, et al 2004; Qvarnberg, Kantola, et al 1992; Sykes, Wilson, et al 1986). Qvarnberg, Kantola, et al 1992 reported the proportion of responders and provided numeric data only for facial pain and facial sensitivity but not for other symptoms. Sykes, Wilson, et al 1986 reported symptoms as the proportion of responders. Dijkstra, Ebbens, et al 2004 reported the median total symptom score but provided neither standard deviations (SDs) nor interquartile ranges. Also, the outcome was presented at two weeks whereas study medication was taken for one year. Furthermore, they provided the number of non-responders who were withdrawn from the trial because of recurrent or persistent disease. We performed a sensitivity analysis by adding Dijkstra, Ebbens, et al 2004 and found that the pooled effect still significantly favoured steroids (risk ratio (RR) 1.40; 95%confidence interval (CI) 1.06 to 1.85).

Subgroup analyses showed no significant differences when steroid was administered to patients with and without surgery. However, a subgroup of patients who had received sinus surgery showed benefit of steroid for both outcomes of symptom

scores and the proportion of responders, whereas a subgroup of patients without sinus surgery showed no benefit. Lund, Black, et al 2004 excluded patients who had sinus surgery within one year before enrolment but did not state the patients' sinus surgery status before that time; therefore we did not pool data from this study. We performed sensitivity analysis by including Lund, Black, et al 2004 to the subgroup of patients without sinus surgery and the same non-significant result was shown. Subgroup analyses show significantly greater effects in 'sinus delivery methods' than 'nasal delivery methods' subgroups. There were no included studies which used large-volume delivery, either as high or low pressure, or any using high-pressure delivery. The findings suggest that sinus delivery (cf nasal) with direct sinus mucosa contact is likely to be more

effective. Both a wide nasal corridor created by sinus surgery and topical delivery methods affect topical delivery and distribution as shown in the literature (Harvey and Schlosser 2009; Harvey, Debnath, et al 2009; Snidvongs, Chaowanapanja, et al 2008). We found no difference in the sinus surgery status subgroups. However, effective sinus distribution requires not only an open sinus system but additional factors such as pressure (positive) and volume. Larger volumes (greater than 100 ml) distribute more effectively to the sinuses (Beule , Athanasiadis, et al 2009). There were no included studies with this volume. Among patients with sinus surgery, various sinus ostial dimensions may also bring about different sinus drug distribution (Singhal, Weitzel, et al 2010). Whether there is any difference between steroid drops and sprays is not known as there were no included studies using steroid drops.

The most common events were epistaxis and headache. Adverse events reported were possibly ambiguous. Headache (Jorissen and Bachert 2009; Lund, Black, et al 2004) could be drug-related, disease-related or coincidental. Sinusitis, rhinitis, common cold and respiratory infection (Giger, Pasche, et al 2003; Jorissen and Bachert 2009; Lund, Black, et al 2004) should be considered as disease symptoms rather than adverse events. Epistaxis, dry nose, nasal burning and nasal irritation are considered to be drug-related events.We acknowledge that rare adverse events are possibly not detected in randomised controlled trials (RCTs). However, they were extremely low and there was no difference in adverse events between the study groups and control groups in any trial. Post-market adverse events for intranasal steroid sprays are very low. However, we have not specifically sought adverse event data from non-RCT studies. Minor adverse events from nasal steroid are commonly tolerated by patients. The amount of benefit clearly outweighs the risk.

Overall completeness and applicability of evidence

We used the standardised mean difference as a summary statistic in this meta-analysis because the included studies assessed the same outcome but measured it in a variety of ways. In these circumstances it is necessary to standardise the results of the studies to a uniform scale before they can be combined. For symptoms, the measurements used were four symptoms rated from 0 to 3 (Furukido, Takeno, et al 2005), five symptoms rated from 0 to 10 (Jorissen and Bachert 2009), three symptoms rated from 0 to 10 (Lavigne, Cameron, et al 2002), five symptoms rated

from 0 to 3 (Lund, Black, et al 2004) and nine symptoms rated by visual analogue scale (Parikh, Scadding, et al 2001).

There was evidence showing beneficial effects of topical steroid over placebo. The standardised mean difference effect estimate for improvement in symptom scores was -0.37 (95% CI -0.60 to - 0.13). The 95% CI was below the null value and favoured topical steroid. The risk ratio for the proportion of patients responding to treatment also favoured the topical steroids group over placebo (RR 1.69; 95% CI 1.21 to 2.37). Subgroup analyses showed significantly greater effects in the sinus delivery methods subgroup. The evidence suggests that topical steroid is effective in symptom control for CRS patients. Sinus delivery methods should be considered to achieve maximum results.

Potential biases in the review process

Questions arose regarding the eligibility criteria and data analyses. The inclusion of trials studying mixed populations of polyps and non-polyps patients possibly brings heterogeneity.We decided to include trials with mixed populations if patients with chronic rhinosinusitis without polyps comprised the majority of the population. Two included trials had mixed polyps and non-polyps populations (Dijkstra, Ebbens, et al 2004; Jorissen and Bachert 2009). We only pooled data from Jorissen and Bachert 2009, which we extracted only from the non-polyps population, for meta-analysis. One included trial had a mixed population of chronic rhinosinusitis and allergic rhinitis (Giger, Pasche, et al 2003). We did not pool these data as topical steroid was not compared with placebo.

Trials required data imputation where standard deviations were missing and we conducted data imputation, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green 2011). Low volume and large volume needed to be defined and we defined a 'large' volume delivery as consisting of at least 60 ml. This represents a full catheter syringe or the smallest nasal irrigation device commercially available. A large number of studies used simple sprays (volumes < 1 ml). The amount of low and large volume was pre-defined based on a previous study (Beule , Athanasiadis, et al 2009) showing how significant volume affects sinus delivery. We did not pool data from trials using volumes of 1 ml to 60ml for subgroup analyses because they were neither low nor large technique by current standards. To be certain that subgroup effects are reliable an interaction effect should be tested, which is not easy to do with published data. The results of the subgroup analyses should therefore be interpreted with caution.

Agreements and disagreements with other studies or reviews

This review included two more studies than a previous non- Cochrane review by some of the same authors (Kalish, Arendts, et al 2009).Most of the included studies in both reviews are the same. However, we excluded one trial from Kalish, Arendts, et al 2009 from this review as the majority of the population had polyps (Mastalerz, Milewski, et al 1997). We also included two more trials (Furukido, Takeno, et al 2005; Jorissen and Bachert 2009). The pooled results of this review differ from Kalish, Arendts, et al 2009 and now reveal evidence favouring the use of topical steroid over placebo. Additional subgroup analyses answer questions not addressed

by the individual studies about the contributing effects of sinus surgery status and topical delivery methods.

Another review of the use of intranasal steroid in chronic rhinosinusitis with and without polyps was performed by Joe et al (Joe, Thambi, et al 2008). However, its results cannot be compared with this review as all the included studies involved participants with polyposis and the primary outcome was polyp size and not a patient-reported outcome (such as symptoms). Intranasal steroid studies were included and intrasinus steroid delivery studies were excluded. The use of concurrent medication and sinus surgery were also exclusion criteria. The review authors found that intranasal steroid was beneficial in chronic rhinosinusitis with polyps.

Conclusion

Implications for practice

Topical steroid may be included in a comprehensive treatment of chronic rhinosinusitis without polyps. The evidence demonstrates that it has beneficial effects on symptom control, with little evidence of significant adverse effects. Direct sinus delivery methods may allow the steroid to contact the sinus mucosa more effectively and this may be a significant contributing factor in its efficacy.

Implications for research

Clinical diversity, including variability in the agents used, patients' sinus surgery status and the topical delivery methods, led to heterogeneity in the studies included

in this review. Subgroup analyses suggested that the beneficial effects were greater with sinus delivery methods, however these findings are only observational as the individuals in the trials were not randomised into these subgroups. Well-conducted randomised controlled trials are required, comparing different methods of topical drug delivery to the sinuses with an appropriate duration of treatment (longer than 12 weeks) and using validated outcome measures. Randomised controlled trials should be pre-registered and their reporting should be according to the latest CONSORT guidelines (Schulz, Altman, et al 2010).

Acknowlegements

We acknowledge ProfMark Jorissen, Prof Claus Bachert and their statisticians for providing raw data from their study.Wewould also like to thank Thanarath Imsuwansri for his kind interpretation of two Japanese articles.

References

Benninger MS, Ferguson BJ, Hadley JA, etal.Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, andpathophysiology.*Otolaryngol Head Neck Surg*2003;129(Suppl 3):S1–32.

Beule A, Athanasiadis T, Athanasiadis E, Field J, WormaldPJ. Efficacy of different techniques of sinonasal irrigation after modified Lothrop procedure. *Am J Rhinol Allergy* 2009;23(1):85–90.

Blackwell DCJ, Coles R. Summary health statistics for U.S.adults: National Health Interview Survey 1997.*Vital andHealth Statistics. Series 10: Data from the National HealthSurvey* 2002;10(205):1–109.

Cuenant G, Stipon JP, Plante-Longchamp G. Efficacy of endonasal neomycin-tixocortolpivalate irrigation in thetreatment of chronic allergic and bacterial sinusitis. *ORL J OtorhinolaryngolRelat Spec* 1986;48(4):226–32.

Dijkstra MD, Ebbens FA, Poublon RML, FokkensWJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis andnasal polyps 1 year after functional endoscopic sinus surgery. *ClinExp Allergy*2004;34(9):1395–400.

Fokkens W, Lund V, Mullol J. European position paper onrhinosinusitis and nasal polyps 2007. *Rhinology* 2007;45(Suppl 20):1–139.

Furukido K, Takeno S, Ueda T, Yajin K. Cytokine profile inparanasal effusions in patients with chronic sinusitis usingthe YAMIK sinus catheter with and without betamethasone.*Eur Arch Otorhinolaryngol* 2005;262(1):50–4.

Giger R, Pasche P, Cheseaux C, et al.Comparison of once- versus twice-daily useof beclomethasonedipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. *Eur Arch Otorhinolaryngol*2003;260(3):135–40.

Gliklich RE, MetsonR. The health impact of chronic sinusitis in patients seeking otolaryngologic care.*Otolaryngol Head Neck Surg*1995;113:104–9.

Grobler A, Weitzel EK, Buele A, et al.Pre- andpostoperative sinus penetration of nasal irrigation. *Laryngoscope*2008;118(11):2078–81.

Hamilos DL. Chronic sinusitis.*J Allergy ClinImmunol*2000;106:213–27.

Harvey RJ, Debnath N, Srubiski A, Bleier B, Schlosser RJ. Fluid residuals and drug exposure in nasal irrigation. *Otolaryngol Head Neck Surg*2009;141(6):757–61.

Harvey RJ, Schlosser RJ. Local drug delivery.*OtolaryngolClin North Am* 2009;42:829–45.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration,2011. Available from www.cochrane-handbook.org.

Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008;139(3):340–7.

Jorissen M, Bachert C. Effect of corticosteroids on wound healing after endoscopic sinus surgery. *Rhinology* 2009;47:280–6.

Kalish LH, Arendts G, Sacks R, Craig JC. Topical steroids in chronic rhinosinusitis without polyps: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*2009;141(6):674–83.

Kennedy DW. Pathogenesis of chronic rhinosinusitis.*Ann OtolRhinolLaryngol Suppl*2004;193:6–9.

Kern RC, Conley DB, Walsh W, etal.Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. *Am J Rhinol*2008;22(6):549–59.

Lanza DC, Kennedy DW. Adult rhinosinusitis defined.*Otolaryngol Head Neck Surg* 1997;117(3Pt2):S1–7.

Lavigne F, Cameron L, Renzi PM, etal.Intrasinusadministration of topical budesonide to allergic patientswith chronic rhinosinusitis following surgery. *Laryngoscope*2002;112(5):858–64.

Linder JA. Health-related quality of life in patients withsinusitis.*Curr Allergy Asthma Rep*2004;4:490–5.

Lund VJ, Black JH, Szabo LZ, Schrewelius C, AkerlundA. Efficacy and

tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. *Rhinology* 2004;42(2):57–62.

Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* 1997;52(9):895–900.

McNally PA, White MW, Kaliner MA. Sinusitis in an allergists' office: analysis of 2000 consecutive cases.*AllergyAsthma Proc*1997;18:169–75.

Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. *Laryngoscope* 2000; Vol. 110, issue3 Pt 3:24–8.

Mullol J. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol AllergyClin North Am*2009;29(4):657–68.

Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. *Rhinology* 2001;39(2):75–9.

Qvarnberg Y, Kantola O, Salo J, Toivanen M, Valtonen H, Vuori E. Influence of topical steroid treatment on maxillary sinusitis. *Rhinology* 1992;30(2):103–12.

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332

Shashy RG, Moore EJ, Weaver A. Prevalence of the chronicsinusitis diagnosis in Olmsted County, Minnesota. *ArchOtolaryngol Head Neck Surg* 2004;130(3):320–3.

Singhal D, Weitzel EK, Lin E, et al.Effect of headposition and surgical dissection on sinus irrigant penetration in cadavers. *Laryngoscope* 2010;120(12):2528–31.

Snidvongs K, Chaowanapanja P, Aeumjaturapat S, ChusakulS, Praweswararat P. Does nasal irrigation enter paranasalsinuses in chronic rhinosinusitis?.*Am J Rhinol*2008;22(5):483–6.

Spector SL, Bernstein IL, Li JT, etal.Parameters for the diagnosis and management of sinusitis. *J Allergy ClinImmunol*1998;102(6 Pt 2):S107–44.

Sok JC, Ferguson BJ.Differential diagnosis of eosinophilic chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2006;6(3):203–14.

Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study.*Lancet* 1986;2(8503):359–60.

Chapter6 Appendix

Appendix6.1

Table 6.2 Characteristics of included studies

Cuenant, Stipon, et al 1986	Methods	Randomised, double-blind, parallel study
	Participants	60 patients Mean age 39 ± 14 years Chronic allergic or bacterial maxillary sinusitis Settings of enrolment: not stated Sinus surgery status: not stated
	Interventions	Treatment group (n = 30) 5 cc injection of 50 mg of tixocortol pivalate (Pivalone) plus 17,000 IU neomycin daily Control group (n = 30) 5 cc injection of 17,000 IU neomycin daily Injections through maxillary sinus cannulation after intrasinus lavage No sinus surgery Taken for 11 days
	Outcomes	Primary: ostial patency (determined by maxillary sinus pressure fluctuation during the normal respiratory cycle, in a vertical U-tube connected to an irrigation system) Secondary: symptoms, rhinoscopy
	Notes	

Cuenant, Stipon, et al 1986	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote “... allocated on a randomised basis”
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment. Quote “...allocated on a randomised basis”
	Blinding (self report outcomes)	Low risk: Quote “... on a double-blind...basis” and “Both treatments looked alike and contained the same excipients”
	Blinding (objective outcomes)	Low risk: Quote “...on a double-blind...basis” and “Both treatments looked alike and contained the same excipients”
	Incomplete outcome data	Low risk: Quote “None of the 60 patients dropped out”
	Selective reporting	High risk: Symptoms and rhinoscopy were efficacy assessment criteria stated in Patients and Methods but they were reported in all treatment groups without separate data
	Other bias	Low risk: Free of other sources of bias

Dijkstra, Ebbens, et al 2004	Methods	Randomised, double-blind, parallel study
	Participants	162 patients Mean age 41 years Requiring FESS for chronic rhinosinusitis or nasal polyps Tertiary care medical centres in the Netherlands Sinus surgery status: with sinus surgery
	Interventions	Treatment group I (n = 53) 100 µl of fluticasone propionate aqueous 400 µg twice daily Treatment group II (n = 53) 100 µl of fluticasone propionate aqueous 800 µg twice daily Control group (n = 56) placebo spray twice daily Nasal spray Administered after sinus surgery Taken for 52 weeks or until withdrawal from the trial
	Outcomes	Primary: VAS symptom scores and recurrence rate Secondary: nasal endoscopy findings, CT scan, adverse events
	Notes	46 patients had been withdrawn from the trial because of recurrent diseases and 32 patients because of persistent symptoms

Dijkstra, Ebbens, et al 2004	Random sequence generation	Unclear risk: Did not describe sequence generation process.Quote "... a randomisation code generated by the statistics department of the Erasmus University Medical Centre Rotterdam. Randomization to treatment groups was equal." Comment: probably computer-generated?
	Allocation concealment	Low risk: Quote "... a randomisation code generated by the statistics department of the Erasmus University Medical Centre Rotterdam."
	Blinding (self report outcomes)	Low risk: Quote "double blind"
	Blinding (objective outcomes)	Low risk Quote "double blind"
	Incomplete outcome data	High risk: In the placebo group, 32/56 were withdrawn (22 due to recurrent or persistent disease). In the FPANS 400 µg group, 34/53 were withdrawn (27 due to recurrent or persistent disease). In the FPANS 800 µg group, 37/53 were withdrawn (29 due to recurrent or persistent disease). Comment: reasons for missing data were related to outcomes. Missing outcome data balanced in numbers across intervention groups.
	Selective reporting	High risk: Quote (in Methods) "Study medication was taken for one year" and "During 11 postoperative visits, VAS scores and nasal endoscopy findings were recorded" Reported in Results: "...median total symptoms score two weeks after FESS". No VAS after one year, no nasal endoscopy reported. Two types of withdrawal listed in Methods, but only one reported.
	Other bias	Low risk: Free of other sources of bias

Furukido, Takeno, et al 2005	Methods	Randomised, single-blind, parallel study
	Participants	25 adults patients Chronic sinusitis Mean age 53.7 years Tertiary care in Japan Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 15) 2 ml betamethasone solution 0.4 mg/ml weekly Control group (n = 10) normal saline solution Through the YAMIK catheter inserted into the nasal cavity after evacuation of effusion No sinus surgery Taken for 4 consecutive weeks
	Outcomes	Primary: symptoms score Secondary: radiographs (ethmoid and maxillary sinuses) and cytokine levels of sinus effusion
	Notes	

Furukido, Takeno, et al 2005	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote “... patients were randomly divided into... ”
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding (self report outcomes)	Low risk: Quote “... we adopted a single blind test...”
	Blinding (objective outcomes)	Low risk: The outcomes (radiographs, cytokines level) are not influenced by lack of blinding
	Incomplete outcome data	Low risk: Quote “...all patients were able to complete the five treatment sessions...”
	Selective reporting	Low risk: All expected outcomes were reported
	Other bias	Low risk: Free of other sources of bias

Giger, Pasche, et al 2003	Methods	Randomised, double-blind, parallel study
	Participants	112 adult patients Mean age 31.8 ± 10.2 and 32.9 ± 10.9 in treatment and control group Allergic rhinitis (n = 52) or non-allergic chronic rhinosinusitis (n = 60) Tertiary cares in Switzerland Sinus surgery status: not stated
	Interventions	Treatment group (n = 55) nasal aqueous beclomethasone dipropionate, 200 µg twice daily Control group (n = 57) nasal aqueous beclomethasone dipropionate, 400 µg in the morning and the matched placebo in the evening Nasal spray No sinus surgery Taken for 12 weeks
	Outcomes	Primary: symptoms score for the 7-day run-in period and for the first 4weeks of treatment Secondary: active anterior rhinomanometry, acoustic rhinometry, morning serum cortisol, adverse events
	Notes	

Giger, Pasche, et al 2003	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote "... patients were randomly assigned..."
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment. Quote "... patients were randomly assigned..."
	Blinding (self report outcomes)	Low risk: Quote "... to receive either intranasal BDP 400 micro g in the morning and the matched placebo in the evening, or at 200 micro g twice daily in the morning and in the evening"
	Blinding (objective outcomes)	Low risk: Quote "This was a randomised, double blind... "
	Incomplete outcome data	Low risk: Quote "Three patients did not have post baseline data... " Of the 112 randomised patients, 3 did not enter the ITT analysis and 13 discontinued the treatment. Missing data did not have an impact on effect size.
	Selective reporting	Low risk: All expected outcomes were reported
	Other bias	Low risk: Free of other sources of bias

Jorissen and Bachert 2009	Methods	Randomised, double-blind, parallel study
	Participants	91 adult patients Mean age 47.4 ± 12.5 years Chronic sinusitis or nasal polyps Tertiary cares in Belgium Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 46) 2mg of betamethasone tablet (7 days) followed by 200 µl of intranasal mometasone furoate 200 µg twice daily Control group (n = 45) placebo tablet and spray Nasal spray Administered 2 weeks after sinus surgery Taken for 6 months
	Outcomes	Primary: endoscopic score Secondary: symptom scores and adverse events
	Notes	

Jorissen and Bachert 2009	Random sequence generation	Low risk: Quote “Randomization to treatment was achieved according to a computer-generated sequential list...”
	Allocation concealment	Low risk Quote: “Randomization to treatment was achieved according to a computer-generated sequential list...”
	Blinding (self report outcomes)	Low risk: Quote “Randomization to treatment...was provided to each participating centre’s pharmacy for distribution of appropriate study medication to the investigator and subsequently to the patient, in a double blinded manner. Betamethasone matching placebo tablets were prepared by the pharmacy at the University Hospital Gent, whereas MFNS (Nasonex) and matching placebo nasal sprays were provided by Schering-Plough.”
	Blinding (objective outcomes)	Low risk: Quote “Randomization to treatment...was provided to each participating centre’s pharmacy for distribution of appropriate study medication to the investigator and subsequently to the patient, in a double blinded manner. Betamethasone matching placebo tablets were prepared by the pharmacy at the University Hospital Gent, whereas MFNS (Nasonex) and matching placebo nasal sprays were provided by Schering-Plough.”
	Incomplete outcome data	Low risk: Quote “... of whom 2/49 and 4/50 patients in the MFNS and placebo group, respectively, did not return to the site for surgery. A further 2 patients (1 in each group) did not start their randomised treatment after surgery” and “Overall, 67 patients (35(76.1%) in the MFNS group and 32 (71.1%) in the placebo group) completed the study”
	Selective reporting	High risk: The patient’ opinion of treatment success was planned in the Methods but not reported.
	Other bias	Low risk: Free of other sources of bias

Lavigne, Cameron, et al 2002	Methods	Randomised, double-blind, parallel study
	Participants	26 adult patients Mean age 46 ± 10.7 years Chronic rhinosinusitis and allergy to house dust mites with previously sinus surgery Tertiary care in Canada Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 13) 3 ml of 256 µg budesonide daily Control group (n = 13) placebo Through a maxillary antrum sinusotomy tube After sinus surgery Taken for 3 weeks
	Outcomes	Primary: symptom scores Secondary: immunocytochemistry
	Notes	

Lavigne, Cameron, et al 2002	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding (self report outcomes)	Low risk: Quote "... topical budesonide...or matched placebo was instilled.." and "... double blind.."
	Blinding (objective outcomes)	Low risk: Quote "... double blind.."
	Incomplete outcome data	Low risk: Quote "Twenty-four of the 29 patients who were recruited completed the study" Comment: missing data balanced across groups
	Selective reporting	Unclear risk: Quote "Twenty-four of the 29 patients who were recruited completed the study" and "Five patients could not complete the study" but 26 patients were reported in results, and 22 patients were reported for VAS in Figure 6
	Other bias	Low risk: Free of other sources of bias

Lund, Black, et al 2004	Methods	Randomised, double-blind, parallel study
	Participants	167 patients Mean age 38 and 43 in treatment and control group Chronic rhinosinusitis Tertiary cares in the United Kingdom, South Africa and Hungary and 1 primary care in South Africa Sinus surgery status: without sinus surgery for 1 year; not stated before that period
	Interventions	Treatment group (n = 81) 100 µl of budesonide 128 µg twice daily Control group (n = 86) placebo Nasal spray No sinus surgery Taken for 20 weeks
	Outcomes	Primary: combined symptom scores Secondary: individual symptom score, Chronic Sinusitis Survey score, SF36, peak nasal inspiratory flow, patients' overall evaluation of efficacy and adverse events
	Notes	

Lund, Black, et al 2004	Random sequence generation	Low risk: Quote "... randomisation was performed in balanced blocks of four by means of a computer program (SAS Software version 6.11)"
	Allocation concealment	Low risk: Quote "... randomisation was performed.at the Department of Biostatistics And Data Management, AstraZeneca R&D Lund, Sweden"
	Blinding (self report outcomes)	Low risk: Quote "BANS and placebo aqueous sprays were identical in appearance and were both administered via the same vehicle"
	Blinding (objective outcomes)	Low risk: Quote "The treatment codes were known only to the person responsible for packaging, who were not involved in the study in any other way. Each bottle of study medication was supplied with a detachable label, which was attached to the Case Report Form when the medication was dispensed."
	Incomplete outcome data	Low risk: Quote "A total of 244 patients were enrolled....77 discontinued during the run-in period....167 patients were eligible for randomisation, of whom 81 were randomised to BANS and 86 to placebo. In total, 134 patients (67 in each group) completed treatment."
	Selective reporting	High risk: Numerical data from SF-36 were not reported
	Other bias	Low risk: Free of other sources of bias

Parikh, Scadding, et al 2001	Methods	Randomised, double-blind, parallel study
	Participants	29 patients Mean age 45.1 ± 10.7 and 48 ± 20 in treatment and control group Chronic rhinosinusitis Tertiary care in the United Kingdom Sinus surgery status: mixed population with and without sinus surgery
	Interventions	Treatment group (n = 14) 100 µl of fluticasone propionate aqueous 2 sprays each side twice daily (400 µg/day) Control group (n = 15) placebo Nasal spray No sinus surgery Taken for 16 weeks
	Outcomes	Primary: VAS symptom score Secondary: diary symptom scoring comparing the first week score with the final week score, acoustic rhinometry, rigid endoscopy scores, middle meatal swabs, blood tests -CRP, ESR, WBC and eosinophil count
	Notes	

Parikh, Scadding, et al 2001	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote “Patients were randomised to... ” and “The randomisation code was generated...” Comment: probably computer-generated?
	Allocation concealment	Low risk: Quote “The randomisation code was generated and maintained by personnel in the pharmacy. The investigators were not involved in the process of randomisation.”
	Blinding (self report outcomes)	Low risk: Quote “Placebo spray had benzalkonium chloride in the same concentration as fluticasone propionate, and both had rose scent to mask any differences in smell.”
	Blinding (objective outcomes)	Low risk: Quote “The study medications were prepared and supplied by Glaxo Wellcome Research and Development Public Limited...”
	Incomplete outcome data	Low risk: Quote “Twenty-nine patients were enrolled, and 22 completed the trial. Of these 13 were re-assessed at 8 weeks only, and 9 at both 8 and 16 weeks. Of the 7 patients not completing the trial, 5 did not attend follow-up, 1 stopped using his trial medication prematurely at 3 weeks (drop out) and 1 patient was withdrawn as his nasal swab taken at the initial visit grew MRSA. A diary card was maintained by the patient who dropped out, and hence data from it was used in analysis.”
	Selective reporting	Low risk All expected outcomes were reported
	Other bias	Low risk Free of other sources of bias

Qvarnberg, Kantola, et al 1992	Methods	Randomised, double-blind, parallel study
	Participants	40 patients Mean age 45.6 and 45.2 in treatment and control group Chronic or recurrent maxillary sinusitis Tertiary hospital in Finland Sinus surgery status: not stated
	Interventions	Treatment group (n = 20) budesonide twice daily, 400 µg per day Control group (n = 20) placebo Aerosol No sinus surgery Taken for 12 weeks
	Outcomes	Primary: symptom scores Secondary outcomes: radiograph, cellular picture and bacteriology
	Notes	

Qvarnberg, Kantola, et al 1992	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote “This trial was carried out as a randomised...”
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment. Quote “This trial was carried out as a randomised...”
	Blinding (self report outcomes)	Low risk: Quote “This trial was carried out as a randomised double-blind... ”
	Blinding (objective outcomes)	Low risk Quote “This trial was carried out as a randomised double-blind... ”
	Incomplete outcome data	Low risk: Quote “Thirty-eight of the 40 patients completed the trial. Two patients, one in each group, had to be withdrawn as a Caldwell-Luc operation was performed before the completion of the 3-month treatment period.”
	Selective reporting	High risk: Symptom scores were pre-specified but incompletely reported so that they cannot be entered in a meta-analysis. Numerical data for facial pain and facial sensitivity, but no other symptoms nor total score were provided.
	Other bias	Low risk: Free of other sources of bias

Sykes, Wilson, et al 1986	Methods	Randomised, double-blind, parallel study
	Participants	50 patients Age 20 to 74 years Chronic rhinosinusitis Tertiary hospital in the United Kingdom Sinus surgery status: not stated
	Interventions	Treatment group I (n = 20) 20 µg dexamethasone, 120 µg tramazoline and 100 µg neomycin Treatment group II (n = 20) 20 µg dexamethasone and 120 µg tramazoline Control group (n = 10) matched placebo Nasal spray No sinus surgery The length of treatment was 2 weeks
	Outcomes	Primary: proportion of patients having improved symptoms Secondary: nasal airway resistance, nasal mucociliary clearance, sinus radiographs and bacteriology
	Notes	

Sykes, Wilson, et al 1986	Random sequence generation	Unclear risk: Did not describe sequence generation process. Quote: “Patients were randomly allocated...”
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment. Quote: “Patients were randomly allocated...”
	Blinding (self report outcomes)	Low risk: Quote “Patients and investigators were unaware of the treatment being given...”
	Blinding (objective outcomes)	Low risk: Quote “Patients and investigators were unaware of the treatment being given...”
	Incomplete outcome data	Low risk: No drop-out
	Selective reporting	Low risk: All expected outcomes were reported
	Other bias	Low risk: Free of other sources of bias

Table 6.2 Characteristics of included studies

Abbreviation

BANS: budesonide aqueous nasal spray

BDP: beclomethasone dipropionate

CRP: C-reactive protein

CT: computed tomography

ESR: erythrocyte sedimentation rate

FESS: functional endoscopic sinus surgery

FPANS: fluticasone propionate aqueous nasal spray

ITT: intention-to-treat

IU: international units

MFNS: mometasone furoate nasal spray

MRSA: methicillin-resistant *Staphylococcus aureus*

VAS: visual analogue scale

WBC: white blood cell count

Chapter 7

Topical steroids for nasal polyps

Topical steroids for nasal polyps (Review)

Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 12

http://www.thecochranelibrary.com

"This study aims to assess the effects of topical steroid for nasal polyps and how sinus surgery and topical delivery method influence the impact of topical steroid."

Abstract

Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents inflammatory changes throughout the nose and sinuses from a group of disorders which all lead to swelling and overgrowth of the nasal mucosa. Topical corticosteroids have been the most widely used treatment, with each clinician using different regimes, at different doses, in different settings and with or without sinus surgery. CRSwNP requires ongoing medical management to prevent recurrence. We aim to assess the effects of topical corticosteroids on CRSwNP and to analyse various subgroups, including patients who had sinus surgery immediately prior to the delivery of the corticosteroids, surgery any time prior to the topical corticosteroids or patients who had never had previous surgery. Also to assess the most effective dose and delivery methods for topical corticosteroids.

Methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 10 April 2012. The selection criteria was randomised controlled trials studying topical corticosteroids for patients with CRSwNP. At least two authors reviewed the search results and selected trials meeting the eligibility criteria, obtaining full texts

and contacting authors. We documented our justification for the exclusion of studies. At least two authors extracted data using a pre-determined, standardised data form.

Results

Forty studies (3624 patients) met the inclusion criteria. The trials were at low (21 trials), medium (13 trials) and high (six trials) risk of bias. The primary outcomes were sino-nasal symptoms, polyp size and polyp recurrence after surgery. When compared to placebo, topical corticosteroids improved overall symptom scores (standardised mean difference (SMD) -0.46; 95% confidence interval (CI) -0.65 to -0.27, P < 0.00001; seven trials, n = 445) and had a higher proportion of patients whose symptoms improved (responders) (risk ratio (RR) 1.71; 95% CI 1.29 to 2.26, P = 0.0002; four trials, n = 234). Topical corticosteroids also decreased the polyp score (SMD -0.73; 95% CI -1.00 to -0.46, P < 0.00001; three trials, n = 237) and had a greater proportion of patients with a reduction in polyp size (responders) (RR 2.09; 95% CI 1.65 to 2.64, P < 0.00001; eight trials, n= 785) when compared to placebo. Topical corticosteroids also prevented polyp recurrence after surgery (RR 0.59; 95% CI 0.45 to 0.79, P = 0.0004; six trials, n = 437). Subgroup analyses by sinus surgery status revealed a greater benefit in reduction of polyp score when topical steroid was administered any time after sinus surgery (SMD -1.19; 95% CI -1.54 to -0.83) compared to patients who had never had surgery (SMD -0.13; 95% CI -0.53 to 0.28, P < 0.00001). There was no difference between groups in terms of adverse events.

Conclusions

Topical corticosteroids are a beneficial treatment for CRSwNP and the adverse effects are minor, with benefits outweighing the risks. They improve symptoms, reduce polyp size and prevent polyp recurrence after surgery. Patients having sinus surgery may have a greater response to topical corticosteroids but further research is required.

Introduction

Description of the condition

Definition

Nasal polyps are a manifestation of chronic inflammation of the mucosa throughout the nose and sinuses from a group of disorders which all lead to swelling and overgrowth of the nasal mucosa (Mygind and Bachert 2000). Polyps generally arise from the mucosa surrounding the middle meatus and often cause nasal blockage and restricted airflow. Chronic rhinosinusitis (CRS) is defined as the presence of two or more symptoms, one of which should be either nasal blockage/ obstruction/ congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure OR reduction or loss of smell. These symptoms need to be present for 12 weeks or more. Chronic rhinosinusitis is further classified as with polyps (CRSwNP) or without polyps (CRSsNP) based on the presence or absence of polyps, on endoscopic view, in the middle meatus (the area between the middle and inferior turbinates into which the maxillary, anterior ethmoid and frontal sinuses drain). This definition accepts that there is a spectrum of disease in CRS which includes polypoid change in the sinuses but which is not evident in the middle meatus and excludes those in the CRSwNP group (Fokkens, Lund, et al. 2012).

Aetiology

The exact mechanisms that cause nasal polyps are largely unknown, possibly because a single, unified cause for the underlying inflammatory process may not exist (Benninger, Ferguson, et al. 2003). It is more likely that many factors contribute to mucosal inflammation and that nasal polyps are a common result of a diverse

group of disorders. Several theories have been suggested. No clear evidence exists for an allergic origin, although there is an established association with asthma and aspirin sensitivity (Slavin 2002). Nasal polyps are also seen in cystic fibrosis, Churg-Strauss syndrome and primary ciliary dyskinesia (Kartagener's syndrome) (Mygind and Bachert 2000). Chronic rhinosinusitis with nasal polyps (CRSwNP) is largely characterised by a T-helper-2 dominated cytokine pattern that includes interleukin-5 and formation of immunoglobulin E, compared to chronic rhinosinusitis without polyps (CRSsNP), which exhibits T-helper-1 biased cytokine release (Fokkens, Lund, et al. 2012). Four processes might contribute to the inflammatory process:

- late-phase allergic inflammation in response to airborne allergens in allergic patients with nasal polyps;
- T-cell activation with production of IL-5, IL-13 and IFN in response to fungal antigens (hyphae) in sinus mucus;
- T-cell activation, cytokine production and local IgE production in response to bacterial superantigens. There is growing evidence that *S. aureus* derived enterotoxins amplify the eosinophilic inflammation in nasal polyps in different ways, including amplification of the release of Th2 cytokines and IgE formation, and down-regulation of T-regulatory cytokines (Bachert, Zhang et al 2008); and
- dysregulation of the sinus epithelium with overproduction of chemokines, such as RANTES, similar to inflammatory findings in asthma (Meltzer, Hamilos et al 2004).

Regardless of aetiology, the increased presence of inflammatory mediators is prominent and consistent in nasal polyps.

Prevalence

The exact prevalence of CRSwNP is uncertain because there have been few epidemiological studies, but the overall prevalence is probably around 2% to 4%. They are rarely seen in children and the incidence gradually increases with age (Klossek, Neukirch et al 2005). They are seen in all ethnic groups and throughout the world, but no comparative studies have been conducted. CRSwNP is more prevalent in individuals with aspirin intolerance, non-allergic asthma and in cystic fibrosis.

Diagnosis

A diagnosis of CRSwNP may be suggested by symptoms of nasal obstruction, watery nasal discharge (rhinorrhoea or post-nasal drip) or loss of smell (anosmia/hyposmia with a concomitant effect on taste). Patients may also report headaches, facial pain and discomfort. Obstruction of the sinus ostia can predispose to infection and symptoms of acute, recurrent or chronic sinusitis may be present.

Nasal polyps most often originate from the mucosa of the lateral wall of the middle meatus as a pale translucent mass of tissue. They may exist with an underlying rhinosinusitis. Polyps can vary widely in size and are most often bilateral. Papillomas, including inverted papillomas, can be confused with polyps, therefore histological examination is important when nasal polyps are unilateral.

There are numerous grading systems but the most widely accepted uses 0 to 3, with grade 0 being no visible polyps; grade 1 being polyps confined to the middle meatus; grade 2 being polyps beyond the middle meatus but not completely obstructing the nasal cavity; and grade 3 being polyps completely obstructing the nasal cavity (Lund and Kennedy 1995).

Microscopically, polyps are characterised by a ciliated pseudostratified columnar epithelium, with areas of transitional or squamous epithelium. They typically show a chronic infiltration of inflammatory cells. Goblet cells, which secrete mucus, and submucous glands are found in lower density than in normal epithelium (Bateman, Fahy et al 2003). Nasal polyps may be histologically classified as eosinophilic polyps, which make up 65% to 90% of total cases, or polyps with a neutrophilic or lymphocytic infiltrate (Hellquist 1996).

The definitive diagnosis of CRSwNP is made by a combination of anterior rhinoscopy, endoscopy and computerised tomography (CT) imaging. Plain sinus X-ray is of little value in the diagnosis of CRSwNP.

As per the definition, the diagnosis of CRSwNP is based on the presence or absence of polyps, on endoscopic view, in the middle meatus (the area between the middle and inferior turbinates into which the maxillary, anterior ethmoid and frontal sinuses drain). It is appreciated that some patients may have polypoid changes in the sinuses NOT evident in the middle meatus but these patients are classified as CRS without polyps. In patients who have had surgery previously, any polyps evident in

the open sinuses are considered CRSwNP. Polyps which are seen in the sinuses after surgery are classified as recurrent polyps.

Description of the intervention

The current consensus among specialists is that CRSwNP should initially be treated conservatively, as many patients may not require surgery. Surgery has a role when the medical treatment fails (Bachert, Watelet et al 2005; Ragab, Lund et al 2004). Both medical and surgical treatments have been shown to have similar efficacy, with an improvement in symptoms and quality of life. However, both methods have high rates of recurrence (Ragab, Lund et al 2004; Scadding 2002).

The main aim of treatment is to relieve nasal symptoms by eliminating or reducing the size of polyps. Relieving nasal symptoms may include improving nasal breathing, improving or restoring the sense of smell, improving hyponasal speech, reducing nasal discharge and reducing the incidence of facial pain and pressure. The first-line medical treatment is corticosteroids, which have a multifactorial effect initiated by their binding to a specific cytoplasmic glucocorticoid receptor. This results in a reduction in the total number of lymphocytes, their activation and cytokine production, reduction of mast cells and the reduction of the influx and total number of eosinophils in polyp tissue (Badia and Lund 2001). New approaches including antibiotic, antifungal, leukotriene modifier and intranasal furosemide treatments are being developed and tested (Fokkens, Lund et al 2012).

Oral corticosteroids for large polyps have been reported to be effective in a small number of trials (Mladina, Clement et al 2005). They have also been used in combination with topical corticosteroids. However, their use has been limited to short periods because of the risk of side effects. The true efficacy of oral corticosteroids for CRSwNP has been reviewed systematically (Martinez-Devesa and Patiar 2011).

Topical corticosteroids have been the most widely used form of corticosteroids. The classes of topical corticosteroids include the first-generation intranasal corticosteroids (beclomethasone dipropionate, triamcinolone acetonide, flunisolide, budesonide) and the newer preparations (fluticasone propionate, mometasone furoate, fluticasone furoate and ciclesonide). Topical corticosteroids have been used for both reducing polyp size as well as preventing recurrence. Common side effects include local irritation and epistaxis. Potential adverse events related to the administration of intranasal corticosteroids are effects on growth, ocular effects, effects on bone and effects on the hypothalamic-pituitary-adrenal axis. Cases of adrenal suppression and Cushing's syndrome from systemic absorption have been reported, but are rare (Bateman, Fahy et al 2003).

Delivery methods may influence the efficacy of the corticosteroids on the polyps. Delivery methods such as nasal drops, aqueous pumps and metered-dose pumps, the spray volume and the formulation are all important considerations when comparing topical corticosteroids (Meltzer 2007). More recently direct drug delivery and the use of rinse bottles and netipots have been applied.

Why it is important to do this review

Nasal corticosteroids have been extensively utilised as a treatment for CRSwNP. There have been a number of randomised controlled trials. However, each has used different regimes, at different doses, in different settings and some with different objectives. There is one meta-analyses on the effectiveness of topical corticosteroids as treatment for CRSwNP but this review only looked at polyp size and not symptoms and other outcomes and therefore only included 13 of the trials we have reviewed (Joe, Thambi et al 2008). Our review aims to assess the strength of evidence supporting the use of topical corticosteroids for a wide range of outcomes and to try to explain any heterogeneity seen in the results.

Objectives

To assess the effects of topical corticosteroids on CRSwNP and to analyse various subgroups, including patients who had sinus surgery immediately prior to the delivery of the corticosteroids, surgery any time prior to the topical corticosteroids or patients who had never had previous surgery. Also to assess the most effective dose and delivery methods for topical corticosteroids.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Inclusion criteria

Patients with CRSwNP diagnosed clinically with either: endoscopic evidence of nasal polyps; and/or radiological evidence of nasal polyps

Exclusion criteria

Antrochoanal polyps (benign polyps originating from the mucosa of the maxillary sinus)

Malignant polyps

Cystic fibrosis

Primary ciliary dyskinesia

Types of interventions

Topical corticosteroids versus no intervention

Topical corticosteroids versus placebo

Topical and oral corticosteroids versus oral corticosteroids only

Low-dose versus high-dose corticosteroids

Types of outcome measures

Primary outcomes

For the purpose of primary treatment: change in symptom scores (overall or nasal obstruction) and polyp size (grade) and participants with reduction in these measures ('responders')

For the purpose of recurrence prevention: proportion with polyp recurrence

Secondary outcomes

Change in nasal air flow

Change in radiological appearance

Change in smell

Quality of life outcomes

Drop-outs

Adverse effects

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the search was 10 April 2012.

Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials

Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 3); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP and Google. We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Higgins and Green 2011)). Search strategies for major databases including CENTRAL are provided in Table7.1 (See Appendix 7.1).

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials.

Data collection and analysis

Selection of studies

We (LK, KS, DC, RS) independently reviewed the titles and abstracts of all studies identified by the search strategy and applied the inclusion and exclusion criteria. When the studies satisfied the inclusion criteria or there was insufficient information

to make a decision, we obtained the full text of the articles. We documented our justification for the exclusion of studies.

Data extraction and management

The review authors independently extracted all data from the studies using a pre-determined, standardised data form. We extracted the following data.

- Characteristics of trials: publication status, year, country of study, funding, setting, design, inclusion and exclusion criteria, recruitment, methods, analysis and results.
- Study methods: method of allocation, blinding and losses after randomisation (follow-up losses and drop-outs).
- Characteristics of participants: study population, number of participants in each arm, age, gender, nationality and diagnostic criteria, prior surgery (extent).
- Characteristics of interventions: preparation used, dose, delivery method, length of treatment and follow-up, compliance, co-interventions and intervention used in control group.
- Outcomes: symptom score, change in endoscopic or radiological findings, complications and adverse events, drop-outs.

Assessment of risk of bias in included studies

We undertook assessment of the risk of bias of the included trials independently. As guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green 2011), we assessed the following domains:

sequence generation (selection bias);

allocation concealment (selection bias);

blinding (performance bias and detection bias);

incomplete outcome data (attrition bias);

selective outcome reporting (reporting bias); and

other sources of bias.

We used the Cochrane 'Risk of bias' tool in Review Manager (RevMan) version 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: high, low and unclear (or unknown) risk of bias. We judged the quality of studies according to their risk of bias in four areas: selection bias, performance and detection bias, attrition bias and reporting bias. We considered trials as having high, medium and low quality as follows: high quality = low risk of bias in three to four of these four key domains; medium quality = low risk of bias in two; and low quality = low risk of bias in one or no domains.

Data synthesis

The authors followed the ENT Group statistical guidelines. Data analysis was on an intention-to-treat basis. We combined comparable data to give a summary measure of effect. We used the standardised mean difference (SMD) and 95% confidence intervals (CIs) for continuous data. We used the risk ratio (RR) and 95% CIs for dichotomous data. We pooled the intervention effects when trials were sufficiently homogeneous. We pooled data using a fixed-effect model. We performed statistical assessments using Review Manager (RevMan) version 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). We assessed the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's Q test for heterogeneity and by a measure of the I2 statistic. An I2 of less than 40%, 40% to 60% and greater than 60% represent low, moderate and substantial heterogeneity. We performed subgroup analysis to explore possible sources of heterogeneity as below. We contacted the study authors via email for raw data in cases of missing data. The analyses were based on intention-to-treat. For missing standard deviations, we used either 95% CIs, standard error, P value, range or interquartile ranges for estimation to impute standard deviations. For missing means, we converted medians.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis for sinus surgery status, topical delivery methods, polyp severity, steroid agents used and quality of studies. We investigated differences between subgroups for fixed-effect analyses based on the inverse-

variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

Results

Description of studies

Characteristics of included studies are displayed in Table 7.2 (See Appendix7.2).

Results of the search

The searches retrieved a total of 953 references. We identified three more records from references of the retrieved studies. We removed 735 of these in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 221 references for further consideration. We screened titles and abstracts and subsequently removed 169 studies. We assessed 52 full texts for eligibility. One ongoing study investigated predictors of response. One paper was an oral steroid study. Three non-randomised studies and two studies failed to compare topical steroid to either placebo or no intervention and we therefore also excluded these. One study is ongoing. We included 40 studies (44 papers; three papers were abstracts of presentations at academic meetings of included studies and one paper pooled data from two included studies for reanalysis). A flow chart of study retrieval and selection is provided in Figure 7.1.

