Changes and Innovations For The Surgical Management of Intracranial Aneurysms

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ABSTRACT

Advancements have been made in the understanding of intracranial aneurysms and their management. Surgical strategies have evolved, with many principles revisited, many approaches reconsidered, and many frontiers successfully conquered. The global expansion of endovascular services has challenged the existence of aneurysm surgery, changing the complexity of aneurysm case mix and volume that are presently referred for surgical repair.

As in the evolution of any type of procedures, innovations arise from the criticisms of currently available techniques. The development and technological maturation of endoscopic surgery in recent years have emboldened neurosurgeons, who are already familiar with the transsphenoidal techniques, to consider expanded endonasal approaches for the treatment of more complex cranial base pathologies. The surgical relevance of an endoscopic transnasal access for the clip reconstruction of intracranial aneurysms is a natural extension of the philosophy underlying this evolution.

This thesis presents a compilation of scientific investigations (through literature reviews, clinical studies and preclinical experiments) that examined the history, evolution and contemporary innovations in the surgical management of intracranial aneurysms. The results of this study have the potential to expand the therapeutic options for intracranial aneurysms.

STATEMENT OF ORIGINALITY

I certify that the research described 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 have been acknowledged in the thesis. This study was approved by the Macquarie University Human Ethics Committee, and was conducted in accordance with institutional ethics committee guidelines.

The protocols used in this research include:

1. The use of a prospectively collected cerebrovascular database for the purpose of surgical audit (Macquarie University Human Ethics reference number: HE26SEP2008-R06107),

2. The effects of hemodynamic insults on vascular wall biology in intracranial aneurysms (Macquarie University Human Ethics reference number: 5201000813),

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4. The use of cadavers for anatomical dissections and surgical procedures under the Anatomy Act 1977 (approved for anatomy laboratory, deLacy Building, St Vincent's Hospital, Sydney; license number H11/5683-2).

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This thesis is dedicated to our patients with intracranial aneurysms

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AUTHOR'S PUBLICATIONS AND BOOK CHAPTERS WRITTEN DURING THE PERIOD OF CANDIDATURE

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ORAL PRESENTATIONS AT SCIENTIFIC MEETINGS RELATED TO THIS THESIS

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1	**Leon Tat Lai**, Behzad Eftekhar, Michael Kerin Morgan Are patients with ruptured posterior circulation aneurysms at increased risk of developing shunt-dependent hydrocephalus? Oral presentation delivered at the Annual Scientific Meeting of Neurosurgical Society of Australasia (NSA), Fiji 2011.
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delivered at the Annual Scientific Meeting of the Australian Society of Otolaryngology Head and Neck Surgery, Adelaide, Australia 2012.

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INVITED LECTURES AT SCIENTIFIC MEETINGS AND COURSES RELATED TO THIS THESIS

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2	**Leon Tat Lai**, Perioperative Complications of the extended endoscopic endonasal skull base surgery. A lecture delivered at the 4th Neurorhinology Course, St Vincent's Hospital, Sydney, Australia 2013.

POSTER PRESENTATIONS AT SCIENTIFIC MEETINGS RELATED TO THIS THESIS

Poster No.	Authors, Presentation Title, Scientific Meeting
1	**Leon Tat Lai**, Michael Kerin Morgan, David CW Chin, Kornkiat Snidvongs, June XZ Huang, Joanne Malek, Matthew Lam, Rohan McLachlan, Richard John Harvey. Endoscopic endonasal transclival approach to the Basilar artery. Poster presentation delivered at the Annual Scientific Meeting of the Australian Society of Otolaryngology Head and Neck Surgery, Adelaide, Australia 2012.
2	**Leon Tat Lai**, Michael Kerin Morgan, Spencer Trooboff, Richard John Harvey. Expanded endoscopic endonasal skull base surgery and the risk of postoperative seizure: a systematic review of published evidence. Poster presentation delivered at the 81st Annual Scientific Congress of the Royal Australasian College of Surgeon, Kuala Lumpur, Malaysia 2012.
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ABBREVIATIONS AND DEFINITIONS