Included studies

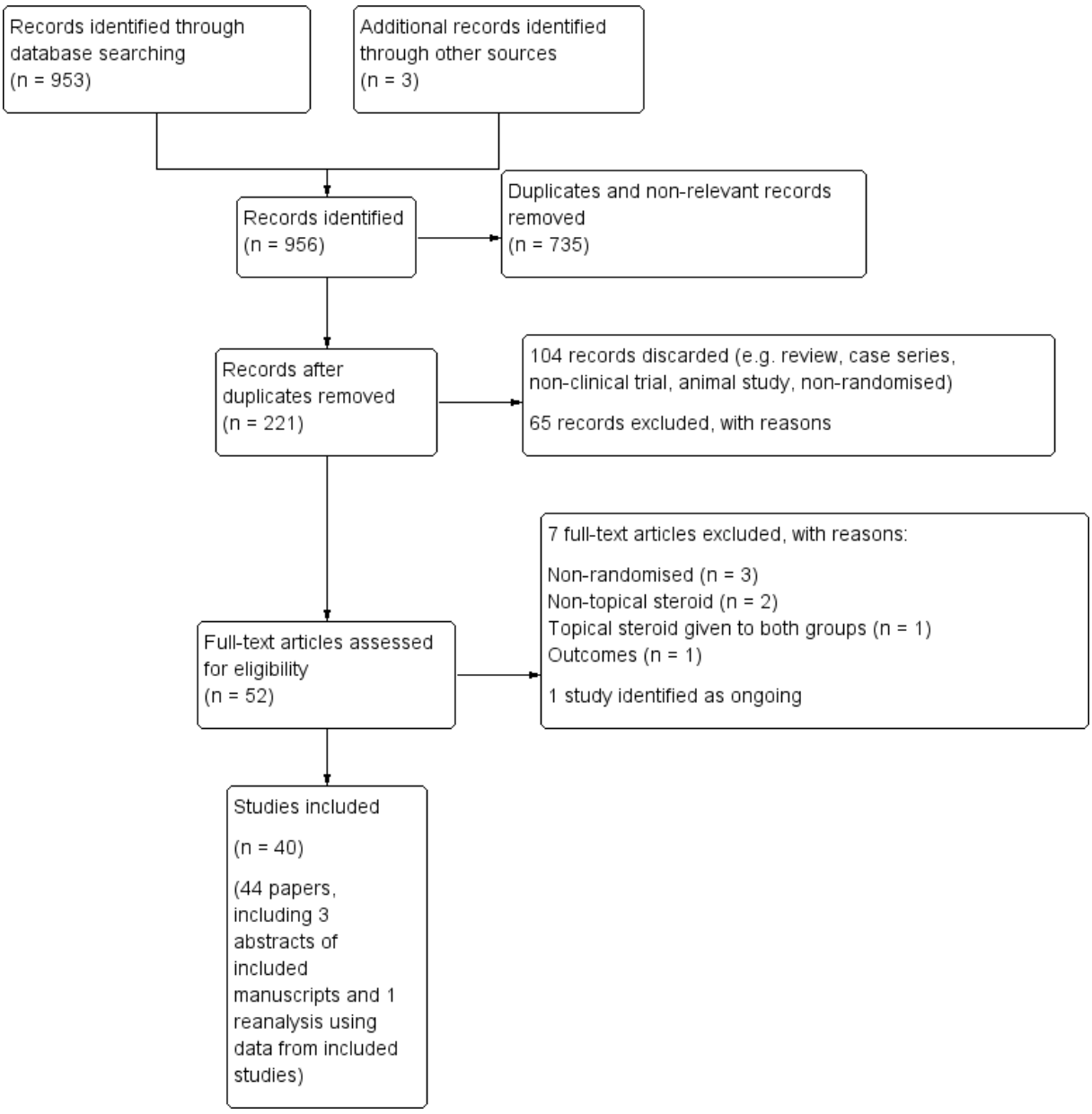


Figure 7.1 Search history flow diagram

Of the 40 included studies, 36 (90%) compared topical steroid against placebo (Aukema, Mulder et al 2005; Bross-Soriano, Arrieta-Gomez et al 2004; Chalton, Mackay et al 1985; Chur, Small et al 2010; Dijkstra, Ebbens et al 2004; Dingsor, Kramer et al 1985; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Keith, Nieminen et al 2000; Lang and McNeill 1983; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Olsson, Ehnhage et al 2010; Passali, Bernstein et al 2003; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009). Among these, nine trials also compared a low dose to a high dose of topical steroid (Chur, Small et al 2010; Dijkstra, Ebbens et al 2004; Filiaci, Passali et al 2000; Jankowski, Schrewelius et al 2001; Lildholdt, Rundcrantz et al 1995; Penttila, Poulsen et al 2000; Small, Hernandez et al 2005; Stjarne, Blomgren et al 2006; Tos, Svendstrup et al 1998) and three trials also compared two steroid agents, fluticasone propionate and beclomethasone dipropionate (Bross-Soriano, Arrieta-Gomez et al 2004; Holmberg, Juliusson et al 1997; Lund, Flood et al 1998).

Four trials (10%) compared topical steroid against no intervention (El Naggar, Kale et al 1995; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Karlsson and Rundcrantz 1982; Rotenberg, Zhang et al 2011).

Twenty-one (52.5%) included studies were fully or partially sponsored by pharmaceutical companies: GlaxoSmithKline (Aukema, Mulder et al 2005; Dijkstra, Ebbens et al 2004; Ehnhage, Olsson et al 2009; Holmberg, Juliusson et al 1997; Keith, Nieminen et al 2000; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Olsson, Ehnhage et al 2010; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005), AstraZeneca (Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Ruhno, Andersson et al 1990; Tos, Svendstrup et al 1998), Rhone-Poulenc Rorer (Vento, Blomgren et al 2012) and Schering Plough (Jorissen and Bachert 2009; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009). The inclusion criteria for these studies and the overall quality of the studies did not vary significantly from the studies which were not sponsored by industry.

Dealing with missing data

We asked the trial authors to provide raw data for any trials containing mixed populations of polyps and non-polyps patients. This was provided for one trial (Jorissen and Bachert 2009). For other missing data, all authors contacted were unable to provide the data (Aukema, Mulder et al 2005; Dijkstra, Ebbens et al 2004; Ehnhage, Olsson et al 2009; Holmström 1999; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Lildholdt, Rundcrantz et

al 1995; Lund, Flood et al 1998; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009). For missing standard deviations, we used standard error (Aukema, Mulder et al 2005; Hartwig, Linden et al 1988; Holmström 1999; Holopainen, Grahne et al 1982; Johansson, Holmberg et al 2002; Mastalerz, Milewski et al 1997; Vlckova, Navrátil et al 2009), 95% confidence intervals (CIs) (Filiaci, Passali et al 2000; Jankowski, Schrewelius et al 2001), range (Ehnhage, Olsson et al 2009) and interquartile ranges (Ehnhage, Olsson et al 2009) for estimation to impute standard deviations. We did not convert standard deviations from P values for differences in mean because P values in the applicable studies were not obtained from t tests or they were reported as non-significant.

For missing means, we converted from medians (Ehnhage, Olsson et al 2009). We calculated the correlation coefficient in the experimental and control groups from Jorissen and Bachert 2009 (for change in symptom scores) and Ehnhage, Olsson et al 2009 (for change in obstruction scores) and used this to calculate the imputation of standard deviation of change in symptom scores for three studies (Holopainen, Grahne et al 1982; Johansson, Holmberg et al 2002; Mastalerz, Milewski et al 1997) and change in obstruction scores for five studies (Aukema, Mulder et al 2005; Dingsor, Kramer et al 1985; Hartwig, Linden et al 1988; Keith, Nieminen et al 2000; Ruhno, Andersson et al 1990).

Participants

There were 3624 participants in total in the 40 included studies. The mean age of the patients was 48.2 years and 64.3% were men. All studies included patients over the age of 18 years.

Sinus surgery status

1. In 26 studies (65%) all or the majority of participants had sinus surgery (Aukema, Mulder et al 2005; Bross-Soriano, Arrieta-Gomez et al 2004; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; El Naggar, Kale et al 1995; Hartwig, Linden et al 1988; Holmberg, Juliusson et al 1997; Holopainen, Grahne et al 1982; Jorissen and Bachert 2009; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Karlsson and Rundcrantz 1982; Keith, Nieminen et al 2000; Lund, Flood et al 1998; Mygind, Pedersen et al 1975; Olsson, Ehnhage et al 2010; Passali, Bernstein et al 2003; Penttila, Poulsen et al 2000; Rotenberg, Zhang et al 2011; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009).

2. In 14 studies included in the above group, the topical steroid was given immediately after sinus surgery, however in the rest of the studies sinus surgery had been performed in the majority of patients but the extent of the surgery and the timing was not always clear.

3. In 14 studies (35%), all or the majority of participants had not had sinus surgery (Chalton, Mackay et al 1985; Chur, Small et al 2010; Filiaci, Passali et al 2000; Holmström 1999; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009;

Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Lang and McNeill 1983; Lildholdt, Rundcrantz et al 1995; Mastalerz, Milewski et al 1997; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006).

Polyp size

1. In seven studies (17.5%) the patient group only had small to medium-size polyps (Holmström 1999; Holopainen, Grahne et al 1982; Johansen, Illum et al 1993; Keith, Nieminen et al 2000; Lang and McNeill 1983; Penttila, Poulsen et al 2000; Vlckova, Navrátil et al 2009).

2. In four studies (10%) all the patients had medium to large-size polyps (Karlsson and Rundcrantz 1982; Mygind, Pedersen et al 1975; Passali, Bernstein et al 2003; Tos, Svendstrup et al 1998).

3. Twenty-nine (72.5%) trials studied polyps of all sizes.

Interventions

Steroid agent

The steroid agents used were different across the studies.

1. Fluticasone propionate was studied in 15 trials (Aukema, Mulder et al 2005; Bross-Soriano, Arrieta-Gomez et al 2004; Dijkstra, Ebbens et al 2004; Ehnhage, Olsson et al 2009; Holmberg, Juliusson et al 1997; Holmström 1999; Jankowski, Klossek et al 2009; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Keith, Nieminen et al 2000; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Olsson, Ehnhage et al

2010; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005; Vlckova, Navrátil et al 2009).

2. Beclomethasone dipropionate was studied in seven trials (Bross-Soriano, Arrieta-Gomez et al 2004; El Naggar, Kale et al 1995; Holmberg, Juliusson et al 1997; Lund, Flood et al 1998; Karlsson and Rundcrantz 1982; Lang and McNeill 1983; Mygind, Pedersen et al 1975).

3. Betamethasone sodium phospate was studied in one trial (Chalton, Mackay et al 1985).

4. Mometasone furoate was studied in seven trials (Chur, Small et al 2010; Jorissen and Bachert 2009; Passali, Bernstein et al 2003; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009).

5. Flunisolide was studied in two trials (Dingsor, Kramer et al 1985; Drettner, Ebbesen et al 1982).

6. Budesonide was studied in nine trials (Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Lildholdt, Rundcrantz et al 1995; Rotenberg, Zhang et al 2011; Ruhno, Andersson et al 1990; Tos, Svendstrup et al 1998).

7. Triamcinolone acetonide was studied in one trial (Vento, Blomgren et al 2012).

Topical delivery method

Steroid agents were administered by various topical delivery methods.

1. Nasal sprays (low volume) in 28 trials (Bross-Soriano, Arrieta-Gomez et al 2004; Chur, Small et al 2010; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; El Naggar, Kale et al 1995; Holmberg, Juliusson et al 1997; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Lang and McNeill 1983; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Passali, Bernstein et al 2003; Rotenberg, Zhang et al 2011; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vlckova, Navrátil et al 2009).

2. Nasal drops (low volume) in seven trials (Aukema, Mulder et al 2005; Chalton, Mackay et al 1985; Ehnhage, Olsson et al 2009; Holmström 1999; Keith, Nieminen et al 2000; Olsson, Ehnhage et al 2010; Penttila, Poulsen et al 2000).

3. Nasal aerosols (low volume) in four trials (Hartwig, Linden et al 1988; Johansen, Illum et al 1993; Mygind, Pedersen et al 1975; Vento, Blomgren et al 2012).

4. Turbuhaler (low volume) in three trials (Filiaci, Passali et al 2000; Lildholdt, Rundcrantz et al 1995; Tos, Svendstrup et al 1998).

5. Nasal irrigation (high pressure and low volume) in one trial (Rotenberg, Zhang et al 2011).

One study (Karlsson and Rundcrantz 1982) used the term "intranasal" without clearly stating the delivery method used.

Outcomes

Primary outcomes

Symptoms

Thirty-three studies (82.5%) reported symptoms as an outcome (Aukema, Mulder et al 2005; Chur, Small et al 2010; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Keith, Nieminen et al 2000; Lang and McNeill 1983; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009). Symptoms were reported in different ways across studies, such as change in overall symptom scores, overall symptom scores, individual symptom scores and proportion of responders for particular symptoms (proportion of patients whose symptoms improved).

Polyp size

Thirty studies (75%) reported polyp size (Aukema, Mulder et al 2005; Chalton, Mackay et al 1985; Chur, Small et al 2010; Dingsor, Kramer et al 1985; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Karlsson and Rundcrantz 1982; Keith, Nieminen et al 2000; Lang and McNeill 1983; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mygind, Pedersen et al 1975; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009). These were reported as either change in polyp score, final score at a defined endpoint or proportion of responders (proportion of patients who had a reduction in polyp size).

Polyp recurrence

Six studies (16%) reported polyp recurrence after sinus surgery (Bross-Soriano, Arrieta-Gomez et al 2004; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; Passali, Bernstein et al 2003; Stjarne, Olsson et al 2009) with follow-up varying from three months to six years.

Secondary outcomes

Change in nasal endoscopic findings

Most studies reported polyp size as the main nasal endoscopic findings. Few studies reported other findings such as oedema and discharge.

Change in radiological appearance

Four studies (10%) reported change in radiographs (Aukema, Mulder et al 2005; Dingsor, Kramer et al 1985; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Rotenberg, Zhang et al 2011).

Change in nasal airflow

Twenty-four studies (60%) reported change in nasal airflow (Aukema, Mulder et al 2005; Chalton, Mackay et al 1985; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Keith, Nieminen et al 2000; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Penttila, Poulsen et al 2000; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009). The outcomes reported were peak nasal inspiratory flow, peak expiratory flow, rhinomanometry, acoustic rhinometry and the proportion of responders (proportion of patients who had an improvement in airflow).

Change in smell

Fifteen studies (37.5%) reported smell function (Chur, Small et al 2010; Ehnhage, Olsson et al 2009; El Naggar, Kale et al 1995; Holmström 1999; Johansen, Illum et al 1993; Keith, Nieminen et al 2000; Lildholdt, Rundcrantz et al 1995; Penttila, Poulsen et al 2000; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998;

Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009). The outcomes reported included the University of Pennsylvania Smell Identification Test (UPSIT), butanol olfactory threshold test or patients' self assessment score.

Quality of life outcomes

Two studies (5%) reported disease-specific quality of life (SNOT-21) (Rotenberg, Zhang et al 2011) and health-related quality of life (SF36) (Olsson, Ehnhage et al 2010).

Drop-outs

Thirty-seven studies (92.5%) reported drop-outs (Aukema, Mulder et al 2005; Bross-Soriano, Arrieta-Gomez et al 2004; Chalton, Mackay et al 1985; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; Ehnhage, Olsson et al 2009; El Naggar, Kale et al 1995; Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Karlsson and Rundcrantz 1982; Keith, Nieminen et al 2000; Lang and McNeill 1983; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Olsson, Ehnhage et al 2010; Penttila, Poulsen et al 2000; Rotenberg, Zhang et al 2011; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009).

Adverse effects

Twenty-seven studies (67.5%) reported adverse events (Chur, Small et al 2010; Dingsor, Kramer et al 1985;Dijkstra, Ebbens et al 2004; Drettner, Ebbesen et al 1982; El Naggar, Kale et al 1995; Filiaci, Passali et al 2000; Hartwig, Linden et al 1988; Holmström 1999; Holopainen, Grahne et al 1982; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Jorissen and Bachert 2009; Keith, Nieminen et al 2000; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Mygind, Pedersen et al 1975; Penttila, Poulsen et al 2000; Rotenberg, Zhang et al 2011; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012; Vlckova, Navrátil et al 2009).

Excluded studies

The majority of the 956 abstracts retrieved from the searches did not focus on the use of topical steroid in CRS with polyps. Of the 221 studies initially identified, 86 studies were reviews, guidelines, case series, non-clinical trials or animal studies. Among the 83 excluded studies, 26 were not randomised nor controlled. The study populations of nine studies did not have CRS with polyps. One trial studied patients with cystic fibrosis. Topical steroid was not the primary study medication in 21 trials. Fourteen studies failed to compare topical steroid to either placebo or no intervention. Twelve studies reported non-clinical efficacy outcomes such as inflammatory mediators or immunohistochemistry.

Risk of bias in included studies

See Table 7.2 (Appendix 7.2) Characteristics of included studies. Our judgements about each risk of bias item are presented as percentages across all the included studies and shown in Figure 7.2 with each 'Risk of bias' item in the individual included studies shown in Figure 7.3. Generally, the included studies had low risk of bias for blinding and incomplete outcome data, medium risk of bias for selective reporting and unclear risk of bias for allocation. The trials were of low (21 trials), medium (13 trials) and high (six trials) risk of bias.

Allocation (selection bias)

Most studies provided insufficient information about the sequence generation process and how investigators could not foresee assignment.

Blinding (performance bias and detection bias)

Most studies blinded both patients and investigators and described study medications as being identical in appearance. Blinding was not performed in studies comparing topical steroid with no intervention.

Incomplete outcome data (attrition bias)

Most studies had a low risk of bias due to either intention-to-treat analysis or the number of missing patients not being large enough to change the effects.

Selective reporting (reporting bias)

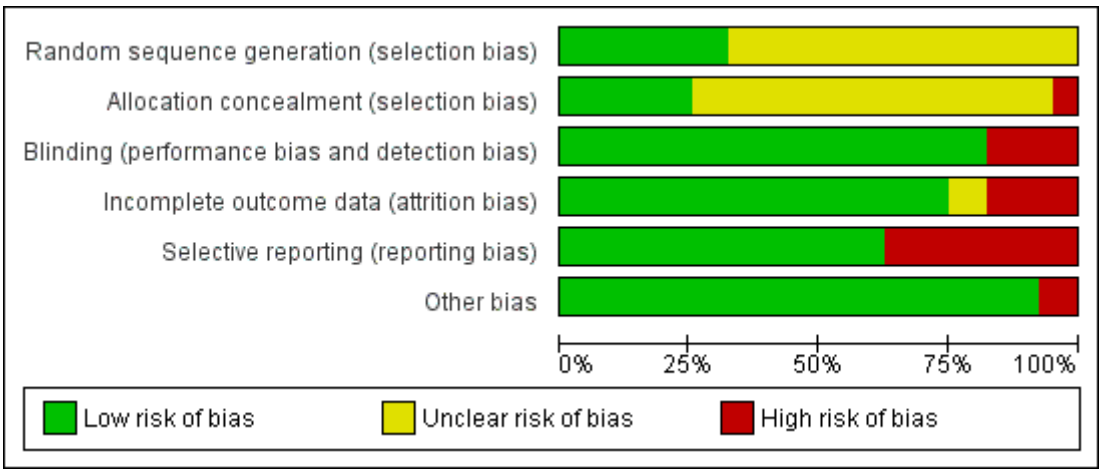


Figure 7.2 Risk of bias graph

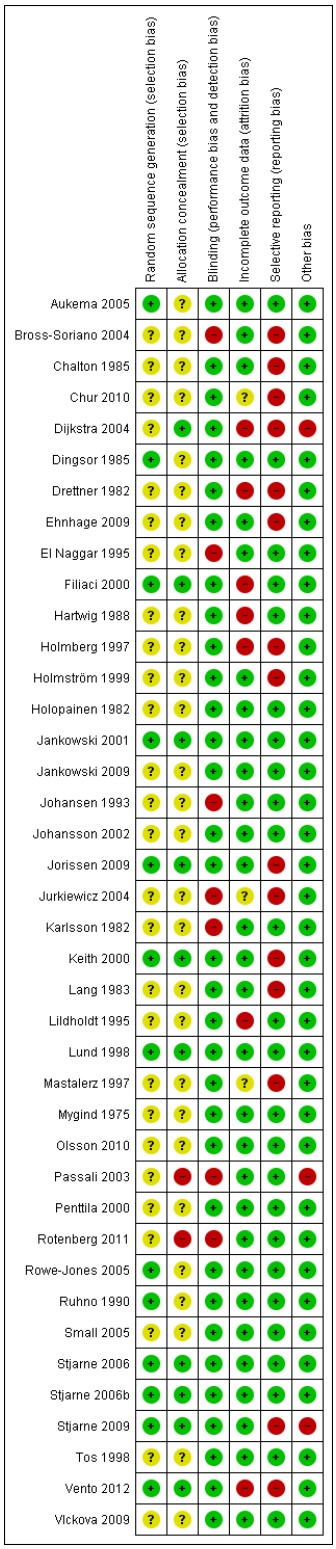


Figure 7.3 Risk of bias summary

About two-thirds of the studies were free of selective reporting. Some pre-specified outcomes were incompletely reported.

Other potential sources of bias

Twenty-one (52.5%) included studies (Aukema, Mulder et al 2005; Dijkstra, Ebbens et al 2004; Ehnhage, Olsson et al 2009; Holmberg, Juliusson et al 1997; Johansen, Illum et al 1993; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Keith, Nieminen et al 2000; Lund, Flood et al 1998; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Olsson, Ehnhage et al 2010; Penttila, Poulsen et al 2000; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012) were fully or partially sponsored by pharmaceutical companies. However, this issue may not affect study quality if the study authors have full authority for publication.

Effects of interventions

1. Topical steroid versus placebo

Symptoms

In the following studies, the data for combined symptoms could not be included in the meta-analysis because the numeric scores for combined symptoms were not provided (Aukema, Mulder et al 2005; Chur, Small et al 2010; Dingsor, Kramer et al 1985; Ehnhage, Olsson et al 2009; Hartwig, Linden et al 1988; Holmström 1999; Jankowski, Klossek et al 2009; Keith, Nieminen et al 2000; Lang and McNeill 1983; Ruhno, Andersson et al 1990 Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009; Vento, Blomgren et al 2012), the standard deviation was not provided or could

not be imputed (Drettner, Ebbesen et al 1982; Jankowski, Schrewelius et al 2001; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Rowe-Jones, Medcalf et al 2005; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Tos, Svendstrup et al 1998), the number of participants per arm was not given (Johansen, Illum et al 1993) or the symptoms were reported at two weeks and not at the endpoint of one year (Dijkstra, Ebbens et al 2004).

In the following studies, the data for nasal obstruction could not be included in the meta-analysis because the numeric scores for nasal obstruction were not provided (Holmberg, Juliusson et al 1997; Holmström 1999; Holopainen, Grahne et al 1982; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Lang and McNeill 1983; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Rowe-Jones, Medcalf et al 2005; Ruhno, Andersson et al 1990; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009) or the standard deviation was not provided or could not be imputed (Filiaci, Passali et al 2000; Jankowski, Schrewelius et al 2001; Jankowski, Klossek et al 2009; Johansen, Illum et al 1993; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006).

Overall symptom scores

Data addressing the change in combined symptom scores were available from seven studies (Filiaci, Passali et al 2000; Holopainen, Grahne et al 1982; Johansson, Holmberg et al 2002; Jorissen and Bachert 2009; Mastalerz, Milewski et al 1997; Mygind, Pedersen et al 1975; Vlckova, Navrátil et al 2009) and could be combined in

the meta-analysis. The pooled results significantly favoured the topical steroid group (standardised mean difference (SMD) -0.46; 95% confidence interval (CI) -0.65 to -0.27, P < 0.00001; seven trials, 445 patients) (Figure 7.4). The confidence intervals for the results of individual studies have poor overlap. Although the overall effect favours the topical steroid, it is not significant for three studies (Holopainen, Grahne et al 1982; Jorissen and Bachert 2009; Mastalerz, Milewski et al 1997). The I2 of74% represents substantial heterogeneity. These seven studies have both clinical diversity for various surgical status and delivery methods and methodological diversity for various risks of bias (see Appendix 7.2 Characteristics of included studies). We performed subgroup analysis to investigate this statistical diversity.

Subgroup analysis: patients with sinus surgery versus without sinus surgery

We found no significant difference when we compared studies including a majority of patients who had previous sinus surgery (SMD -0.32; 95% CI -0.58 to -0.07) and those without a history of sinus surgery (SMD -0.64; 95% CI -0.93 to -0.35) (P = 0.11) (Figure 7.5). The I2 in the 'patients with sinus surgery subgroup' of 82% still represents substantial heterogeneity. Four studies used four different steroid agents: budesonide (Holopainen, Grahne et al 1982), mometasone furoate (Jorissen and Bachert 2009), beclomethasone (Mygind, Pedersen et al 1975) and fluticasone propionate (Vlckova, Navrátil et al 2009). Aerosol was used for Mygind, Pedersen et al 1975 while others used nasal spray.

The I2 in the 'patients without sinus surgery subgroup' of 49% represents moderate heterogeneity. Filiaci, Passali et al 2000 used budesonide

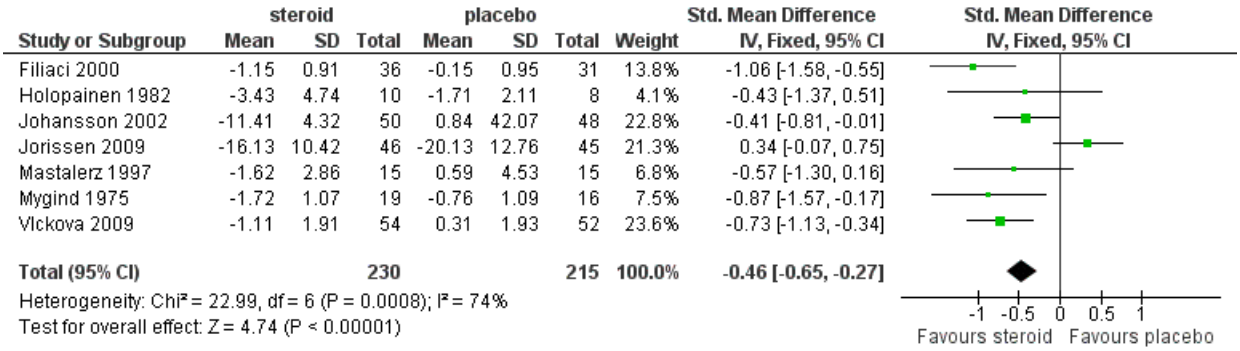


Figure 7.4 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores

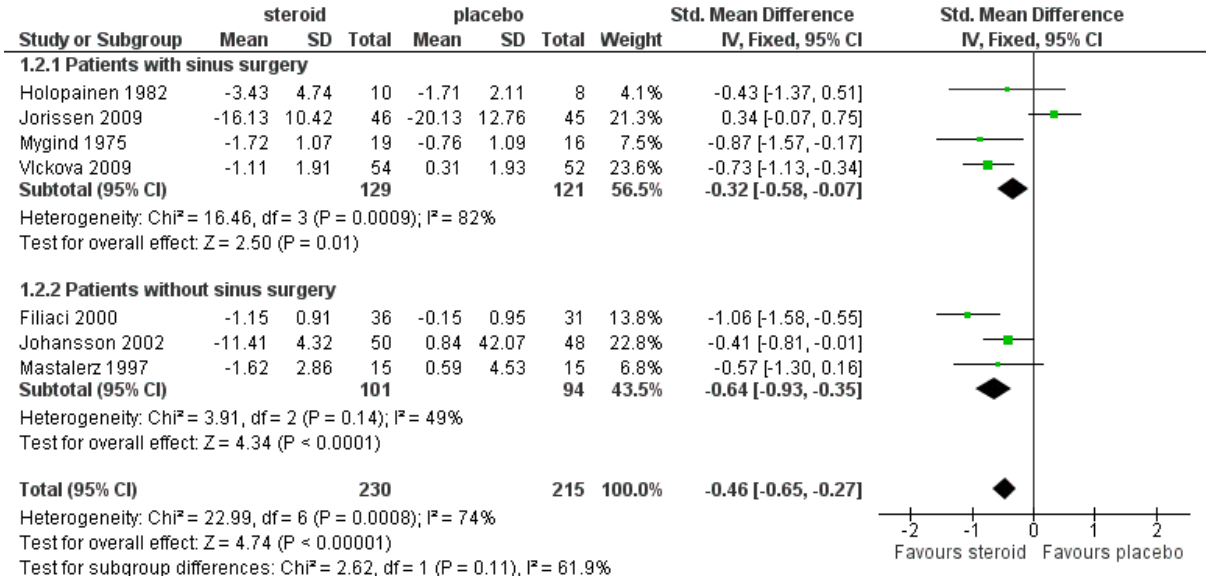


Figure 7.5 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by sinus surgery

turbuhaler while Johansson, Holmberg et al 2002 used budesonide spray and Mastalerz, Milewski et al 1997 used fluticasone propionate spray. The risk of bias is low for Filiaci, Passali et al 2000, medium for Johansson, Holmberg et al 2002 and high for Mastalerz, Milewski et al 1997.

Subgroup analysis: topical delivery methods

When we performed subgroup analyses we found that although nasal steroid spray was effective, its effect (SMD -0.32; 95% CI -0.53 to -0.10) was significantly smaller than nasal aerosol (SMD -0.87; 95% CI -1.57 to -0.17) (P = 0.002) and turbuhaler (SMD -1.06; 95% CI -1.58 to -0.55) (P = 0.004). Although it must be noted that there was only one trial for analysis in each of the nasal aerosol and turbuhaler groups (Figure 7.6) The I2 in the nasal spray subgroup of 82% still represents substantial heterogeneity. Studies are diverse in terms of sinus surgery status, steroid agent used and risk of bias. Holopainen, Grahne et al 1982, Jorissen and Bachert 2009 and Vlckova, Navrátil et al 2009 studied patients with sinus surgery while Johansson, Holmberg et al 2002 and Mastalerz, Milewski et al 1997 studied patients without sinus surgery.

Subgroup analysis by polyp severity

When we performed subgroup analyses we found that studies only including patients with large-size polyps (SMD -0.87; 95% CI -1.57 to -0.17) have a greater symptom improvement response than studies with patients with small polyps only (SMD -0.69; 95% CI -1.05 to -0.33) (P = 0.0007) and studies including all polyp sizes (SMD -0.32; 95% CI -0.56 to -0.08) (P = 0.03) (Figure 7.7). There is no heterogeneity in

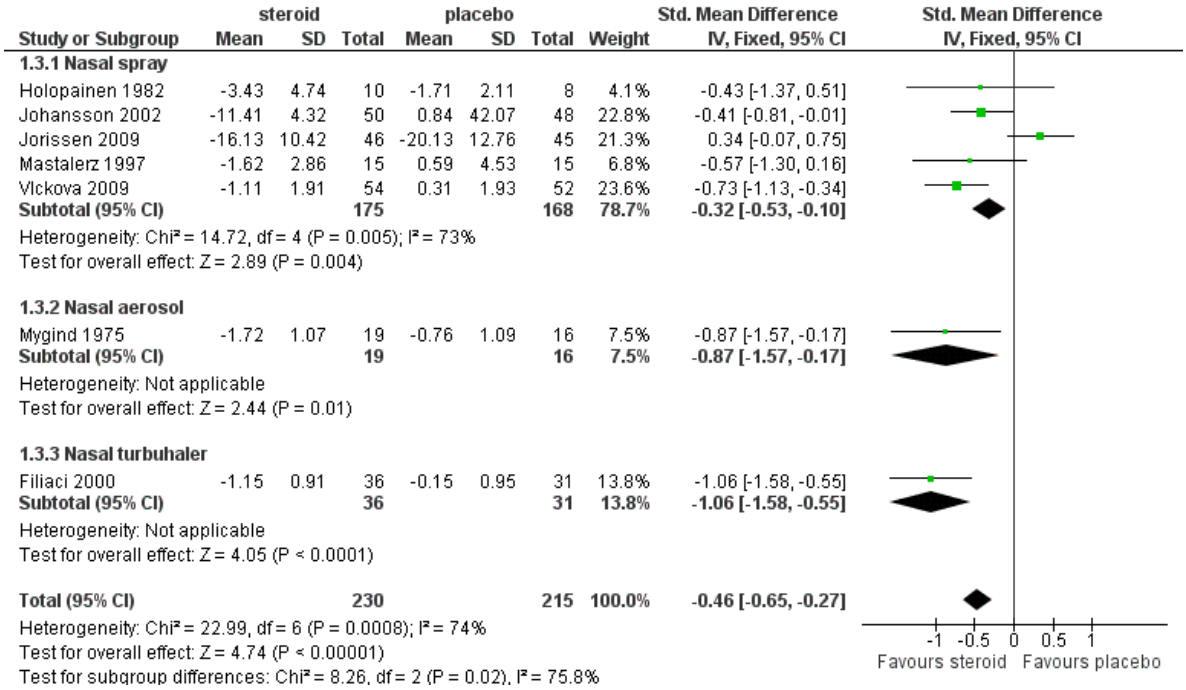


Figure 7.6 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by topical delivery methods

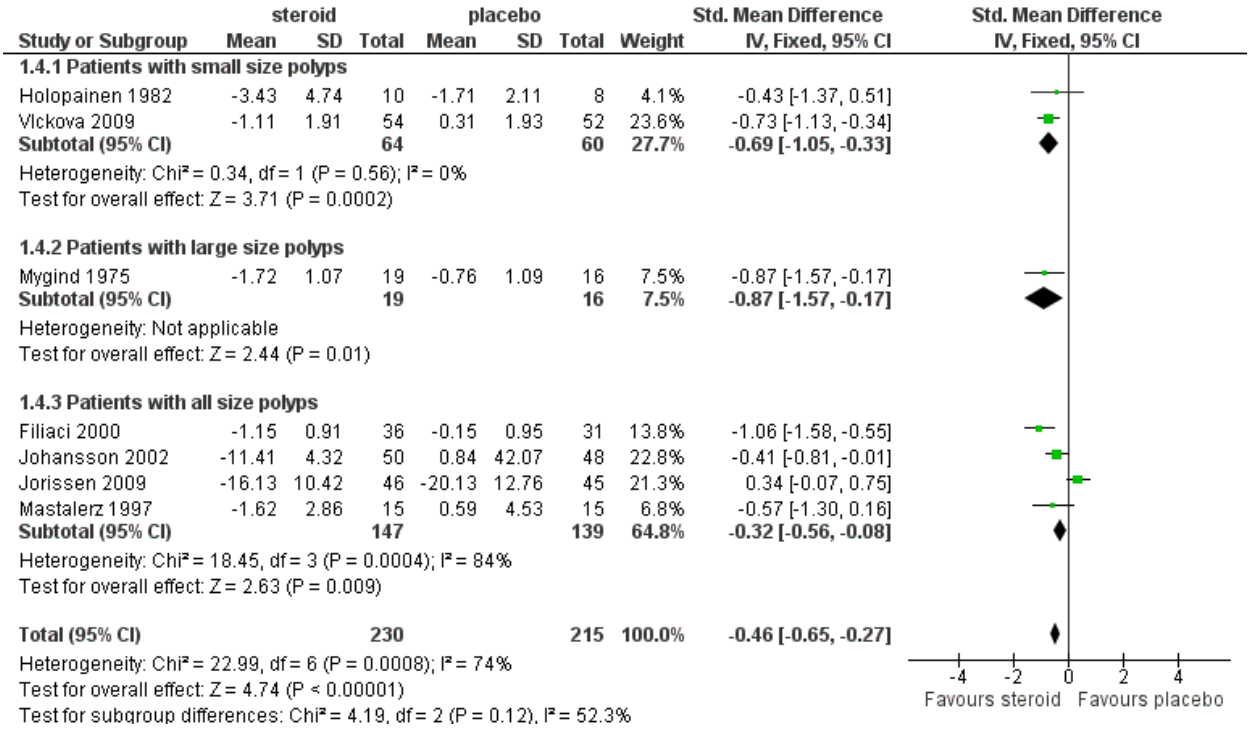


Figure 7.7 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by polyp severity

subgroups studying small-size and large-size polyps, whereas the subgroup studying all size polyps has substantial heterogeneity with an I2 of 84%. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias. Jorissen and Bachert 2009 studied patients with sinus surgery while Filiaci, Passali et al 2000, Johansson, Holmberg et al 2002 and Mastalerz, Milewski et al 1997 studied patients without sinus surgery.

Subgroup analysis by steroid agent

When we performed subgroup analyses we found that there was significant heterogeneity between the studies of different steroid agents, such as polyp severity, surgical state and product delivery. A meaningful meta-analysis was not applicable (Figure 7.8).

Subgroup analysis by quality of studies

We found no significant difference when we compared studies with high quality (SMD -0.45; 95% CI -0.65 to -0.26) and studies with low quality (SMD -0.57; 95% CI -1.30 to 0.16) (P = 0.77) (Figure 7.9).

Proportion of patients with overall improvement in symptoms (responders)

Data addressing the proportion of patients who showed improvement in symptoms (responders) were available from four studies (Filiaci, Passali et al 2000; Holmberg, Juliusson et al 1997; Mygind, Pedersen et al 1975; Penttila, Poulsen et al 2000). The pooled results significantly favoured the topical steroid group (risk ratio (RR) 1.71;95% CI 1.29 to 2.26, P = 0.0002; four trials, n = 234) (Figure 7.10). The I2 of 0% suggests this is a consistent result.

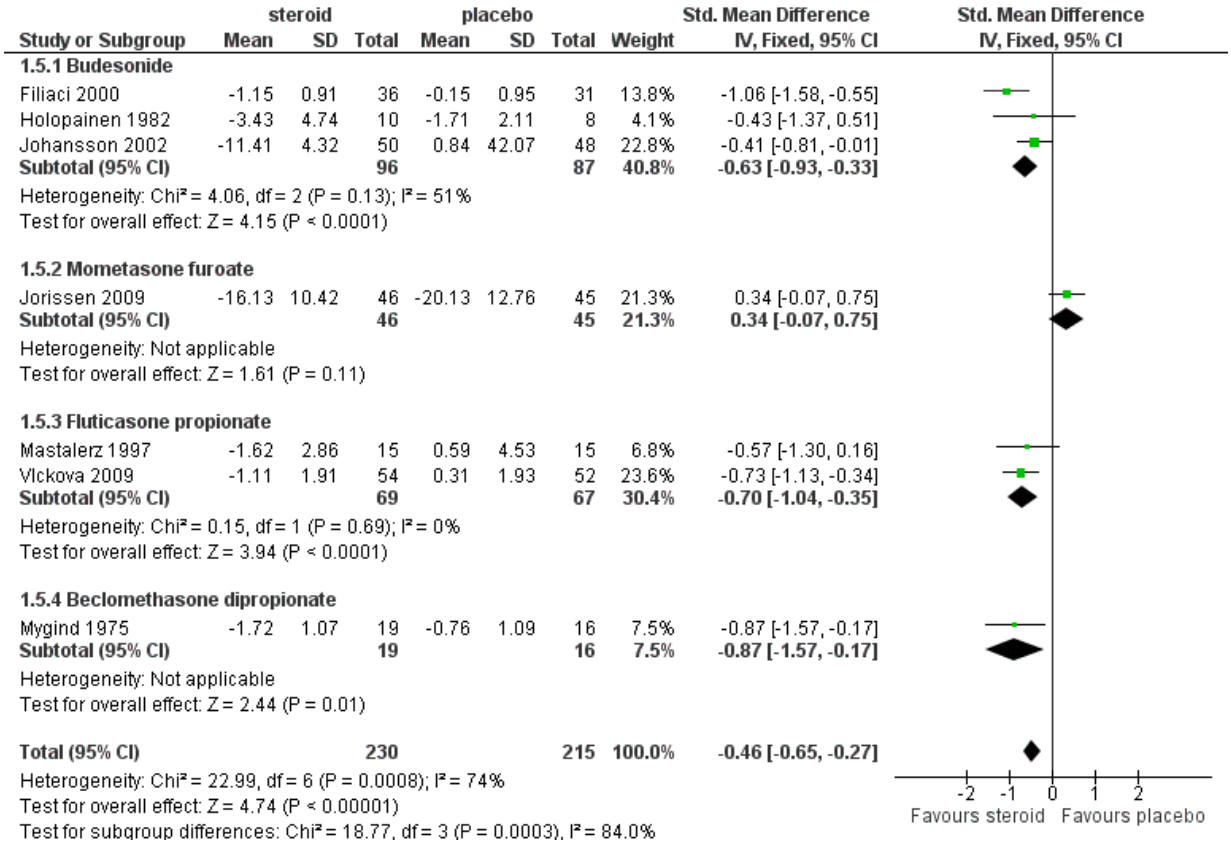


Figure 7.8 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by steroid agent

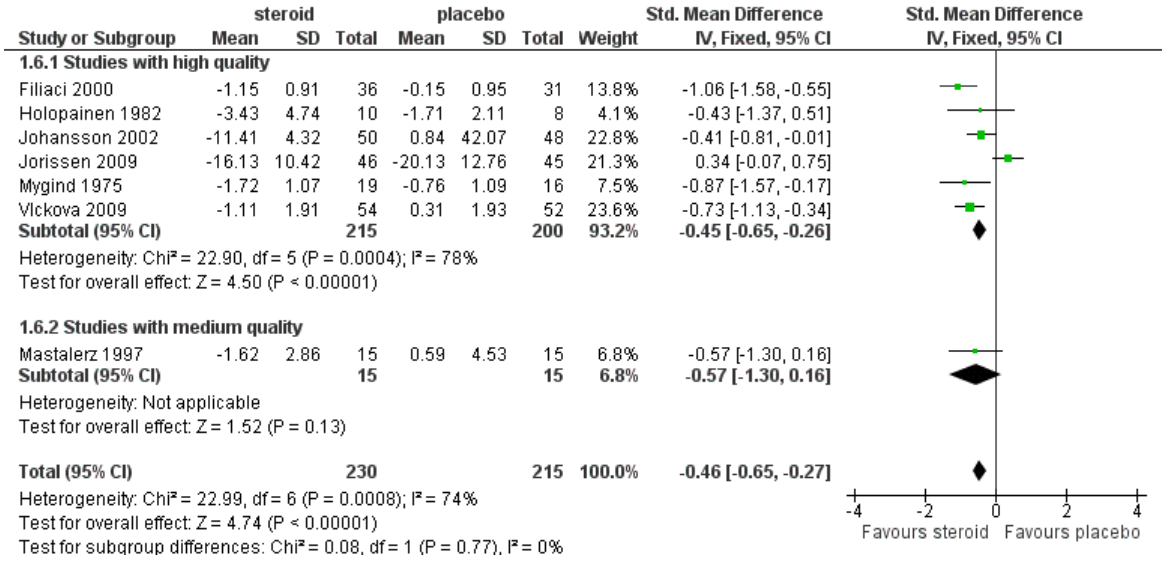


Figure 7.9 Forest plot of comparison: Topical steroids versus placebo, outcome: overall symptom scores by quality of studies

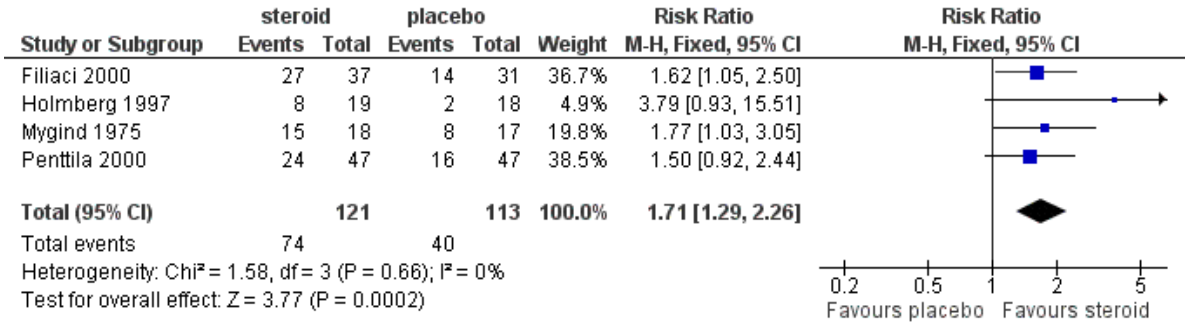


Figure 7.10 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders

Nasal obstruction

Change in nasal obstruction score

Data addressing the change in obstruction score were available from seven studies (Aukema, Mulder et al 2005; Dingsor, Kramer et al 1985; Ehnhage, Olsson et al 2009; Hartwig, Linden et al 1988; Keith, Nieminen et al 2000; Ruhno, Andersson et al 1990; Vlckova, Navrátil et al 2009). The pooled results significantly favoured the topical steroid group (SMD -0.81; 95% CI -1.01 to -0.62, P < 0.00001) (Figure 7.11). The I2 of 89% represents substantial heterogeneity. Studies are diverse in terms of topical delivery methods, steroid agent used and risk of bias.

Subgroup analysis: patients with versus those without sinus surgery

Subgroup analysis could not be performed because all seven studies included patients who had had previous surgery (Figure 7.12).

Subgroup analysis: topical delivery methods

We found no significant difference between nasal drops (SMD -1.00; 95% CI -1.28 to -0.71) and nasal sprays (SMD -0.90; 95% CI -1.21 to -0.59), whereas nasal aerosol showed a non-significant effect (SMD -0.16; 95% CI -0.62 to 0.30) (Figure 7.13).

Subgroup analysis by polyp severity

When we performed subgroup analyses we found that there was no difference (P = 0.26) between studies including patients with small-size polyps (SMD -0.94; 95% CI -1.23 to -0.65) and studies including all polyp sizes (SMD -0.71; 95% CI -0.97 to -0.46) (Figure 7.14).

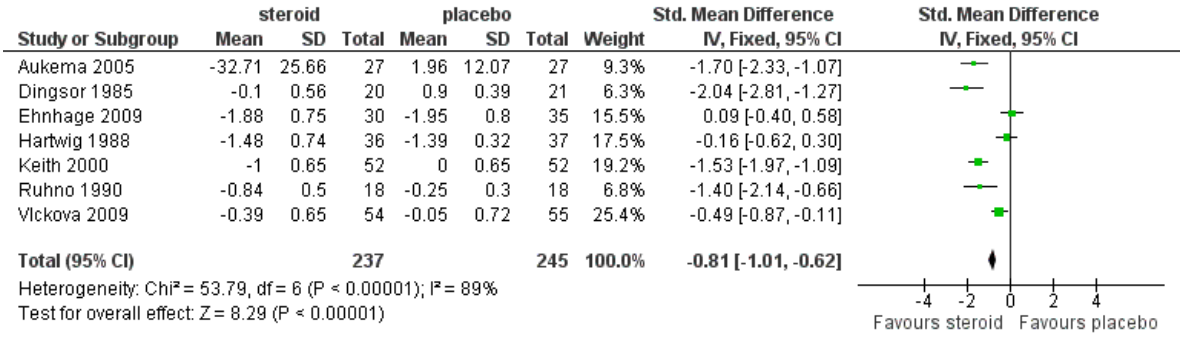


Figure 7.11 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score

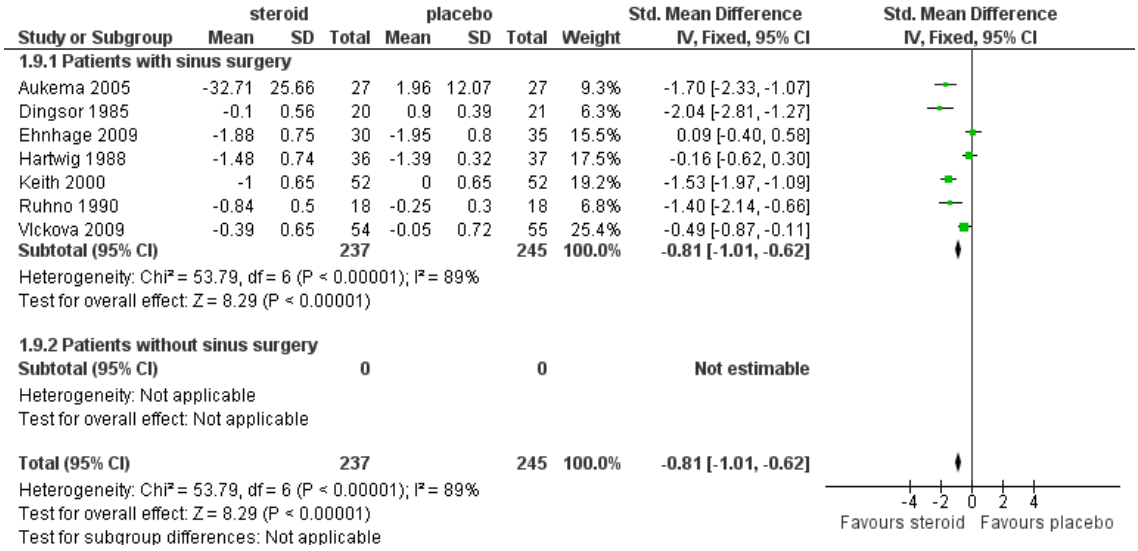


Figure 7.12 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by sinus surgery status

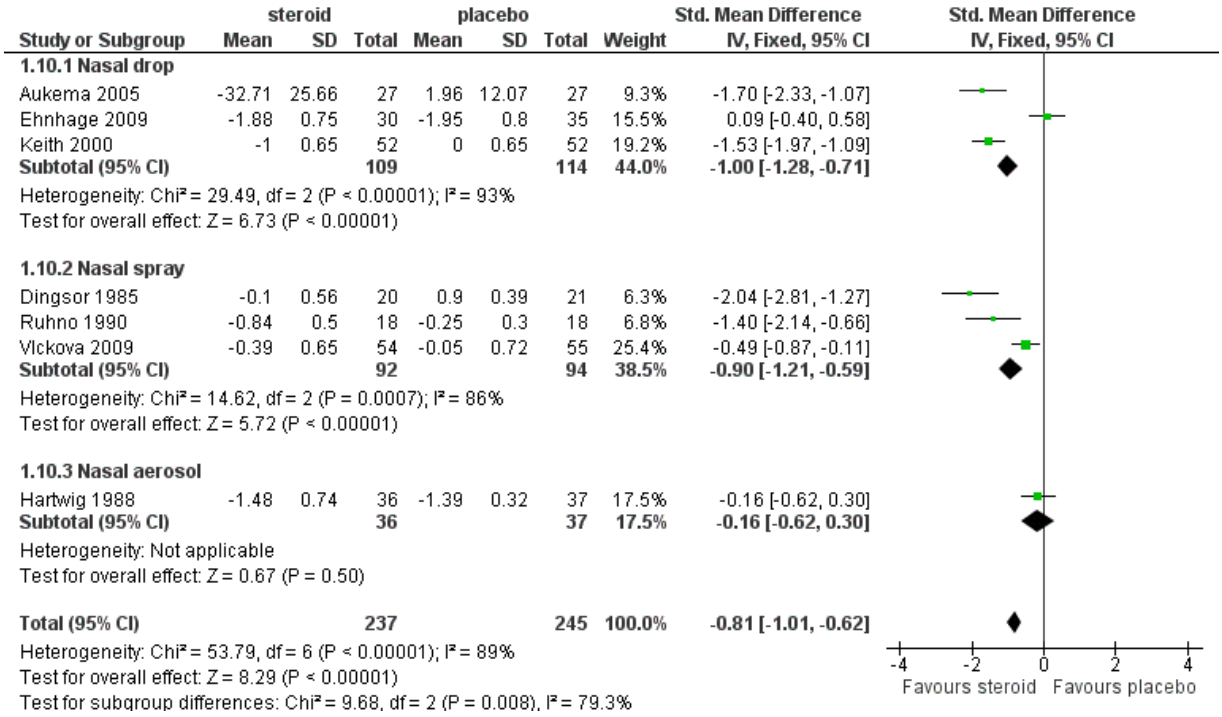


Figure 7.13 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by topical delivery method

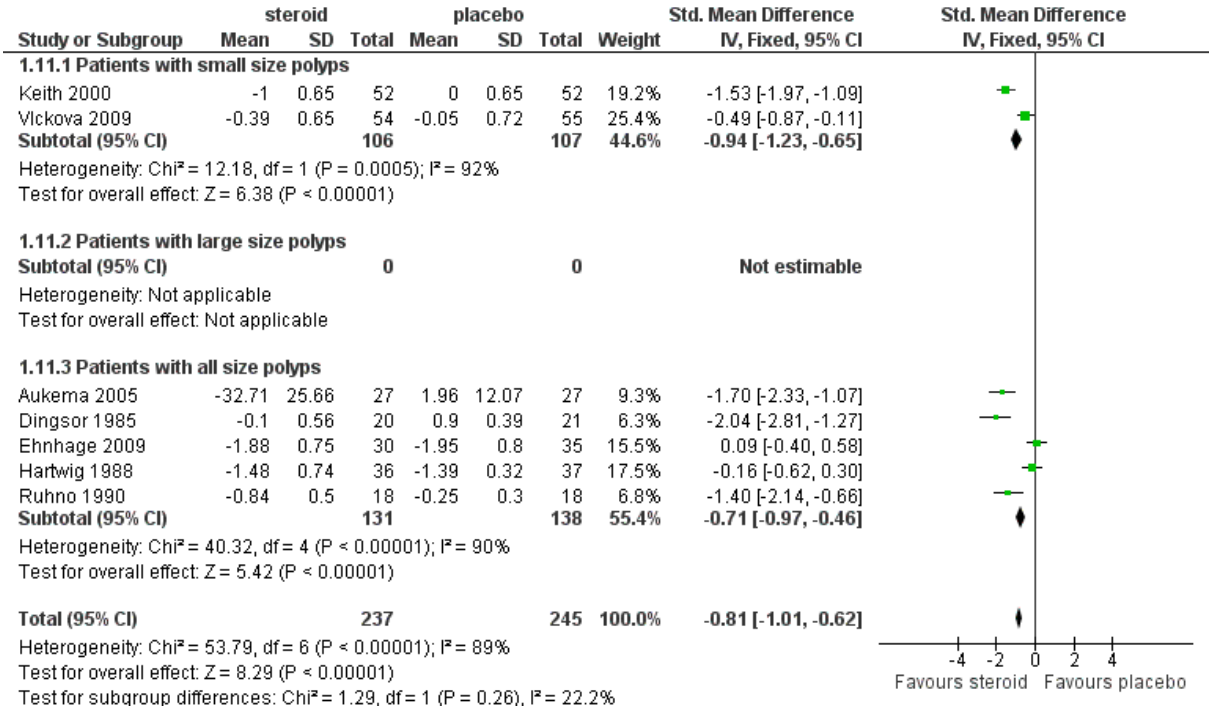


Figure 7.14 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by polyp severity

Subgroup analysis by steroid agent

We found the single study with flunisolide (SMD -2.04; 95% CI -2.81 to -1.27) had greater effects than the combined studies with fluticasone propionate (SMD -0.81; 95% CI -1.04 to -0.58) (P = 0.0003) and budesonide (SMD -0.50; 95% CI -0.89 to -0.11) (P = 0.0005) (Figure 7.15). The I2 values of 91% and 87% in the fluticasone propionate and budesonide subgroups, respectively, represent substantial heterogeneity. Studies are diverse in terms of topical delivery methods and risk of bias.

Subgroup analysis by quality of studies

We found that the effects significantly favoured the use of topical corticosteroids only in studies with high quality (SMD -1.19; 95% CI -1.43 to -0.96) but not in studies with medium quality (SMD -0.04; 95% CI -0.38 to 0.29) (P < 0.00001) (Figure 7.16). The I2 of 82% in the studies with high quality subgroup still represents substantial heterogeneity. While the I2 of 0% in the medium quality subgroup suggests that heterogeneity might not be important.

Proportion of patients with improvement in nasal obstruction (responders)

Data addressing the proportion of responders in nasal obstruction were available from five studies (Drettner, Ebbesen et al 1982; Keith, Nieminen et al 2000; Penttila, Poulsen et al 2000; Stjarne, Blomgren et al 2006; Stjarne, Olsson et al 2009). The pooled results significantly favoured the topical steroid group (RR 1.43; 95% CI 1.27 to 1.61, P < 0.00001) (Figure 7.17). The I2 of 91% represents substantial heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias. Drettner, Ebbesen et al 1982,

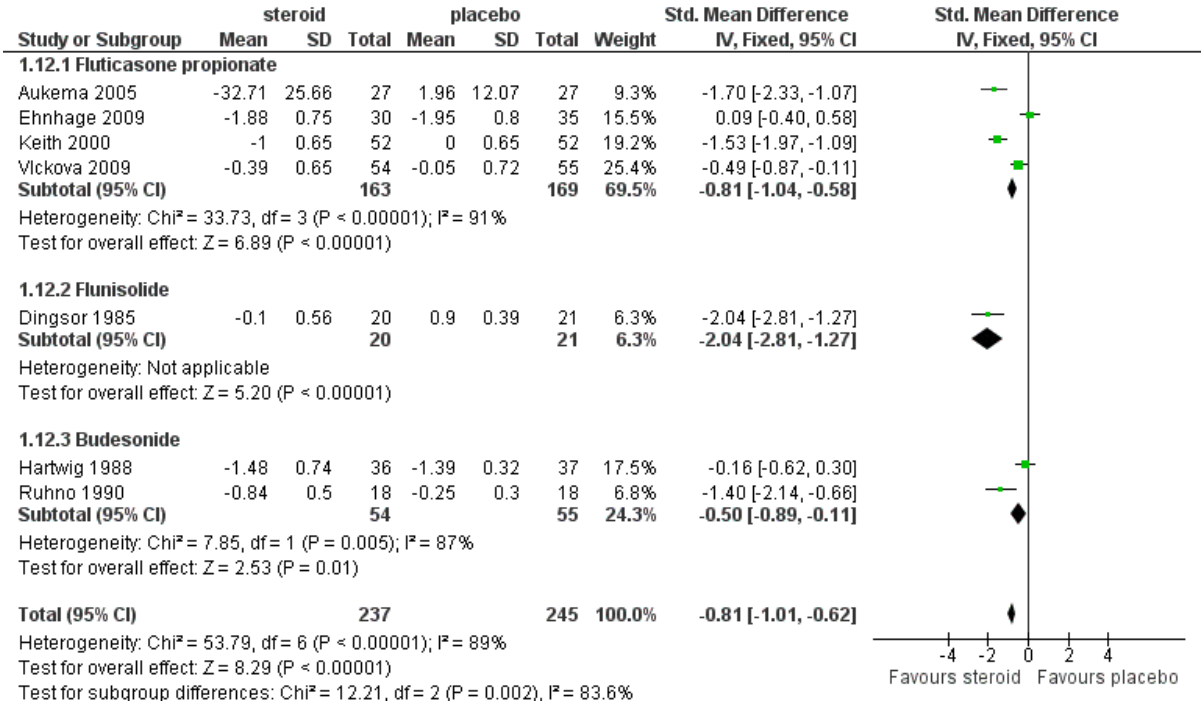


Figure 7.15 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by steroid agent

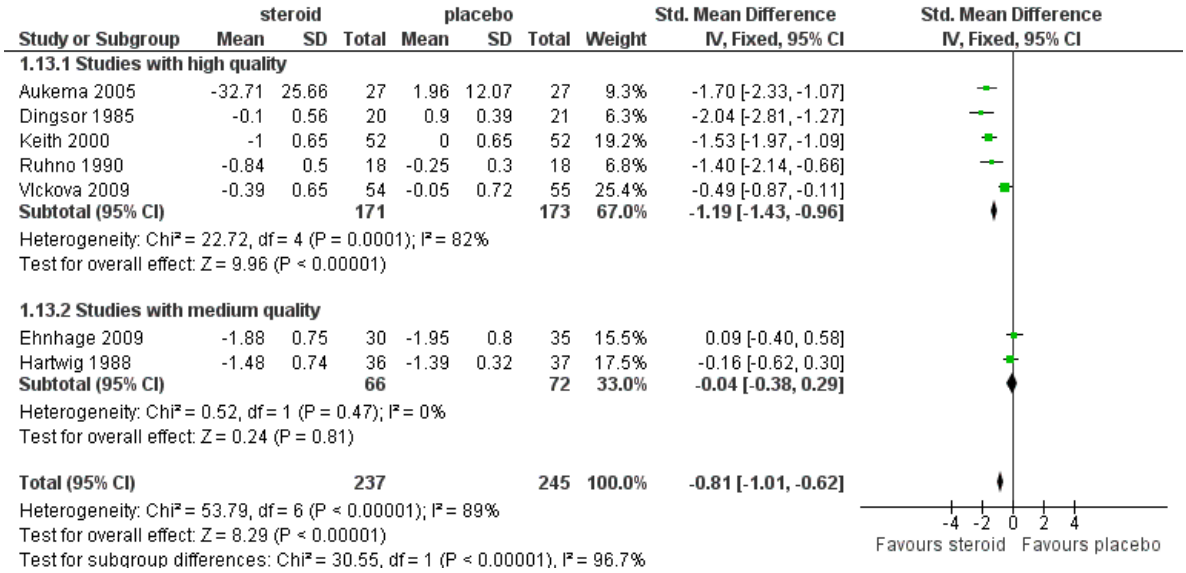


Figure 7.16 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal obstruction score by quality of studies

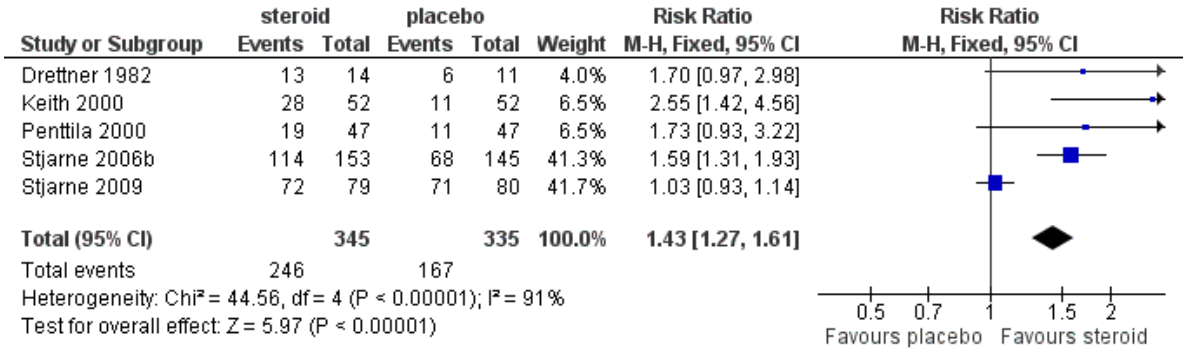


Figure 7.17 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders

Keith,Nieminen et al 2000, Penttila, Poulsen et al 2000 and Stjarne, Olsson et al 2009 studied patients with sinus surgery while Stjarne, Blomgren et al 2006 studied patients without sinus surgery.

Polyp size

In the following studies, the data could not be combined with the others because the numeric scores for polyp size were not provided (Aukema, Mulder et al 2005; Chur, Small et al 2010; Ehnhage, Olsson et al 2009; Holmberg, Juliusson et al 1997; Jankowski, Klossek et al 2009; Stjarne, Olsson et al 2009; Vento, Blomgren et al 2012), or the standard deviation was not provided or could not be imputed (Drettner, Ebbesen et al 1982; Filiaci, Passali et al 2000; Karlsson and Rundcrantz 1982; Lildholdt, Rundcrantz et al 1995; Lund, Flood et al 1998; Rowe-Jones, Medcalf et al 2005; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Tos, Svendstrup et al 1998) or the number of participants per arm was not given (Johansen, Illum et al 1993).

Polyp score

Data addressing the final value of the polyp score at the endpoint were available from three studies (Dingsor, Kramer et al 1985; Hartwig, Linden et al 1988; Johansson, Holmberg et al 2002) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.49; 95% CI -0.77 to -0.21, P = 0.0007) (Figure 7.18). The I2 of 59% represents moderate heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias.

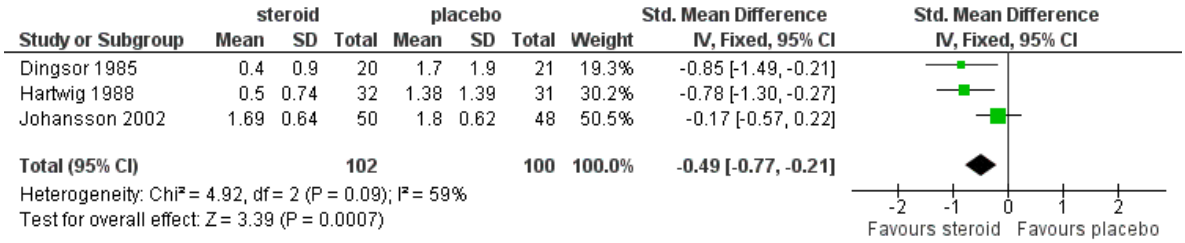


Figure 7.18 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score

Subgroup analysis: patients who had sinus surgery versus those without sinus surgery

When we performed subgroup analyses we found that the effect of topical steroid was significantly greater for patients with sinus surgery (SMD -0.81; 95% CI -1.21 to -0.41) than patients without sinus surgery (SMD -0.17; 95% CI -0.57 to 0.22) (P = 0.03) (Figure 7.19). The I2 of 0% may explain the heterogeneity in polyp score analysis.

Subgroup analysis: topical delivery methods

We found no significant difference when we compared the effect of nasal spray (SMD -0.36; 95% CI -0.70 to -0.02) to nasal aerosol (SMD -0.78; 95% CI -1.30 to -0.27) (P = 0.18) (Figure 7.20).

Change in polyp score

Data addressing the change in polyp score were available from three studies

(Jankowski, Schrewelius et al 2001; Mygind, Pedersen et al 1975; Vlckova, Navrátil et al 2009) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.73; 95% CI -1.00 to -0.46, P < 0.00001) (Figure 7.21). The I2 of 87% represents substantial heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods and steroid agent used.

Subgroup analysis: patients who had sinus surgery versus those without sinus surgery

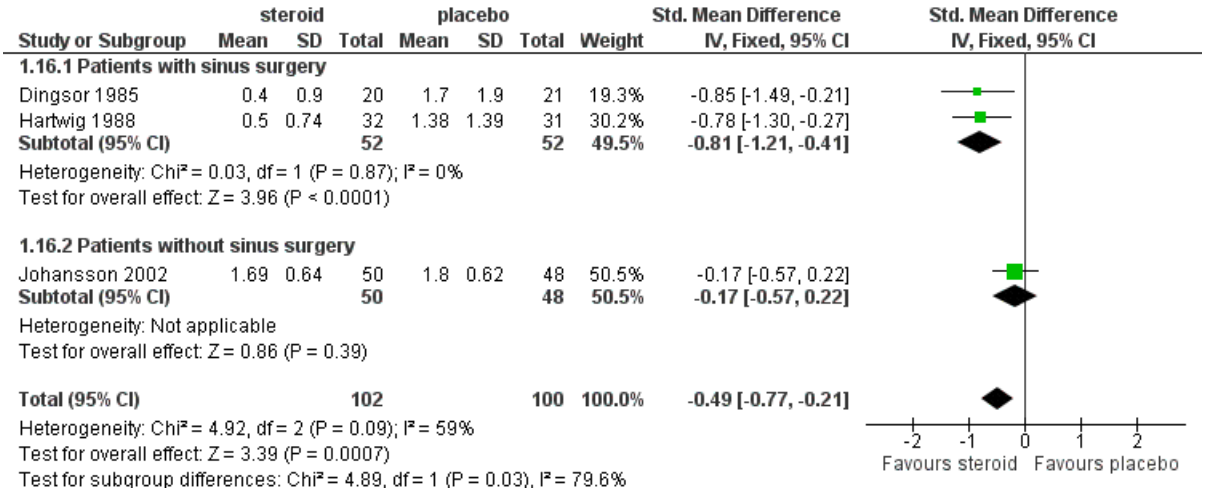


Figure 7.19 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score by sinus surgery

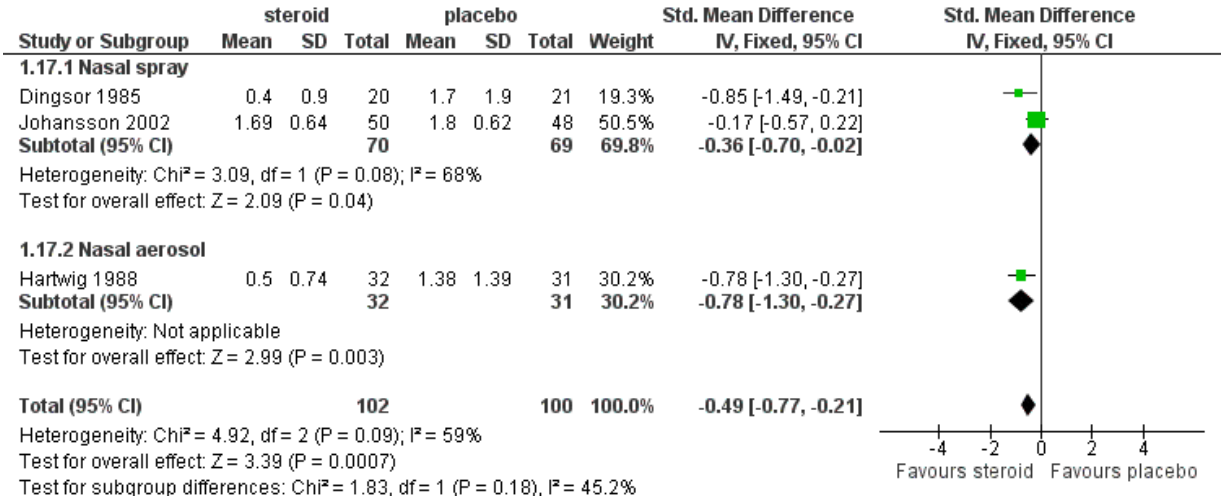


Figure 7.20 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp score by topical delivery methods

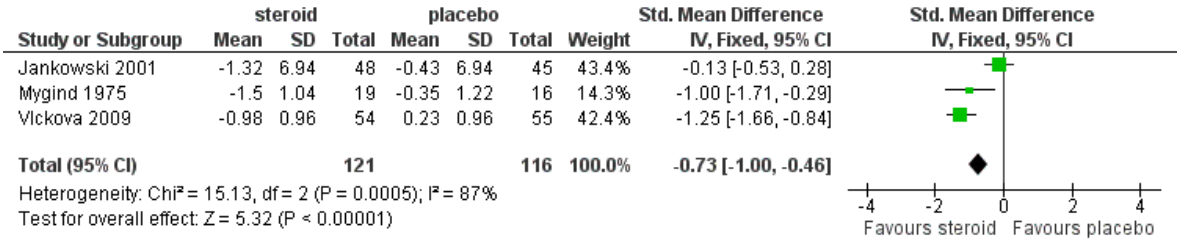


Figure 7.21 Forest plot of comparison: Topical steroids versus placebo, outcome: change in polyp score

When we performed subgroup analyses we found that the effect of topical steroid was significantly greater for patients with sinus surgery (SMD -1.19; 95% CI -1.54 to -0.83) than patients without sinus surgery (SMD -0.13; 95% CI -0.53 to 0.28) (P = 0.0001) (Figure 7.22).

The I2 of 0% in the 'patients with sinus surgery' subgroup again suggests that sinus surgery may explain the heterogeneity seen in polyp score analysis.

Proportion of patients who had a reduction in polyp size (responders)

Data addressing the proportion of responders in polyp size was available from eight studies (Chalton, Mackay et al 1985; Holmström 1999; Holopainen, Grahne et al 1982; Keith, Nieminen et al 2000; Lang and McNeill 1983; Penttila, Poulsen et al 2000; Stjarne, Blomgren et al 2006; Vlckova, Navrátil et al 2009) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (RR 2.09; 95% CI 1.65 to 2.64), P < 0.00001; eight trials, n = 785) (Figure 7.23). The I2 of 53% represents moderate heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias.

Subgroup analysis: patients who had had sinus surgery versus those without sinus surgery

When we performed subgroup analyses we found that the effect of topical steroid was significantly greater for patients who had had sinus surgery (RR 3.22; 95% CI 2.10 to 4.93) than for patients without sinus surgery (RR 1.63; 95% CI 1.23 to 2.17)

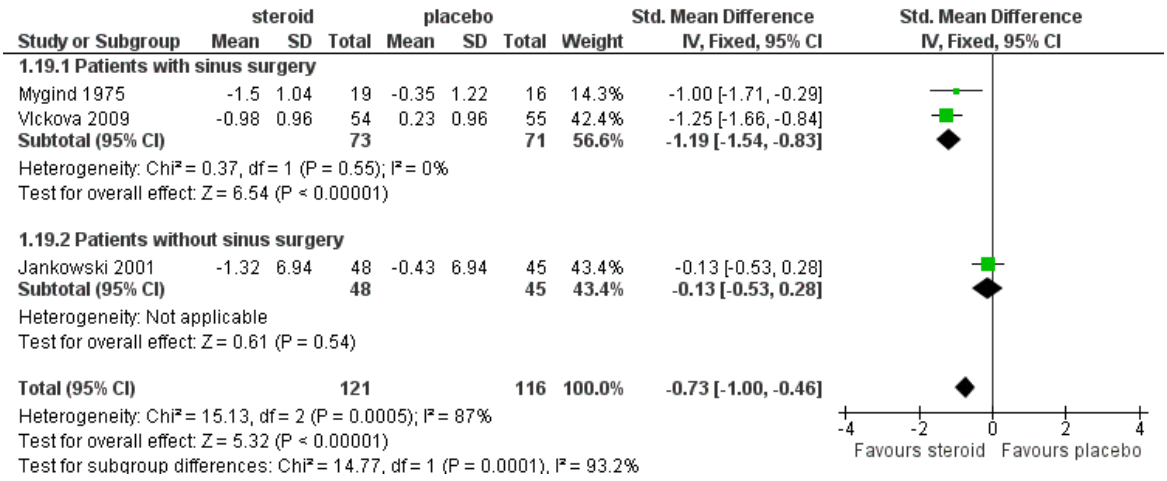


Figure 7.22 Forest plot of comparison: Topical steroids versus placebo, outcome: change in polyp score by sinus surgery status

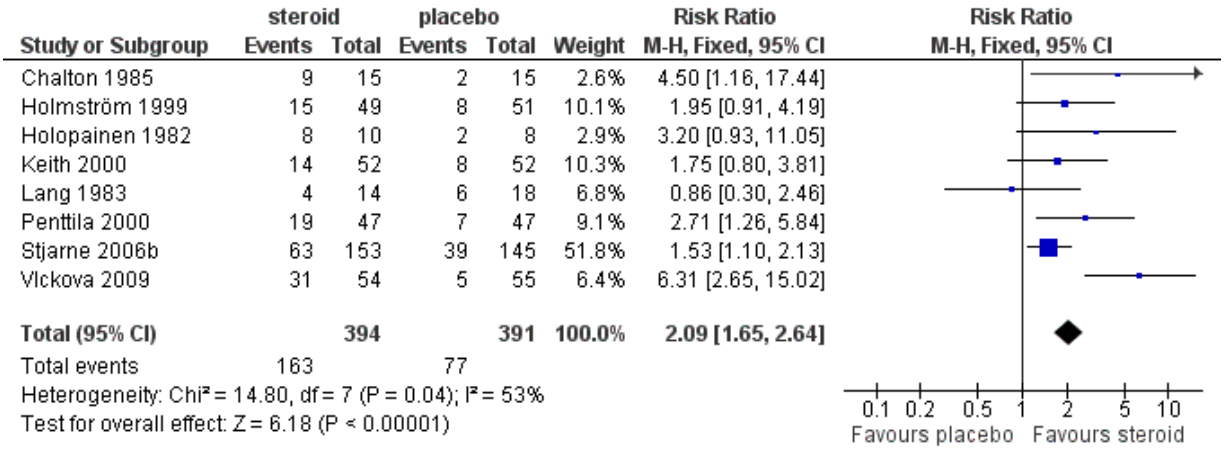


Figure 7.23 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size)

(P = 0.009) (Figure 7.24). The I2 statistics of 38% and 24% for the subgroups of 'patients with sinus surgery' and 'without', respectively suggest that surgical status again explains the heterogeneity seen in the analysis of ‘proportion of patients who had a reduction in polyp size’.

Subgroup analysis: topical delivery methods

We found no significant difference when we compared the effect of nasal drops (RR 2.31; 95% CI 1.52 to 3.50) to nasal sprays (RR 1.99; 95% CI 1.50 to 2.63) (P = 0.56) (Figure 7.25).

Subgroup analysis: polyp severity

We found no significant difference when we compared studies including patients with small polyp size (RR 2.59; 95% CI 1.83 to 3.65) to studies including patients with all size polyps (RR 1.67; 95% CI 1.22 to 2.30) (P = 0.07) (Figure 7.26).

Subgroup analysis: steroid agent

When we performed subgroup analyses we found that the effect was not significant for the beclomethasone subgroup (RR 0.86; 95% CI 0.30 to 2.46) and the budesonide subgroup (RR 3.20; 95% CI 0.93 to 11.05), whereas it significantly favoured topical steroid for fluticasone propionate (RR 2.86; 95% CI 1.94 to 4.22), mometasone furoate (RR 1.53; 95% CI 1.10 to 2.13) and betamethasone (RR 4.50; 95% CI 1.16 to 17.44) (Figure 7.27). The I2 of 48% in the fluticasone propionate subgroup still represents moderate heterogeneity.

Subgroup analysis: quality of studies

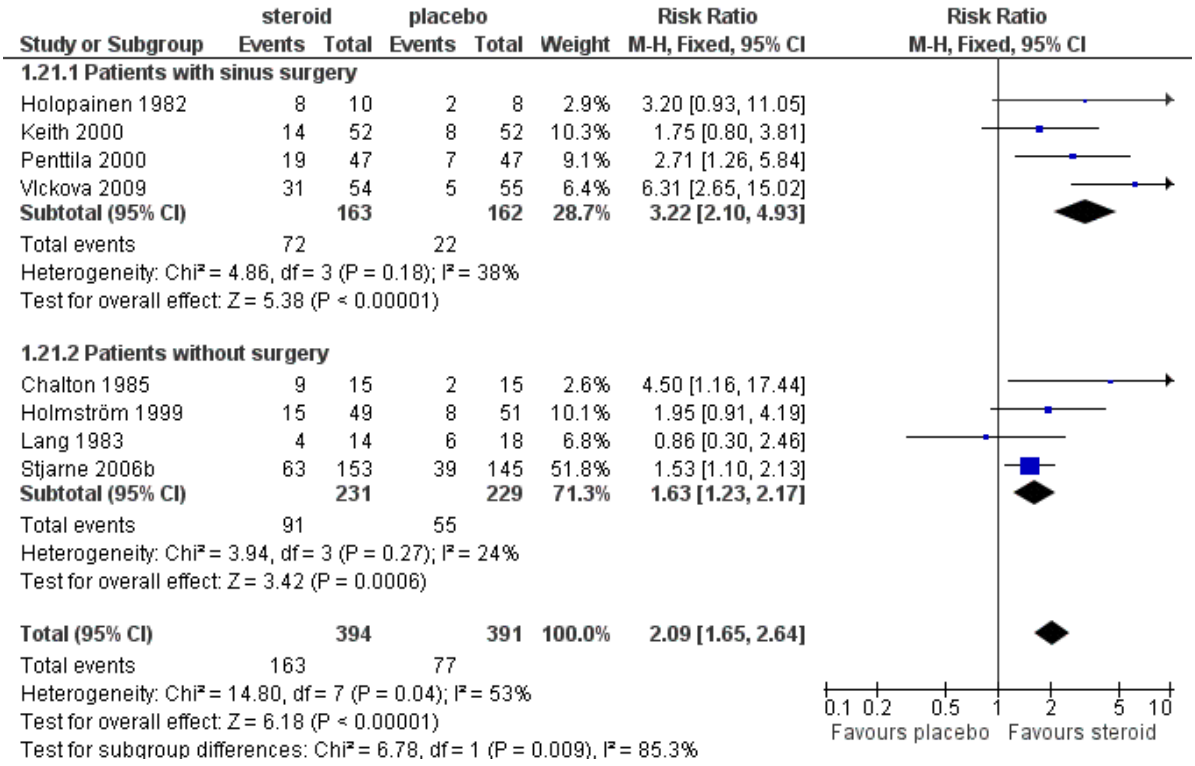


Figure 7.24 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by sinus surgery status

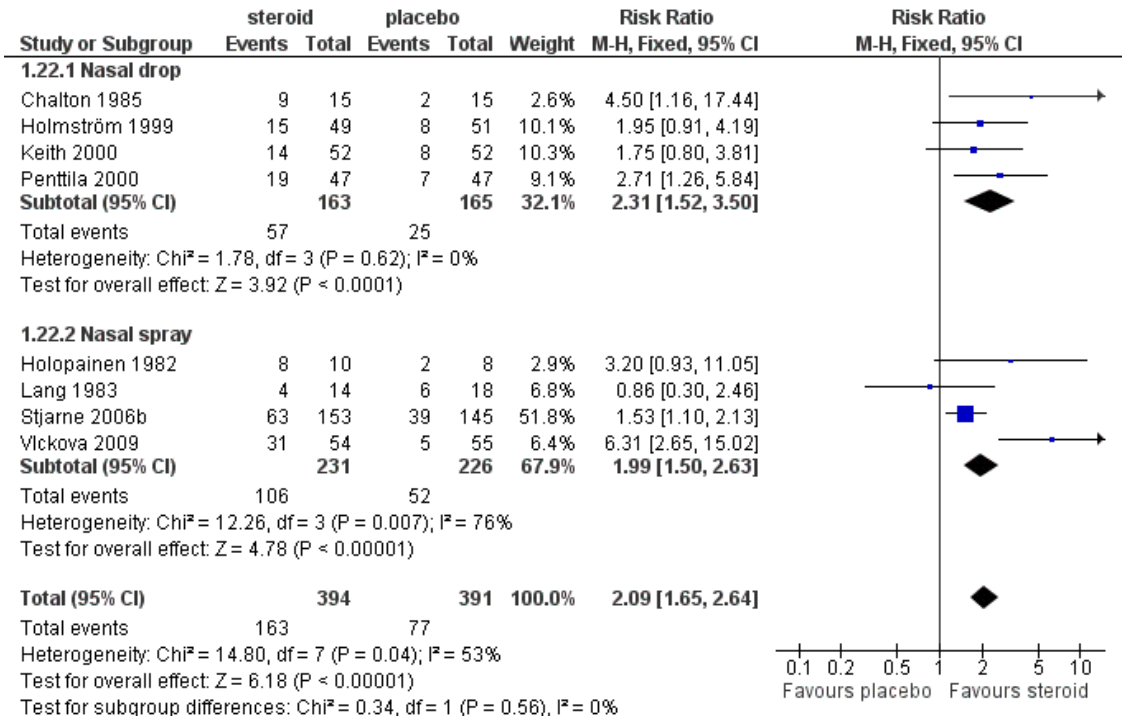


Figure 7.25 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by topical delivery methods

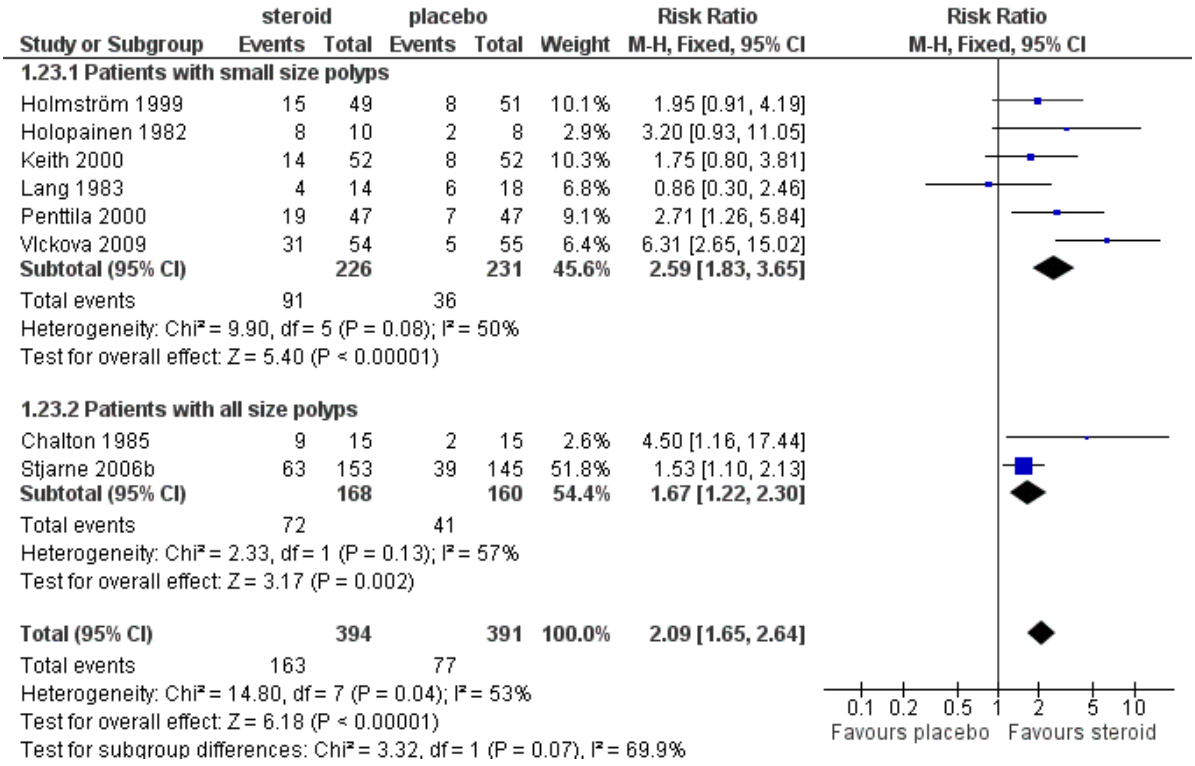


Figure 7.26 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by polyp severity

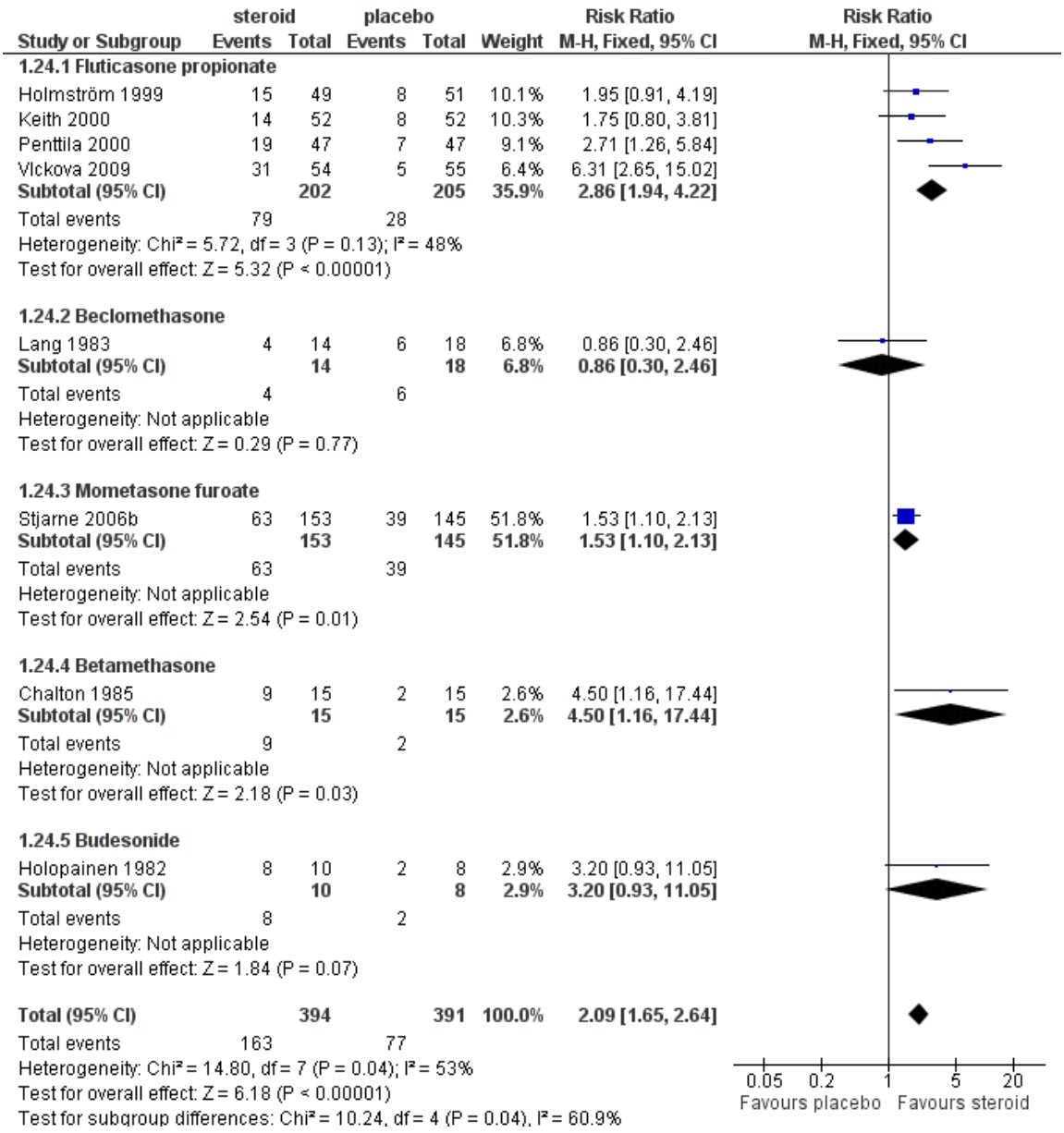


Figure 7.27 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by steroid agent

We found no significant difference when we compared studies with high quality (RR 2.13; 95% CI 1.65 to 2.76) and studies with medium quality (RR 1.91; 95% CI 1.11 to 3.29) (P = 0.72) (Figure 7.28).

Polyp recurrence after surgery

Data addressing polyp recurrence after surgery were available from six studies (Bross-Soriano, Arrieta-Gomez et al 2004; Dingsor, Kramer et al 1985; Dijkstra, Ebbens et al 2004;Drettner, Ebbesen et al 1982; Passali, Bernstein et al 2003; Stjarne, Olsson et al 2009) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (RR 0.59; 95% CI 0.45 to 0.79, P = 0.0004) (Figure 7.29). The I2 of 25% suggests that heterogeneity might not be important.

Subgroup analysis by quality of studies

We found no significant difference when we compared studies with high quality (RR 0.68; 95% CI 0.47 to 0.98) and studies with medium or low quality (RR 0.51; 95% CI 0.33 to 0.79) (P = 0.33) (Figure 7.30).

Nasal airflow

In the following studies, the data could not be combined with the others in the meta-analysis because the numeric data were not provided (Drettner, Ebbesen et al 1982; Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Stjarne, Olsson et al 2009), or the standard deviations were not provided or could not be imputed (Holmberg, Juliusson et al 1997; Jankowski, Schrewelius et al 2001; Keith, Nieminen et al 2000; Lildholdt,

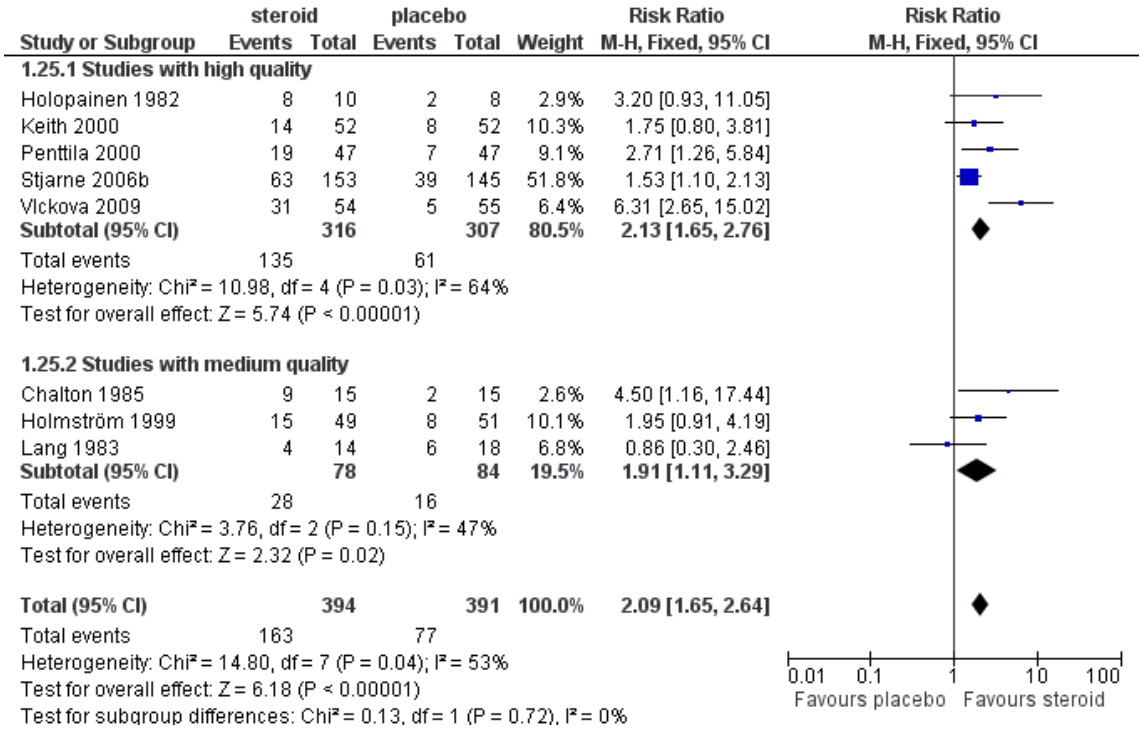


Figure 7.28 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (reduction in polyp size) by quality of studies

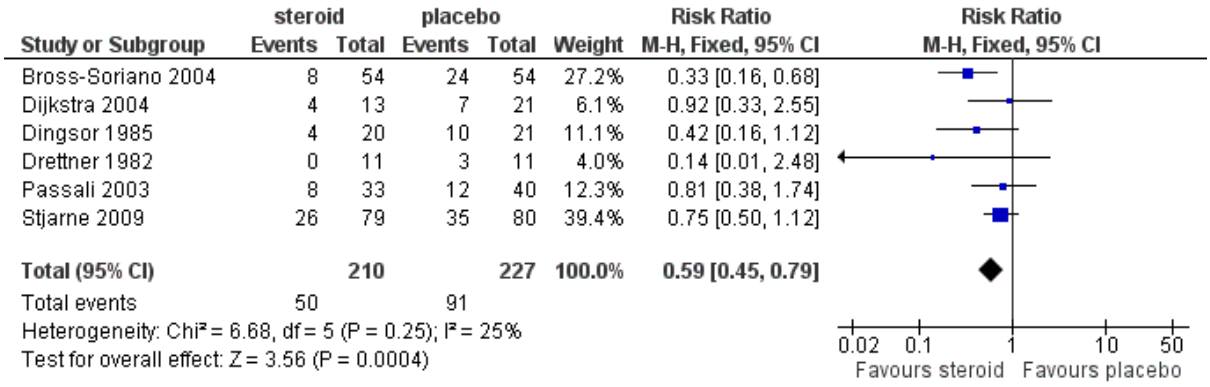


Figure 7.29 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp recurrence after surgery

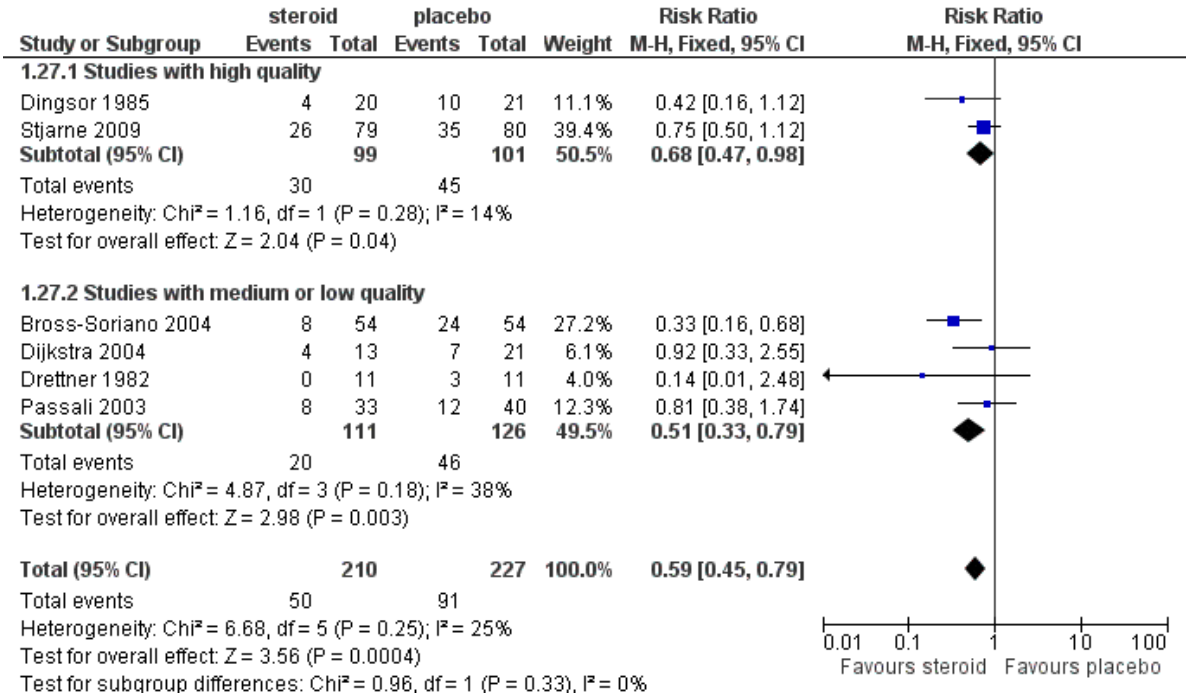


Figure 7.30 Forest plot of comparison: Topical steroids versus placebo, outcome: polyp recurrence after surgery by quality of studies

Rundcrantz et al 1995; Lund, Flood et al 1998; Penttila, Poulsen et al 2000; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Blomgren et al 2006; Vento, Blomgren et al 2012) or the number of participants per arm was not given (Johansen, Illum et al 1993).

Peak nasal inspiratory flow

Data addressing the peak nasal inspiratory flow were available from seven studies (Aukema, Mulder et al 2005; Holopainen, Grahne et al 1982; Jankowski, Klossek et al 2009; Johansson, Holmberg et al 2002; Mastalerz, Milewski et al 1997; Ruhno, Andersson et al 1990; Vlckova, Navrátil et al 2009) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (mean difference (MD) 22.04; 95% CI 13.29 to 30.80, P < 0.00001) (Figure 7.31). The I2 of 49% represents moderate heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias.

Subgroup analysis: patients who had had sinus surgery versus those without sinus surgery

We found no significant difference when we compared patients with surgery (MD 24.01; 95% CI 9.85 to 38.17) and without sinus surgery (MD 20.83; 95% CI 9.69 to 31.97) (P = 0.73) (Figure 7.32).

Subgroup analysis: topical delivery methods

We found no significant difference when we compared the effect of nasal drops (MD 50.00; 95% CI -5.42 to 105.42) to nasal spray (MD 22.62; 95% CI 14.60 to 30.64) (P = 0.32) (Figure 7.33).

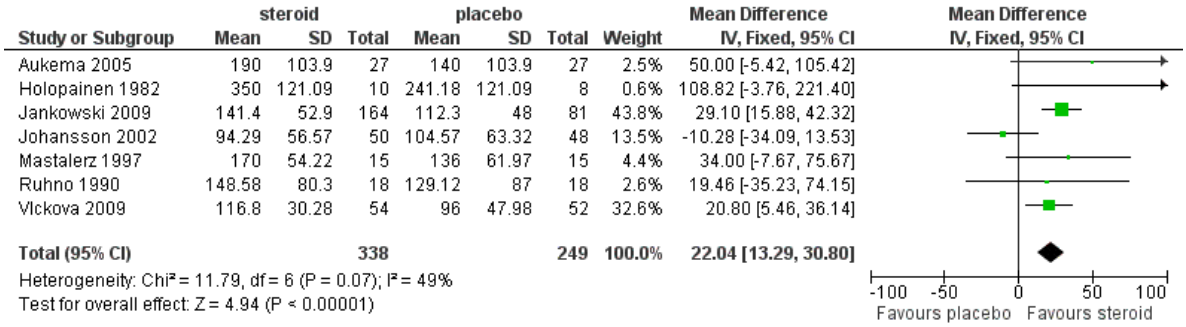


Figure 7.31 Forest plot of comparison: Topical steroids versus placebo, outcome: peak nasal inspiratory flow

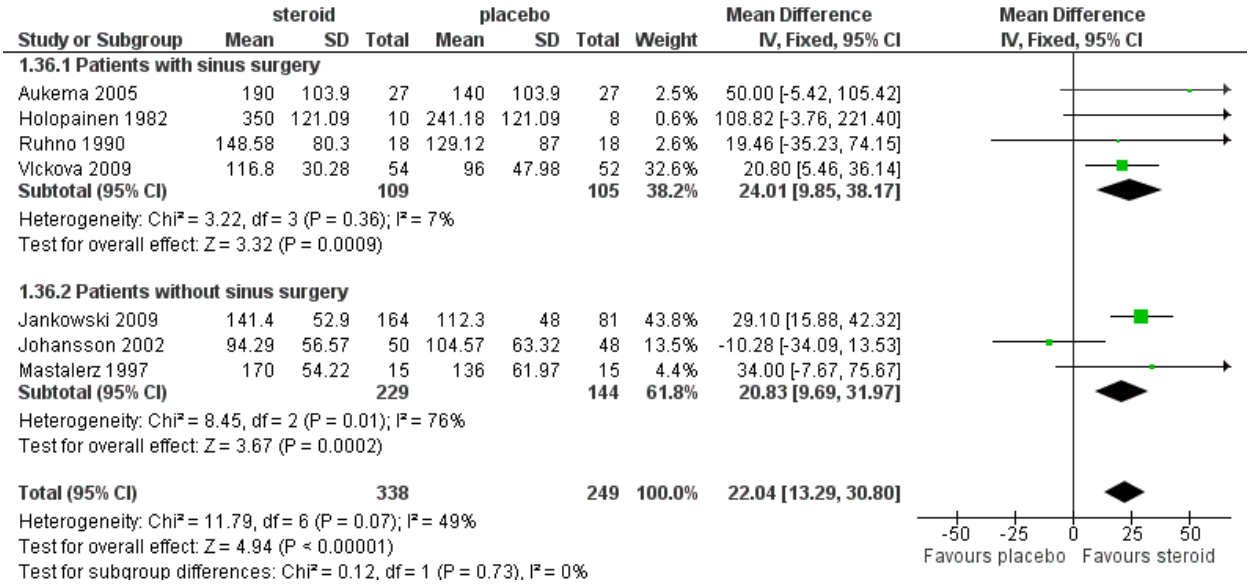


Figure 7.32 Forest plot of comparison: Topical steroids versus placebo, outcome: peak nasal inspiratory flow by sinus surgery status

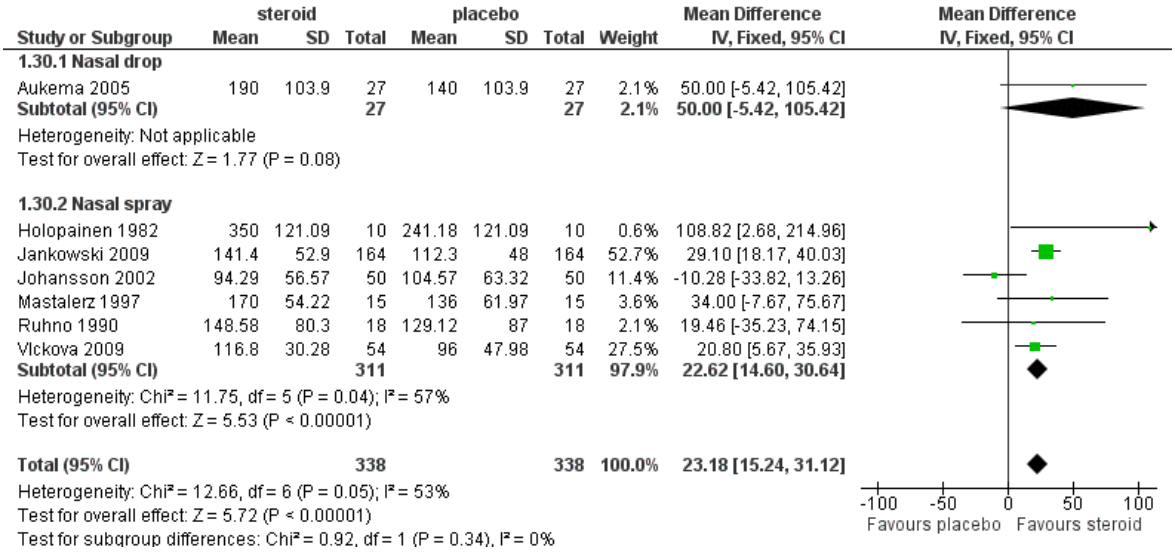


Figure 7.33 Forest plot of comparison: Topical steroids versus placebo, outcome: peak nasal inspiratory flow by topical delivery methods

Change in nasal airflow

Data addressing the change in nasal airflow were available from three studies (Ehnhage, Olsson et al 2009; Holmström 1999; Ruhno, Andersson et al 1990) and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.57; 95% CI -0.85 to -0.29, P = 0.0001) (Figure 7.34). The I2 of 59% still represents moderate heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias. Ehnhage, Olsson et al 2009 and Ruhno, Andersson et al 1990 studied patients with sinus surgery while Holmström 1999 studied patients without sinus surgery.

Proportion of patients with improvement in nasal airflow (responders)

Data addressing the proportion of responders in nasal airflow were available from two studies (Chalton, Mackay et al 1985; Ruhno, Andersson et al 1990), which significantly favoured the topical steroid group (RR 1.91; 95% CI 1.13 to 3.22, P = 0.02) (Figure 7.35). The I2 of 77% represents moderate heterogeneity. Studies are diverse in terms of sinus surgery status, topical delivery methods, steroid agent used and risk of bias. Ruhno, Andersson et al 1990 studied patients with sinus surgery while Chalton, Mackay et al 1985 studied patients without sinus surgery.

Change in CT score

Data addressing the change in CT score were available from one study (Aukema 2005) which showed no significant effect (MD -1.02; 95% CI -3.31 to 1.27, P = 0.38) (Figure 7.36).

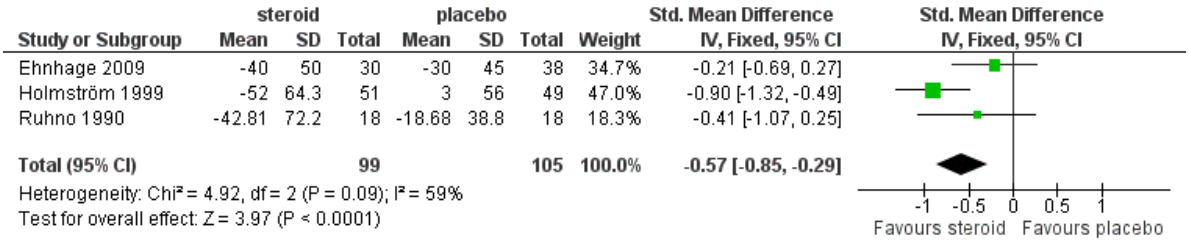


Figure 7.34 Forest plot of comparison: Topical steroids versus placebo, outcome: change in nasal airflow

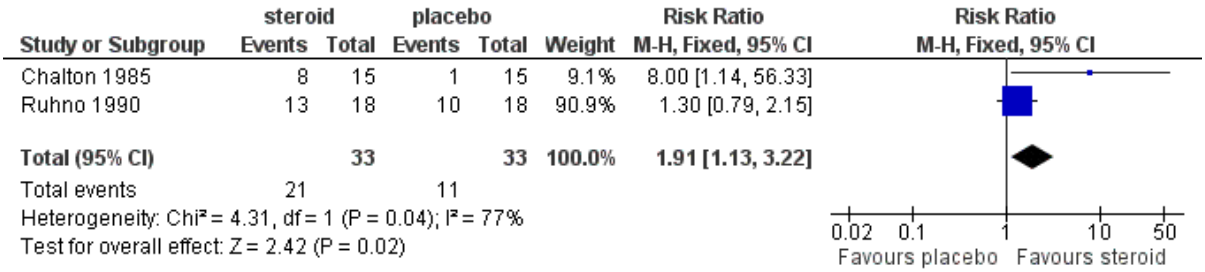


Figure 7.35 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of patients with improvement in nasal airflow

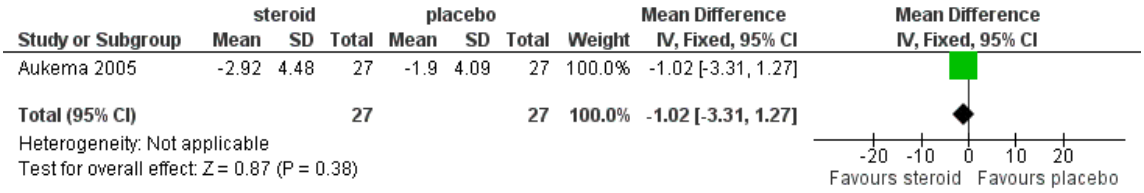


Figure 7.36 Forest plot of comparison: Topical steroids versus placebo, outcome: change in CT score

Sense of smell

In the following studies, the data could not be combined with the others in the meta-analysis because the numeric data were not provided (Chur, Small et al 2010; Holmström 1999; Johansen, Illum et al 1993; Keith, Nieminen et al 2000; Penttila, Poulsen et al 2000), or the standard deviations were not provided or could not be imputed (Lildholdt, Rundcrantz et al 1995; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Stjarne, Olsson et al 2009; Tos, Svendstrup et al 1998; Vento, Blomgren et al 2012).

Change in olfactory threshold test

Data addressing the change in olfactory threshold test were available from one study (Ehnhage, Olsson et al 2009) which showed no significant effect (MD -1.50; 95% CI -3.05 to 0.05, P = 0.06) (Figure 7.37).

Proportion of responders (improvement in olfaction - subjective)

Data addressing the proportion of responders with improvement in olfaction were available from one study (Stjarne, Blomgren et al 2006), which significantly favoured the topical steroid group (RR 1.66; 95% CI 1.15 to 2.40, P = 0.007) (Figure 7.38).

Olfactory score

Data addressing the change in olfaction score were available from one study (Vlckova, Navrátil et al 2009) which significantly favoured the topical steroid group (MD -0.45; 95% CI -0.64 to -0.26, P < 0.00001) (Figure 7.39).

Quality of life

Quality of life (SF36): physical component summary (PCS)

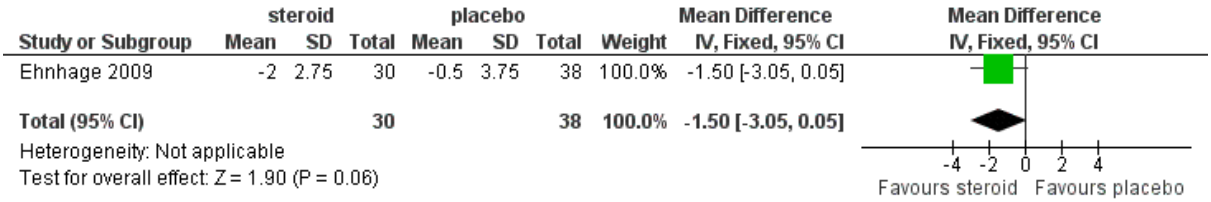


Figure 7.37 Forest plot of comparison: Topical steroids versus placebo, outcome: change in olfactory threshold test

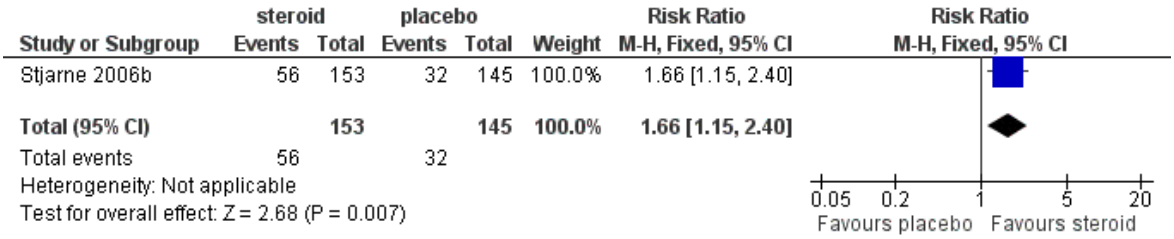


Figure 7.38 Forest plot of comparison: Topical steroids versus placebo, outcome: proportion of responders (improvement in olfaction)

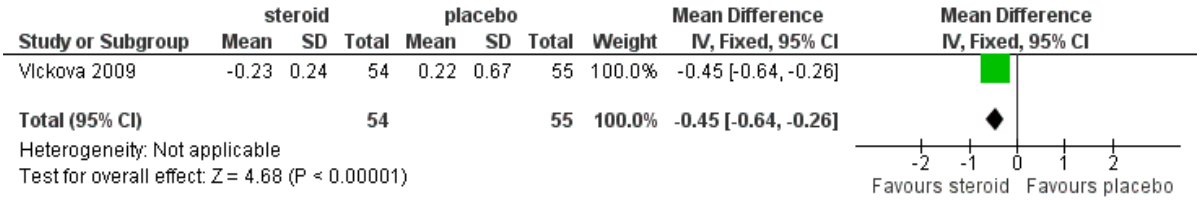


Figure 7.39 Forest plot of comparison: Topical steroids versus placebo, outcome: olfactory score

Data addressing quality of life (SF36) PCS were available from one study (Olsson 2010), which showed no significant effect (MD -2.00; 95% CI 2.39 to -6.39, P = 0.37) (Figure 7.40).

Quality of life (SF36): mental component summary (MCS)

Data addressing quality of life (SF36) MCS were available from one study (Olsson 2010), which significantly favoured the topical steroid group (MD -5.00; 95% CI -0.69 to -9.31, P = 0.02) (Figure 7.41).

Drop-outs

Data addressing drop-outs were available from 34 out of 36 (94.4%) studies. Most studies reported no difference in the number of drop-outs between the topical steroid group and the placebo group. (See Table 7.3).

Adverse events

Data addressing adverse events were available from 26 out of 36 (72.2%) studies. Most studies reported no difference in adverse events between the topical steroid group and the placebo group. (See Table 7.4, Appendix 7.3).

2. Topical steroid versus no intervention

In the following studies, the data could not be pooled for meta-analysis because the standard deviation was not provided and we were not be able to impute it (Jurkiewicz, Zielnik-Jurkiewicz et al 2004; Karlsson and Rundcrantz 1982). The University of Pennsylvania Smell Identification Test (UPSIT) is a test designed to test both nostrils simultaneously. We did not use the UPSIT score from El Naggar, Kale

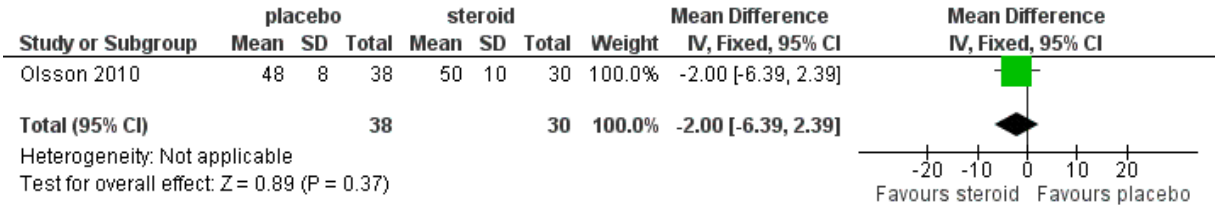


Figure 7.40 Forest plot of comparison: Topical steroids versus placebo, outcome: quality of life (SF36): physical component summary (PCS)

Study	Steroid group 1 n (%)	Placebo group n (%)	No intervention group n (%)	Steroid group 2 n (%)
Aukema, Mulder et al 2005	1 (3.7)	6 (22.2)		
Bross-Soriano, Arrieta-Gomez et al 2004	0 (0)	0 (0)		0 (0)
Chalton, Mackay et al 1985	0 (0)	0 (0)		
Dijkstra, Ebbens et al 2004	4 (30.8)	7 (33.3)		14 (54.3)
Dingsor, Kramer et al 1985	3 (15)	2 (9.5)		
Drettner, Ebbesen et al 1982	3 (21.4)	0 (0)		
El Naggar, Kale et al 1995	0 (0)		0 (0)	
Ehnhage, Olsson et al 2009	7 (23.3)	6 (17.1)		
Filiaci, Passali et al 2000	3 (7.7)	6 (16.2)		2 (4.9)
Hartwig, Linden et al 1988	4 (11.1)	6 (16.2)		
Holmberg, Juliusson et al 1997	4 (21.1)	7 (38.9)		2 (11.1)
Holmström 1999	1 (1.9)	2 (3.8)		
Holopainen, Grahne et al 1982	0 (0)	1 (11.1)		
Jankowski, Schrewelius et al 2001	7 (14.6)	5 (11.1)		
Jankowski, Klossek et al 2009	27 (16.5)	19 (23.5)		
Johansen, Illum et al 1993	NA	NA		
Johansson, Holmberg et al 2002	0 (0)	0 (0)		
Jorissen and Bachert 2009	11 (23.9)	13 (28.9)		
Karlsson and Rundcrantz 1982	0 (0)		0 (0)	

Keith, Nieminen et al 2000	1 (1.9)	5 (9.6)		
Lang and Mcneill 1983	0 (0)	0 (0)		
Lildholdt, Rundcrantz et al 1995	2 (4.5)	2 (5)		2 (4.8)
Lund, Flood et al 1998	3 (30)	4 (44.4)		0 (0)
Mastalerz, Milewski et al 1997	0 (0)	0 (0)		
Mygind, Pedersen et al 1975	0 (0)	0 (0)		
Olsson, Ehnhage et al 2010	4 (13.3)	4 (10.5)		
Penttila, Poulsen et al 2000	4 (8.5)	10 (21.3)		2 (4.2)
Rotenberg, Zhang et al 2011	1 (4.8)		1 (4.5)	2 (9.5)
Rowe-Jones, Medcalf et al 2005	11 (20)	26 (48.1)		
Ruhno, Andersson et al 1990	0 (0)	0 (0)		
Small, Hernandez et al 2005	14 (12.2)	22 (18.8)		
Stjarne, Mosges et al 2006	8 (7.8)	19 (17.9)		9 (8.8)
Stjarne, Blomgren et al 2006	19 (12.4)	19 (17.9)		
Stjarne, Olsson et al 2009	36 (45.6)	43 (53.8)		
Tos, Svendstrup et al 1998	0 (0)	0 (0)		0 (0)
Vento, Blomgren et al 2012	9 (30)	8 (26.7)		
Vlckova, Navrátil et al 2009	0 (0)	3 (5.5)		

Table 7.3 Drop-outs

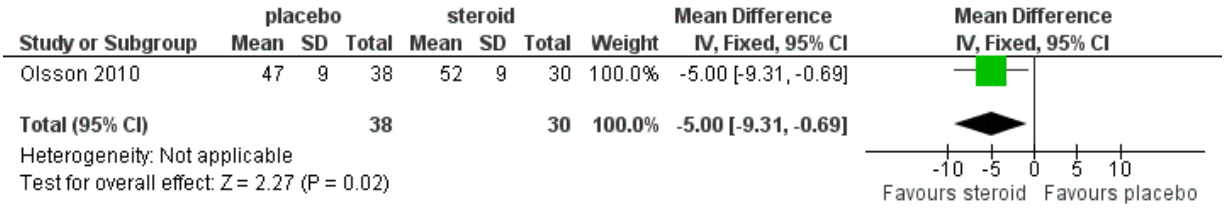


Figure 7.41 Forest plot of comparison: Topical steroids versus placebo, outcome: quality of life (SF36): mental component summary (MCS)

et al 1995 for analysis when it was tested in each nostril separately. This study delivered steroid to one nostril and used the other as a control.

Symptoms

Jurkiewicz, Zielnik-Jurkiewicz et al 2004 reported symptoms ($P < 0.01$) being significantly improved in the topical steroid group compared to no intervention.

Polyp size

Karlsson and Rundcrantz 1982 reported the mean polyp score being significantly improved in the topical steroid group compared to no intervention ($P = 0.003$). El Naggar, Kale et al 1995 reported the UPSIT test being not significantly different between groups ($P = 0.31$).

Polyp recurrence

Jurkiewicz, Zielnik-Jurkiewicz et al 2004 reported polyp recurrence ($P < 0.01$) being significantly improved in the topical steroid group compared to no intervention.

Change in endoscopy score

Data addressing the change in endoscopy score were available from one study (Rotenberg, Zhang et al 2011), which showed no significant effect (MD 0.40; 95% CI -0.11 to 0.91) (Figure 7.42).

Change in CT score

Data addressing the change in CT score were available from one study

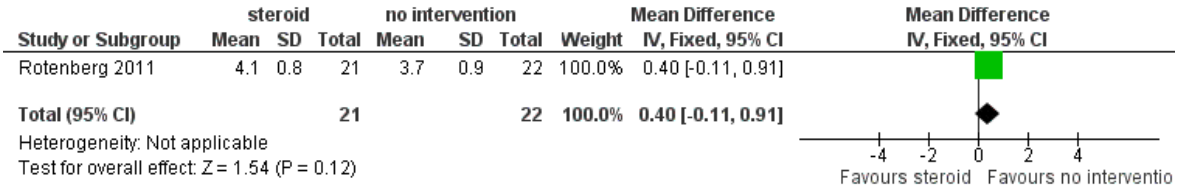


Figure 7.42 Forest plot of comparison: Topical steroids versus no intervention, outcome: change in endoscopy score

(Rotenberg, Zhang et al 2011), which showed no significant effect (MD 0.90; 95% CI -1.02 to 2.82) (Figure 7.43).

Quality of life

Data addressing disease-specific quality of life (SNOT-21) were available from one study (Rotenberg, Zhang et al 2011), which showed no significant effect (MD 5.40; 95% CI -3.40 to 14.20) (Figure 7.44).

Drop-outs

Data addressing drop-outs were available from two (50%) studies (El Naggar, Kale et al 1995; Rotenberg, Zhang et al 2011). Both studies reported no difference in the number of drop-outs between the topical steroid group and the placebo group. (See Table 7.3)

Adverse events

Data addressing adverse events were available from one out of four studies (25%) (Rotenberg, Zhang et al 2011). No difference between groups was reported. (See Table 7.4, Appendix 7.3)

3.Topical and oral corticosteroids versus oral corticosteroids only

No studies addressed this comparison.

4. Low-dose steroid versus high-dose steroid

Symptoms

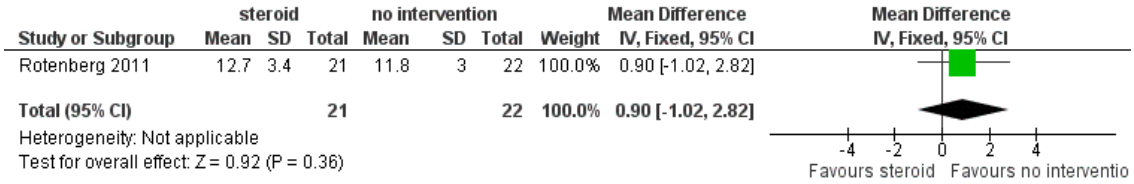


Figure 7.43 Forest plot of comparison: Topical steroids versus no intervention, outcome: change in CT score

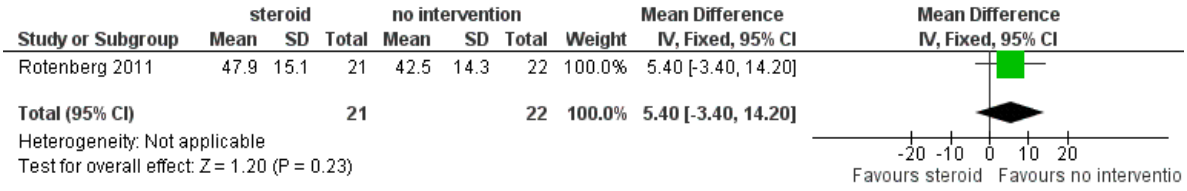


Figure 7.44 Forest plot of comparison: Topical steroids versus no intervention, outcome: quality of life

In the following studies, the data could not be combined with the others in the meta-analysis because the numeric scores of combined symptoms were not provided (Chur, Small et al 2010), or standard deviation was not provided and could not be imputed (Jankowski, Schrewelius et al 2001; Lildholdt, Rundcrantz et al 1995; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Tos, Svendstrup et al 1998) or symptoms were reported at two weeks, and not at the endpoint of one year (Dijkstra, Ebbens et al 2004).

Symptom scores

Data addressing the change in combined symptom scores were available from one study (Filiaci, Passali et al 2000), which showed no significant effect (SMD -0.29; 95% CI -0.73 to 0.15, P = 0.20) (Figure 7.45).

Proportion of patients with overall improvement in symptoms (responders)

Data addressing the proportion of responders in symptoms was available from two studies (Filiaci, Passali et al 2000; Penttila, Poulsen et al 2000), which showed no significant effect (RR 0.94; 95% CI 0.74 to 1.21, P = 0.65) (Figure 7.46).

Polyp size

In the following studies, the data could not be combined with the others because the numeric scores for polyp size were not provided (Chur, Small et al 2010), or standard deviation was not provided and could not be imputed (Filiaci, Passali et al 2000; Lildholdt, Rundcrantz et al 1995; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Tos, Svendstrup et al 1998).

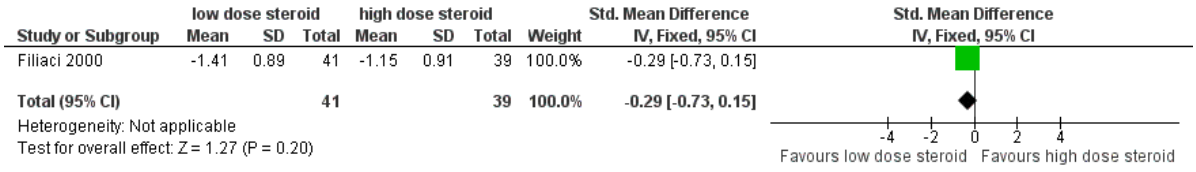


Figure 7.45 Forest plot of comparison: Low-dose steroid versus high-dose steroid, outcome: symptom scores

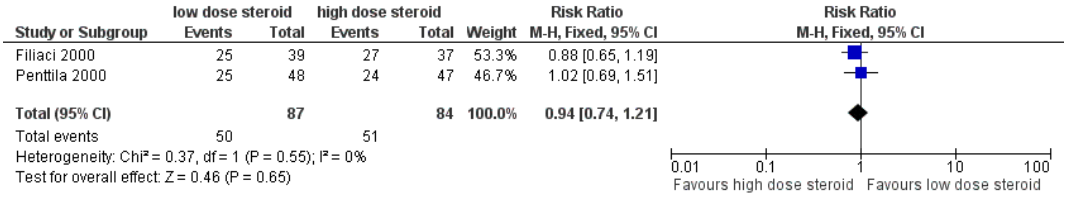


Figure 7.46 Forest plot of comparison: Low-dose steroid versus high-dose steroid, outcome: proportion of responders (improvement in symptom)

Change in polyp score

Data addressing the change in polyp score were available from one study (Jankowski, Schrewelius et al 2001), which showed no significant effect (SMD -0.04; 95% CI -0.44 to 0.36, P = 0.84) (Figure 7.47)

Proportion of patients who had a reduction in polyp size (responders)

Data addressing the proportion of responders in polyp size were available from one study (Penttila, Poulsen et al 2000), which showed no significant effect (RR 0.57; 95% CI 0.30 to 1.06, P = 0.07) (Figure 7.48).

Polyp recurrence after surgery

Data addressing polyp recurrence after surgery were available from one study (Dijkstra, Ebbens et al 2004), which showed no significant effect (RR 0.46; 95% CI 0.19 to 1.10, P = 0.08) (Figure 7.49).

Discussion

Summary of main results

Due to the limited number of included studies that could be pooled for meta-analysis, we also provide a summary table showing trial outcomes. When topical steroid was compared to placebo, pooled data analyses of symptoms, polyp size, polyp recurrence and nasal airflow all demonstrated significant benefit in the topical steroid group. Although these outcomes were reported in various ways across studies, such as the final score, the change of score and the proportion of responders, all meta-analyses show a consistency of results favouring topical steroid. Although these data consistently favoured topical corticosteroids there was also significant heterogeneity

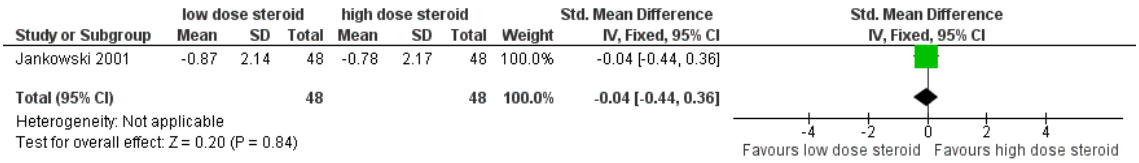


Figure 7.47 Forest plot of comparison: Low-dose steroid versus high-dose steroid, outcome: change in polyp score

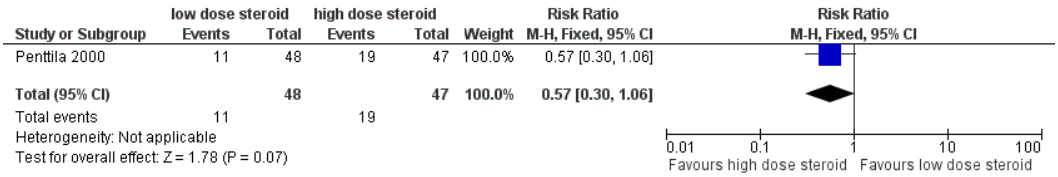


Figure 7.48 Forest plot of comparison: Low-dose steroid versus high-dose steroid, outcome: proportion of responders (reduction in polyp size)

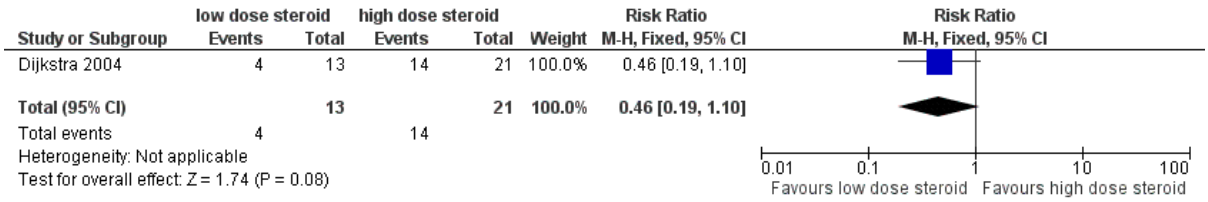


Figure 7.49 Forest plot of comparison: Low-dose steroid versus high-dose steroid, outcome: polyp recurrence after surgery

seen and variability in the effect size. To better explore this, we performed various subgroup analyses.

The 36 included studies were diverse, both clinically and methodologically. Variability included sinus surgery status, topical delivery methods, polyp severity, steroid agent used, dosing and study quality. We therefore used these subgroups for analysis. Patients who had had prior sinus surgery any time before the topical corticosteroids were given, that is either immediately before or at some time in their past, showed significantly better reduction in polyp size for all three outcomes (final polyp score, change in polyp score and proportion of responders in polyp reduction) compared to patients who had never had sinus surgery. When the heterogeneity within each subgroup was explored, low heterogeneity existed for these subgroups (polyp score: I2 = 0%, change in polyp score: I2 = 0%, responders in polyp size: I2 = 38% (with sinus surgery) and 20% (without sinus surgery)) suggesting that the surgery status of the patients may explain the heterogeneity in the primary analysis. The other subgroup analyses were unable to eliminate the heterogeneity.

The number of patients who had polyp recurrence when topical corticosteroids were administered immediately after surgery was performed also significantly favoured topical corticosteroids and this result also had low heterogeneity in contrast to most other analyses, again suggesting the role of surgery prior to administering topical corticosteroids is beneficial. Similarly for nasal obstruction scores, topical steroid was again favoured over placebo and all these studies included patients with previous surgery. Other subgroup analyses were not able to explain the heterogeneity seen.

There was not enough information regarding the extent of previous surgery for us to consider the role of simple polypectomy versus more comprehensive sinus surgery. For overall symptom improvement, heterogeneity was found but this was not adequately explained by any of the subgroup analyses, including surgical status. Although there was no difference in the degree of improvement in overall symptom scores between surgical state subgroups, there were considerable differences evident in the individual studies, making an analysis of the subgroups unreliable. The effect size of nasal aerosol and turbuhaler was greater than nasal spray in overall symptom control. However, nasal spray had a greater effect size than aerosol in the control of nasal obstruction. There was only a single trial using aerosol and conclusions may be limited. Also, there was no difference in polyp size reduction and nasal airway across various types of topical delivery methods. Patients with large polyps showed a significant decrease in symptoms compared to patients with small-sized polyps. This may be due to greater symptom severity in the baseline of the large polyp subgroup. The potential for greater polyp surface area and exposure to simple low-volume delivery techniques may further explain this effect. Both subgroups had the same response to steroid in overall polyp size reduction.

There was no difference between studies with high quality and medium quality in the outcomes of symptom scores, polyp size and polyp recurrence. However, for the nasal obstruction score, the effects significantly favoured topical steroid only in studies with high quality but not in studies with medium quality.

Although there are 36 trials included (for this comparison), data from only a limited number of studies could be pooled for meta-analysis. Many studies do not provide complete reporting of data such as standard deviations, standard error, 95% confidence interval, range or interquartile range, for baseline, final or change in outcomes.

When topical steroid was compared to no intervention, the included studies showed improvement of symptoms, reduction in polyp size and prevention of polyp recurrence in the topical steroid group but no difference from the control group for endoscopy, CT score and quality of life. In the meta-analysis we performed we could pool data from only one study.

When a low dose was compared to a high dose of topical steroid, no difference was evident for symptom control, polyp size and polyp recurrence.

The most common adverse events were epistaxis and nasal irritation including itching, sneeze, dry nose and rhinitis. Adverse events may be difficult to distinguish from the underlying pathology treated as rhinitis, itching and sneeze are well-described symptoms in CRS. We acknowledge that rare adverse events may not be detected in randomised controlled trials (RCTs). However, they were extremely infrequent and there was no difference in adverse

events between the study groups and control groups in any trial. Post-market adverse events (Lanier, Kai et al 2007) for intranasal steroid sprays are uncommon at recommended dosages. However, we have not specifically sought adverse event data from non-RCT studies. Minor adverse events from nasal corticosteroids are well tolerated by patients. The benefit appears to outweigh the risk.

Potential biases in the review process

Questions arose regarding the eligibility criteria and data analyses. The inclusion of trials studying mixed populations of polyps and non-polyps patients possibly brings heterogeneity. We decided to include trials with mixed populations if data for the polyps population were reported separately from non-polyps (Dijkstra, Ebbens et al 2004), or we were able to extract information from unpublished data received from the authors (Jorissen and Bachert 2009) or patients with chronic rhinosinusitis with polyps comprised the majority of the population (Mastalerz, Milewski et al 1997; Rowe-Jones, Medcalf et al 2005).

Mastalerz, Milewski et al 1997 conducted a cross-over trial with an allocation of each participant to a sequence of two interventions. We pooled data for meta-analysis as we believe an intervention does not have a lasting effect which persists into a subsequent period, thus interfering with the effects of a different subsequent intervention. We analysed data as if the trial was a parallel-group trial. The confidence interval may be too wide and the trial may receive too little weight. Nevertheless, the error might be regarded as less serious than some other types of

unit of analysis error when the study is under-weighted rather than over-weighted (Higgins and Green 2011).

El Naggar, Kale et al 1995 delivered topical steroid into one nostril and left the other nostril without treatment as control. UPSIT was tested via each nostril separately whereas UPSIT is a test designed to test both nostrils simultaneously. We did not pool these data for meta-analysis.

As for polyp recurrence, time to relapse was also reported (Stjarne, Olsson et al 2009) but it is not appropriate to analyse mean time to relapse using methods for continuous outcomes. This is because the relevant times are only known for the subset of participants who have had the event (Higgins and Green 2011).

When we pooled data from trials studying more than one regime of topical steroid (Chur, Small et al 2010; Dijkstra, Ebbens et al 2004; Filiaci, Passali et al 2000; Jankowski, Schrewelius et al 2001; Lildholdt, Rundcrantz et al 1995; Penttila, Poulsen et al 2000; Small, Hernandez et al 2005; Stjarne, Mosges et al 2006; Tos, Svendstrup et al 1998) and data from trials studying two delivery methods (Johansen, Illum et al 1993; Rotenberg, Zhang et al 2011; Tos, Svendstrup et al 1998) for meta-analysis, only data from one steroid arm could be pooled to compare with placebo. It was difficult to determine which arm (low dose or high dose, once daily or twice daily dose and various types of topical delivery methods) the data should be taken from. We collected data from the first arm of each study for analysing the effects against placebo.

Symptoms were scored differently across included studies. We used overall symptom score and nasal obstruction for meta-analysis. Nasal obstruction is recognised as the major symptom of patients with nasal polyps. Data from trials reporting any other individual symptoms were not pooled.

Agreements and disagreements with other studies or reviews

In agreement with a previous systematic review (Joe, Thambi et al 2008), the change in polyp size was significantly improved by topical steroid over placebo. Data pooled for meta-analysis in Joe, Thambi et al 2008 were extracted from studies reporting change in polyp size. Those studies included the same study (Jankowski, Schrewelius et al 2001) as our review and also some different trials. This is because we did not impute standard deviations from P values when the actual values were not obtained from t tests or when levels of significance were reported (such as P = non-significant) rather than exact P values (Higgins and Green 2011). However, the results in both reviews are similar.

A previous Cochrane review (Snidvongs, Kalish et al 2011) studying topical steroids for chronic rhinosinusitis without polyps also performed subgroup analysis by sinus surgery status and topical delivery methods. Only patients with sinus surgery had symptom improvement both in symptom score (standardised mean difference (SMD) -0.54; 95% confidence interval (CI) -1.03 to -0.06) and the proportion of responders (risk ratio (RR) 2.75; 95% CI 1.18 to 6.42) but not for those without surgery (SMD -0.10; 95% CI -0.90 to 0.71) and (RR 1.50; 95% CI 0.78 to 2.88). Those with direct sinus delivery performed better than those with simple nasal delivery methods (P =

0.04). In agreement with this review, sinus surgery status revealed more benefit in reduction of polyp score (P < 0.00001) when steroid was administered after sinus surgery. Both reviews reveal evidence as to how topical drug access and distribution bring effective delivery of steroid to the sinuses with more beneficial effects.

Conclusion

Implications for practice

Topical nasal steroid should be considered part of medical treatment for chronic rhinosinusitis with polyps. The evidence demonstrates that it has beneficial effects on symptom control, polyp size and polyp recurrence, with little evidence of significant adverse effects. The effect on polyp size may be greater when the topical steroid is administered after sinus surgery.

Implications for research

Clinical diversity, including variability in the agents used, patients' sinus surgery status and topical delivery methods, led to heterogeneity across studies in this review. Subgroup analyses suggested that the beneficial effects are greater when steroid is administered after sinus surgery. However, these findings are only observational as the individuals in the trials were not randomised into these subgroups. Well-conducted randomised controlled trials are required, comparing different methods of topical drug delivery to the sinuses with an appropriate duration of treatment (longer than 12 weeks) and using validated outcome measures, including quality of life outcomes. Complete reporting of outcome data is essential for all future studies as this was a limitation for meta-analysis. Randomised controlled

trials should be pre-registered and their reporting should be according to the latest CONSORT guidelines (Schulz, Altman et al 2010).

Acknowledgements

We acknowledge Prof Mark Jorissen, Prof Claus Bachert and their statisticians for providing raw data from their study.

References

Aukema AAC, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol* 2005;115:1017- 23.

Bachert C, Watelet JB, Gevaert P, Van Cauwenberge P. Pharmacological management of nasal polyposis.*Drugs* 2005;65(11):1537-52.

Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. *Curr Opin Allergy Clin Immunol* 2008;8:34-8.

Badia L, Lund V. Topical steroids in nasal polyposis. *Drugs* 2001;61(5):573-8.

Bateman ND, Fahy C, Woolford TJ. Nasal polyps: still more questions than answers. *J Laryngol Otol* 2003;117(1):1-9.

Benninger MS, Ferguson BJ, Hadley JA, et al.Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;129(Suppl 3):S1–32.

Bross-Soriano D, Arrieta-Gomez JR, Prado-Calleros H. Infections after endoscopic polypectomy using nasal steroids. *Otolaryngol Head Neck Surg* 2004;130(3):319-22.

Chalton R, Mackay I, Wilson R, Cole P. Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. *BMJ* 1985;291:788.

Chur V, Small CB , Stryszak P, Teper A. Mometasone furoate nasal spray is safe for the treatment of nasal polyps in pediatric subjects 6-17 years of age. *J Allergy Clin Immunol* 2010;25(2 Suppl2):AB101.

Dijkstra MD, Ebbens FA, Poublon RM, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. *Clin Exp Allergy* 2004;34(9):1395-400.

Dingsor G, Kramer J, Olsholt R, Soderstrom T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. *Rhinology* 1985;23(1):49.

Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. *Rhinology* 1982;20(3):149-58.

Ehnhage A, Olsson P, Kölbeck KG, Skedinger M, Dahlén B, Alenius M, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. *Allergy* 2009;64(5):762-9.

El NM, Kale S, Aldren C, Martin F. Effect of Beconase nasal spray on olfactory function in post-nasal polypectomy patients: a prospective controlled trial. J Laryngol Otol 1995;109(10):941-4.

Filiaci F, Passali D, Puxeddu R, Schrewelius C. A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. *Rhinology* 2000;38(4):185-90.

Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps Group. European Position Paper on Nasal Polyps 2012. *Rhinol Suppl*. 2012 Mar;(23):3 p preceding table of contents, 1-298.

Hartwig S, Linden M, Laurent C, Vargo A-K, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). *J Laryngol Otol* 1988;102(2):148-51.

Hellquist HB. Nasal polyps update Histopathology. *Allergy Asthma Proc* 1996;17(5):237-42.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. *Ann Allergy Asthma Immunol* 1997;78(3):270-6.

Holmström M. Clinical performance of fluticasone propionate nasal drops. *Allergy* 1999;54(Suppl 53):21-5.

Holopainen E, Grahne B, Malmberg H. Budesonide in the treatment of nasal polyposis. *Eur J Respir Dis* 1982;63(Suppl 122):221-8.

Jankowski R, Schrewelius C, Bonfils P, Saban Y, Gilain L, Prades JM, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. *Arch Otolaryngol Head Neck Surg* 2001;127:447-52.

Jankowski R, Klossek JM, Attali V, Coste A, Serrano E. Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. *Allergy* 2009;64(6):944-50.

Johansen LV, Illum P, Kristensen S, Winther L, Vang Petersen S, Synnerstad B. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. *Clin Otolaryngol Allied Sci* 1993;18(6):524-7.

Johansson L, Holmberg K, Melen I, Stierna P, Bende M. Sensitivity of a new grading system for studying nasal polyps with the potential to detect early changes in polyp size after treatment with a topical corticosteroid (budesonide). *Acta Otolaryngol* 2002;122(1):49-53.

Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008;139:340-7.

Jorissen M, Bachert C. Effect of steroids on wound healing after endoscopic sinus surgery. *Rhinology* 2009;47(3):280-6.

Jurkiewicz D, Zielnik-Jurkiewicz B, Wojdas A. Effectiveness of fluticasone propionate in nasal polyps treatment. *Internat Rev Allergol Clin Immunol* 2004;10(1):22-4.

Karlsson G, Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. *Rhinology* 1982;20(3):144-8.

Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 mug daily compared with placebo for the treatment of bilateral polyposis in adults. *Clin Exp Allergy* 2000;30(10):1460-8.

Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al.

Prevalence of nasal polyposis in France: a cross-sectional, case-control study. *Allergy* 2005;60(2):233-7.

Lang DA, McNeill J. Double blind controlled study of effect of topical steroids on nasal polyps. *Clin Otolaryngol* 1983;8:139.

Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. *Ann Allergy Asthma Immunol* 2007;99(6):473-9.

Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol Allied Sci* 1995;20(1):26-30.

Lund VJ, Kennedy DW. Quantification for staging sinusitis. *Ann Otol Rhinol Laryngol.Suppl* 1995;167(104):17-21.

Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. *Arch Otolaryngol Head Neck Surg* 1998;124(5):513-8.

Martinez-Devesa P, Patiar S. Oral steroids for nasal polyps. *Cochrane Database of Syst Rev* 2011, Issue 7. Art. No.: CD005232. DOI: 10.1002/14651858.CD005232.pub3

Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* 1997;52(9):895-900.

Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004;131(6Suppl):S1-S62.

Meltzer EO. Formulation considerations of intranasal steroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol* 2007;98(1):12-21.

Mladina R, Clement P, Lopatin A, Mann W, Passali D. International Consensus on Nasal Polyposis 2002-2004. *Eur Arch Otorhinolaryngol* 2005;262(6):519-21.

Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin Allergy* 1975;5(2):159-64.

Mygind ND, Bachert RC. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax* 2000;55(Suppl 2):79-83.

Olsson P, Ehnhage A, Nordin S, Stjarne P. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. *Rhinology* 2010;48(3):325-30.

Passali D, Bernstein JM, Passali FM, Damiani V, Passali GC, Bellussi L. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2003;129(6):656-9.

Penttila M, Holmstrom M, Poulsen P, Hollingworth K. The efficacy and tolerability of fluticasone propionate (FP) nasal drops 400 microg once daily and twice daily compared with placebo in the treatment of nasal polyposis. *Allergy* 1998;53 (Suppl 43):509

Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. *Clin Exp Allergy* 2000;30(1):94-102.

Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope* 2004;114(5):923-30.

Rotenberg BW, Zhang I, Arra I, Payton KB. Postoperative care for Samter' s triad patients undergoing endoscopic sinus surgery: a double-blinded, randomized controlled trial. *Laryngoscope* 2011;121:2702 5.

Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology* 2005;43(1):2-10.

Ruhno J, Andersson B, Denburg J, Anderson M, Hitch D, Lapp P, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. *J Allergy Clin Immunol* 1990;86:946-53.

Scadding GK. Comparison of medical and surgical treatment of nasal polyposis. Curr Allergy Asthma Rep 2002;2(6):494-9.

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

Slavin RG. Nasal polyps and sinusitis. *Clin Allergy Immunol* 2002;16:295-309.

Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryszak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol* 2005;116(6):1275-81.

Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ. Topical steroid for chronic rhinosinusitis without polyps.*Cochrane Database Syst Rev* 2011, Issue 8. Art. No.: CD009274. DOI: 10.1002/14651858.CD009274.

Stjarne P, Mosges R, Jorissen M, Passali D, Bellussi L, Staudinger H, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006;132:179-85.

Stjarne P, Blomgren K, Caye-Thomasen P, Salo S, Soderstrom T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2006;126(6):606-12.

Stjarne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 2009;135(3):296-302.

Tos M, Svendstrup F, Arndal H, Orntoft S, Jakobsen J, Borum P, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. *Am J Rhinol* 1998;12(3):183-9.

Vento SI, Blomgren K, Hytonen M, Simola M, Malmberg H. Prevention of relapses of nasal polyposis with intranasal triamcinolone acetonide after polyp surgery: a prospective double-blind, placebo-controlled, randomised study with a 9-month follow-up. *Clin Otolaryngol* 2012;37:117 23.

Vlckova I, Navrátil P, Kana R, Pavlicek P, Chrbolka P, Djupesland PG. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. *Rhinology* 2009;47(4):419-26.

Chapter7 Appendix

Appendix7.1

Table 7.1 Search strategy

Appendix7.2

Table 7.2 Characteristics of included studies

Appendix7.3

Table 7.4 Adverse events

1	exp steroid/
2	exp anti-inflammatory agent/
3	exp nonsteroid antiinflammatory agent/ or OCULAR-ANTIINFLAMMATORY-AGENT/
4	2 not 3
5	(STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID*).mp
6	BETAMETHASONE.mp.or 378-44-9.rn. or BETAMETASONE.mp. or BETADEXAMETHASONE.mp. or FLUBENISOLONE.mp. or CELESTO*.mp.
7	(HYDROCORTISONE or CORTISOL).mp. or 50-23-7.rn.
8	DEXAMETHASONE.mp.or 50-02-2.rn. or DEXAMETASONE.mp. or HEXADECADROL.mp. or DECADRON.mp. or DEXACORT.mp. or DEXASONE.mp. or HEXADROL.mp. or METHYLFLUORPREDNI SOLONE.mp. or MILLICORTEN.mp. or ORADEXON.mp.
9	BUDESONIDE.mp. or 51333-22-3.rn. or HORACORT.mp. or PULMICORT.mp. or RHINOCORT.mp.
10	FLUNISOLIDE.mp. or 3385-03-3.rn. or NASALIDE.mp. or NASAREL.mp. or RHINALAR.mp.
11	FLUTICASONE.mp. or 90566-53-3.rn. or 80474-14-2.rn. or FLONASE.mp. or FLOUNCE.mp. or FLIXONASE.mp.
12	MOMETASONE.mp. or 105102-22-5.rn. or NASONEX.mp.

13	((TRIAMCINOLONE.mp. or 124-94-7.rn. or NASACORT.mp. or TRI.mp.) adj NASAL.mp.) or ARISTOCORT.mp. or VOLON.mp.
14	BECLOMETHASONE.mp. or 4419-39-0.rn. or BECLAMET.mp. or BECLOCORT.mp. or BECOLMETASONE.mp. or BECOTIDE.mp. or BECONASE.mp. or VANCENASE.mp.
15	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	nose polyp/
17	polyp/ or polyposis/
18	(polyp* or papillom*).tw.
19	17 or 18
20	exp *nose/
21	(NOSE* or NASAL* or NASI or INTRANASAL* or SINONASAL* or PARANASAL*).tw.
22	20 or 21
23	19 and 22
24	rhinopolyp*.tw.

25	16 or 23 or 24
26	15 and 25
27	exp intranasal drug administration/
28	nebulization/ or nebulizer/
29	(spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical*).tw.
30	27 OR 28 OR 29
31	26 AND 30

Table7.1 Search strategy

Aukema, Mulder et al 2005	Methods	Randomised, double-blind, parallel study
	Participants	54 patients Mean age: 44 years Chronic rhinosinusitis with polyps requiring sinus surgery Setting: tertiary care in the Netherlands Sinus surgery status: majority of patients (45/54; 83.3%) had previous sinus surgery. Extent of surgery and timing was not stated.
	Interventions	Treatment group (n = 27) fluticasone propionate 400 µg daily Control group (n = 27) placebo Nasal drop No sinus surgery Taken for 12 weeks
	Outcomes	Primary: number of patients who finally need ESS Secondary: 6 symptoms VAS score, PNIF, CT score, polyp size
	Notes	Funding: GlaxoSmithKline

Aukema, Mulder et al 2005	Random sequence generation	Low risk: Quote "Medications were numbered by means of computerized randomization and were assigned in numeric order"
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "Double-blind randomization to FPNDs or placebo took place " and "Randomization codes were not disclosed until a year after all patients had finished the study."
	Incomplete outcome data	Low risk: Quote "In the intent-to-treat population " Comment: missing data have been imputed using appropriate methods
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Bross-Soriano, Arrieta-Gomez et al 2004	Methods	Randomised, double-blind, parallel study
	Participants	162 patients Mean age: 40.4 years Chronic rhinosinusitis with polyps Setting: tertiary care in Mexico Sinus surgery status: with sinus surgery
	Interventions	Treatment group 1 (n = 54) fluticasone propionate 400 µg daily after nasal lavage Treatment group 2 (n = 54) beclomethasone dipropionate 600 µg daily after nasal lavage Control group (n = 54) nasal lavage Nasal spray Administered after sinus surgery (endoscopic polypectomy) Taken for 78 weeks
	Outcomes	Primary: prevalence of nose and paranasal sinuses infection Secondary: polyp recurrence
	Notes	Funding: not stated

Bross-Soriano, Arrieta-Gomez et al 2004	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	High risk Quote: "..the first group were treated with saline lavage only. ...the second group also received fluticasone propionate ... the third group received beclomethasone dipropionate ... after lavage."
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	High risk: The length of the study was 18 months but the primary outcome was reported at 3 months and the secondary outcome was reported at 12 months after surgery
	Other bias	Low risk: The study appears to be free of other sources of bias

Chalton, Mackay et al 1985	Methods	Randomised, double-blind, parallel study
	Participants	30 patients Mean age: 42 years Chronic rhinosinusitis with polyps Setting: tertiary care in UK Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 15) betamethasone sodium phospate 100 µg twice daily Control group (n = 15) placebo Nasal drop No sinus surgery Taken for 4 weeks
	Outcomes	Primary: polyp size (proportion of responders) Secondary: nasal air flow (number of improved patients)
	Notes	Funding: not stated

Chalton, Mackay et al 1985	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote: "...participate in a double blind, placebo controlled study"
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	High risk: The size of the polyps was the outcome described in Methods but not reported. Disappearance of visible nasal polyps was reported instead.
	Other bias	Low risk: The study appears to be free of other sources of bias

Chur, Small et al 2010	Methods	Randomised, double-blind, parallel study
	Participants	127 patients Mean age: not stated, range 6 to 17 years Chronic rhinosinusitis with polyps Setting: multinational, multicentre (Guatemala and USA) Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 50) mometasone furoate once daily (100 µg or 200 µg up to the age) Treatment group 2 (n = 51) mometasone furoate twice daily (100 µg or 200 µg up to the age) Control group (n = 26) placebo Nasal spray No sinus surgery Taken for 16 weeks
	Outcomes	Primary: 24-hour urinary free cortisol (UFC) change from baseline Secondary: 24-hour UFC corrected for creatinine, adverse events, polyp size, nasal symptoms, sense of smell, investigator-evaluated therapeutic response
	Notes	Funding: not stated

Chur, Small et al 2010	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk Quote: "A 4-month, multinational, double-blind (to treatment) study randomized subjects "
	Incomplete outcome data	Unclear risk: Did not address the incomplete outcome data
	Selective reporting	High risk: Pre-specified sense of smell was not reported
	Other bias	Low risk: The study appears to be free of other sources of bias

Dijkstra, Ebbens et al 2004	Methods	Randomised, double-blind, parallel study
	Participants	162 patients Mean age: 41 years Chronic rhinosinusitis with and without polyps requiring sinus surgery (only data from polyps patients were used for analysis) Setting: tertiary care medical centres in the Netherlands Sinus surgery status: with sinus surgery
	Interventions	Treatment group I (n = 53) 100 µl of fluticasone propionate aqueous 400 µg twice daily Treatment group II (n = 53) 100 µl of fluticasone propionate aqueous 800 µg twice daily Control group (n = 56) placebo spray twice daily Nasal spray Administered after sinus surgery (endoscopic sinus surgery) Taken for 52 weeks or until withdrawal from the trial
	Outcomes	Primary: VAS symptom scores and recurrence rate Secondary: nasal endoscopy findings, adverse events
	Notes	Funding: GlaxoSmithKline

Dijkstra, Ebbens et al 2004	Random sequence generation	Unclear risk: Quote " ... a randomisation code generated by the statistics department of the Erasmus University Medical Centre Rotterdam. Randomization to treatment groups was equal." Comment: did not describe sequence generation process, probably computer-generated?
	Allocation concealment	Low risk: Quote: ... a randomisation code generated by the statistics department of the Erasmus University Medical Centre Rotterdam.
	Blinding	Low risk: Quote: double blind
	Incomplete outcome data	High risk: In the placebo group, 32/56 were withdrawn (22 due to recurrent or persistent disease). In the FPANS 400 µg group, 34/53 were withdrawn (27 due to recurrent or persistent disease). In the FPANS 800 µg group, 37/53 were withdrawn (29 due to recurrent or persistent disease). Comment: reasons for missing data were related to outcomes.Missing outcome data balanced in numbers across intervention groups.
	Selective reporting	High risk: Quote" (in Methods) Study medication was taken for one year and During 11 postoperative visits, VAS scores and nasal endoscopy findings were recorded. Reported in Results: ...median total symptoms score two weeks after FESS" Comment: no VAS after 1 year, no nasal endoscopy reported. Two types of withdrawal listed in Methods, but only one reported.
	Other bias	High risk: High drop-out rate: 103/162 (64%)

Dingsor, Kramer et al 1985	Methods	Randomised, double-blind, parallel study
	Participants	41 patients Mean age: 49 years Chronic rhinosinusitis with polyps Setting: 2 hospitals in Norway Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 20) flunisolide 100 µg twice daily Control group (n = 21) placebo Nasal spray Polypectomy Taken for 52 weeks
	Outcomes	Primary: polyp number, polyp size, symptom Secondary: radiograph, adverse events, ACTH test
	Notes	Funding: not stated

Dingsor, Kramer et al 1985	Random sequence generation	Low risk: Quote " placebo controlled, double blind, parallel design " and "patients were randomly assigned to one of the two treatment groups, according to a computer-generated code"
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote: "It was a placebo controlled, double blind, parallel design " and "The placebo was administered as a vehicle spray identical in appearance to that containing flunisolide."
	Incomplete outcome data	Low risk: Quote: "Patients dropping out because of side effects or lack of effect were to be included in the final analysis"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Drettner, Ebbesen et al 1982	Methods	Randomised, double-blind, parallel study
	Participants	25 patients Mean age: 43.8 years Chronic rhinosinusitis with polyps Setting: not stated Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 14) flunisolide 100 µg twice daily Control group (n = 11) placebo (propyleneglycol and polyethylenglycol) Nasal spray Administered 4 weeks after sinus surgery (polypectomy) Taken for 12 weeks
	Outcomes	Primary: symptom scores and polyp size Secondary: rhinoscopy score, nasal airflow (by rhinomanometry), adverse events
	Notes	Funding: not stated

Drettner, Ebbesen et al 1982	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "The code was not broken until the study was completed" and "The placebo treatment consisted of the vehicle propyleneglycol and polyethylenglycol in the same concentration as in the flunisolide solution and was given exactly in the same way as the active treatment."
	Incomplete outcome data	High risk As-treated analysis. 3/14 (21.4%) patients from the intervention group dropped out whereas none from the control group. Reasons for missing patients were not clear.
	Selective reporting	High risk: Rhinoscopic score (for nasal obstruction, nasal secretion and the state of nasal mucosa) was mentioned under Methods but not reported.
	Other bias	Low risk: The study appears to be free of other sources of bias

Ehnhage, Olsson et al 2009	Methods	Randomised, double-blind, parallel study
	Participants	68 patients Mean age: 51.6 years Chronic rhinosinusitis with polyps with asthma Setting: one tertiary university hospital in Sweden Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 30) fluticasone propionate 400 µg twice daily Control group (n = 38) placebo Nasal drop Administered after sinus surgery (endoscopic sinus surgery) Taken for 10 weeks
	Outcomes	Primary: nasal and asthma symptoms Secondary: polyp size, PNIF, butanol threshold test, peak expiratory flow rate, as needed ß2-agonists for asthma, pulmonary function and bronchial histamine sensitivity, adverse events
	Notes	Funding: GlaxoSmithKline, Swedish Association of Otorhinolaryngology, Head and Neck Surgery, the Acta Otolaryngologica Foundation, Swedish Heart Lung Foundation, Swedish Asthma and Allergy Association, Swedish Medical Research Council

Ehnhage, Olsson et al 2009	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk Quote: "A randomized, double-blind, placebo-controlled phase " and "Both placebo and FPND were produced by (the third party) GlaxoSmithKline (GSK) Australia, and packed in Bad Oldesloe,GSK Germany."
	Incomplete outcome data	Quote: "All randomized patients were included in the statistical analyses, according to the intent-to-treat principle"
	Selective reporting	High risk: Polyp score was reported incompletely
	Other bias	Low risk: The study appears to be free of other sources of bias

El Naggar, Kale et al 1995	Methods	Randomised, double-blind, parallel study
	Participants	29 patients Mean age: 51.5 years Chronic rhinosinusitis with polyps Setting: not stated Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 29 nostril) beclomethasone dipropionate 100 µg twice daily Control group (n = 29 nostril) no treatment Nasal spray Administered after sinus surgery (polypectomy) Taken for 6 weeks
	Outcomes	Primary: University of Pennsylvania Smell Identification Test (UPSIT)
	Notes	Funding: not stated

El Naggar, Kale et al 1995	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	High risk: Steroid treatment versus no treatment
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	Low risk: The study s pre-specified outcome was reported in the pre-specified way
	Other bias	Low risk The study appears to be free of other sources of bias

Filiaci, Passali et al 2000	Methods	Randomised, double-blind, parallel study
	Participants	157 patients Mean age: 47.9 years Chronic rhinosinusitis with polyps Setting: multicentre; 7 tertiary university hospitals in Spain and Italy Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 39) budesonide 140 µg twice daily Treatment group 2 (n = 40) budesonide 280 µg once daily Treatment group 3 (n = 41) budesonide 140 µg once daily Control group (n = 37) placebo Turbuhaler No sinus surgery Taken for 8 weeks
	Outcomes	Primary: polyp size; Secondary: symptom, patients overall evaluation of treatment, adverse events
	Notes	Funding: not stated

Filiaci, Passali et al 2000	Random sequence generation	Low risk: Quote "The trial was a randomized, double-blind, placebo-controlled, parallel-group study" and "On enrolment, patients were allocated a sequential enrolment number. At the end of the run-in period, randomization was performed in balanced blocks of four by allocating these numbers to the four treatment groups in consecutive order"
	Allocation concealment	Low risk: Quote "Details of the treatment received by each patient were held in secure but accessible locations in each centre; the treatment code could only be broken in an emergency, if necessary for the appropriate management of the patient."
	Blinding	Low risk: Quote "Inhalers used for placebo and budesonide treatment were identical in appearance, and labelled with the patient enrolment number. Details of the treatment received by each patient were held in secure but accessible locations in each centre; the treatment code could only be broken in an emergency, if necessary for the appropriate management of the patient."
	Incomplete outcome data	High risk: No imputation of data was performed for withdrawn patients. Reasons for missing outcome data (13/157 or 8.3%) including disease deteriorated or not improved or adverse events were possibly related to true outcomes.
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk The study appears to be free of other sources of bias

Hartwig, Linden et al 1988	Methods	Randomised, double-blind, parallel study
	Participants	73 patients Mean age: 54.2 years Chronic rhinosinusitis with polyps Setting: not stated Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 36) budesonide 200 µg twice daily Control group (n = 37) placebo Nasal aerosol Administered after sinus surgery (polypectomy) Taken for 24 weeks
	Outcomes	Primary: polyp score Secondary: nasal obstruction, adverse events
	Notes	Funding: not stated

Hartwig, Linden et al 1988	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "...placebo-controlled, double-blind, parallel group type" and "The placebo spray was identical in all respects."
	Incomplete outcome data	High risk As-treated analysis was performed. Number of patients at the 3-month follow-up visit shown in Figure (70) did not equal to the text (71).
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk The study appears to be free of other sources of bias

Holmberg, Juliusson et al 1997	Methods	Randomised, double-blind, parallel study
	Participants	55 patients Mean age: 54 years Chronic rhinosinusitis with polyps Setting: not stated Sinus surgery status: with sinus surgery (polypectomy)
	Interventions	Treatment group 1 (n = 19) fluticasone propionate 200 µg twice daily Treatment group 2 (n = 18) beclomethasone dipropionate 200 µg twice daily Control group (n = 18) placebo Nasal spray No sinus surgery Taken for 26 weeks
	Outcomes	Primary: symptom, polyp score Secondary: PNIF, adverse events
	Notes	Funding: Glaxo Wellcome PLC, England and the Torsten and Ragnar Söderberg Foundation, Sweden

Holmberg, Juliusson et al 1997	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk Quote: "...designed as a double-blind, placebo-controlled study with parallel groups" and "The placebo solution was therefore identical to the active treatments but did not contain any active drug."
	Incomplete outcome data	High risk Reason for missing outcome data likely to be related to true outcome, with imbalance in numbers for missing data across intervention groups (39% missing in placebo group, 11% missing in beclomethasone and 21% missing in fluticasone propionate)
	Selective reporting	High risk: Polyp score was pre-specified but not reported.
	Other bias	Low risk: The study appears to be free of other sources of bias

Holmström 1999	Methods	Randomised, double-blind, parallel study
	Participants	104 patients Mean age: not stated Chronic rhinosinusitis with polyps, small and medium size (grade 1 to 2) Setting: multicentre Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 52) fluticasone propionate 400 µg once daily Control group (n = 52) placebo Nasal drop No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size Secondary: peak nasal inspiratory flow, symptom scores, olfactory function, use of rescue medications and need for polypectomy
	Notes	Funding: not stated

Holmström 1999	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "the patients underwent.. double-blind treatment"
	Incomplete outcome data	Low risk: As-treated analysis. Four missing patients out of 104 (3.8%) was not enough to have impact on the intervention effect estimate.
	Selective reporting	High risk: The need for polypectomy was pre-specified but not reported.
	Other bias	Low risk: There are 2 studies (called Study 1 and Study 2) reported in this paper. Only data from Study 1 were recorded in this table. Although data from Study 1 appeared similar to Keith, Nieminen et al 2000 (including number of patients in each arm, patient characteristic of having small and medium size polyp, study drug, dosage, delivery method of nasal drop, the length of treatment, outcomes and results), there is no evidence that these two are the same study. Study 2 was subsequently reported in 2 papers: Penttila, Holmstrom et al 1998 and Penttila, Poulsen et al 2000. Holmstrom was the last author of Penttila, Poulsen et al 2000

Holopainen, Grahne et al 1982	Methods	Randomised, double-blind, parallel study
	Participants	19 patients Mean age: 42 years Chronic rhinosinusitis with polyps, small size with perennial nasal symptoms Setting: tertiary university hospital in Finland Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 10) budesonide 200 µg twice daily Control group (n = 9) placebo Nasal spray Administered after sinus surgery (polypectomy) Taken for 16 weeks
	Outcomes	Primary: symptoms Secondary: polyp size (number of noses having small, medium, large polyps), polyp number (number of patients with increased and decreased number), peak nasal inspiratory flow, morning plasma cortisol, adverse events
	Notes	Funding: not stated

Holopainen, Grahne et al 1982	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "The trial was conducted as a double-blind, placebo-controlled parallel study" and "The placebo was identical with the active spray but without budesonide."
	Incomplete outcome data	Low risk As-treated analysis. One missing patient out of 19 (5%) was not enough to have impact on the intervention effect estimate.
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Jankowski, Schrewelius et al 2001	Methods	Randomised, double-blind, parallel study
	Participants	183 patients Mean age: 44 years Chronic rhinosinusitis with polyps Setting: multicentre (16 study centres in France) Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 48) budesonide 128 µg once daily Treatment group 2 (n = 42) budesonide 128 µg twice daily Treatment group 3 (n = 48) budesonide 256 µg once daily Control group (n = 45) placebo Nasal spray No sinus surgery Taken for 8 weeks
	Outcomes	Primary: polyp size; Secondary: peak nasal inspiratory flow, symptoms, adverse events
	Notes	Funding: not stated

Jankowski, Schrewelius et al 2001	Random sequence generation	Low risk: Quote "...patients were randomized according to a balanced-block design "
	Allocation concealment	Low risk: Quote "Treatment codes for individual patients were kept in secure locations at each study centre"
	Blinding	Low risk: Quote "The trial was a randomized, double blind, placebo-controlled, parallel group study" and "All study medication was identical in appearance."
	Incomplete outcome data	Low risk: Missing outcome data balanced in numbers across intervention groups (7, 5, 5, 5 in treatment group 1, 2, 3 and control group, respectively) and seem not enough (22/183) to have a clinically relevant impact on the intervention effect estimate.
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk The study appears to be free of other sources of bias

Jankowski, Klossek et al 2009	Methods	Randomised, double-blind, parallel study
	Participants	242 patients Mean age: 51 years Chronic rhinosinusitis with polyps Setting: multicentre in France Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 161) fluticasone propionate 100 µg twice daily Control group (n = 81) placebo Nasal spray No sinus surgery Taken for 4 weeks
	Outcomes	Primary: peak nasal inspiratory flow Secondary: polyp size, symptoms, adverse events
	Notes	Funding: not stated

Jankowski, Klossek et al 2009	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "This was a multi-centre, randomized, double-blind, parallel group, placebo-controlled, 8-month study"
	Incomplete outcome data	Low risk Quote: "The Intent-to-Treat (ITT) population, defined as primary population for analyses, consisted of all patients randomized to treatment "
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Johansen, Illum et al 1993	Methods	Randomised, double-blind, parallel study
	Participants	Randomised, double-blind, parallel study Participants 91 patients Mean age: 52 years Chronic rhinosinusitis with polyps, small and medium sized Setting: multicentre, 5 in Denmark and 1 in Sweden Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (number not given) budesonide aqua 200 µg twice daily Treatment group 2 (number not given) budesonide aerosol 200 µg twice daily Control group (number not given) placebo Nasal spray (for Treatment group 1) and aerosol (for Treatment group 2) No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size; Secondary: symptoms, sense of smell, peak inspiratory flow, peak expiratory flow, adverse events
	Notes	Funding: Astra Danmark A/S and Astra Draco AB, Sweden

Johansen, Illum et al 1993	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	High risk Comment: although was stated to be double-blind (Quote"...placebo controlled double-blind study"), there was no description how the authors blinded patients receiving 2 different delivery methods (spray and aerosol). Patients in control group may receive either spray or aerosol (Quote: "The patients were treated with either...placebo aqua or aerosol"). There was a also comparison between steroid spray and steroid aerosol.
	Incomplete outcome data	Low risk Missing outcome data seem not enough (5.5%) to have a clinically relevant impact on the intervention effect estimate
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk The study appears to be free of other sources of bias

Johansson, Holmberg et al 2002	Methods	Randomised, double-blind, parallel study
	Participants	98 patients Mean age: 56 years Chronic rhinosinusitis with polyps Setting: tertiary university hospital in Sweden Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 50) budesonide 128 µg twice daily Control group (n = 48) placebo Nasal spray No sinus surgery Taken for 2 weeks
	Outcomes	Primary: polyp size, symptoms, peak nasal inspiratory flow
	Notes	Funding; AstraZeneca supplied the study drugs. Funds from the Central Hospital of Skovde

Johansson, Holmberg et al 2002	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "...in a double-blind fashion"
	Incomplete outcome data	Low risk: One missing patient out of 98 (1%) was not enough to have impact on the intervention effect estimate
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Jorissen and Bachert 2009	Methods	Randomised, double-blind, parallel study
	Participants	41 patients Mean age: 47.4 years Chronic rhinosinusitis with and without polyps (only data from polyps patients was used for analysis) Setting: multicentre (2 tertiary university hospitals in Belgium) Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 16) betamethasone 2 mg tablets for 7 days, followed by mometasone furoate 200 µg once daily Control group (n = 25) placebo tablets and spray Nasal spray Administered after sinus surgery (endoscopic sinus surgery) Taken for 24 weeks
	Outcomes	Primary: endoscopic score Secondary outcomes: symptoms, combination endoscopic score for inflammation, oedema and polyps, the percentage of patients requiring rescue medication, patients' opinion of treatment success, adverse events
	Notes	Funding: Schering-Plough Corp

Jorissen and Bachert 2009	Random sequence generation	Low risk: Quote "This was a 2-arm, randomized, double-blind, placebo-controlled, prospective study" and "Randomization to treatment was achieved according to a computer-generated sequential list "
	Allocation concealment	Low risk: Quote "Randomization to treatment was achieved according to a computer-generated sequential list, which was provided to each participating centre s pharmacy for distribution of appropriate study medication to the investigator and subsequently to the patient, in a double-blinded manner"
	Blinding	Low risk: Quote "...distribution of appropriate study medication to the investigator and subsequently to the patient, in a double-blinded manner"
	Incomplete outcome data	Low risk: Quote "Analyses of efficacy assessments were performed on the intent-to-treat (ITT) population "
	Selective reporting	High risk: The patient' opinion of treatment success was planned in the Methods but not reported.
	Other bias	Low risk: The study appears to be free of other sources of bias

Jurkiewicz, Zielnik-Jurkiewicz et al 2004	Methods	Randomised, double-blind, parallel study
	Participants	86 patients Mean age: not stated, range 26 to 72 years Chronic rhinosinusitis with polyps Setting: tertiary care in Poland Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 46) fluticasone propionate 400 µg twice daily Control group (n = 40) no treatment Nasal spray Administered after sinus surgery (polypectomy) Taken for 52 weeks
	Outcomes	Primary: symptoms Secondary outcomes: rhinomanometry, CT, laryngological exam, endoscopy
	Notes	Funding: not stated

Jurkiewicz, Zielnik-Jurkiewicz et al 2004	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	High risk Quote: " first group was treated after polypectomy with Flixonase during one year second group underwent surgical treatment of nasal polyps only"
	Incomplete outcome data	Unclear risk: Insufficient reporting of attrition/exclusions to permit judgement of Yes or No
	Selective reporting	High risk: Rhinomanometry and CT scan were pre-specified outcomes but not reported
	Other bias	Low risk: The study appears to be free of other sources of bias

Karlsson and Rundcrantz 1982	Methods	Randomised, double-blind, parallel study
	Participants	40 patients Mean age: 49 years Chronic rhinosinusitis with polyps, severe Setting: not stated Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 20) beclomethasone dipropionate 400 µg once daily for 1 month then 200 µg once daily for 29 months Control group (n = 20) no treatment Intranasal, delivery method: not stated Administered after sinus surgery (polypectomy) Taken for 120 weeks
	Outcomes	Primary: polyp size Secondary outcomes: adverse events
	Notes	Funding: not stated

Karlsson and Rundcrantz 1982	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	High risk: Quote "One group received no medical treatment after the polypectomy other 20 patients were treated postoperatively with beclomethasone dipropionate "
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Keith, Nieminen et al 2000	Methods	Randomised, double-blind, parallel study
	Participants	104 patients Mean age: 48 years Chronic rhinosinusitis with polyps, small and medium size (grade 1 to 2) Setting: multicentre in 11 study centres in Canada and Finland Sinus surgery status: with sinus surgery. Majority of patients (72/104; 69%) had previous sinus surgery. Extent of surgery was not stated.
	Interventions	Treatment group (n = 52) fluticasone propionate 400 µg once daily Control group (n = 52) placebo Nasal drop No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size Secondary: symptoms, peak nasal inspiratory flow, University of Pennsylvania Smell Identification Test (UPSIT), butanol threshold smell test, use of rescue medications and adverse events
	Notes	Funding: Glaxo Wellcome plc, UK

Keith, Nieminen et al 2000	Random sequence generation	Low risk: Quote "..a block of treatments, pre-coded with computer randomized numbers"
	Allocation concealment	Low risk: Quote "Each investigator was given a block of treatments, pre-coded with computer randomized numbers, which were assigned"
	Blinding	Low risk: Quote "This was an international multicentre, double-blind, randomized, parallel group study " and "FPND ..and placebo solution were supplied in identical opaque nasal drop containers, in a foil pack."
	Incomplete outcome data	Low risk: Quote "The primary population for the analysis of efficacy and safety was the intent to treat population"
	Selective reporting	High risk: The polyp size using 4-point scoring system which was the primary endpoint was not reported.
	Other bias	Low risk: The study appears to be free of other sources of bias

Lang and McNeill 1983	Methods	Randomised, double-blind, parallel study
	Participants	32 patients Mean age: 42 years Chronic rhinosinusitis with polyps, small and medium size (the term used in the paper is 'simple polyps') Setting: not stated Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 14) beclomethasone dipropionate 400 µg twice daily Control group (n = 18) placebo Nasal spray No sinus surgery Taken for 104 weeks
	Outcomes	Primary: symptoms, polyp size
	Notes	Funding: not stated

Lang and McNeill 1983	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "This allocation was kept blind from both patient and investigator"
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	High risk Subjective assessment of nasal obstruction, sneezing and nasal discharge was not reported. Grade of nasal polyp described under Methods was not reported.
	Other bias	Low risk: The study appears to be free of other sources of bias

Lildholdt, Rundcrantz et al 1995	Methods	Randomised, double-blind, parallel study
	Participants	93 patients Mean age: 51 years Chronic rhinosinusitis with polyps Setting: multicentre in Denmark and Sweden Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 40) budesonide 200 µg twice daily Treatment group 2 (n = 44) budesonide 400 µg twice daily Control group (n = 42) placebo Powder insufflation (turbuhaler) No sinus surgery Taken for 4 weeks
	Outcomes	Primary: polyp size Secondary: symptoms, nasal and oral expiratory peak flows, semi-quantitative test of smell, overall assessment of treatment efficacy, adverse events
	Notes	Funding: not stated

Lildholdt, Rundcrantz et al 1995	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "This double-blind, placebo-controlled trial "
	Incomplete outcome data	High risk: Reasons for drop-out were disease deterioration and side effects which may have impact on the intervention effect estimate. The number of discontinued patients did not balance across study groups.
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Lund, Flood et al 1998	Methods	Randomised, double-blind, parallel study
	Participants	29 patients Mean age: 49.3 years Chronic rhinosinusitis with polyps requiring sinus surgery Setting: tertiary centre in London Sinus surgery status: with sinus surgery. Majority of patients (19/29; 65.5%) had previous sinus surgery (polypectomy)
	Interventions	Treatment group 1 (n = 10) fluticasone propionate 400 µg twice daily Treatment group 2 (n = 10) beclomethasone dipropionate 400 µg twice daily Control group (n = 9) placebo Nasal spray No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size Secondary: symptoms, PNIF, acoustic rhinometry, adverse events
	Notes	Funding: Glaxo Wellcome research and development public limited

Lund, Flood et al 1998	Random sequence generation	Low risk: Quote " randomly allocated, using a computer-generated random code and a block size "
	Allocation concealment	Low risk: Quote "Patients were randomly allocated, using a computer-generated random code and a block size of 6, to receive 1 of 3 treatments "
	Blinding	Low risk: Quote " randomized, double-blind the placebo was identical to the active formulations "
	Incomplete outcome data	Low risk Quote: "...results expressed in this study involve using the last-value-carried-forward technique to avoid treatment bias"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Mastalerz, Milewski et al 1997	Methods	Randomised, double-blind, parallel study
	Participants	15 patients Mean age: 44.7 years Aspirin sensitivity including 9/15 (60%) patients of chronic rhinosinusitis with polyps Setting: tertiary university hospital in Poland Sinus surgery status: without sinus surgery
	Interventions	Treatment group (n = 15) fluticasone propionate 400 µg once daily Control group (n = 15) placebo Nasal spray No sinus surgery Taken for 4 weeks
	Outcomes	Primary: nasal L-ASA provocation test Secondary: symptoms, PNIF, pulmonary function test
	Notes	Funding: Glaxo Wellcome, Poland

Mastalerz, Milewski et al 1997	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "Then the patients received FP or placebo in a randomized, double-blind, crossover design" and "Placebo solution, identical in appearance to FP, was administered in the same way"
	Incomplete outcome data	Unclear risk: Insufficient reporting of attrition/exclusions to permit judgement of Yes or No
	Selective reporting	High risk Lung function tests (FEV1, FVC and MEF50) were mentioned in Methods but not reported in Results.
	Other bias	Low risk: The study appears to be free of other sources of bias

Mygind, Pedersen et al 1975	Methods	Randomised, double-blind, parallel study
	Participants	35 patients Mean age: 51 years Chronic rhinosinusitis with polyps, moderate to severe Setting: 2 tertiary university hospitals in Denmark Sinus surgery status: with sinus surgery. On average, polyp was removed 8 times in each patient.
	Interventions	Treatment group (n = 19) beclomethasone dipropionate 100 µg 4 times daily Control group (n = 16) placebo Aerosol No sinus surgery Taken for 3 weeks
	Outcomes	Primary: symptoms Secondary: polyp size, adverse events
	Notes	Funding: Glaxo, Copenhagen provided the aerosols

Mygind, Pedersen et al 1975	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "In a double-blind trial "
	Incomplete outcome data	Low risk: No missing outcome data
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Olsson, Ehnhage et al 2010	Methods	Randomised, double-blind, parallel study
	Participants	68 patients Mean age: 51.6 years Chronic rhinosinusitis with polyps with asthma Setting: 1 tertiary university hospital in Sweden Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 30) fluticasone propionate 400 µg twice daily Control group (n = 38) placebo Nasal drop Administered after sinus surgery (endoscopic sinus surgery) Taken for 10 weeks
	Outcomes	Primary: quality of life
	Notes	Funding: GlaxoSmithKline, the Swedish Association of Otorhinolaryngology, Head and Neck Surgery, the Acta Otolaryngologica Foundation, and the Swedish Asthma and Allergy Association

Olsson, Ehnhage et al 2010	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "This randomized, double-blind, placebo-controlled study "
	Incomplete outcome data	Low risk: Quote "According to the Intent-to-treat principle "
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Passali, Bernstein et al 2003	Methods	Randomised, double-blind, parallel study
	Participants	170 patients Mean age: 37.3 years Chronic rhinosinusitis with polyps, severe stage 3 Setting: 1 tertiary university hospital in Italy Sinus surgery status: with sinus surgery
	Interventions	Treatment group 1 (n = 97) intranasal furosemide 200 µg once daily Treatment group 2 (n = 33) mometasone furoate 400 µg once daily Control group (n = 40) placebo Nasal spray Administered after sinus surgery (endoscopic sinus surgery) Taken for 1 to 9 years for Treatment group 1, 1 to 3 years for Treatment group 2, and 1 to 6 years for control group
	Outcomes	Primary: polyp recurrence Secondary: adverse event
	Notes	Funding: not stated

Passali, Bernstein et al 2003	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	High risk: Quote "From January 7, 1991, to December 22, 1997, we assigned patients to furosemide treatment (group 1) or placebo (group 2). Subsequently, considering the positive results obtained with furosemide, we decided to compare the efficacy of this drug with that of a topical corticosteroid (mometasone), ... we continued to enrol patients into the furosemide group, ceased to enrol patients into group 2 (placebo), and began to enrol patients into the mometasone group (group 3)."
	Blinding	High risk: Quote "Group 2 received no specific treatment" and "group 1 follow-up range, 1-9 years; group 2, 1-6 years; and group 3, 1-3 years" Comment: no mention about blinding in the study
	Incomplete outcome data	Low risk: Quote "no patient abandoned therapeutic protocols" Comment: no missing outcome data
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	High risk: Had a potential source of bias related to the specific study design used, as no blinding and different time frames for collecting patients, i.e. the steroid patients were only analysed for 3 years compared to 9 years for furosemide

Penttila, Poulsen et al 2000	Methods	Randomised, double-blind, parallel study
	Participants	142 patients Mean age: 51 years Chronic rhinosinusitis with polyps, mild to moderate Setting: multinational, multicentre in 12 centres in Denmark (3), Finland (1) and Sweden (8) Sinus surgery status: with sinus surgery. Majority of patients (102/142; 72%) had previous sinus surgery. Extent of surgery was not stated.
	Interventions	Treatment group 1 (n = 47) fluticasone propionate 400 µg twice daily Treatment group 2 (n = 48) fluticasone propionate 400 µg once daily Control group (n = 47) placebo Nasal drop No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size, symptoms, PNIF, degree of nasal blockage Secondary: butanol threshold test, UPSIT test, adverse events
	Notes	Funding: Glaxo Wellcome plc, UK

Penttila, Poulsen et al 2000	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "Active and placebo nasal drops were provided in identical single-dose containers"
	Incomplete outcome data	Low risk: Quote "The primary population for the analysis of efficacy and safety was the Intent-to-Treat Population which included all randomized patients who took at least one dose of study medication"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Rotenberg, Zhang et al 2011	Methods	Randomised, double-blind, parallel study
	Participants	64 patients Mean age: 47.5 years Chronic rhinosinusitis with polyps with Samter's triad Setting: tertiary university hospital in Canada Sinus surgery status: with sinus surgery
	Interventions	Treatment group 1 (n = 21) nasal irrigation 60 ml each nostril twice daily plus budesonide nasal spray 128 µg twice daily Treatment group 2 (n = 21) nasal irrigation 60 ml each nostril twice daily plus budesonide 500 µg added twice daily Control group (n = 22) nasal irrigation 60 ml each nostril twice daily Nasal spray (Treatment group 1) and nasal irrigation (Treatment group 2) Administered after sinus surgery (endoscopic sinus surgery) Taken for 1 year
	Outcomes	Primary: disease-specific quality of life (SNOT-21); Secondary: endoscopy score, CT score, intraocular pressure, adrenocorticotropic hormone levels
	Notes	Self funding

Rotenberg, Zhang et al 2011	Random sequence generation	Unclear risk: Quote "We conducted a triple-arm, randomized, blinded, controlled trial" Comment: insufficient information to permit judgement of Yes or No
	Allocation concealment	High risk: Quote "When the prescriptions were filled they were placed in a series"
	Blinding	High risk: One group used nasal saline irrigation only while the other group used nasal irrigation plus nasal spray
	Incomplete outcome data	Low risk: 'As-treated' analysis. Four missing patients out of 64 (6.25%) was not enough to have impact on the intervention effect estimate.
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Row-Jones, Medcalf et al 2005	Methods	Randomised, double-blind, parallel study
	Participants	109 patients Mean age: 41 years Chronic rhinosinusitis with polyps (71%) and without polyps (29%) Setting: tertiary university hospital in UK Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 55) fluticasone propionate 200 µg twice daily Control group (n = 54) placebo Nasal spray Administered after sinus surgery (endoscopic sinus surgery) Taken for 5 years
	Outcomes	Primary: symptoms, polyp size Secondary: rescue medication requirements and the number of failures in each treatment group
	Notes	Funding: GlaxoSmithKline

Row-Jones, Medcalf et al 2005	Random sequence generation	Low risk: Quote "...were randomly allocated by computer generated number to FPANS or placebo postoperatively for five years"
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote " a prospective, stratified, randomised, double-blind, placebo controlled, parallel group study" and "Placebo spray comprised all the constituents of the standard FPANS spray, excluding fluticasone propionate"
	Incomplete outcome data	Low risk: Quote "The values recorded at their time of failure were brought forward for inclusion in each subsequent postoperative time period analysis. This last value carried forward analysis also included the last data from patients were lost to follow-up over the study but who had not failed"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Ruhno, Andersson et al 1990	Methods	Randomised, double-blind, parallel study
	Participants	36 patients Mean age: 46.6 years Chronic rhinosinusitis with polyps Setting: tertiary university hospital in Canada Sinus surgery status: with sinus surgery. Majority of patients had previous sinus surgery with the mean number of previous surgery of 5.6 times.
	Interventions	Treatment group (n = 18) budesonide 400 µg twice daily Control group (n = 18) placebo Nasal spray No sinus surgery Taken for 4 weeks
	Outcomes	Primary: symptom score, symptom frequency Secondary: investigators' assessment nasal obstruction score, overall assessment, PNIF, lung function test, adverse events
	Notes	Funding: Draco AB, Lund, Sweden

Ruhno, Andersson et al 1990	Random sequence generation	Low risk Quote: "..randomized parallel group design" and "Patients...were enrolled serially to receive..."
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote "Budesonide and placebo was provided in identical nasal applicator"
	Incomplete outcome data	Low risk: Quote "...all patients completed the study according to the protocol"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Small, Hernandez et al 2005	Methods	Randomised, double-blind, parallel study
	Participants	354 patients Mean age: 47.5 years Chronic rhinosinusitis with polyps Setting: multinational, multicentre in 44 centres Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 115) mometasone furoate 200 µg once daily Treatment group 2 (n = 122) mometasone furoate 200 µg twice daily Control group (n = 117) placebo Nasal spray No sinus surgery Taken for 16 weeks
	Outcomes	Primary: polyp size, congestion/obstruction score Secondary: loss of smell, anterior rhinorrhoea, posterior nasal drip, PNIF, subjective improvement of obstruction and symptomatic therapeutic response, adverse events
	Notes	Funding: the Schering-Plough Research Institute

Small, Hernandez et al 2005	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk: Quote: "A randomized, double-blind, double-dummy, placebo-controlled study was carried out "
	Incomplete outcome data	Low risk Quote: "Analyses and summaries were based on all randomized subjects (intent-to-treat principle) and were performed "
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Stjarne, Mosges et al 2006	Methods	Randomised, double-blind, parallel study
	Participants	Methods Randomised, double-blind, parallel study Participants 310 patients Mean age: 48.6 years Chronic rhinosinusitis with polyps Setting: multinational, multicentre in 24 centres, 17 countries Sinus surgery status: without sinus surgery
	Interventions	Treatment group 1 (n = 102) mometasone furoate 200 µg once daily Treatment group 2 (n = 102) mometasone furoate 200 µg twice daily Control group (n = 106) placebo Nasal spray No sinus surgery Taken for 16 weeks
	Outcomes	Primary: polyp size, obstruction score; Secondary: loss of smell, anterior rhinorrhoea, posterior nasal drip, PNIF, subjective improvement of obstruction and symptomatic response, adverse events
	Notes	Funding: the Schering-Plough Research Institute

Stjarne, Mosges et al 2006	Random sequence generation	Low risk: Quote "Randomization was performed in blocks of 3 using random numbers ... with seed based on clock time. Randomization was stratified by the presence or absence of concurrent asthma."
	Allocation concealment	Low risk Quote: "Randomization was ...generated by SAS function UNIFORM (SAS Institute, Cary, NC) with seed based on clock time."
	Blinding	Low risk: Quote "Treatment was administered for 4 months in a blinded manner "
	Incomplete outcome data	Low risk: Quote "Summaries of data were based on all randomized subjects (intent-to-treat principle)"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Stjarne, Blomgren et al 2006	Methods	Randomised, double-blind, parallel study
	Participants	298 patients Mean age: 53 years Chronic rhinosinusitis with polyps Setting: multinational multicentre in 12 centres in Denmark, Finland, Norway and Sweden Sinus surgery status: without sinus surgery. Minority of patients (61/298; 20.5%) had previous sinus surgery.
	Interventions	Treatment group (n = 153) mometasone furoate 200 µg once daily Control group (n = 145) placebo Nasal spray No sinus surgery Taken for 16 weeks
	Outcomes	Primary: congestion/obstruction score Secondary: polyp size, loss of smell, rhinorrhoea, PNIF, symptomatic therapeutic response, olfactory threshold, adverse events
	Notes	Funding: Schering-Plough

Stjarne, Blomgren et al 2006	Random sequence generation	Low risk: Quote "They were subsequently randomized at the baseline visit " and "...according to a computer-generated code to receive..."
	Allocation concealment	Low risk Quote: "The randomization schedule for the blinded treatments was maintained by the sponsor and only disclosed after the study was completed and the database closed."
	Blinding	Low risk Quote: "This randomized, double-blind, double-dummy, placebo-controlled trial "
	Incomplete outcome data	Low risk Quote: "All analyses and summaries are based on the intent-to-treat (ITT) population "
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Stjarne, Olsson et al 2009	Methods	Randomised, double-blind, parallel study
	Participants	159 patients Mean age: 48.5 years Chronic rhinosinusitis with polyps Setting: multicentre in 10 centres in Sweden Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 79) mometasone furoate 200 µg once daily Control group (n = 80) placebo Nasal spray Administered after sinus surgery (endoscopic sinus surgery) Taken for 24 weeks
	Outcomes	Primary: time to relapse, polyp size Secondary: symptoms, PNIF, butanol olfactory threshold test, adverse events
	Notes	Funding: Schering-Plough

Stjarne, Olsson et al 2009	Random sequence generation	Low risk: Quote "...those who met entry criteria were assigned a study number and randomized in a 1:1 ratio to receive " and "...according to a computer-generated code created by a statistician (M.Å.)" and "Randomization was performed in blocks of 4 by means of a random number generated by SAS function and based on clock time"
	Allocation concealment	Low risk: Quote "according to a computer-generated code created by a statistician (M.Å.)." Comment: M.Å. was the last author but probably was not involved in administering the interventions and outcomes assessment
	Blinding	Low risk: Quote "All participants, investigators, and staff administering the interventions and staff assessing the outcomes were blinded to group assignment" Comment: group assignment was done by the last author who probably was not involved in administering the interventions and outcomes assessment
	Incomplete outcome data	Low risk: Quote "The intent-to-treat (ITT) population included all subjects who received 1 or more doses of the study medication and had baseline and post baseline data"
	Selective reporting	High risk: Polyp size and extension (mentioned in Methods) were not reported
	Other bias	High risk: High drop-out rate (46% drop-out in the steroid arm and 54% drop-out in the placebo arm)

Tos, Svendstrup et al 1998	Methods	Randomised, double-blind, parallel study
	Participants	138 patients Mean age: not stated, range 20 to 82 years Chronic rhinosinusitis with polyps, moderate or severe Setting: multicentre in 4 centres in Denmark Sinus surgery status: with sinus surgery. Patients in all groups had multiple previous polyp removals.
	Interventions	Treatment group 1 (n = 46) budesonide 128 µg twice daily Treatment group 2 (n = 45) budesonide 200 µg twice daily Control group 1 (n = 24) placebo Control group 2 (n = 23) placebo Nasal spray for Treatment group 1 and turbuhaler for Treatment group 2 No sinus surgery Taken for 6 weeks
	Outcomes	Primary: polyp size; Secondary: symptoms, sense of smell, patients' overall evaluation of treatment of efficacy, adverse events
	Notes	Funding: Astra Draco, AB Sweden

Tos, Svendstrup et al 1998	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk Quote: "The study was of double-blind (with respect to each of the active groups and placebo)" and "...there was no blinding between the two formulations, Rhinocort Aqua and Rhinocort Turbuhaler" Comment: no blinding between groups of Rhinocort Turbuhaler and Rhinocort Aqua, however keeping our primary objective in mind, blinding would still be low risk comparing placebo to nasal corticosteroids
	Incomplete outcome data	Low risk: Quote "The Intent To Treat analysis included all 138 randomized patients"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Vento, Blomgren et al 2012	Methods	Randomised, double-blind, parallel study
	Participants	60 patients Mean age: 51.4 years Chronic rhinosinusitis with polyps Setting: tertiary university hospital in Finland Sinus surgery status: with sinus surgery
	Interventions	Treatment group (n = 30) triamcinolone acetonide 220 µg daily Control group (n = 30) placebo 220 µg daily Nasal aerosol Administered after sinus surgery (endoscopic sinus surgery) Taken for 9 months
	Outcomes	Primary outcomes: polyp size, olfactory threshold, active anterior rhinomanometry and acoustic rhinometry Secondary outcomes: symptoms, use of rescue medication, adverse effects
	Notes	Funding: Rhone-Poulenc Rorer

Vento, Blomgren et al 2012	Random sequence generation	Low risk: Quote "A statistician drew up a computer-generated randomisation list"
	Allocation concealment	Low risk Quote: "The pharmacy supplied the investigators with identical bottles, numbered according to the randomisation list"
	Blinding	Low risk: Quote "The pharmacy supplied the investigators with identical..."
	Incomplete outcome data	High risk: 'As-treated' analysis. 17 out of 69 (24.6%) was not big enough to have impact on the intervention effect estimate
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Vlckova, Navrátil et al 2009	Methods	Randomised, double-blind, parallel study
	Participants	109 patients Mean age: 47.9 years Chronic rhinosinusitis with polyps, mild to moderate Setting: multicentre in 5 centres in the Czech Republic Sinus surgery status: with sinus surgery. Majority of patients (71/109; 65.1%) had previous sinus surgery. Extent of surgery was not stated.
	Interventions	Treatment group (n = 54) fluticasone propionate 400 µg twice daily Control group (n = 55) placebo Nasal spray using breath-actuated bi-directional delivery device No sinus surgery Taken for 12 weeks
	Outcomes	Primary: polyp size Secondary: PNIF, symptoms, patients' sense of smell, use of rescue medication, adverse events
	Notes	Funding: not stated

Vlckova, Navrátil et al 2009	Random sequence generation	Unclear risk: Did not describe sequence generation process
	Allocation concealment	Unclear risk: Did not describe allocation sequence concealment
	Blinding	Low risk Quote: "prospective, randomized, double-blind, placebo-controlled, parallel group study" and "Opt-FP and placebo breath-actuated bi-directional delivery devices were identical in appearance" and "The placebo aqueous nasal spray was formulated to match FP exactly, except for the active ingredient"
	Incomplete outcome data	Low risk: Quote "All 109 subjects received at least one dose of study medication and underwent one baseline and one post-baseline assessment, allowing inclusion in the ITT population for efficacy analyses and the safety population"
	Selective reporting	Low risk: All of the study s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	Other bias	Low risk: The study appears to be free of other sources of bias

Table 7.2 Characteristics of included studies

Footnotes

CT: computerised tomography

ESS: endoscopic sinus surgery

FEV1: forced expiratory volume in one second FP: fluticasone propionate

FPANS: fluticasone propionate aqueous nasal spray

FPND: fluticasone propionate nasal drops

FVC: forced vital capacity

ITT: intention-to-treat

PNIF: peak nasal inspiratory flow

UFC: urinary free cortisol

UPSIT: University of Pennsylvania Smell Identification Test

VAS: visual analogue scale

Study ID	Steroid group n (%)	Placebo group n (%)	Description of events reported	Remarks
Chur, Small et al 2010				There was no difference in 24-hour urinary free cortisol change in all groups
Dijkstra, Ebbens et al 2004				The incidence of epistaxis was not higher in the steroid group
Dingsor, Kramer et al 1985	6 (30)	10 (48)	Itching, sore throat, sneeze, blood traces, nausea	No patients had abnormal plasma cortisol
Drettner, Ebbesen et al 1982	4 (36)	7 (64)	Nasal irritation, blood stained mucus, nasal crust, eye irritation, cataract, pharynx irritation	
Ehnhage, Olsson et al 2009	22 (73)	18 (47)		70% mild, 23% moderate, 7% serious severity
Filiaci, Passali et al 2000			Viral infection, abdominal pain, bronchitis, respiratory infection	80% are mild to moderate
Hartwig, Linden et al 1988	9 (25)	1 (3)	Nose bleed, nasal irritation	
Holmström 1999	14 (14)	18 (18)	Epistaxis, throat irritation, nose dryness	There was no change in morning serum cortisol and no difference between treatment groups in the overall frequency of adverse events

Holopainen, Grahne et al 1982			Transient nasal stinging and slight throat irritation	Mean morning plasma cortisol was not different between before and 4 months after treatment in both groups. Local SE were mild in both groups.
Jankowski, Schrewelius et al 2001	16 (33)	5 (11)	Blood-tinged nasal secretion, headache, bronchospasm	Most events are mild or moderate
Jankowski, Klossek et al 2009				The incidence of adverse events was similar in all groups
Johansen, Illum et al 1993			Dry nose, headache, epistaxis	No differences between treatment groups
Jorissen and Bachert 2009	10 (63)	16 (62)	Headache, sinusitis, cold	Rare serious events
Keith, Nieminen et al 2000	12 (23)	9 (17)	Epistaxis, headache, viral respiratory infection	No serious events. No difference between groups in serum cortisol level.
Lildholdt, Rundcrantz et al 1995			Epistaxis, dryness	No serious events
Lund, Flood et al 1998	7 (70)	3 (33)	Asthma, respiratory infection, headache	No serious events
Mygind, Pedersen et al 1975	8 (44)	0 (0)	Nasal infection	
Penttila, Poulsen et al 2000	21 (45)	27 (57)	Respiratory infection, epistaxis	No serious events. No difference in incidence of events between groups.
Ruhno, Andersson et al 1990	6 (33.3)	5 (27.8)	Headache, epistaxis, dizziness	No serious events
Small, Hernandez et al 2005	56 (49)	64 (55)	Epistaxis and headache	Most adverse events are mild or moderate and unrelated to study treatment

Stjarne, Mosges et al 2006	54 (53)	54 (51)	Respiratory infection, headache, epistaxis	Most adverse events are mild or moderate
Stjarne, Blomgren et al 2006	93 (61)	68 (47)	Epistaxis	Most adverse events are mild or moderate. All epistaxis were mild.
Stjarne, Olsson et al 2009	11 (14)	9 (11)	Epistaxis, dyspepsia, obstruction, headache, sneezing, nausea, nasal congestion, rhinorrhoea, skin irritation	Most adverse events are mild or moderate
Tos, Svendstrup et al 1998			Respiratory infection, nasal mucosal blood, rhinitis, bronchospasm, headache	No serious events
Vento, Blomgren et al 2012	13-17 (43-57)	16-19 (55-63)	Drying, crusting, blood in secretion	No serious events. No differences between treatment groups.
Vlckova, Navrátil et al 2009	13 (24)	11 (20)	Epistaxis	No serious adverse events. Morning plasma cortisol was not changed.

Table 7.4 Adverse events

Chapter 8

Sinus surgery and delivery method influence the effectiveness of topical corticosteroid for chronic rhinosinusitis; systematic review and meta-analysis


Sinus surgery and delivery method influence the effectiveness of topical corticosteroid for chronic rhinosinusitis: Systematic review and meta-analysis

Kornkiat Snidvongs, M.D.,[1,2] Larry Kalish, M.D., M. Med. (Clin Epi),[3,4] Raymond Sacks, M.D.,[1,3,4] Rahuram Sivasubramaniam, M.D.,[5] Daron Cope, M.D.,[6] and Richard J Harvey, M.D.[1,6,7]

ABSTRACT

MATERIALS AND METHODS

Search Methods for Identification of Studies

Criteria for Included Studies

American Journal of Rhinology & Allergy 1

"This study aims to assess the effects of topical steroid for CRS and how sinus surgery and topical delivery method influence the impact of topical steroid."

Abstract

Background

Published randomized controlled trials (RCTs) on the efficacy of intranasal corticosteroid (INCS) in chronic rhinosinusitis (CRS) use either nasal delivery (nasal drop, nasal spray) or sinus delivery (sinus catheter, sinus irrigation) in patients with or without sinus surgery. This influences topical drug delivery and distribution. The effect of these factors on the published results of RCTs is assessed.

Objectives

This systematic review explores the strength of evidence supporting the influence of sinus surgery and delivery methods on the effectiveness of topical steroids in studies for CRS with meta-analyses.

Methods

A systematic review was conducted of RCTs comparing INCS with either placebo or no intervention for treating CRS. Data were extracted for meta-analysis and subgroup analyses by sinus surgery status and topical delivery methods.

Results

Forty-eight studies (3961 patients) met the inclusion criteria. INCS improved overall symptoms (standardized mean difference (SMD) -0.49, p <0.00001) and the proportion of responders (risk ratio (RR) 0.59, p<0.00001) compared to placebo. It decreased polyp size with a greater proportion of responders (RR 0.48, p <0.00001) and prevented polyp recurrence (RR 0.59, p= 0.0004) compared with placebo. Reduction of polyp size was greater in patients with sinus surgery (RR 0.31; 95%CI (0.20, 0.48)) than those without (RR 0.61; 95%CI (0.46, 0.81)), p=0.009. Greater

symptom improvement occurred when sinus delivery methods (SMD -1.32; 95%CI (-2.26,-0.38)) were compared to nasal delivery methods (SMD -0.38; 95%CI (-0.55,-0.22), $p < 0.00001$).

Conclusions

INCS is effective for CRS. Prior sinus surgery and direct sinus delivery appear to enhance the effectiveness of INCS in CRS.

Introduction

Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Anti-inflammatory therapy, including corticosteroid(Snidvongs, Pratt et al. 2012), doxycycline(Van Zele, Gevaert et al. 2010) and low-dose macrolides(Harvey, Wallwork et al. 2009), plays a significant role in the treatment of CRS. Compared to oral corticosteroid administration, topical corticosteroids are more widely used as a treatment as they can be given for longer periods without the associated systemic side effects and potentially achieve better drug concentration in the sinus mucosa.

However, simply applying topical steroid through the nostrils does not imply delivery of the drug into the sinus. To deliver topical medicine into the sinuses, an appropriate access and delivery is required. Sinus surgery greatly affects the amount of corticosteroid, which comes into contact with paranasal sinus mucosa(Grobler, Weitzel et al. 2008; Harvey, Goddard et al. 2008; Thomas, Harvey et al. 2013). The oedematous inflammatory mucosa and ostiomeatal occlusion often seen in CRS allows less than 1% of solution volume to enter the sinus cavities prior to surgery(Snidvongs, Chaowanapanja et al. 2008). The extent of sinus surgery varies across institutions. This difference brings about variable access and sinus penetration. An adequate ostial dimension, has been shown to be necessary for appropriate topical drug distribution(Grobler, Weitzel et al. 2008; Harvey and Schlosser 2009; Singhal, Weitzel et al. 2010; Brenner, Abadie et al. 2011). Additionally, an appropriate device and delivery technique is required for adequate administration(Grobler, Weitzel et al. 2008; Harvey and Schlosser 2009). Simple

nasal delivery methods such as drops, sprays, aerosols, nebulisers and atomisers, provide good nasal cavity contact but poor sinus delivery. Nasal irrigation, with squeeze bottles and neti pots, along with direct sinus cannulation are likely to provide better delivery to the sinuses, especially in the post-sinus surgery setting(Grobler, Weitzel et al. 2008; Harvey, Goddard et al. 2008).

Studies investigating topical steroid for CRS have a high level of heterogeneity and systematic reviews (Joe, Thambi et al. 2008; Kalish, Arendts et al. 2009; Rudmik, Schlosser et al. 2012) rarely discuss or explore this heterogeneity of patient groups and outcomes. Trials studying the effectiveness of topical corticosteroid used various topical delivery methods and. patient with both non-surgical and post endoscopic sinus surgery (ESS) cavities. This systematic review aims to assess the strength of evidence supporting the influence of sinus surgery and delivery methods on the benefit of topical steroids in CRS.

Material and Methods

Search methods for identification of studies

Electronic systematic searches for randomized-controlled trials were conducted with no language, publication year, nor publication status restrictions. A search strategy was used with a combination of MESH terms and key words in collaboration with the Cochrane ENT disorders group. The Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews;

Cambridge Scientific Abstracts; mRCT; and additional sources were searched for published and unpublished trials. The date of the last search was 10 April 2012.

Criteria for Included studies

Types of studies

Randomized controlled trials (RCTs), which fulfilled the criteria described below, were included.

Types of participants

Both adults and children with CRS as defined by either European Position Paper on Rhinosinusitis and Nasal Polyps 2007(Fokkens, Lund et al. 2007); or Rhinosinusitis Task Force Report(Lanza and Kennedy 1997) and its revision(Benninger, Ferguson et al. 2003) were included; All candidates had chronic sino-nasal symptoms for longer than 12 weeks. Antrochoanal polyps, cystic fibrosis and primary ciliary dyskinesia were excluded.

Types of interventions

Studies involving topical steroid therapies versus either placebo or no treatment were considered. Trials using any co-interventions including oral steroid, antihistamines, decongestants, antibiotics (topical or intravenous) were included when the co-interventions were equally applied in both groups.

Types of outcome measures

The outcomes were sino-nasal symptoms, polyp size, polyp recurrence and adverse effects.

Statistical analysis

Data synthesis

Comparable data were combined to give a summary measure of effect. The standardised mean difference (SMD) and 95% CIs were used for continuous data. The risk ratio (RR) and 95% CIs were used for dichotomous data. A fixed-effect model was used. Statistical assessments were performed using Review Manager (RevMan) version 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). The I^2 of less than 40%, 40-60% and greater than 60% represent low, moderate and substantial heterogeneity.

Subgroup analysis

When heterogeneity was present, subgroup analysis was performed for sinus surgery status (patients with versus without sinus surgery) and topical delivery methods (sinus delivery such as direct cannulation, irrigation post-surgery versus nasal delivery such as sprays, drops, and nebulisers). We investigated differences between the two subgroups for fixed-effect analyses based on the inverse-variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

Dealing with missing data

The study authors were contacted via email for raw data in cases of missing data(Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Lund, Flood et al. 1998; Holmstrom 1999; Jankowski, Schrewelius et al. 2001; Dijkstra, Ebbens et al. 2004; Aukema, Mulder et al. 2005; Furukido, Takeno et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Ehnhage,

Olsson et al. 2009; Jankowski, Klossek et al. 2009; Stjarne, Olsson et al. 2009). The analyses were based on intention-to-treat. For missing standard deviations, either 95% confidence intervals (CIs) (Filiaci, Passali et al. 2000; Jankowski, Schrewelius et al. 2001; Lund, Black et al. 2004), standard error(Holopainen, Grahne et al. 1982; Hartwig, Linden et al. 1988; Mastalerz, Milewski et al. 1997; Holmstrom 1999; Johansson, Holmberg et al. 2002; Aukema, Mulder et al. 2005; Vlckova, Navratil et al. 2009), p-value(Lund, Flood et al. 1998), range(Ehnhage, Olsson et al. 2009) or interquartile ranges(Furukido, Takeno et al. 2005; Ehnhage, Olsson et al. 2009) was used for estimation to impute standard deviations. For missing means, medians were converted(Furukido, Takeno et al. 2005; Ehnhage, Olsson et al. 2009). The correlation coefficient was calculated in the experimental and control groups from some studies (Lavigne, Cameron et al. 2002; Jorissen and Bachert 2009) and was used to calculate the imputation of standard deviation of change in symptom scores for other studies(Holopainen, Grahne et al. 1982; Mastalerz, Milewski et al. 1997; Johansson, Holmberg et al. 2002; Furukido, Takeno et al. 2005).

Results

Results of the search

A total of 1537 references were identified. Four more records were identified from the references of these studies. 1276 of these were excluded after screening the title, 279 studies were removed after abstract were analysed and 18 further studies were removed after full text assessment, leaving forty-eight studies included. A flow chart of study retrieval and selection is displayed in Figure 8.1.

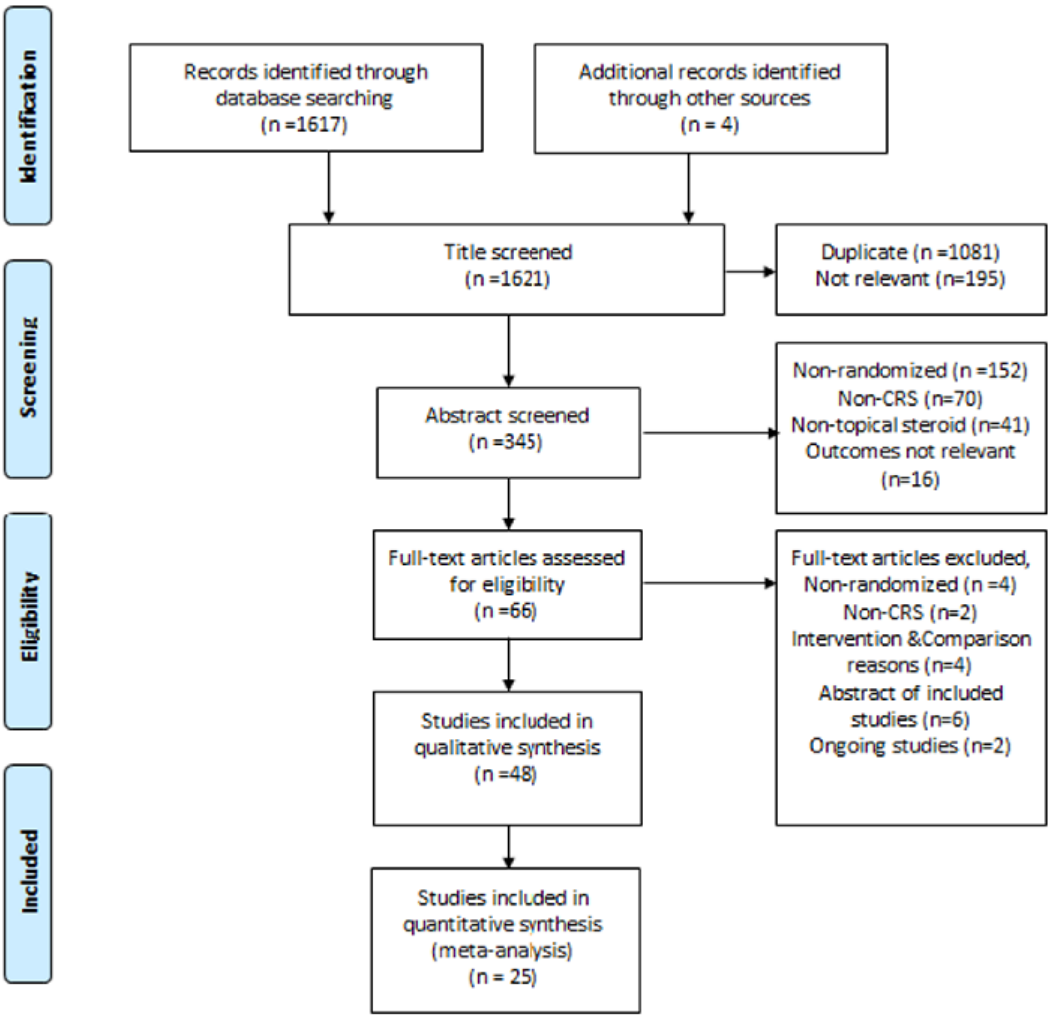


Figure 8.1: Flow chart of study retrieval and selection on topical steroid for CRS

Included studies

There were 48 studies fulfilling the inclusion criteria for trials of topical steroid for CRS. Forty-two (87.5%) trials compared topical steroid against placebo(Mygind, Pedersen et al. 1975; Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Lang and McNeill 1983; Chalton, Mackay et al. 1985; Dingsor, Kramer et al. 1985; Sykes, Wilson et al. 1986; Hartwig, Linden et al. 1988; Ruhno, Andersson et al. 1990; Qvarnberg, Kantola et al. 1992; Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Holmberg, Juliusson et al. 1997; Mastalerz, Milewski et al. 1997; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Holmstrom 1999; Filiaci, Passali et al. 2000; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Jankowski, Schrewelius et al. 2001; Parikh, Scadding et al. 2001; Johansson, Holmberg et al. 2002; Lavigne, Cameron et al. 2002; Passali, Bernstein et al. 2003; Bross-Soriano, Arrieta-Gomez et al. 2004; Dijkstra, Ebbens et al. 2004; Lund,Black et al. 2004; Aukema, Mulder et al. 2005; Furukido, Takeno et al. 2005; Rowe-Jones, Medcalf et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Ehnhage, Olsson et al. 2009; Jankowski, Klossek et al. 2009; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Chur, Small et al. 2010; Olsson, Ehnhage et al. 2010; Vento, Blomgren et al. 2012). Five trials (10.4%) compared topical steroid against no intervention (Karlsson and Rundcrantz 1982; Cuenant, Stipon et al. 1986; El, Kale et al. 1995; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004; Rotenberg, Zhang et al. 2011). One trial (2.1%) compared two different treatment regimens for steroid administration (Giger, Pasche et al. 2003). See Table 6.2 (Appendix 6.1) and Table 7.2 (Appendix 7.2) for the

studies characteristics.

Participants

There were 3,961 participants in total. The mean age of the patients was 46.9 years and 63.9% were men.

For twenty-seven trials (56.3%)(Mygind, Pedersen et al. 1975; Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Karlsson and Rundcrantz 1982; Dingsor, Kramer et al. 1985; Hartwig, Linden et al. 1988; Ruhno, Andersson et al. 1990; El, Kale et al. 1995; Holmberg, Juliusson et al. 1997; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Lavigne, Cameron et al. 2002; Passali, Bernstein et al. 2003; Bross-Soriano, Arrieta-Gomez et al. 2004; Dijkstra, Ebbens et al. 2004; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004; Aukema, Mulder et al. 2005; Rowe-Jones, Medcalf et al. 2005; Ehnhage, Olsson et al. 2009; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Olsson, Ehnhage et al. 2010; Rotenberg, Zhang et al. 2011; Vento, Blomgren et al. 2012), patients (all or the majority) had sinus surgery prior to administering steroid either as a co-intervention or they had previous surgery documented. In 15 (31.3%) studies(Lang and McNeill 1983; Chalton, Mackay et al. 1985; Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Mastalerz, Milewski et al. 1997; Holmstrom 1999; Filiaci, Passali et al. 2000; Jankowski, Schrewelius et al. 2001; Johansson, Holmberg et al. 2002; Furukido, Takeno et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Jankowski, Klossek et al. 2009; Chur, Small et al. 2010) , patients (all or

the majority) had not had previous sinus surgery. Mixed populations of patients with an undefined proportion having previous surgeries were presented in six trials (12.5%)(Cuenant, Stipon et al. 1986; Sykes, Wilson et al. 1986; Qvarnberg, Kantola et al. 1992; Parikh, Scadding et al. 2001; Giger, Pasche et al. 2003; Lund, Black et al. 2004).

Interventions

The steroid agents used differed across the studies. They were tixocortol pivalate(Cuenant, Stipon et al. 1986), fluticasone propionate(Holmberg, Juliusson et al. 1997; Mastalerz, Milewski et al. 1997; Lund, Flood et al. 1998; Holmstrom 1999; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Parikh, Scadding et al. 2001; Bross-Soriano, Arrieta-Gomez et al. 2004; Dijkstra, Ebbens et al. 2004; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004; Aukema, Mulder et al. 2005; Rowe-Jones, Medcalf et al. 2005; Ehnhage, Olsson et al. 2009; Jankowski, Klossek et al. 2009; Vlckova, Navratil et al. 2009; Olsson, Ehnhage et al. 2010), betamethasone(Chalton, Mackay et al. 1985; Furukido, Takeno et al. 2005), beclomethasone dipropionate(Mygind, Pedersen et al. 1975; Karlsson and Rundcrantz 1982; Lang and McNeill 1983; El, Kale et al. 1995; Holmberg, Juliusson et al. 1997; Lund, Flood et al. 1998; Giger, Pasche et al. 2003; Bross-Soriano, Arrieta-Gomez et al. 2004), mometasone furoate(Passali, Bernstein et al. 2003; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Chur, Small et al. 2010), budesonide(Holopainen, Grahne et al. 1982; Hartwig, Linden et al. 1988; Ruhno, Andersson et al. 1990;

Qvarnberg, Kantola et al. 1992; Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Tos, Svendstrup et al. 1998; Filiaci, Passali et al. 2000; Jankowski, Schrewelius et al. 2001; Johansson, Holmberg et al. 2002; Lavigne, Cameron et al. 2002; Lund, Black et al. 2004; Rotenberg, Zhang et al. 2011), flunisolide(Drettner, Ebbesen et al. 1982; Dingsor, Kramer et al. 1985), triamcinolone acetonide(Vento, Blomgren et al. 2012) and dexamethasone(Sykes, Wilson et al. 1986).

Three trials used a direct sinus delivery technique whereby the drug was instilled directly into the sinus through a sinusotomy tube, in one study(Lavigne, Cameron et al. 2002), intrasinus lavage in one study(Cuenant, Stipon et al. 1986) and postoperative nasal irrigation in one study(Rotenberg, Zhang et al. 2011).

Thirty trials delivered the topical steroid via a nasal spray(Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Lang and McNeill 1983; Dingsor, Kramer et al. 1985; Sykes, Wilson et al. 1986; Ruhno, Andersson et al. 1990; Johansen, Illum et al. 1993; El, Kale et al. 1995; Holmberg, Juliusson et al. 1997; Mastalerz, Milewski et al. 1997; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Jankowski, Schrewelius et al. 2001; Parikh, Scadding et al. 2001; Johansson, Holmberg et al. 2002; Giger, Pasche et al. 2003; Passali, Bernstein et al. 2003; Bross-Soriano, Arrieta-Gomez et al. 2004; Dijkstra, Ebbens et al. 2004; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004; Lund, Black et al. 2004; Rowe-Jones, Medcalf et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Jankowski, Klossek et al. 2009; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Chur, Small et al. 2010), seven trials used

nasal drops(Chalton, Mackay et al. 1985; Holmstrom 1999; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Aukema, Mulder et al. 2005; Ehnhage, Olsson et al. 2009; Olsson, Ehnhage et al. 2010), one trial instilled the drug through an intranasal tube(Furukido, Takeno et al. 2005), five trials used aerosol(Mygind, Pedersen et al. 1975; Hartwig, Linden et al. 1988; Qvarnberg, Kantola et al. 1992; Johansen, Illum et al. 1993; Vento, Blomgren et al. 2012), three trials used turbuhalers(Lildholdt, Rundcrantz et al. 1995; Tos, Svendstrup et al. 1998; Filiaci, Passali et al. 2000) and one study(Karlsson and Rundcrantz 1982) used the term "intranasal" without clearly stating the delivery method used.

Outcomes

Forty-one studies (85.4%) of trials reported symptoms as an outcome(Mygind, Pedersen et al. 1975; Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Lang and McNeill 1983; Dingsor, Kramer et al. 1985; Cuenant, Stipon et al. 1986; Sykes, Wilson et al. 1986; Hartwig, Linden et al. 1988; Ruhno, Andersson et al. 1990; Qvarnberg, Kantola et al. 1992; Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Holmberg, Juliusson et al. 1997; Mastalerz, Milewski et al. 1997; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Holmstrom 1999; Filiaci, Passali et al. 2000; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Jankowski, Schrewelius et al. 2001; Parikh, Scadding et al. 2001; Johansson, Holmberg et al. 2002; Lavigne, Cameron et al. 2002; Giger, Pasche et al. 2003; Dijkstra, Ebbens et al. 2004; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004; Lund, Black et al. 2004; Aukema, Mulder et al. 2005; Furukido, Takeno et al. 2005; Rowe-Jones,

Medcalf et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Ehnhage, Olsson et al. 2009; Jankowski, Klossek et al. 2009; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Chur, Small et al. 2010; Vento, Blomgren et al. 2012). Symptoms were reported in different ways across studies such as change in symptom scores, combined symptom scores, individual symptom scores and proportion of responders for particular symptoms.

Thirty studies reported polyp size (Mygind, Pedersen et al. 1975; Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Karlsson and Rundcrantz 1982; Lang and McNeill 1983; Chalton, Mackay et al. 1985; Dingsor, Kramer et al. 1985; Hartwig, Linden et al. 1988; Johansen, Illum et al. 1993; Lildholdt, Rundcrantz et al. 1995; Holmberg, Juliusson et al. 1997; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Holmstrom 1999; Filiaci, Passali et al. 2000; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Jankowski, Schrewelius et al. 2001; Johansson, Holmberg et al. 2002; Aukema, Mulder et al. 2005; Rowe-Jones, Medcalf et al. 2005; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Ehnhage, Olsson et al. 2009; Jankowski, Klossek et al. 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Chur, Small et al. 2010). These were reported as either change in polyp score, final score at a defined endpoint or proportion of responders having a reduction in polyp size. Six studies reported polyp recurrence(Drettner, Ebbesen et al. 1982; Dingsor, Kramer et al. 1985; Passali, Bernstein et al. 2003; Bross-Soriano, Arrieta-Gomez et al. 2004; Dijkstra, Ebbens et al. 2004; Stjarne, Olsson et al. 2009). Adverse events were reported in thirty

trials(Mygind, Pedersen et al. 1975; Drettner, Ebbesen et al. 1982; Holopainen, Grahne et al. 1982; Dingsor, Kramer et al. 1985; Hartwig, Linden et al. 1988; Ruhno, Andersson et al. 1990; Johansen, Illum et al. 1993; El, Kale et al. 1995; Lildholdt, Rundcrantz et al. 1995; Lund, Flood et al. 1998; Tos, Svendstrup et al. 1998; Holmstrom 1999; Filiaci, Passali et al. 2000; Keith, Nieminen et al. 2000; Penttila, Poulsen et al. 2000; Jankowski, Schrewelius et al. 2001; Lavigne, Cameron et al. 2002; Giger, Pasche et al. 2003; Dijkstra, Ebbens et al. 2004; Lund, Black et al. 2004; Small, Hernandez et al. 2005; Stjarne, Blomgren et al. 2006; Stjarne, Mosges et al. 2006; Jankowski, Klossek et al. 2009; Jorissen and Bachert 2009; Stjarne, Olsson et al. 2009; Vlckova, Navratil et al. 2009; Chur, Small et al. 2010; Rotenberg, Zhang et al. 2011; Vento, Blomgren et al. 2012).

Effects of interventions

Topical steroid versus placebo

When data were pooled for meta-analysis, topical steroids significantly improved overall symptoms when compared to placebo (combined standardised mean difference (SMD) -0.49; 95% confidence interval (CI) -0.64, -0.34, $p < 0.00001$, 12 trials) and provided a greater proportion of responders in symptom control (RR 0.59; 95% CI 0.47, 0.73, $p < 0.00001$, 8 trials). (Figure 8.2). Both forest plots show low heterogeneity of 35% and 0% respectively.

Data addressing polyp size were combined in the meta-analysis. The pooled results significantly favoured the topical steroid group for the proportion of responders (patients who had a reduction in polyp size) (RR 0.48; 95% CI 0.38, 0.60,

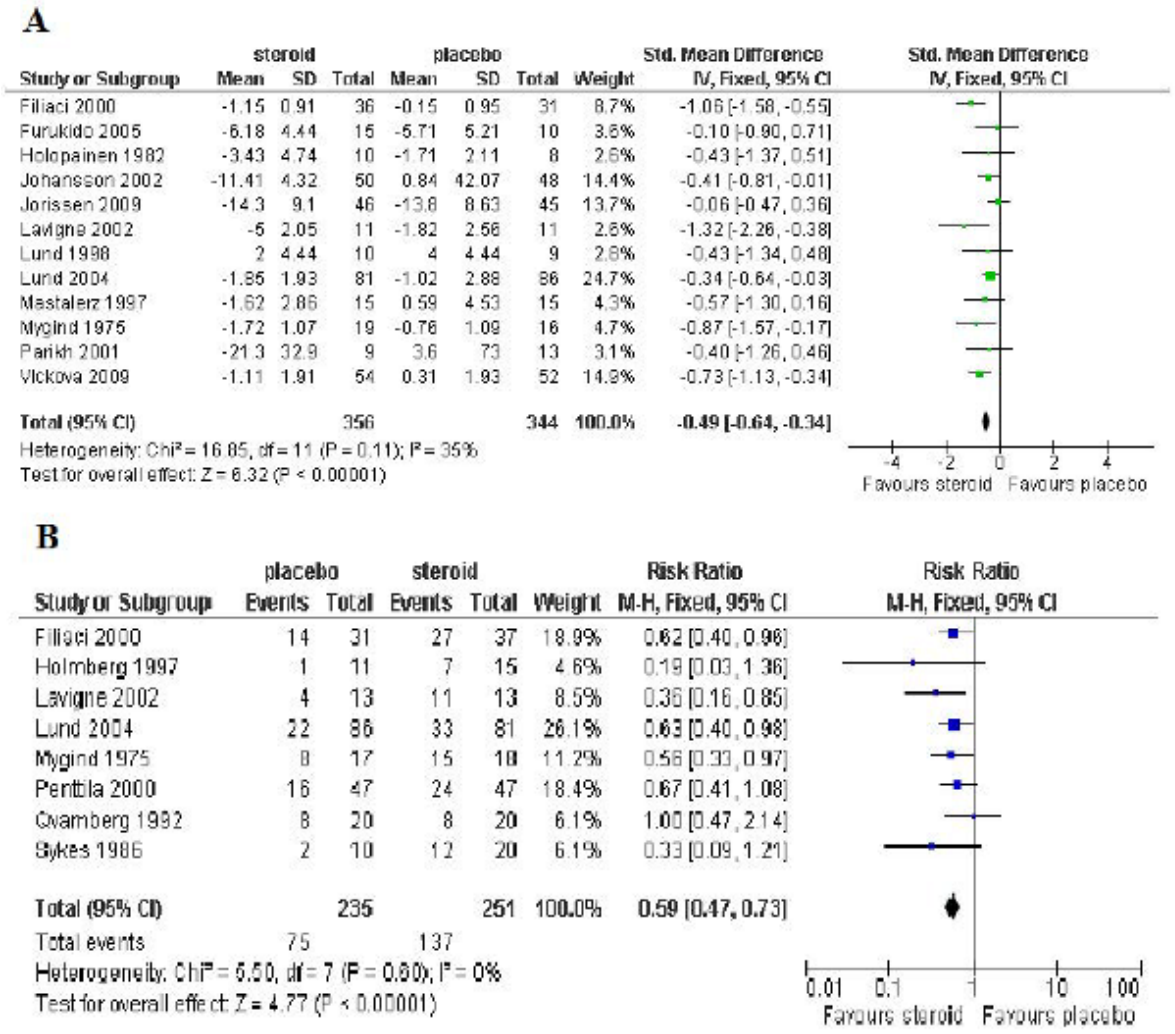


Figure 8.2: Meta-analysis of topical steroid versus placebo in patients with CRS (A) symptom improvement (B) proportion of responders in symptoms

p<0.00001, 8 trials). The $I^2$of 53% suggests moderate heterogeneity. Data addressing polyp recurrence after surgery were combined in the meta-analysis with results again significantly favouring the topical steroid group (RR 0.59; 95% CI 0.45, 0.79, p=0.0004, 6 trials). (Figure 8.3). The $I^2$of 25% also suggests low heterogeneity.

Subgroup analysis: patients with sinus surgery versus without sinus surgery

Subgroup analyses were performed to explore heterogeneity of symptom improvement ($I^2$of 35%) and proportion of responders in polyp size reduction ($I^2$of 53%). The beneficial effects of steroid in patients who had received sinus surgery were similar to those without sinus surgery for symptom improvement (SMD -0.52; 95% CI -0.76, -0.29 versus SMD-0.47; 95% CI -0.67, -0.27, p=0.73). The heterogeneity within subgroups was moderate for patients with surgery (I^2=49%) and low for patients without surgery (I^2=27%). However, the effect of topical steroid in polyp size reduction was significantly greater in patients with sinus surgery (RR 0.31; 95%CI 0.20, 0.48) than those without (RR 0.61; 95%CI 0.46, 0.81), p=0.009 (Figure 8.4). The heterogeneity within subgroups was low (I^2=38% and 24% for patients with and without surgery)

Subgroup analysis: by topical delivery methods

Greater symptom improvement could be demonstrated when sinus delivery (direct sinus cannulation or post-operative sino-nasal irrigation) methods (SMD -1.32; 95% CI -2.26, -0.38) was compared to nasal delivery (simple sprays/ low volume) methods (SMD -0.38; 95%CI -0.55, -0.22, p < 0.00001)

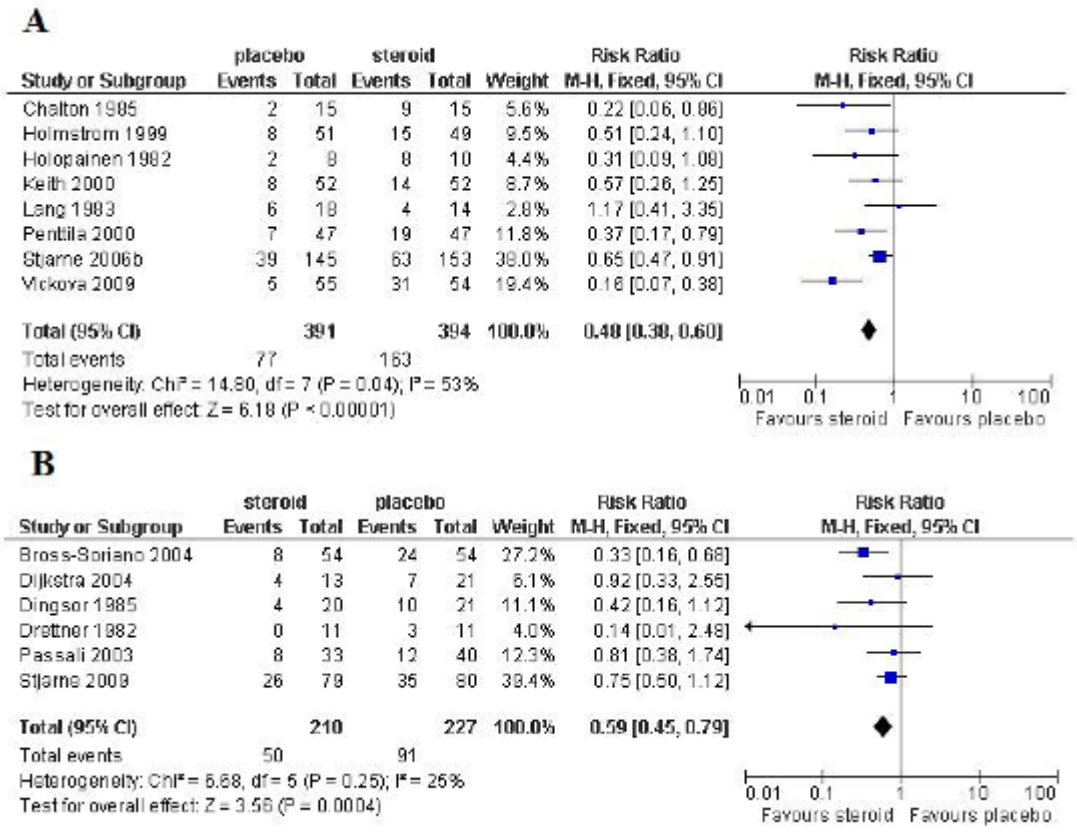


Figure 8.3: Meta-analysis of topical steroid versus placebo in patients with CRS (A) proportion of responders in polyp size (B) polyp recurrence after surgery

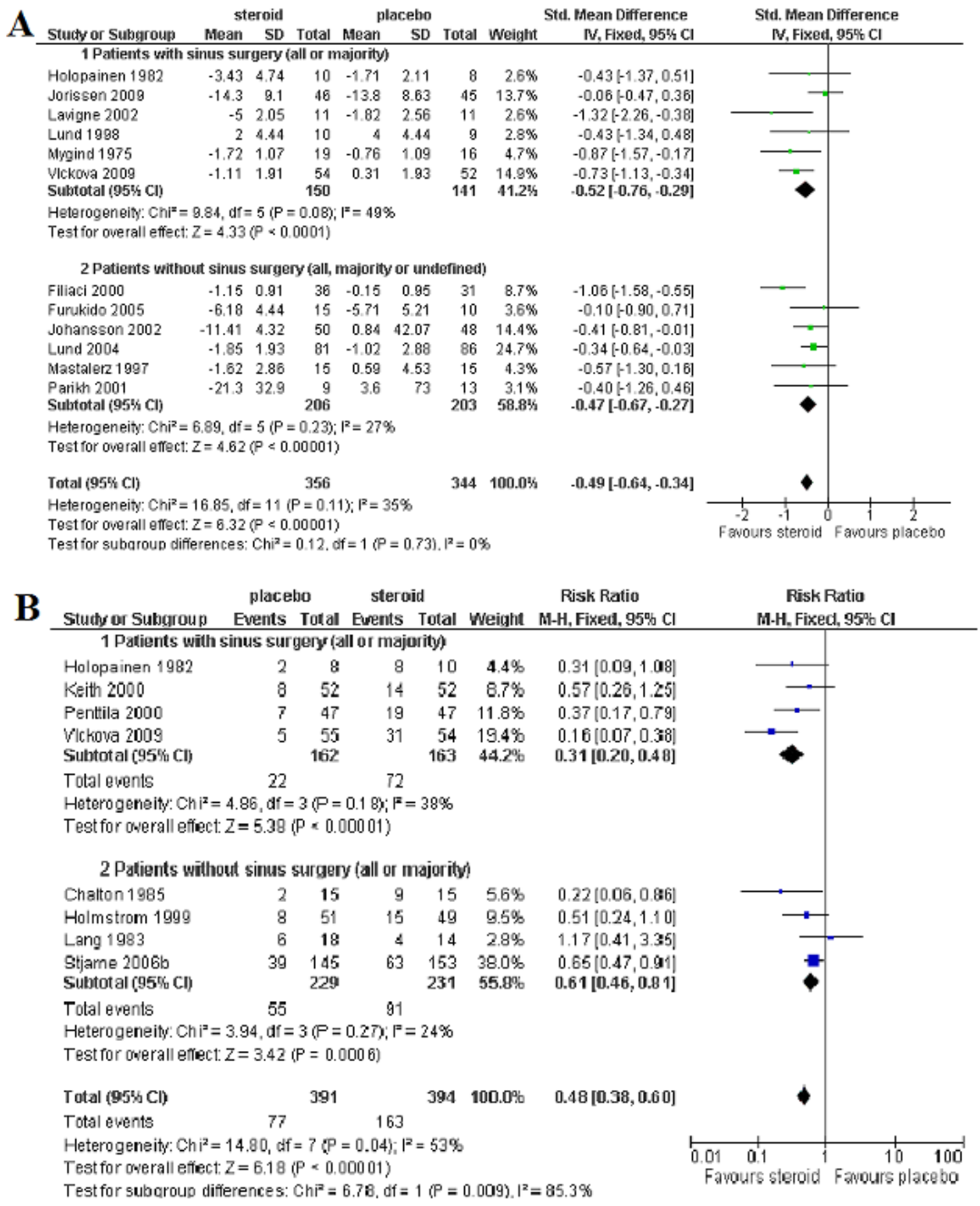


Figure 8.4: Subgroup analysis by surgical status in patients with CRS (A) symptom improvement (B) proportion of responders in polyp size

and nasal aerosol/ turbuhaler (SMD -1.00; 95%CI -1.41, -0.58, p < 0.00001). Heterogeneity was low (I^2=0%) within these subgroups. For the proportion of responders in polyp size reduction, there are no studies using sinus delivery or nasal aerosol/ turbuhaler. No significance difference was found for polyp size reduction between nasal spray (RR 0.50; 95%CI 0.38, 0.67) and nasal drop (RR 0.43; 95%CI 0.29, 0.66, p=0.56). Heterogeneity was substantial within nasal spray subgroup (I^2=76%) but low within nasal drop subgroup (I^2=0%). (Figure 8.5)

Topical steroid versus no treatment

Data could not be pooled for meta-analysis from any study. One trial reported symptoms as all groups' symptoms without separate data(Cuenant, Stipon et al. 1986). Symptoms, polyp size or polyp recurrence were not reported in one trial(Rotenberg, Zhang et al. 2011). Two trials did not provide standard deviation or any alternative(Karlsson and Rundcrantz 1982; Jurkiewicz, Zielnik-Jurkiewicz et al. 2004) and one trial reported University of Pennsylvania Smell Identification Test in each nostril separately(El, Kale et al. 1995).

In summary for these studies, symptoms(Jurkiewicz, Zielnik-Jurkiewicz et al. 2004) (p<0.01), polyp score (p=0.003)(Karlsson and Rundcrantz 1982) and polyp recurrence(Jurkiewicz, Zielnik-Jurkiewicz et al. 2004) (p<0.01) were reported as significant improvement in the topical steroid group compared to no intervention. UPSIT test was not significantly different between groups(El, Kale et al. 1995) (p=0.31). Disease-specific quality of life, endoscopy and CT score were not significantly different between groups(Rotenberg, Zhang et al. 2011).

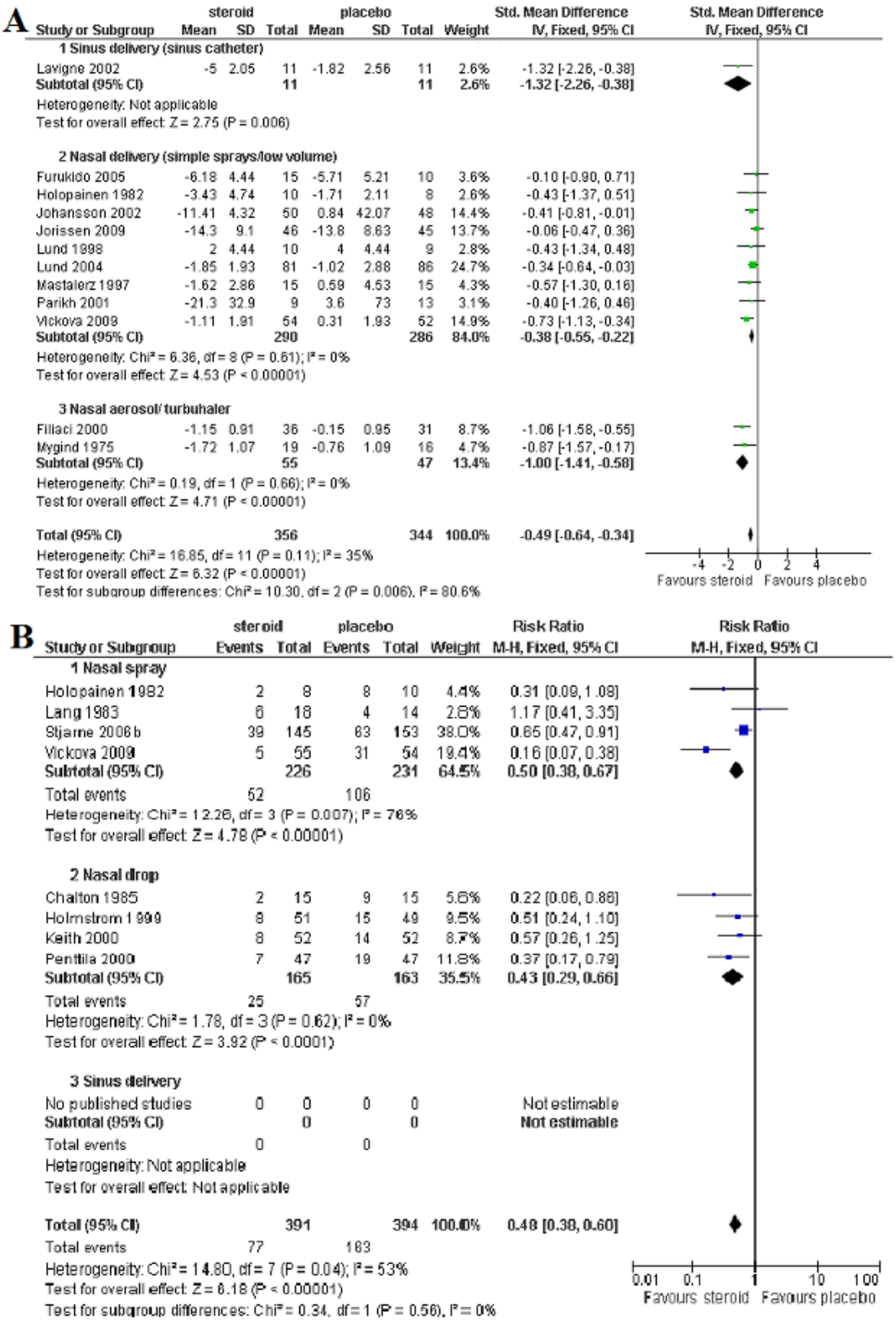


Figure 8.5: Subgroup analysis by topical delivery methods in patients with CRSs (A) symptom improvement (B) proportion of responders in polyp size

Adverse events

There was no difference between the study group and control in any trial. Most adverse events were mild and moderate. Few were considered to be due to study medication. The most common event was headache. Data were displayed in Table 6.3 and Table 7.4 (Appendix 7.3).

Discussion

Topical steroids are beneficial in treating CRS for symptom control, reduction in polyp size and prevention of polyp recurrence after ESS. The effect for polyp size reduction demonstrates significant heterogeneity between included studies. Subgroup analyses were performed to explore this heterogeneity. One possible explanation is the surgical state of the patient at the time of topical steroid delivery. When this was taken into consideration, greater polyp size reduction was seen in patients having had surgery compared to those without sinus surgery and the heterogeneity in the analysis resolved. There was very little heterogeneity in the studies all showing reduced polyp recurrence with topical steroids when used in the immediate post surgical state. The actual surgical state is not often defined and can be variable enough to account for some of the heterogeneity seen.

The heterogeneity was similarly resolved when subgroup analysis by topical delivery methods was performed for symptom improvement. Direct sinus delivery shows significantly better symptom improvement and suggests an attempt at sinus delivery (cf nasal) with direct sinus mucosa contact is more likely to be effective. Both a wide

nasal corridor created by sinus surgery and the methods of topical delivery affects distribution to sinuses and such findings are not surprising.(Harvey, Goddard et al. 2008; Snidvongs, Chaowanapanja et al. 2008; Harvey and Schlosser 2009; Snidvongs, Pratt et al. 2012). However there was no clear benefit to symptoms for INCS within the ESSsubgroup.. On subgroup analysis by sinus surgery for symptom improvement, the heterogeneity was even higher within a 'subgroup of patients with sinus surgery'. The variability of what is actually occurs when surgeons perform ESS is likely to account for the increase in heterogeneity of this 'surgery subgroup'. There is also variability between different delivery methods in the studies analysed. Effective sinus distribution requires multiple factors(Rudmik, Schlosser et al. 2012) such as positive pressure, large volumes(Beule, Athanasiadis et al. 2009) , and various sinus ostial dimensions after ESS(Singhal, Weitzel et al. 2010). Greatest distribution is likely to be achieved when a wide post-ESS corridor has been created regardless of delivery method(Snidvongs, Pratt et al. 2012; Virgin, Rowe et al. 2012).

Attempts to examine both variables--the effect of surgery and sinus delivery methods were performed in two studies. Rotenberg and colleagues (Rotenberg, Zhang et al. 2011) reported no difference when budesonide irrigation was compared to a normal saline irrigation. In this study, however, the surgical technique of polypectomy and limited sinus surgery, is unlikely to create appropriate access for drug topicalization in a severely affected samter's triad (asthma, polyps and aspirin sensitivity) subpopulation. The delivery volume of 60ml is also inadequate according to data from Buele's study which proposed using a volume of 100ml for an effective irrigation(Beule, Athanasiadis et al. 2009). Data were not available for meta-analysis

as there was no placebo group as per the other included RCTs. In contrast to the Rotenberg study, Lavigne and colleagues (Lavigne, Cameron et al. 2002) reported positive outcomes when 256 mcg of budesonide was administered through a maxillary sinus catheter in post-operative CRS patients. The dosage used is no higher compared to many other studies, but the delivery is guaranteed directly into the sinus through the catheter. Although not a commonly performed delivery technique it is a controlled method of assessing the effect of the steroid by insuring its delivery to the affected mucosa. Supporting this approach, recent cohort studies of varying eosinophillic CRS subtypes found that postoperative corticosteroid irrigation(Snidvongs, Pratt et al. 2012) or placement of steroid-infused carboxymethylcellulose foam(Pletcher and Goldberg 2010) improved symptoms and endoscopy findings. Similar findings were seen with large volume irrigations and wide endoscopic sinus surgery in a cystic fibrosis population(Virgin, Rowe et al. 2012). . In the post-surgically setting, even anatomically directed steroid drops, resulted in a higher percentage of frontal ostia patency when compared to steroid spray(Hong, Jang et al. 2012), although distribution of simple drops to the remaining sinus cavities remains limited. Unfortunately, no current randomised placebo controlled trial of long duration large volume steroid irrigation post sinus surgery has been published.

Adverse events reported were often ambiguous. Headache could be drug-related, disease-related or coincidental. Sinusitis, rhinitis, common cold andrespiratory infection should be considered as disease symptoms rather than adverse events. Epistaxis, dry nose, nasal burning and nasal irritation are considered to be drug-

related events. Minor adverse events from nasal steroid are commonly tolerated by patients. The benefit appears to outweigh the risk.

Conclusion

Topical nasal steroids are considered an essential part of the medical treatment of chronic rhinosinusitis but their effect size is often small. There is consistent evidence, although not comprehensive across all outcomes, that the effects of INCS are greater when topical steroid is administered after sinus surgery. The impact on polyp reduction was consistent across studies. Attempts at more direct sinus delivery, such as the catheter method, appears to have a greater impact on symptoms.

A well-conducted placebo controlled randomised trial is required, comparing effective topical drug delivery methods to the sinuses, post sinus surgery, with an appropriate duration of treatment (preferably 12months) and using validated outcome measures. Randomised controlled trials should be pre-registered and their reporting should be according to the latest CONSORT guidelines.

References

Aukema, A. A. C., P. G. Mulder and W. J. Fokkens Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol* 2005; 115: 1017-1023.

Benninger, M. S., B. J. Ferguson, J. A. Hadley, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003; 129(3 Suppl): S1-32.

Beule, A., T. Athanasiadis, E. Athanasiadis, J. Field and P. J. Wormald Efficacy of different techniques of sinonasal irrigation after modified Lothrop procedure. *Am J Rhinol Allergy* 2009; 23(1): 85-90.

Brenner, P. S., W. M. Abadie, E. K. Weitzel, R. F. Thomas and K. C. McMains Unexpected consequences of transnasal balloon dilation of the maxillary ostium. *International forum of allergy & rhinology* 2011; 1(6): 466-470.

Bross-Soriano, D., J. R. Arrieta-Gomez and H. Prado-Calleros Infections after endoscopic polypectomy using nasal steroids. *Otolaryngol Head Neck Surg* 2004; 130(3): 319-322.

Chalton, R., I. Mackay, R. Wilson and P. Cole Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. *BMJ* 1985; 291: 788-788.

Chur, V., C. B. Small, P. Stryszak and A. Teper Mometasone Furoate Nasal Spray is Safe for the Treatment of Nasal Polyps in Pediatric Subjects 6-17 Years of Age. *J Allergy Clin Immunol* 2010; 125(2): AB101.

Cuenant, G., J. P. Stipon, G. Plante-Longchamp, C. Baudoin and Y. Guerrier Efficacy of endonasal neomycin-tixocortol pivalate irrigation in the treatment of

chronic allergic and bacterial sinusitis. *ORL J Otorhinolaryngol Relat Spec* 1986; 48(4): 226-232.

Dijkstra, M. D., F. A. Ebbens, R. M. Poublon and W. J. Fokkens Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. *Clin Exp Allergy* 2004; 34(9): 1395-1400.

Dingsor, G., J. Kramer, R. Olsholt and T. Soderstrom Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. *Rhinology* 1985; 23(1): 49-58.

Drettner, B., A. Ebbesen and M. Nilsson Prophylactive treatment with flunisolide after polypectomy. *Rhinology* 1982; 20(3): 149-158.

Ehnhage, A., P. Olsson and a. l. Kolbeck K-G et Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. *Allergy* 2009; 64(5): 762-769.

El, N. M., S. Kale, C. Aldren and F. Martin Effect of Beconase nasal spray on olfactory function in post-nasal polypectomy patients: A prospective controlled trial. *J Laryngol Otol* 1995; 109(10): 941-944.

Filiaci, F., D. Passali, R. Puxeddu and C. Schrewelius A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. *Rhinology* 2000; 38(4): 185-190.

Fokkens, W., V. Lund and J. Mullol European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007; (20): 1-136.

Furukido, K., S. Takeno, T. Ueda and K. Yajin Cytokine profile in paranasal effusions in patients with chronic sinusitis using the YAMIK sinus catheter with and without betamethasone. *Eur Arch Otorhinolaryngol* 2005; 262(1): 50-54.

Giger, R., P. Pasche, C. Cheseaux, et al. Comparison of once- versus twice-daily use of beclomethasone dipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. *Eur Arch Otorhinolaryngol* 2003; 260(3): 135-140.

Grobler, A., E. K. Weitzel, A. Buele, et al. Pre- and postoperative sinus penetration of nasal irrigation. *Laryngoscope* 2008; 118(11): 2078-2081.

Hartwig, S., M. Linden, C. Laurent, A. K. Vargo and N. Lindqvist Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). *J Laryngol Otol* 1988; 102(2): 148-151.

Harvey, R. J., J. C. Goddard, S. K. Wise and R. J. Schlosser Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008; 139(1): 137-142.

Harvey, R. J. and R. J. Schlosser Local drug delivery. *Otolaryngol Clin North Am* 2009; 42(5): 829-845.

Harvey, R. J., B. D. Wallwork and V. J. Lund Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. *Immunology and allergy clinics of North America* 2009; 29(4): 689-703.

Holmberg, K., S. Juliusson, B. Balder, et al. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. *Ann Allergy Asthma Immunol* 1997; 78(3): 270-276.

Holmstrom, M. Clinical performance of fluticasone propionate nasal drops. *Allergy* 1999; Supplement 54(53): 21-25.

Holmstrom, M. Clinical performance of fluticasone propionate nasal drops. *Allergy: European Journal of Allergy and Clinical Immunology* 1999; Supplement 54(53): 21-25.

Holopainen, E., B. Grahne and H. Malmberg Budesonide in the treatment of nasal polyposis. *Eur J Resp Dis* 1982; 63(Suppl 122): 221-228.

Hong, S. D., J. Y. Jang, J. H. Kim, et al. The effect of anatomically directed topical steroid drops on frontal recess patency after endoscopic sinus surgery: a prospective randomized single blind study. *Am J Rhinol Allergy* 2012; 26(3): 209-212.

Jankowski, R., J. M. Klossek, V. Attali, A. Coste and E. Serrano Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. *Allergy* 2009; 64(6): 944-950.

Jankowski, R., C. Schrewelius, P. Bonfils, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. *Arch Otolaryngol Head Neck Surg* 2001; 127(4): 447-452.

Joe, S. A., R. Thambi and J. Huang A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008; 139(3): 340-347.

Johansen, L., P. Illum, S. Kristensen, et al. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. *Clin Otolaryngol Allied Sci* 1993; 18(6): 524-527.

Johansson, L., K. Holmberg, I. Melen, P. Stierna and M. Bende Sensitivity of a new grading system for studying nasal polyps with the potential to detect early changes in polyp size after treatment with a topical corticosteroid (budesonide). *Acta Oto-Laryngologica* 2002; 122(1): 49-53.

Jorissen, M. and C. Bachert Effect of corticosteroids on wound healing after endoscopic sinus surgery. *Rhinology* 2009; 47(3): 280-286.

Jurkiewicz, D., B. Zielnik-Jurkiewicz and A. Wojdas Effectiveness of fluticasone propionate in nasal polyps treatment. *Int Rev Allergol Clin Immunol* 2004; 10(1): 22-24.

Kalish, L. H., G. Arendts, R. Sacks and J. C. Craig Topical steroids in chronic rhinosinusitis without polyps: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2009; 141(6): 674-683.

Karlsson, G. and H. Rundcrantz A randomized trial in intranasal beclomethasone dipropionate after polypectomy. *Rhinology* 1982; 20(3): 144-148.

Keith, P., J. Nieminen, K. Hollingworth and J. Dolovich Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. *Clin Exp Allergy* 2000; 30(10): 1460-1468.

Lang, D. A. and J. McNeill Double blind controlled study of effect of topical steroids on nasal polyps. *Clin Otolaryngol* 1983; 8: 135-143.

Lanza, D. C. and D. W. Kennedy Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997; 117(3 Pt 2): S1-7.

Lavigne, F., L. Cameron, P. M. Renzi, et al. Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. *Laryngoscope* 2002; 112(5): 858-864.

Lildholdt, T., H. Rundcrantz and N. Lindqvist Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol Allied Sci* 1995; 20(1): 26-30.

Lund, V. J., J. H. Black, L. Z. Szabo, C. Schrewelius and A. Akerlund Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. *Rhinology* 2004; 42(2): 57-62.

Lund, V. J., J. Flood, A. P. Sykes and D. H. Richards Effect of fluticasone in severe polyposis. *Arch Otolaryngol Head Neck Surg* 1998; 124(5): 513-518.

Mastalerz, L., M. Milewski, M. Duplaga, E. Nizankowska and A. Szczeklik Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* 1997; 52(9): 895-900.

Mygind, N., C. B. Pedersen, S. Prytz and H. Sorensen Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin Allergy* 1975; 5(2): 159-164.

Olsson, P., A. Ehnhage, S. Nordin and P. Stjarne Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. *Rhinology* 2010; 48(3): 325-330.

Parikh, A., G. K. Scadding, Y. Darby and R. C. Baker Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial

using fluticasone propionate aqueous nasal spray. *Rhinology* 2001; 39(2): 75-79.

Passali, D., J. M. Bernstein, F. M. Passali, et al. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2003; 129(6): 656-659.

Penttila, M., P. Poulsen, K. Hollingworth and M. Holmstrom Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 mug once daily and twice daily in the treatment of bilateral nasal polyposis: A placebo-controlled randomized study in adult patients. *Clin Exp Allergy* 2000; 30(1): 94-102.

Pletcher, S. D. and A. N. Goldberg Treatment of recurrent sinonasal polyposis with steroid-infused carboxymethylcellulose foam. *Am J Rhinol Allergy* 2010; 24(6): 451-453.

Qvarnberg, Y., O. Kantola, J. Salo, et al. Influence of topical steroid treatment on maxillary sinusitis. *Rhinology* 1992; 30(2): 103-112.

Rotenberg, B. W., I. Zhang, I. Arra and K. B. Payton Postoperative care for Samter's triad patients undergoing endoscopic sinus surgery: a double-blinded, randomized controlled trial. *Laryngoscope* 2011; 121(12): 2702-2705.

Rowe-Jones, J. M., M. Medcalf, S. R. Durham, D. H. Richards and I. S. Mackay Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology* 2005; 43(1): 2-10.

Rudmik, L., R. J. Schlosser, T. L. Smith and Z. M. Soler Impact of topical nasal steroid therapy on symptoms of nasal polyposis: a meta-analysis. *Laryngoscope* 2012; 122(7): 1431-1437.

Ruhno, J., B. Andersson, J. Denburg, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. *J Allergy Clin Immunol* 1990; 86(6 Pt 1): 946-953.

Singhal, D., E. K. Weitzel, E. Lin, et al. Effect of head position and surgical dissection on sinus irrigant penetration in cadavers. *Laryngoscope* 2010; 120(12): 2528-2531.

Small, C. B., J. Hernandez, A. Reyes, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol* 2005; 116(6): 1275-1281.

Snidvongs, K., P. Chaowanapanja, S. Aeumjaturapat, S. Chusakul and P. Praweswararat Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol* 2008; 22(5): 483-486.

Snidvongs, K., E. Pratt, D. Chin, et al. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2012; 2(5): 415-421.

Stjarne, P., K. Blomgren, P. Caye-Thomasen, S. Salo and T. Soderstrom The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2006; 126(6): 606-612.

Stjarne, P., R. Mosges, M. Jorissen, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006; 132(2): 179-185.

Stjarne, P., P. Olsson and M. Alenius Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 2009; 135(3): 296-302.

Sykes, D. A., R. Wilson, K. L. Chan, I. S. Mackay and P. J. Cole Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study. *Lancet* 1986; 2(8503): 359-360.

Thomas, W. W., R. J. Harvey, L. Rudmik, P. H. Whang and R. J. Schlosser Distribution of topical agents to the paranasal sinuses: An evidenced based review with recommendations. *Otolaryngol Head Neck Surg* 2013; in press.

Tos, M., F. Svendstrup, H. Arndal, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. *Am J Rhinol* 1998; 12(3): 183-189.

Van Zele, T., P. Gevaert, G. Holtappels, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol* 2010; 125(5): 1069-1076

Vento, S., K. Blomgren, M. Hytonen, M. Simola and H. Malmberg Prevention of relapses of nasal polyposis with intranasal triamcinolone acetonide after polyp surgery: A prospective double-blind, placebo-controlled, randomised study with a 9-month follow-up. *Clin Otolaryngol* 2012; 37(2): 117-123.

Virgin, F. W., S. M. Rowe, M. B. Wade, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. *Am J Rhinol Allergy* 2012; 26(1): 70-75.

Vlckova, I., P. Navratil, R. Kana, et al. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. *Rhinology* 2009; 47(4): 419-426.

Chapter 9

Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis

ORIGINAL ARTICLE

Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis

Komkiat Snidvongs, MD[1,2], Eleanor Pratt, BSc BA[3], David Chin, MD[4], Raymond Sacks, MD[1,3], Peter Earls, MBBS, FRCPA[3,5] and Richard J. Harvey, MD[1,6]

Background: Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Corticosteroid therapy has been widely used in CRS. Effective topical delivery has been previously problematic. The post-endoscopic sinus surgery (ESS) corridor is essential for adequate topical drug access. Devices delivering large volume with positive pressure allow better distribution to sinus mucosa. The objective of this study is to evaluate the efficacy of postoperative topical sinonasal steroid irrigations for CRS.

Methods: Patients with CRS undergoing ESS after failing previous medical therapy were recruited. Structured histopathology including markers of eosinophilia was performed. After surgery, patients received either budesonide 1 mg or betamethasone 1 mg delivered in a 240-mL squeeze bottle daily. Outcomes of the symptom score, Sino-Nasal Outcome Test 22 (SNOT-22) score, and endoscopy score were recorded.

Results: A total of 111 patients (mean 50.1 ± 13.5 standard deviation [SD] years, 40.5% female) were included. Mean follow-up was 55.5 ± 33.9 weeks. Baseline and post-treatment symptom scores (2.6 ± 1.1 vs 1.2 ± 1.0), SNOT-22 scores (2.2 ± 1.1 vs 1.0 ± 0.8), and endoscopy scores (6.7 ± 3.0 vs 2.5 ± 2.0) revealed significant improvement (all, $p < 0.001$). Contrary to previous publications, patients with high tissue eosinophilia (>10/high power field [HPF]) had significantly more improvement on symptom score (1.9 ± 1.4 vs 1.1 ± 1.0, $p = 0.04$), SNOT-22 score (1.6 ± 1.3 vs 1.0 ± 0.8, $p = 0.03$), and endoscopy score (5.12 ± 3.4 vs 3.06 ± 3.0, $p = 0.01$) than those without.

Conclusion: The philosophical approach to ESS in CRS is evolving. Topical therapies, when used appropriately, are highly effective for the most challenging eosinophilic patients. Although corticosteroid is a nonspecific therapy, it is effective when appropriately delivered. © 2012 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; corticosteroid; irrigations; endoscopic sinus surgery; budesonide; betamethasone; eosinophilic

How to Cite this Article:
Snidvongs K, Pratt E, Chin D, Sacks R, Earls P, Harvey RJ. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol*, 2012; 2:415–421.

[1]*Macquarie University, Sydney, Australia;* [2]*Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;* [3]*University of Sydney, Sydney, Australia;* [4]*Otolaryngology Head Neck Skull Base Surgery, St Vincent's Hospital, Sydney, Australia;* [5]*Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia;* [6]*University of New South Wales, Sydney, Australia*

Correspondence to: Komkiat Snidvongs, MD, FRCOT, 2 Technology Place, Macquarie University, NSW2109, Australia; e-mail: drkomkiat@yahoo.com

Potential conflict of interest: R.J.H. has served on an advisory board for Schering Plough and Glaxo-Smith-Kline, and was previously a consultant with Medtronic, on the speakers bureau for Merek Sharp Dolme and Arthrocare, and has received grant support from NeilMed. R.S. is a consultant for Medtronic and is on the speakers bureau for Merek Sharp Dolme.

Received: 2 February 2012; Revised: 13 March 2012; Accepted: 20 March 2012
DOI: 10.1002/alr.21047
View this article online at wileyonlinelibrary.com.

Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Topical steroid is currently used for treatments of CRS, both chronic rhinosinusitis without polyps (CRSsNP) and chronic rhinosinusitis with polyps (CRSwNP). The mechanism of corticosteroids combines suppression of gene transcription suppression for proinflammatory products and reduction of inflammatory cell migration, cell chemotactic factors, and adhesion molecules.[1] Recent meta-analyses reveal that topical steroid is effective for sinonasal symptoms for patients with CRSsNP,[2] decreases polyp size,[3,4] and prevents polyp recurrence in CRSwNP[5] but the influence of delivery and sinus surgery are important factors in effectiveness.

Delivery techniques, surgical state of the sinus cavity, delivery device, and fluid dynamics have a significant impact on the distribution of topical therapies to the sinus mucosa.[2] Delivery devices for topical steroid

"Sinus surgery and sinus delivery method have been demonstrated influencing on the effects of topical steroid. The new treatment of 'corticosteroid nasal irrigation after sinus surgery' is proposed for patients with CRS. Its effectiveness and subgroup analysis by tissue eosinophilia are investigated."

Abstract

Background:

Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Corticosteroid therapy has been widely used in CRS. Effective topical delivery has been previously problematic. The post endoscopic sinus surgery (ESS) corridor is essential for adequate topical drug access. Devices delivering large volume with positive pressure allow better distribution to sinus mucosa. The objective of this study is to evaluate the efficacy of post-operative topical sino-nasal steroid irrigations for CRS.

Methods:

Patients with CRS undergoing ESS after failing previous medical therapy were recruited. Structured histopathology including markers of eosinophilia was performed. After surgery, patients received either budesonide 1mg or betamethasone 1 mg delivered in a 240 mL squeeze bottle daily. Outcomes of symptom score, Sino-Nasal Outcome Test 22 (SNOT-22) and endoscopy scores were recorded.

Results:

111 patients (mean 50.1 ±13.5 years, 40.5% female) were included. Mean follow up was 55.5 ± 33.9 weeks. Baseline and post-treatment symptom scores (2.6±1.1 versus 1.2±1.0), SNOT-22 (2.2±1.1 versus 1.0±0.8,) and endoscopy scores (6.7±3.0

versus 2.5±2.0) revealed significant improvement (all, p<0.001). Contrary to previous publications, patients with high tissue eosinophilia (>10/HPF) had significantly more improvement on symptom score (1.9±1.4 versus 1.1±1.0, p=0.04), SNOT-22 (1.6±1.3 versus 1.0±0.8, p=0.03) and endoscopy score (5.12±3.4 versus 3.06±3.0, p=0.01) than those without.

Conclusion:

The philosophical approach to ESS in CRS is evolving. Topical therapies, when used appropriately, are highly effective for the most challenging eosinophilic patients. Although corticosteroid is a non-specific therapy, it is effective when appropriately delivered.

Key words:

chronic rhinosinusitis, corticosteroid, irrigations, endoscopic sinus surgery, budesonide, betamethasone, eosinophilic

Introduction

Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Topical steroid is currently used for treatments of CRS, both chronic rhinosinusitis without polyps (CRSsNP) and chronic rhinosinusitis with polyps (CRSwNP). The mechanism of corticosteroids combines suppression of gene transcription for pro-inflammatory products and reduction of inflammatory cell migration, cell chemotactic factors and adhesion molecules(Mullol, Obando et al. 2009). Recent meta-analyses reveal that topical steroid improves sino-nasal symptoms for patients with CRSsNP(Snidvongs, Kalish et al. 2011), decreases polyp size(Joe, Thambi et al. 2008; Snidvongs, Kalish et al. 2012) and prevents polyp recurrence in CRSwNP(Snidvongs, Kalish et al. 2012) but the influence of delivery and sinus surgery are important factors in effectiveness.

Delivery techniques, surgical state of the sinus cavity, delivery device, and fluid dynamics have a significant impact on the distribution of topical therapies to the sinus mucosa(Harvey and Schlosser 2009). Delivery devices for topical steroid administration are diverse in volume and pressure. Simple nasal delivery methods such as drops, sprays, aerosols, nebulizers and atomizers deliver low volume of steroid under low pressure. They are effective devices for nasal cavity therapy for conditions such as allergic rhinitis and when polyps protrude into the nasal airway. Devices delivering large volume (netipots, squeeze bottles and bulb syringes) under high pressure (squeeze bottles and bulb syringes) provide better options for treating chronic sinus mucosal inflammation. For long term CRS treatment, the post sinus

surgery corridor is essential to provide drug exposure to sinus mucosa(Snidvongs, Chaowanapanja et al. 2008; Harvey, Debnath et al. 2009).

From subgroup analysis in a recent Cochrane review, topical steroid delivery for patients with CRSsNP had a greater proportion of responders and more beneficial effects in symptom control when delivered directly to sinus cavities compared to simple nasal sprays(Snidvongs, Kalish et al. 2011). There is good data for the safety of nasal corticosteroid irrigations(Sachanandani, Piccirillo et al. 2009; Welch, Thaler et al. 2010) but the evidence for the effectiveness of topical steroid delivered through a wide post-operative sino-nasal corridor with a high pressure, high volume device is limited(Steinke, Payne et al. 2009). The objectives of this study are to evaluate the efficacy of post-operative topical sino-nasal steroid irrigation for CRS and to investigate the responsiveness of histopathologic subgroups.

Material and Methods

Patients with CRS requiring endoscopic sinus surgery (ESS) in a tertiary referral hospital were recruited. CRS patients were defined according to EP3POS(Fokkens, Lund et al. 2007). The study had ethical approval from the institutional review board. All patients underwent ESS after failing previous medical therapy. All patients had diffused mucosal changes. No patient with simple single sinus disease was recruited.

Inflammatory characterization

Structured histopathology reporting was performed. Markers of eosinophilia reported were tissue eosinophilia (<5 per high power field (HPF), 5-10 per HPF, >10 per HPF), Charcot-Leyden Crystals (absent, present) and eosinophil aggregates

(absent, present). Patients received a preoperative evaluation including clinical history, co-morbidities of asthma and aspirin (ASA) sensitivity, seromarkers and paranasal sinus computed tomography (CT). Co-morbidity of asthma was defined as clinically using an inhaled β-agonist or corticosteroid. Patients with suspected aspirin sensitivity on history were confirmed with a nasal lysine aspirin challenge as per the European Guidelines(Nizankowska-Mogilnicka, Bochenek et al. 2007). Preoperative CT scans were scored using the Lund-MacKay radiographic staging system. The seromarkers reported were eosinophil count ($x10^9$/L) and total IgE (kU/L).

Extent of ESS and surgical technique

All patients had more than simple osteomeatal complex disease. The philosophy of the institution is to provide a single sinus cavity in which all frontal, ethmoid, maxillary and sphenoid sinuses are in communication. Obstructive phenomenon is eliminated with this approach and fundamentally a “simple neo-sinus” is created in which eosinophilic hypersecretion can be removed and topical steroid can be delivered throughout the entire cavity. This is still mucosal preserving surgery. There is no drilling (except that as part of endoscopic modified Lothrop procedure) or intentional mucosal stripping but complete partition removal. The surgical endpoint is a single cavity with complete partition removal and not simple sinus openings providing ventilation (Figure 9.1).

Corticosteroid nasal irrigations

Patients received once daily nasal irrigation therapy of either budesonide (1 mg) or betamethasone dipropionate (1 mg) in 240 mL of normal saline solution. Once daily

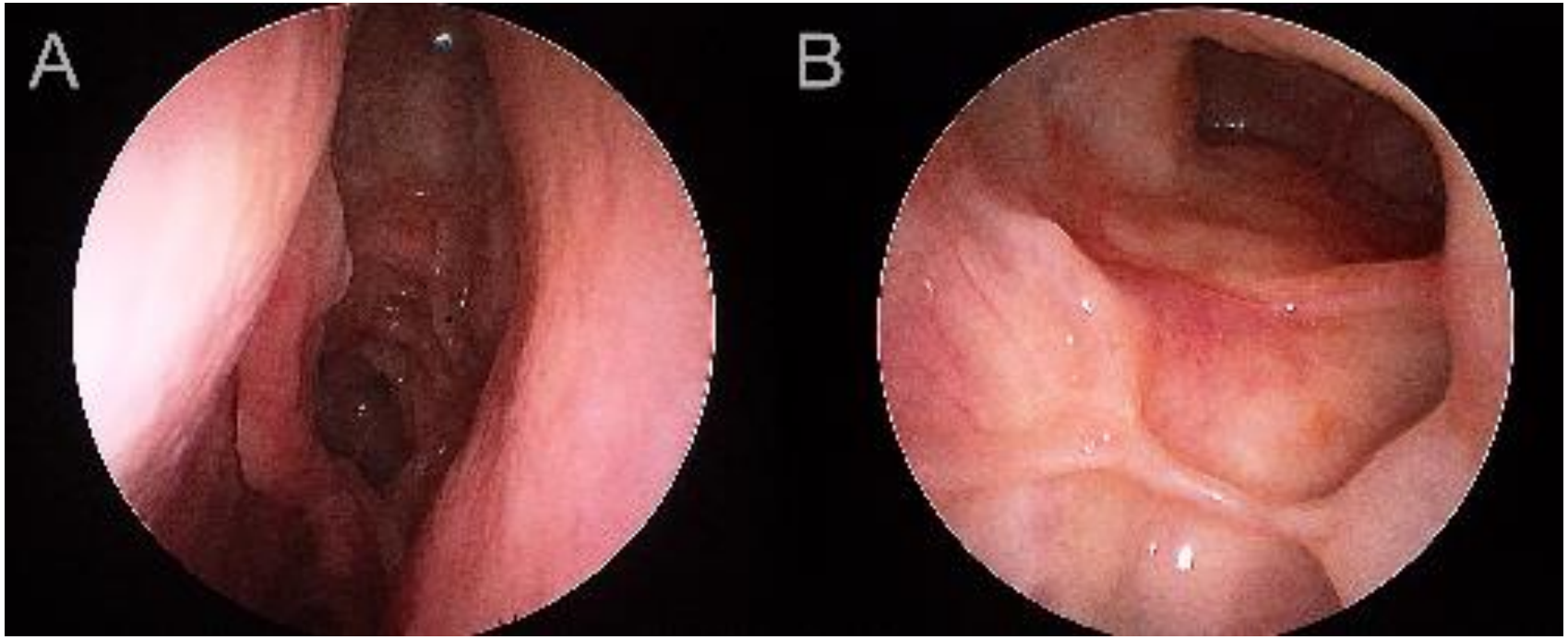


Figure 9.1: Post ESS single cavity with complete partition removal (A) sphenoethmoid cavity (B) frontoethmoid cavity

steroid irrigation was maintained for the first 3 months but after 3 months patients self tapered to alternate days or twice/ weekly as dictated by disease control. There was no limit to maximal duration. These devices allow much better steroid contact with sinus mucosa and provide a small (2.5±1.6%) fluid residual(Harvey, Debnath et al. 2009). Overall steroid exposure is limited in this approach as most patients receive less than 5% of total drug (50 mcg), equivalent to that delivered by simple nasal sprays. This is very different to studies of nasal steroid drop therapy which involved large doses with 100% residual(Chalton, Mackay et al. 1985; DelGaudio and Wise 2006).

Outcomes

The primary outcomes were a symptom score and the Sino-Nasal Outcome Test 22(SNOT-22)(Hopkins, Gillett et al. 2009). Five item symptom score of the following was used: nasal obstruction, post nasal discharge, thick nasal discharge, loss of smell and taste, facial pain and pressure. These were recorded on a Likert scale from 0 (no symptom) to 5 (very severe). Secondary outcomes were Lund-Kennedy endoscopy scores, the need for revision surgery and any long term requirement of oral steroid. The endoscopic assessor was blinded to the histopathology status of the patient.

Statistical analysis

Descriptive data was presented as percentage and mean±SD. Paired T-test (two-tailed) was used for comparisons of paired parametric data. Intention-to-treat analysis was performed. Student's T-test (two-tailed) was used for comparisons of

unrelated groups of parametric data. Statistical analyses were performed using SPSS v 17.0 (Statistical Package for the Social Sciences, Chicago, IL).

Results

Patient population

One hundred and eleven patients with a mean age of 50.1 ±13.5 years were assessed. Forty-five (40.5%) patients were female. Eight (7.2%) patients were smokers and thirty-five (31.5%) had asthma. Six (5.4%) patients had aspirin hypersensitivity. Forty-nine (44.1%) patients were diagnosed as CRSsNP. The mean baseline Lund-Mackay CT score was 13.7±6.3. The mean serum total IgE was 172.7±218.0 kU/L. The mean serum eosinophil count was 0.3±0.4 $x10^3$/mL. Fifty-one (45.9%) were revision surgical patients. The mean follow up was 55.5 ± 33.9 weeks. Seven (6.3%) were lost to follow-up.

Clinical outcomes

Baseline and post-treatment symptom score (2.6±1.1 versus 1.2±1.0) SNOT-22 (2.2±1.1 versus 1.0±0.8) and endoscopy scores (6.4±3.1 versus 2.5±2.0) revealed significant improvement (all, $p<0.001$). Data of each subgroup regarding to the presence of various markers of eosinophilic inflammation was displayed in Table 9.1.

Six out of 111 (5.4%) failed the treatment and required disease control by oral steroid. All of these six patients had some degree of glucocorticoid resistance for both their asthma and upper airway disease. Two of these still had significant symptoms despite receiving 20 mg of prednisone and two subsequently underwent

revision surgery. One patient underwent a revision polypectomy in a cavity that had had all partitions previously removed. The other had poor frontal sinus control and required an endoscopic modified Lothrop procedure. No patient ceased therapy due to adverse effects.

Subgroup analysis

There was a better performance of the eosinophilic CRS patients in the study. Patients with high tissue eosinophilia (>10/HPF) compared to those with low tissue eosinophilia (<10/HPF) had significantly more improvement in symptom (mean change -1.9±1.4 versus -1.1±1.0), p=0.04 (Figure 9.2), SNOT-22 (mean change -1.6±1.3 versus -1.0±0.8), p=0.03 (Figure 9.3) and in endoscopy scores (mean change -5.1$\pm$3.4 versus -3.1$\pm$3.0), p=0.01 (Figure 9.4). Patients with high serum eosinophilia (≥0.3x10^9/L) had significantly more improvement in endoscopic score than those without (mean change -5.7$\pm$3.4 versus -3.2$\pm$2.9), p=0.002 but the symptom improvement (-1.8±1.6 versus -1.4±1.1, p=0.43) and SNOT-22 improvement (-1.5±1.4 versus -1.2±1.0, p=0.30) were similar.

Patients with CRSwNP had significantly more improvement in symptoms (-1.7±1.4 versus -1.1±1.1, p=0.05) (Figure 9.5) and endoscopy scores (mean change -4.86$\pm$3.8 versus -2.63$\pm$2.3, p<0.001) than CRSsNP (Figure 9.6) and had similar SNOT-22 improvement (-1.3±1.3 versus -1.1±0.9, p=0.36) (Figure 9.7). Patients with asthma and patients with ASA hypersensitivity had similar symptom, SNOT-22 and endoscopy improvement when compared with those without (p>0.05, Table 9.2).The

Markers for eosinophilic inflammation		symptom score			SNOT-22 score			endoscopy score		
		baseline	post-treatment	p-value	baseline	post-treatment	p-value	Baseline	post-treatment	p-value
Tissue eosinophilia	<10/HPF	2.5±0.7	1.3±1.1	<0.001	2.0±0.8	1.0±0.9	<0.001	5.1±2.2	2.0±1.6	<0.001
	≥10/HPF	2.6±1.3	0.7±0.5	<0.001	2.3±1.2	0.8±0.7	<0.001	8.1±3.0	2.8±2.4	<0.001
Asthma	negative	2.4±1.1	1.1±1.0	<0.001	2.0±0.9	0.7±0.6	<0.001	5.8±3.0	1.8±1.5	<0.001
	positive	2.9±1.0	1.4±1.1	<0.001	2.3±1.3	1.2±0.8	<0.001	7.2±2.8	3.4±2.4	<0.001
ASA sensitivity	ASA tolerance	2.5±1.1	1.2±1.0	<0.001	2.1±1.0	1.0±0.6	<0.001	6.2±3.0	2.4±2.0	<0.001
	positive by test	2.8±1.5	1.0±1.2	<0.001	2.6±1.8	0.4±0.4	<0.001	7.8±2.7	2.4±0.5	<0.001

CRS subtype	CRSsNP	2.5±1.1	1.4±1.0	<0.001	2.3±1.1	1.2±0.9	<0.001	4.3±2.0	1.9±1.6	<0.001
	CRSwNP	2.6±1.2	0.9±0.9	<0.001	2.0±1.1	0.7±0.8	<0.001	8.3±2.8	2.9±2.3	<0.001
Serum eosinophilia	$<0.3x10^9$/L	2.5±1.0	1.0±0.8	<0.001	2.0±1.0	0.9±0.8	<0.001	5.4±2.5	1.8±1.4	<0.001
	$\geq 0.3x10^9$/L	2.8±1.2	1.2±1.1	<0.001	2.3±1.1	0.9±0.8	<0.001	8.2±3.0	3.3±2.5	<0.001
Serum IgE	<100kU/L	2.4±1.1	1.1±1.1	<0.001	2.1±1.0	0.9±0.9	<0.001	6.1±2.7	2.3±2.5	<0.001
	≥100kU/L	3.0±1.0	1.1±0.8	<0.001	2.3±1.1	0.9±0.7	<0.001	7.5±3.2	2.7±1.7	<0.001
Charcot Leyden	negative	2.4±1.0	1.0±0.9	<0.001	2.2±0.9	0.8±0.7	<0.001	6.0±2.5	1.9±1.5	<0.001
	positive	2.6±1.2	1.1±1.1	<0.001	2.0±1.0	0.6±0.5	<0.001	8.9±3.2	3.0±3.1	<0.001
Eosinophil aggregates	Negative	2.5±1.0	1.1±0.9	<0.001	2.2±0.9	0.9±0.6	<0.001	5.9±2.2	1.8±1.4	<0.001
	positive	2.5±1.1	1.0±1.1	<0.001	2.0±1.2	0.5±0.5	<0.001	8.7±3.2	2.9±2.8	<0.001

Table 9.1 Outcomes by various markers of eosinophilic inflammation

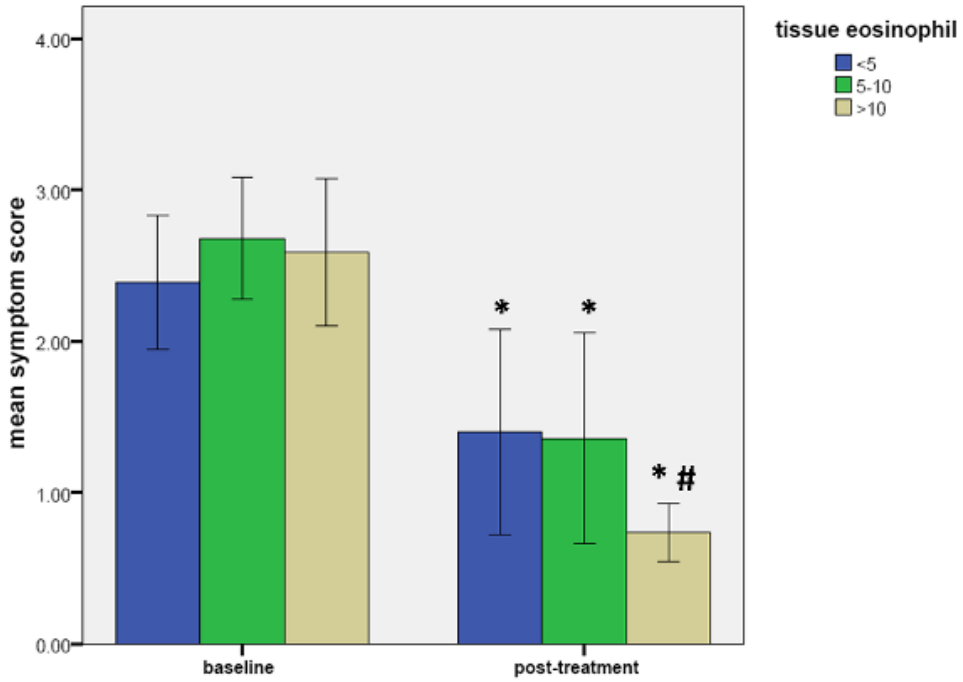


Figure 9.2: Symptom improvement by tissue eosinophil (/HPF); asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; number sign (#) indicates p<0.05 when mean change in symptom was compared between patients with high tissue eosinophilia (≥10/HPF) and those without.

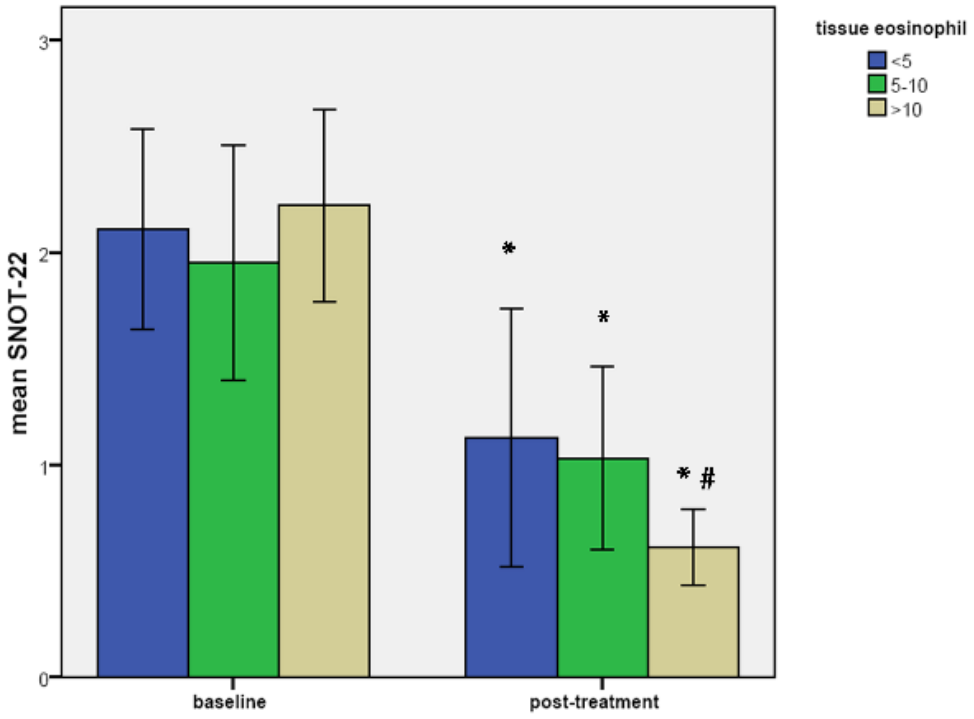


Figure 9.3: Disease specific quality of life (SNOT-22) improvement by tissue eosinophil (/HPF); asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; number sign (#) indicates p<0.05 when mean change in SNOT-22 was compared between patients with high tissue eosinophilia (≥10/HPF) and those without.

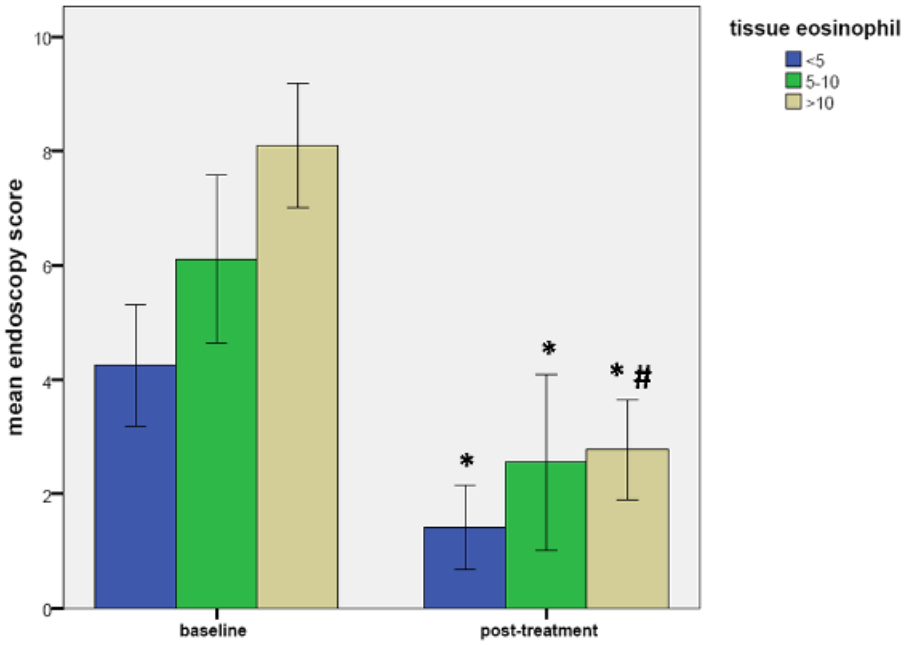


Figure 9.4: Endoscopy score improvement by tissue eosinophil (/HPF); asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; number sign (#) indicates p<0.05 when mean change in endoscopy score was compared between patients with high tissue eosinophilia (≥10/HPF) and those without.

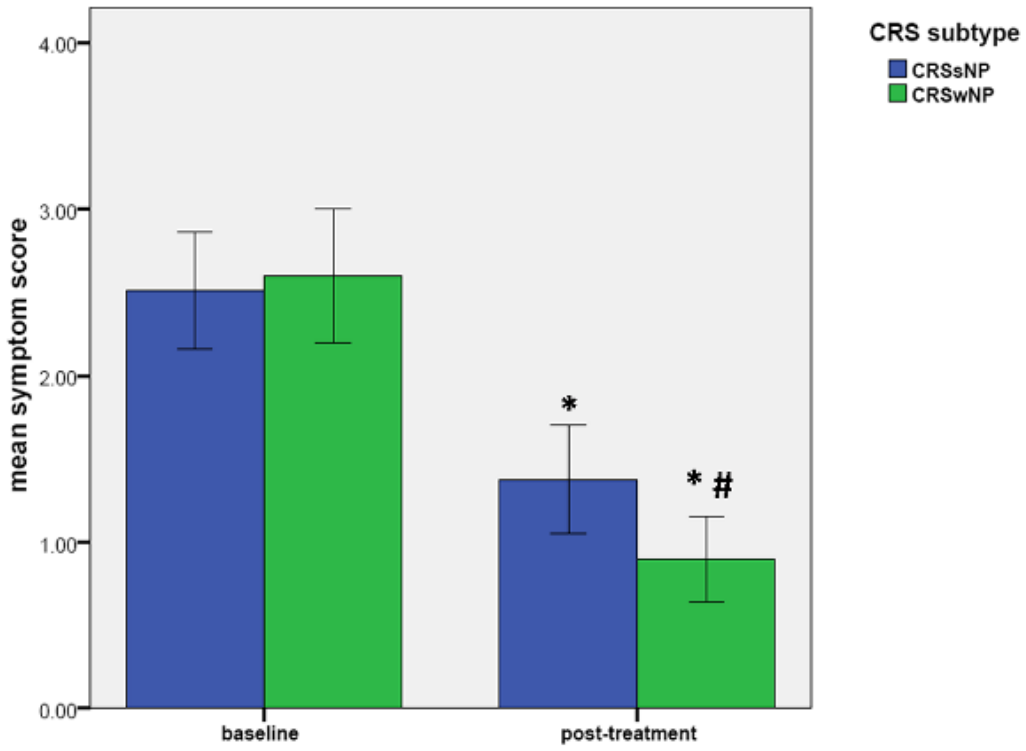


Figure 9.5: Symptom improvement by CRS subtype; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; number sign (#) indicates p<0.05 when mean change in symptom was compared between CRS subtypes.

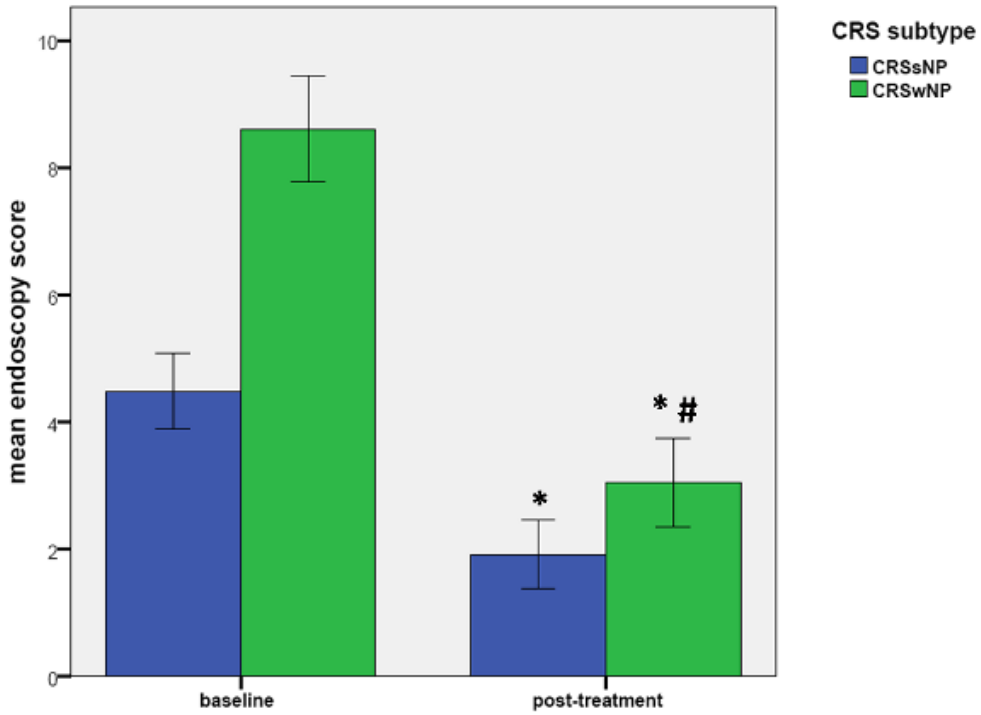


Figure 9.6: Endoscopy score improvement by CRS subtype; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; number sign (#) indicates p<0.05 when mean change in endoscopy score was compared between CRS subtype.

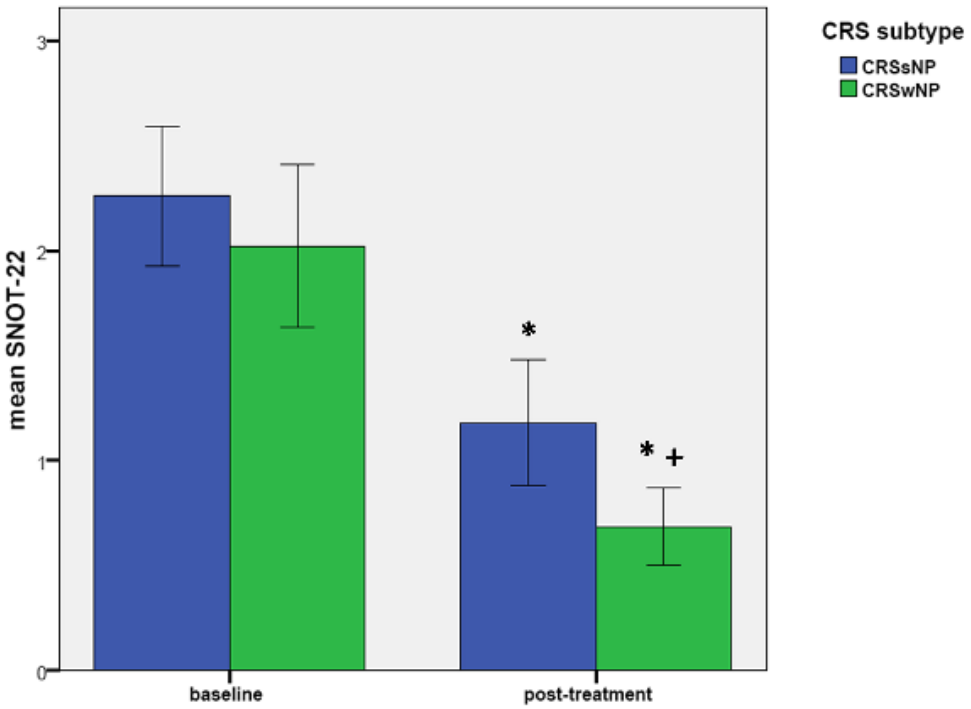


Figure 9.7: Disease specific quality of life (SNOT-22) improvement by CRS subtype; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; plus sign (+) indicates non-significance when mean change in SNOT-22 was compared between CRS subtype.

Markers for eosinophilic inflammation		change in symptom score		change in SNOT-22 score		change in endoscopy score	
		mean	p-value	mean	p-value	mean	p-value
Tissue eosinophilia	<10/HPF	1.1±1.0	0.04	1.0±0.8	0.03	3.1±3.0	0.01
	≥10/HPF	1.9±1.4		1.6±1.3		5.1±3.4	
Asthma	negative	1.3±1.2	0.41	1.2±0.9	0.81	4.0±3.3	1.0
	positive	1.5±1.3		1.1±1.4		4.0±3.9	
ASA sensitivity	ASA tolerance	1.3±1.2	0.35	1.1±1.0	0.34	3.9±3.6	0.22
	ASA hypersensitivity	2.2±1.5		2.2±1.8		5.3±3.0	
CRS subtype	CRSsNP	1.1±1.1	0.05	1.1±0.9	0.36	2.6±2.3	<0.001
	CRSwNP	1.7±1.4		1.3±1.3		5.1±4.0	

Serum eosinophilia	$<0.3x10^9/L$	1.4±1.1	0.43	1.2±1.0	0.30	3.2±2.9	0.002
	$\geq 0.3x10^9/L$	1.8±1.6		1.5±1.4		5.7±3.4	
Serum IgE	<100kU/L	1.2±1.3	0.07	1.1±1.0	0.27	3.7±3.2	0.19
	≥100kU/L	1.9±1.3		1.5±1.3		4.7±3.3	
Charcot Leyden	negative	1.5±1.2	0.44	1.4±1.1	0.78	4.4±2.5	0.59
	positive	1.9±1.6		1.3±1.1		5.1±4.7	
Eosinophil aggregates	Negative	1.4±1.3	0.35	1.3±1.1	0.77	4.3±2.5	0.32
	positive	1.8±1.4		1.4±1.3		5.3±4.4	

Table 9.2 Comparison of mean change in symptom, SNOT-22 and endoscopy between subgroups

comparison between subgroups in the improvement in symptom score, SNOT 22 and endoscopy score is shown in Table 9.2.

Discussion

The impact of surgery from the steroid irrigation cannot be separated in our study. However, they are not separate treatments but intended to function together as a combined therapy. Delivery of steroid via nasal irrigation combines the general therapeutic goals of topical management in providing pharmaceutical delivery and simultaneous mechanical lavage(Harvey, Debnath et al. 2009). Complete sinus distribution is achieved when a wide post ESS corridor has been created(Harvey, Goddard et al. 2008). High-volume positive pressure solutions allow pharmaceutical preparations to better contact sinus mucosa and may enhance the mechanical removal of mucus, inflammatory products, and bacteria/biofilms (Harvey and Schlosser 2009). Corticosteroid irrigations are not offered to un-operated patients in our centre as they are seen as limited treatments without prior wide sinus surgery. Patients with prior minimally invasive procedures, such balloon sinuplasty, are not offered the steroid irrigations as such procedures have not been shown to increase distribution and may even limit it(Brenner, Abadie et al. 2011). There is a need for a randomized controlled trial in steroid irrigation versus simple spray in the post-surgical setting to fully define the influence of the proposed steroid delivery. Such a trial is currently underway but will not be concluded for some time.

Although topical steroid has been recommended in treating CRS(Fokkens, Lund et al. 2007) and widely accepted, not all well designed studies report positive outcomes

over placebo (Parikh, Scadding et al. 2001; Furukido, Takeno et al. 2005). In a recent Cochrane meta-analysis, trials studying the effectiveness of topical corticosteroids demonstrated patient variation due to surgical status. These differences have been shown to greatly affect topical delivery and distribution (Snidvongs, Chaowanapanja et al. 2008; Harvey, Debnath et al. 2009).

The meta-analysis of topical steroid versus placebo showed that a subgroup of patients with sinus surgery had greater polyp score reduction than those without(Snidvongs, Kalish et al. 2012). When steroid was administered directly to the sinuses for CRSsNP, symptoms were more improved than with simple nasal delivery(Snidvongs, Kalish et al. 2011). These findings well explain the positive results of corticosteroid nasal irrigations after ESS in this study.

Overall steroid exposure is limited in this approach as most patients receive less than 5% of total drug as a residual in their sinuses(50mcg)(Harvey, Debnath et al. 2009) and equivalent to that delivered by simple nasal sprays. This dosage is equivalent to 0.11-0.18mgof prednisone (0.42 mg topically and assumed 30-40% absorption) which is 40-70 fold lower than the dosage of 7.5 mg which may result in adrenal suppression. The safety of budesonide added to nasal irrigations has been reported by previous studies on serum and urinary cortisol levels(Welch, Thaler et al. 2010), which demonstrated no objective suppression. Combined with our knowledge of the limited residual(Harvey, Debnath et al. 2009) from steroid irrigations, Sachanandani and his colleagues reported an adequate adrenal response to cosyntropin test after budesonide irrigations(Sachanandani, Piccirillo et al. 2009). This is contrary to studies using nasal drops, which have reported Cushing

syndrome(Stevens 1988; Findlay, Macdonald et al. 1998) and adrenal suppression(Flynn, Beasley et al. 1992; Gill, Swift et al. 2001) induced by betamethasone therapy. Patients in some nasal drop studies(Chalton, Mackay et al. 1985) received large doses with 100% residual being swallowed and absorbed by the gastrointestinal tract. The failure rate of post-ESS corticosteroid irrigation in this study is 5.4%. Patients with glucocorticoid resistance may not be good candidates for this treatment and poor response to oral prednisone pre-ESS should be a flag for these patients. No comparison was performed between the effects of budesonide and betamethasone. There is an allocation bias, due to

prescribing patterns, with asthmatic patients receiving budesonide. This makes an interpretation of outcomes between agents of limited benefit. Betamethasone and budesonide have similar glucocorticoid affinities(Johansson, Andersson et al. 1982; Derendorf and Meltzer 2008).

Eosinophilic chronic rhinosinusitis (ECRS), commonly defined as having tissue eosinophil greater than 10 cells/HPF(Snidvongs, Lam et al. 2012 in press) is associated with clinical severity(Snidvongs, Lam et al. 2012 in press), poor outcome(Soler, Sauer et al. 2010) and high recurrent rate(Gelardi, Fiorella et al. 2009; Tosun, Arslan et al. 2010) after endoscopic sinus surgery. This subgroup, in particular, is likely to require long term anti-inflammatory therapy and thus single modality therapies such as ESS alone is unlikely to produce satisfactory results. The purpose of ESS for this subgroup is to create the access for topical therapies rather than the fundamental concept of relieving osteomeatal obstruction. It was the most challenging subgroup in this study that had favorable outcomes and even greater

improvement than the non ECRS subgroup. Significant improvement was shown for patients with nasal polyps over those without and for patients with serum eosinophilia over those without. Patients with the co-morbidity of asthma, ASA hypersensitivity responded to post-ESS corticosteroid irrigation as well as those without. These findings suggest that local mucosal inflammation can be well controlled when pharmaceutical solution is effectively delivered. ECRS may potentially be considered a condition to “control” similar to asthma and this concept will be included in future European Guidelines on managing CRS. At present, regular effective nasal steroid use may be the optimal therapy to control this condition. The majority of patients in this trial were still using routine steroid irrigations. However, many patients are able to reduce this use to as low as 1-2/week. The influence of frequency and maintenance dose is not addressed in our study and is the focus of future research. Endoscopy has been shown to predict the need for recurrent surgery(Senior, Kennedy et al. 1998) and it may be a comparable tool for monitoring ECRS and associated mucosal inflammation, similar to the use of peak expiratory flow rate in asthma monitoring.

Conclusion

The philosophical approach to ESS in CRS is evolving. Topical therapies when used appropriately are highly effective against the most challenging eosinophilic patients. Although corticosteroid is a blunt tool, it is effective when effectively delivered.

References

Brenner, P. S., W. M. Abadie, E. K. Weitzel, R. F. Thomas and K. C. McMains Unexpected consequences of transnasal balloon dilation of the maxillary ostium. *Intl forum allergy rhinol* 2011; 1(6): 466-470.

Chalton, R., I. Mackay, R. Wilson and P. Cole Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. *Br Med J (Clin Res Ed)* 1985; 291(6498): 788.

DelGaudio, J. M. and S. K. Wise Topical steroid drops for the treatment of sinus ostia stenosis in the postoperative period. *Am J Rhinol* 2006; 20(6): 563-567.

Derendorf, H. and E. O. Meltzer Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy* 2008; 63(10): 1292-1300.

Findlay, C. A., J. F. Macdonald, A. M. Wallace, N. Geddes and M. D. Donaldson Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions. *BMJ* 1998; 317(7160): 739-740.

Flynn, M. D., P. Beasley and J. E. Tooke Adrenal suppression with intranasal betamethasone drops. *J Laryngol Otol* 1992; 106(9): 827-828.

Fokkens, W., V. Lund and J. Mullol European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007; (20): 1-136.

Furukido, K., S. Takeno, T. Ueda and K. Yajin Cytokine profile in paranasal effusions in patients with chronic sinusitis using the YAMIK sinus catheter with and without betamethasone. *Eur Arch Otorhinolaryngol* 2005; 262(1): 50-54.

Gelardi, M., R. Fiorella, M. L. Fiorella, et al. Nasal-sinus polyposis: clinical-cytological grading and prognostic index of relapse. *J Biol Regul Homeost Agents* 2009; 23(3): 181-188.

Gill, G., A. Swift, A. Jones, D. Strain and P. Weston Severe adrenal suppression by steroid nasal drops. *J R Soc Med* 2001; 94(7): 350-351.

Harvey, R. J., N. Debnath, A. Srubiski, B. Bleier and R. J. Schlosser Fluid residuals and drug exposure in nasal irrigation. *Otolaryngol Head Neck Surg* 2009; 141(6): 757-761.

Harvey, R. J., J. C. Goddard, S. K. Wise and R. J. Schlosser Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008; 139(1): 137-142.

Harvey, R. J. and R. J. Schlosser Local drug delivery. *Otolaryngol Clin North Am* 2009; 42(5): 829-845.

Hopkins, C., S. Gillett, R. Slack, V. J. Lund and J. P. Browne Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009; 34(5): 447-454.

Joe, S. A., R. Thambi and J. Huang A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008; 139(3): 340-347.

Johansson, S. A., K. E. Andersson, R. Brattsand, E. Gruvstad and P. Hedner Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur J Clin Pharmacol* 1982; 22(6): 523-529.

Mullol, J., A. Obando, L. Pujols and I. Alobid Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol Allergy Clin North Am* 2009; 29(4): 657-668.

Nizankowska-Mogilnicka, E., G. Bochenek, L. Mastalerz, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007; 62(10): 1111-1118.

Parikh, A., G. K. Scadding, Y. Darby and R. C. Baker Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. *Rhinology* 2001; 39(2): 75-79.

Sachanandani, N. S., J. F. Piccirillo, M. A. Kramper, S. E. Thawley and A. Vlahiotis The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 2009; 135(3): 303-307.

Senior, B. A., D. W. Kennedy, J. Tanabodee, et al. Long-term results of functional endoscopic sinus surgery. *Laryngoscope* 1998; 108(2): 151-157.

Snidvongs, K., P. Chaowanapanja, S. Aeumjaturapat, S. Chusakul and P. Praweswararat Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol* 2008; 22(5): 483-486.

Snidvongs, K., L. Kalish, R. Sacks, J. C. Craig and R. J. Harvey Topical steroid for chronic rhinosinusitis without polyps. *Cochrane Database Syst Rev* 2011; (8): 1-59.

Snidvongs, K., L. Kalish, R. Sivasubramaniam, et al. Topical steroid for nasal polyps. *Cochrane Database Syst Rev* 2012; in press.

Snidvongs, K., M. Lam, R. Sacks, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol* 2012 in press.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010; 142(1): 64-71.

Steinke, J. W., S. C. Payne, M. E. Tessier, et al. Pilot study of budesonide inhalant suspension irrigations for chronic eosinophilic sinusitis. *J Allergy Clin Immunol* 2009; 124(6): 1352-1354

Stevens, D. J. Cushing's syndrome due to the abuse of betamethasone nasal drops. *J Laryngol Otol* 1988; 102(3): 219-221.

Tosun, F., H. H. Arslan, Y. Karslioglu, M. S. Deveci and A. Durmaz Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol* 2010; 119(7): 455-459.

Welch, K. C., E. R. Thaler, L. L. Doghramji, J. N. Palmer and A. G. Chiu The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. *Am J Rhinol Allergy* 2010; 24(1): 26-28.

Chapter 9 Appendix

Appendix9.1 Corticosteroid nasal irrigations after endoscopic sinus surgery on the management of chronic Rhinosinusitis and the influence on osteitis

Figure 9.8: Symptom improvement by the presence of osteitis

Figure 9.9: Disease specific quality of life (SNOT-22) improvement by the presence of osteitis

Figure 9.10: Endoscopy score improvement by the presence of osteitis

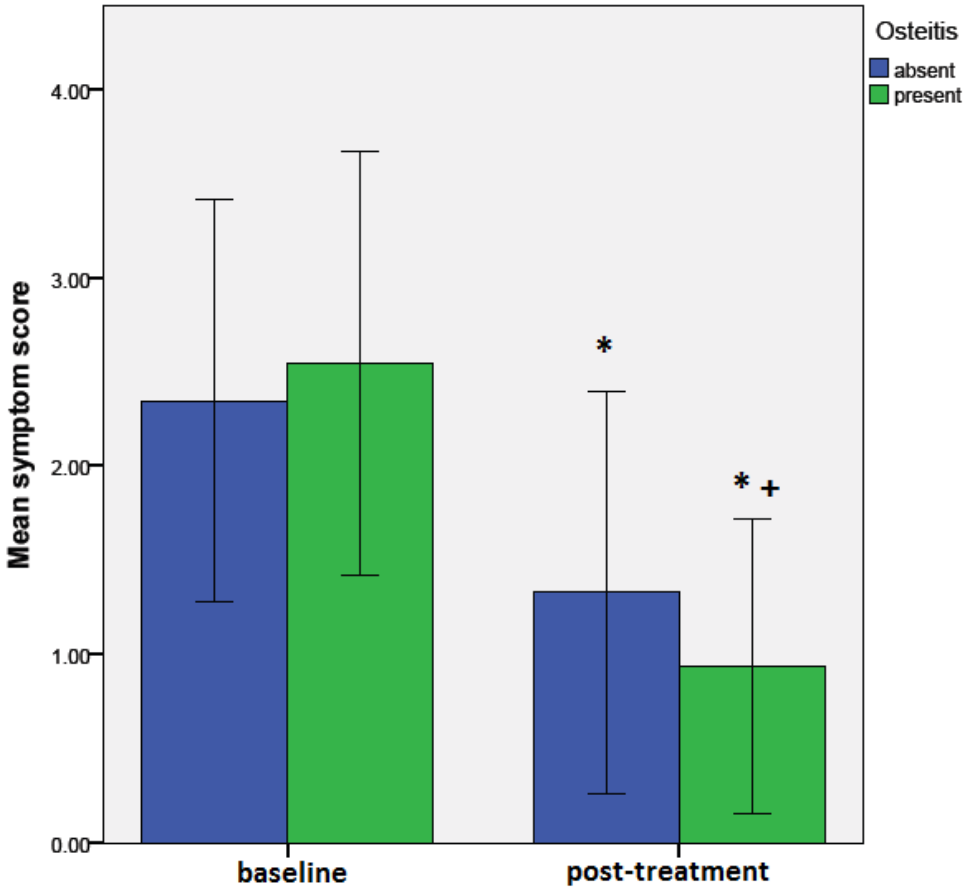


Figure 9.8: Symptom improvement by the presence of osteitis; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; plus sign (+) indicates p>0.05 when mean change in symptom was compared between CRS subtypes.

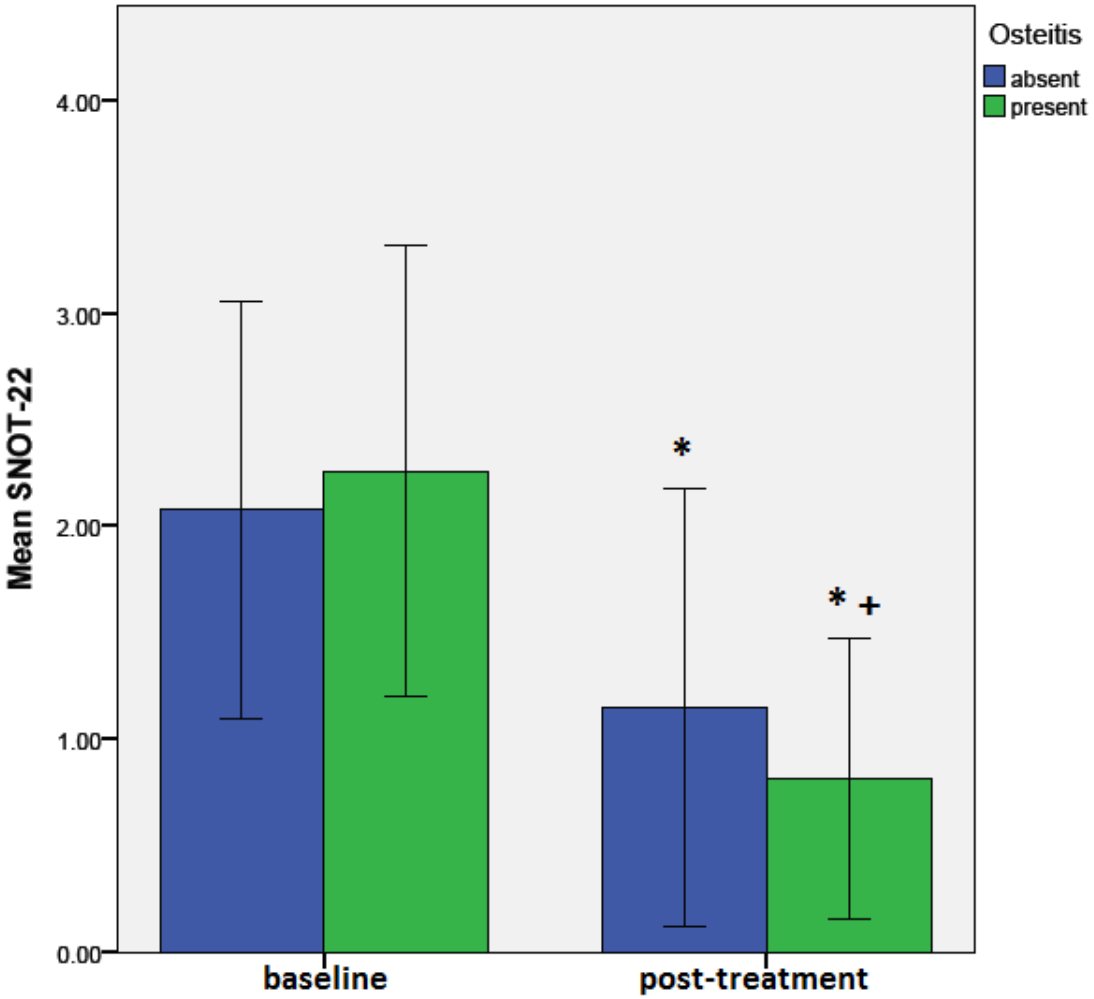


Figure 9.9: Disease specific quality of life (SNOT-22) improvement by the presence of osteitis; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; plus sign (+) indicates p>0.05 when mean change in symptom was compared between CRS subtypes.

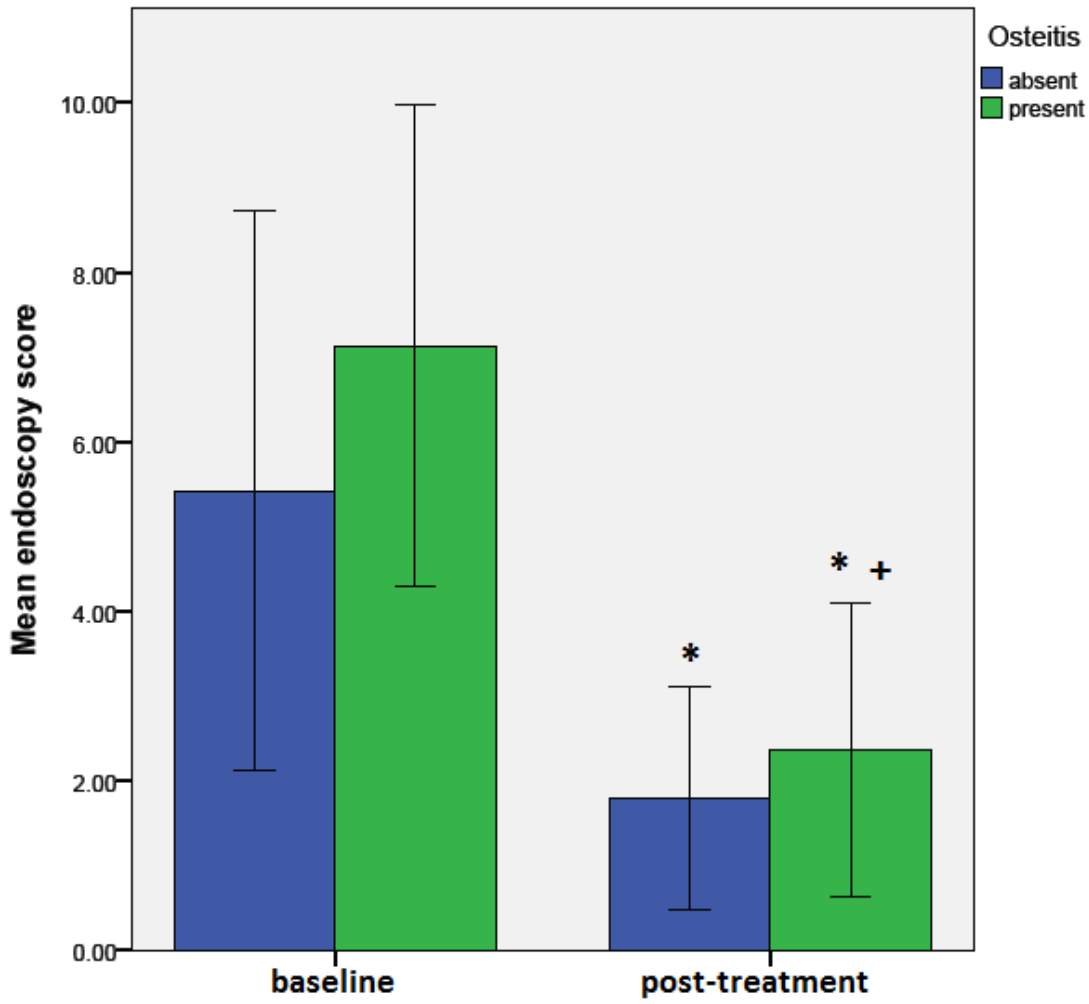


Figure 9.10: Endoscopy score improvement by the presence of osteitis; asterisk (*) indicates p<0.001 when post-treatment was compared with baseline; plus sign (+) indicates p>0.05 when mean change in symptom was compared between CRS subtypes.

Chapter10 Thesis discussion and conclusion

Summation of thesis results

Eosinophilic chronic rhinosinusitis

Patients with eosinophilic chronic rhinosinusitis (ECRS), when defined as tissue eosinophilia of >10/HPF, have significantly worse endoscopic scores (6.0±2.1) when compared to non-ECRS (3.8±2.7), p=0.004. Similarly the mean CT scores of ECRS (15.1±6.2) were significantly more severe than non-ECRS (8.8±5.5), p=0.001. Additionally, patients with ECRS have higher osteitis score (4.0(1.0-6.0)) than those without (1.0(0.0-5.8), p=0.04). Patients with osteitis also have greater endoscopy scores (6.1±2.9 versus 4.4±3.6, p=0.03) and CT scores (14.0±6.0 versus 10.1±5.7, p<0.01) than those without osteitis.

Nasal polyps (x^2=25.76, p<0.01) and serum eosinophilia at >0.30 $x10^9$/L (r=0.33, p=0.03) well predict high tissue eosinophilia. High serum eosinophilia has a good positive predictive value for ECRS. However, the absence of polyps and a normal serum eosinophil count are both poor predictors of non ECRS as high tissue eosinophilia (>10/HPF) is also seen in 19% of non-polyp patients.

When CRS is considered as an inflammatory disease and a subclassification of ECRS is made, the traditional etiological factors to chronic sinus dysfunction appear to play a less significant role. All patients with ECRS, regardless of the status of ostiomeatal complex (OMC) occlusion, have maxillary sinus diseases and there are 36.2% without OMC occlusion. In contrast to ECRS, patients with non-ECRS, have maxillary sinus diseases in 50% of those without OMC occlusion and 96.2% of those

with OMC occlusion (odd ratio (OR) =25.0 (2.77, 226.08); p<0.001). It appears that mucosal ostial obstruction is linked to only small subgroup of non-ECRS patients. Such findings in the ECRS group of both diagnostic and etiological differences to other forms of CRS challenges the traditional concepts of treatment interventions.

Sinus surgery and delivery method influence the effectiveness of topical corticosteroid for chronic rhinosinusitis

In patients with chronic rhinosinusitis without polyps (CRSsNP), topical steroid improves symptom scores when compared to placebo, (standardised mean difference -0.37; 95%confidence interval (CI) -0.60 to -0.13, p = 0.002; five trials, n = 286) and has a greater proportion of responders (risk ratio 1.69; 95% CI 1.21 to 2.37, p = 0.002; four trials, n = 263). However, the effect size is heterogeneous and often small. Only on subgroup analysis of ‘patients with sinus surgery’ versus ‘patients without sinus surgery’ is some of this heterogeneity explained. The effect of topical steroid over placebo is only significant in the subgroup of ‘patients with sinus surgery’ (p=0.002) but not in the subgroup of ‘patients without sinus surgery’ (p=0.82). Subgroup analysis by topical delivery method also reveals more benefit when steroid is administered 'directly to the sinuses' than with 'simple nasal delivery' (p = 0.04).

In patients with chronic rhinosinusitis with polyps (CRSwNP), topical steroid improves overall symptom scores (standardised mean difference (SMD) -0.46; 95% confidence interval (CI) -0.65 to -0.27, p < 0.00001; seven trials, n = 445) and has a higher proportion of patients whose symptoms improved (responders) (risk ratio (RR)

1.71; 95% CI 1.29 to 2.26, p = 0.0002; four trials, n = 234). Topical steroid also decreases the polyp score (SMD -0.73; 95% CI -1.00 to -0.46, p < 0.00001; three trials, n = 237), has a greater proportion of patients with a reduction in polyp size (responders) (RR 2.09; 95% CI 1.65 to 2.64, p < 0.00001; eight trials, n= 785) and prevents polyp recurrence after surgery (RR 0.59; 95% CI 0.45 to 0.79, p = 0.0004; six trials, n = 437) when compared to placebo. Once again, the effect is heterogeneous and often small. Subgroup analysis by sinus surgery status reveals a greater benefit in reduction of polyp score when topical steroid is administered after sinus surgery (SMD -1.19; 95% CI -1.54 to -0.83 versus SMD -0.13; 95% CI -0.53 to 0.28, p < 0.00001).

When both CRS subtypes are combined, topical steroid is beneficial when compared to placebo for treating patients with CRS. It improves overall symptoms (standardized mean difference (SMD) -0.49, p <0.00001) and the proportion of responders (risk ratio (RR) 0.59, p<0.00001). It decreased polyp size with a greater proportion of responders (RR 0.48, p <0.00001) and prevented polyp recurrence (RR 0.59, p= 0.0004). Reduction of polyp size is greater in patients with sinus surgery (RR 0.31; 95%CI (0.20, 0.48)) than those without (RR 0.61; 95%CI (0.46, 0.81)), p=0.009. Greater symptom improvement occurred when sinus delivery methods (SMD -1.32; 95%CI (-2.26,-0.38)) are compared to nasal delivery methods (SMD -0.38; 95%CI (-0.55,-0.22), p < 0.00001).

Although not overwhelming, there is evidence that some of the heterogeneity in published studies on the use of intranasal corticosteroid may be explained by both the ability of topical agents to access and be effectively delivered to the sinus

cavities. There would appear to be a poorest performing group of patient cohorts using simple nasal sprays (with the intent of sinus delivery) in a pre-surgical state. This clinical finding is in keeping with our understanding of experimental studies into the most effective way to delivery topical agents to the sinus cavity (Harvey, Goddard et al. 2008, Snidvongs, Chaowanapanja et al. 2008, Harvey and Schlosser 2009).

Corticosteroid nasal irrigations after endoscopic sinus surgery are beneficial for all subtypes of chronic rhinosinusitis

In bringing together the concepts of effective therapy for an inflammatory condition by remodelling the sinus cavity with surgery and delivering topical corticosteroid with high volume positive pressure device, a significant treatment benefit is seen. Significant improvement is demonstrated between baseline and post-treatment symptom scores (2.6±1.1 versus 1.2±1.0), SNOT-22 (2.2±1.1 versus 1.0±0.8,) and endoscopy scores (6.7±3.0 versus 2.5±2.0) (all, $p<0.001$) for CRS patients. Patients with high tissue eosinophilia (>10/HPF) have significantly more improvement on symptom score (1.9±1.4 versus 1.1±1.0, p=0.04), SNOT-22 (1.6±1.3 versus 1.0±0.8, p=0.03) and endoscopy score (5.12$\underline{+}$3.4 versus 3.06$\underline{+}$3.0, p=0.01) than those without. Patients with osteitis have similar improvement on symptom score (1.6±1.1 versus 1.0±1.2, p=0.07), SNOT-22 (1.4±1.2 versus 0.9±0.8, p=0.06) and endoscopy score (4.6±3.1 versus 3.9±3.1, p=0.39) with patients without osteitis (See Chapter9 Appendix).

Discussion

In agreement with other authors (Kountakis, Arango et al. 2004; Soler, Sauer et al. 2009), this study demonstrates that patients with ECRS have more disease severity. Additionally high tissue eosinophilia is associated with osteitis and this is also true among patients without previous sinus surgery subgroup (35%). Similar results have been reported by other authors(Mehta, Campeau et al. 2008; Bhandarkar, Mace et al. 2011). Patients with osteitis have more disease severity than those without osteitis. Thus it is crucial to define ECRS which is the challenging subgroup in practice. Where the prevalence of “occult’ high tissue eosinophilia among non-polyps, non-asthmatic CRS is as high as 19%, the integration of a structured histopathology report is beneficial in routine practice.

ECRS is not a disease of OMC occlusion. Thus simple surgical interventions which aim to manipulate OMC occlusion such as minimally invasive sinus technique (MIST), balloon sinuplasty and simple antral washouts are unlikely to provide a long term modulation on the pathophysiology of patients with ECRS or alter the dynamics of postsurgical topical therapy. Diffuse eosinophilic inflammation requires corticosteroid therapy rather than the promotion of sinus ventilation and drainage. Although topical steroid is effective in treating CRS, it can only penetrate paranasal sinus system via positive pressure, high volume devices, not via simple nasal spray delivery. Sinus surgery and delivery method influence the effectiveness of topical corticosteroid for chronic rhinosinusitis. This has been shown by meta-analyses of this thesis together with findings from other previous studies(Grobler, Weitzel et al.

2008; Harvey, Goddard et al. 2008; Snidvongs, Chaowanapanja et al.2008; Harvey and Schlosser 2009; Singhal, Weitzel et al. 2010; Rudmik, Schlosser et al. 2012).

Corticosteroid nasal irrigations after endoscopic sinus surgery have been shown beneficial for all subtypes of chronic rhinosinusitis. In contrast to other studies on ECRS (Baudoin, Cupic et al. 2006; Matsuwaki, Ookushi et al. 2008; Gelardi, Fiorella et al. 2009; Sun, Joo et al. 2009; Soler, Sauer et al. 2010; Tosun, Arslan et al. 2010), patients with ECRS in this study have favorable outcomes and even greater improvement than the non ECRS subgroup. Additionally, when subgroup analysis by the presence of osteitis is analyzed, this study demonstrates similar favorable outcomes between the two subgroups. This is in contrast to other studies(Kim, Dhong et al. 2006; Bhandarkar, Mace et al. 2011) reporting patients with osteitis have inferior outcomes post endoscopic sinus surgery when compared to those without. Patients with ECRS and osteitis have been acknowledged having poorer treatment outcomes. This concept is not always true as it depends on which maintenance treatments are given. Topical therapies when used appropriately are highly effective against the most challenging eosinophilic and osteitic patients.

The impact of surgery from the steroid irrigation cannot be separated in our study. However, they are not separate treatments but intended to function together as a combined therapy in a local inflammatory disorder of the airway. Delivery of steroid via nasal irrigation combines the general therapeutic goals of topical management in providing pharmaceutical delivery and simultaneous mechanical lavage(Harvey, Debnath et al. 2009). Complete sinus distribution is achieved when a wide post ESS

corridor has been created(Harvey, Goddard et al. 2008). High-volume positive pressure solutions allow pharmaceutical preparations to better contact sinus mucosa and may enhance the mechanical removal of mucus, inflammatory products, and bacteria/biofilms(Harvey and Schlosser 2009). The philosophy of sinus surgery for patients with ECRS has evolved away from simple infection and obstruction models of disease pathogenesis. Interventions are directed to provide a single sinus cavity in which all frontal, ethmoid, maxillary and sphenoid sinuses are in communication. Obstructive phenomena are eliminated with this approach and fundamentally a simple “neo-sinus” is created in which eosinophilic hypersecretion can be removed and topical steroid effectively delivered throughout the entire cavity. The surgical endpoint is a single cavity with complete partition removal and mucosal preservation. The remodelling empowers the patient to self-treat the condition with locally delivery medications rather than relying on systemic therapies.

Future direction: implications for practice

Defining histopathology subtypes of patients with CRS is beneficial in routine practice. It predicts disease severity (greater disease severity for patients with ECRS) and directs treatment implications (macrolide therapy for neutrophilic CRS and aggressive local corticosteroid therapy for ECRS). Traditional features of the ECRS phenotype are not necessarily reliable markers for the presence of tissue eosinophilia. The use of structured histopathology reporting in CRS allows for the accurate diagnosis of ECRS and identifies other future prognostic markers.

Osteitis is associated with tissue and serum eosinophilia in both patients with and without prior surgery. Patients with these features may benefit from post-operative corticosteroid therapy. Kennedy Osteitis Score is a simple, easy and reproducible scale in radiologically assessing osteitic bones in patients with CRS and can predict measures of severity in eosinophilic rhinosinusitis.

The extension of sinus surgery for patients with ECRS and non-ECRS is based on two different philosophies. Simple surgical interventions which aim to manipulate OMC occlusion such as minimally invasive sinus technique (MIST), balloon sinuplasty and simple antral washouts are still effective but only for patients with non-ECRS in which ostia occlusion is primary disease factor. As for patients with ECRS, a single sinus cavity with complete partition removal in which all sinuses are in communication should be created. Thus eosinophilic hypersecretion can be removed and topical steroid effectively delivered throughout the entire cavity.

Corticosteroid nasal irrigations after endoscopic sinus surgery bring favorable outcomes for patients with ECRS and patients with osteitis in a long term. A wide post sinus surgery corridor allows the steroid to contact the sinus mucosa effectively and enhance the mechanical removal of thick eosinophilic mucin. Simple nasal sprays and limited surgery appear to have a limited role in the management of ECRS.

Future direction: implications for research

A well-conducted placebo controlled randomised trial is required, comparing effective topical drug delivery methods to the sinuses, post sinus surgery, with an

appropriate duration of treatment (preferably 12months) and using validated outcome measures. Randomised controlled trials should be pre-registered and their reporting should be according to the latest CONSORT guidelines(Schulz, Altman et al. 2010).

Thesis conclusion

The diagnosis of ECRS has unique prognostic implications. Traditional features of the ECRS phenotype are not necessarily reliable markers for the presence of tissue eosinophilia. The routine use of a simple structured histopathology reporting in CRS is recommended. Osteitis is associated with tissue and serum eosinophilia in both patients with and without prior surgery. Kennedy Osteitis Score is simple, easy and reproducible in assessing osteitic bones in patients with CRS. OMC occlusion is not associated with draining sinuses for patients with ECRS. Diffuse eosinophilic inflammation is unlikely to be predisposed by anatomical OMC blockage. Simple interventions manipulating the OMC are unlikely to be beneficial to this common subgroup.

The effects of topical steroid are greater when it is administered after sinus surgery. Attempts at more direct sinus delivery appear to have a greater impact on symptoms. Corticosteroid nasal irrigations after endoscopic sinus surgery are proposed in this study. This appraoch brings favorable long term outcomes for patients with ECRS and patients with osteitis. Topical therapies when used appropriately are highly effective against the most challenging eosinophilic patients. Although corticosteroid is a blunt tool, it is effective when effectively delivered.

References

Baudoin, T., H. Cupic, G. Geber, et al. Histopathologic parameters as predictors of response to endoscopic sinus surgery in nonallergic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;134(5): 761-766.

Bhandarkar, N. D., J. C. Mace and T. L. Smith. The Impact of Osteitis on Disease Severity Measures and Quality of Life Outcomes in Chronic Rhinosinusitis. *Int Forum Allergy Rhinol* 2011;1(5): 372-378.

Gelardi, M., R. Fiorella, M. L. Fiorella, et al. Nasal-sinus polyposis: clinical-cytological grading and prognostic index of relapse. *J Biol Regul Homeost Agents* 2009;23(3): 181-188.

Grobler, A., E. K. Weitzel, A. Buele, et al. Pre- and postoperative sinus penetration of nasal irrigation. *Laryngoscope* 2008;118(11): 2078-2081.

Harvey, R. J., N. Debnath, A. Srubiski, B. Bleier and R. J. Schlosser. Fluid residuals and drug exposure in nasal irrigation. *Otolaryngol Head Neck Surg* 2009;141(6): 757-761.

Harvey, R. J., J. C. Goddard, S. K. Wise and R. J. Schlosser. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008;139(1): 137-142.

Harvey, R. J. and R. J. Schlosser. Local drug delivery. *Otolaryngol Clin North Am* 2009;42(5): 829-845.

Kim, H. Y., H. J. Dhong, H. J. Lee, et al. Hyperostosis may affect prognosis after primary endoscopic sinus surgery for chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2006;135(1): 94-99.

Kountakis, S. E., P. Arango, D. Bradley, Z. K. Wade and L. Borish. Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope* 2004;114(11): 1895-1905.

Matsuwaki, Y., T. Ookushi, D. Asaka, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. *Int Arch Allergy Immunol* 2008;146 Suppl 1: 77-81.

Mehta, V., N. G. Campeau, H. Kita and J. B. Hagan. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. *Mayo Clin Proc* 2008;83(6): 671-678.

Rudmik, L., R. J. Schlosser, T. L. Smith and Z. M. Soler. Impact of topical nasal steroid therapy on symptoms of nasal polyposis: a meta-analysis. *Laryngoscope* 2012;122(7): 1431-1437.

Schulz, K. F., D. G. Altman, D. Moher and C. Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340: c332.

Singhal, D., E. K. Weitzel, E. Lin, et al. Effect of head position and surgical dissection on sinus irrigant penetration in cadavers. *Laryngoscope* 2010;120(12): 2528-2531.

Snidvongs, K., P. Chaowanapanja, S. Aeumjaturapat, S. Chusakul and P. Praweswararat. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol* 2008;22(5): 483-486.

Soler, Z. M., D. Sauer, J. Mace and T. L. Smith. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 2010;142(1): 64-71.

Soler, Z. M., D. A. Sauer, J. Mace and T. L. Smith. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2009;141(4): 454-461.

Sun, D. I., Y. H. Joo, H. J. Auo and J. M. Kang. Clinical significance of eosinophilic cationic protein levels in nasal secretions of patients with nasal polyposis. *Eur Arch Otorhinolaryngol* 2009;266(7): 981-986.

Tosun, F., H. H. Arslan, Y. Karslioglu, M. S. Deveci and A. Durmaz. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol* 2010;119(7): 455-459.

Appendix

Ethics approval letter

Subject:	External Approval Noted- Harvey (5201200048)
From:	Ethics Secretariat (ethics.secretariat@mq.edu.au)
To:	richard.harvey@mq.edu.au;
Cc:	kornkiat.snidvongs@students.mq.edu.au;
Date:	Thursday, 9 February 2012 9:47 AM

Dear Dr Harvey

Re: "Mometasone irrigation in the treatment of CRS"

The above application was considered by the Executive of the Human Research Ethics Committee. In accordance with section 5.5 of the National Statement on Ethical Conduct in Human Research (2007) the Executive noted the final approval from St. Vincent Hospital and your right to proceed under their authority.

Please do not hesitate to contact the Ethics Secretariat if you have any questions or concerns.

Please do not hesitate to contact the Ethics Secretariat at the address below, if you require a hard copy letter of the above notification.

Please retain a copy of this email as this is your official notification of external approval being noted.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

COPY
19/08/10.

St Vincent's Hospital

A facility of
St. Vincents & Mater Health Sydney

St. Vincent's Hospital Sydney Ltd
ABN 77 054 038 872
390 Victoria Street
Darlinghurst NSW 2010 Australia

T +61 2 8382 1111
F +61 2 9332 4142
www.stvincents.com.au

18 June 2010

A/Prof Richard Harvey
Sydney ENT Clinic
354 Victoria St
Darlinghurst NSW 2010

Dear Richard

SVH File Number: 10/011
Project Title: Mometasone/Fluticasone/Budesonide irrigation in the treatment of chronic rhinosinusitis
(HREC Ref: HREC/10/SVH/10)

Thank you for submitting the above project for ethical and scientific review. The project was first considered by the St Vincent's Hospital HREC at its meeting held on 11 February 2010. This HREC has been accredited by NSW Department of Health as a lead HREC under the model for single ethical and scientific review.

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the Committee at an Executive meeting on 9 June 2010 has granted ethical and scientific approval of the above multi-centre project.

You are reminded that this letter constitutes *ETHICAL* and scientific approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at the following NSW Public Health sites:

- St Vincent's Hospital
- Concord Repatriation General Hospital

The Committee also granted ethical approval of the above project for the following non-NSW Public Health Organisation sites:

- Sydney Ear Nose and Throat Clinic
- St Vincent's Clinic

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documentation has been reviewed and approved by the HREC:

- Protocol Version 2: dated 3 March 2010
- Master Participant Information Sheet and Consent Form Version 3: dated 16 June 2010
- Product Information Ciclesonide August 2005
- Highlights of Prescribing Information July 2008
- Nasal VAS Score Version 1: dated 3 March 2010

Please note the Clinical Trial Notification (CTN) Form signed by St Vincent's Hospital has been forwarded to Study Coordinator, Ellie Pratt.

The National Ethics Application Form (NEAF) document reviewed by the HREC was:
NEAF AB/15329/1.

Please note the following conditions of approval:

- HREC requires that you furnish it with annual reports on the study's progress beginning in June 2011.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by study participants regarding the conduct of the study.
- Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review, in the specified format.
- The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- The Co-ordinating Investigator will provide a progress report, in the specified format, annually to the HREC as well as at the completion of the study.
- HREC approval is valid for 5 years from the date of this letter.

Investigators holding an academic appointment (including conjoint appointments) at the University of New South Wales are required to provide a copy of the application form, all approved documents and a copy of this letter to the UNSW HREC for ratification. These documents should be sent to UNSW, Ethics Secretariat, Research Services, Rupert Myers Building, 3rd floor, Kensington 2052.

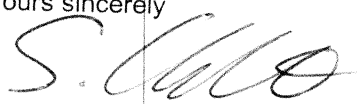
Please note it is the responsibility of the sponsor or the principal (or co-ordinating) investigator of the project to register this study on a publicly available online registry (eg Australian Clinical Trial Registry www.actr.org.au).

Should you have any queries about your project please contact the Research Office, Tel: 8382-2075, email research@stvincents.com.au. The HREC Terms of Reference, Standard Operating Procedures, HREC Membership and standard forms are available via the research/education link on the St Vincent's Hospital website: internal address: http://**ex**wwwsvh.stvincents.com.au external address: http://wwwsvh.stvincents.com.au

Please quote **SVH File Number 10/011** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely



Sarah Charlton
HREC Executive Officer
Research Office
L6 deLacy Building

CC: Ellie Pratt
D/2010/8954

Nose, Sinus and Allergy
Endoscopic sinus, tumour and
Skull Base Surgery

A/Prof Richard Harvey MBBS FRACS
SYDNEY EAR NOSE & THROAT CLINIC

12 January 2011

HREC Executive Officer
Research Office
Level 6, deLacy Building
St Vincent's Hospital
390 Victoria Street
Darlinghurst NSW 2010

St Vincent's Hospital

HREC Executive Committee Meeting: 31/1/2012

Action: Noted additional co-investigator however not conducting study related procedures at SVH HREC Approved sites.

Name: S. CHARLTON Signature:

SVH file reference: 10/011
Mometasone irrigation in the treatment of chronic rhinosinusitis
HREC reference: HREC/10/SVH/10

Dear Sarah

This letter is to notify the HREC Executive Committee that an external application approval form has been submitted to the Macquarie University Human Research Ethics Committee for the above study. Details are as follows:

Site: Macquarie University

Principal Investigator: A/Prof Richard Harvey

In addition, Dr Kornkiat Snidvongs, a PhD student under the supervision of A/Profs Richard Harvey and Raymond Sacks, will be a co-investigator at Macquarie. Please find the Notification of Changes in Research Personnel form, and a short CV for Dr Snidvongs enclosed with this letter.

Please do not hesitate to contact me if you require further information.

Yours sincerely

Richard Harvey

FRACS Fellow of the Royal Australasian College of Surgeons

354 Victoria Street
Darlinghurst NSW 2010
Australia

Tel: +61 2 9360 4811
Fax: +61 2 9360 9919
Email: enquiries@sydneyentclinic.com
Web: http://sydneyentclinic.com
ABN: 37 128 790 321