A1	Proximal Segment of Anterior Cerebral Artery
A2	Distal Segment of Anterior Cerebral Artery
ABS	Australian Bureau of Statistics
AED	Antiepileptic Drug
AICA	Anterior Inferior Cerebellar Artery
AIHW	Australian Institute of Health and Welfare
ACA	Anterior Cerebral Artery
ACF	Anterior Cranial Fossa
AChA	Anterior Choroidal Artery
ACoA	Anterior Communicating Artery
ACP	Anterior Clinoid Process
ACROSS	Australasian Cooperative Research on Subarachnoid Hemorrhage Study
aSAH	Aneurysmal Subarachnoid Hemorrhage
AVM	Arteriovenous Malformation
BA	Basilar Artery
BB	Basilar Bifurcation
BRAT	Barrow Ruptured Aneurysm Trial
C	Clivus
CCA	Common Carotid Artery
CI	Confidence Interval
cnIII	Oculomotor Nerve
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTA	Computed Tomography Angiography
dm	Dural Mata
DR	Dural Ring
DSA	Digital Subtraction Angiography

ECA	External Carotid Artery
EC-IC	Extracranial-Intracranial
EDH	Extradural Haematoma
EESB	Endoscopic Endonasal Skull Base
EVD	External Ventricular Drain
FIA	Familial Intracranial Aneurysm
GDC	Guglielmi Detachable Coil
GOS	Glasgow Outcome Score
ICA	Internal Carotid Artery
ICD	International Classification of Diseases
ICD-10-AM	International Classification of Diseases and related Health Problems, Tenth revision, Australian Modification
ICG	Indocyanine Green
ICGVA	Indocyanine Green Videoangiography
ICH	Intracerebral Hemorrhage
ICU	Intensive Care Unit
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysm
IVH	Intraventricular Hemorrhage
MCA	Middle Cerebral Artery
MeSH	Medical Subject Headings
MP	Medial Pterygoid
MRA	Magnetic Resonance Angiography
MSAC	Medical Services Advisory Committee
mRS	Modified Rankin Score
NA	Not Available/Assessed
NEMESIS	North East Melbourne Stroke Incidence Study
NHMD	National Hospital Morbidity Database
NIR	Near-Infrared
NR	Not Reported

OCR	Optico-Carotid Recess
OR	Odds Ratio
OA	Ophthalmic Artery
PCA	Posterior Cerebral Artery
PCF	Posterior Cranial Fossa
PCoA	Posterior Communicating Artery
PICA	Posterior Inferior Cerebellar Artery
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RACS	Royal Australasian College of Surgeon
RCT	Randomized Controlled Trial
SAH	Subarachnoid Hemorrhage
SCA	Superior Cerebellar Artery
SD	Standard Deviation
SDH	Subdural Haematoma
SF	Sella Floor
SHA	Superior Hypophyseal Artery
SPSS	Statistical Software for Social Sciences
UIA	Unruptured Intracranial Aneurysm
VA	Vertebral Artery
VB	Vertebrobasilar
VBJ	Vertebrobasilar Junction

CHAPTER 1

THE HISTORY AND EVOLUTION OF INTRACRANIAL ANEURYSM SURGERY

PREFACE TO CHAPTER 1

This chapter outlines the historical milestones in the surgical treatment of intracranial aneurysms and considers the evolutionary factors influencing the contemporary practice of aneurysm surgery. The work presented here represents a review of the literature relevant to this thesis and set the scene for the experimental and clinical studies undertaken in subsequent chapters.

This chapter will be submitted for publication.

AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Evolution in the surgical treatment of intracranial aneurysms is driven by the success and failure of the techniques and technologies in the past. This select review outlines historical milestones in the surgical treatment of intracranial aneurysms and considers the important factors influencing the evolution and practice of contemporary aneurysm surgery.

METHODS: A review of the academic literature (Medline, EMBASE, Scopus and Cochrane Collaboration Database) into the history and evolution of intracranial aneurysm surgery was undertaken. Articles and book chapters were identified through relevant bibliographies. An independent meta-analysis of the randomized controlled trials was performed to compare endovascular coiling to neurosurgical clipping of intracranial aneurysms in patients with subarachnoid hemorrhage.

RESULTS: From an early application of the Hunterian carotid ligation principle to present day practice of extracranial-intracranial bypass procedures, the establishment of aneurysm surgery symbolises an amalgam of technical maturation and technological innovations. The development of cranial base approaches, sophistication of aneurysm clip designs and dedicated microsurgical instruments (among others) have led to the evolution and gradual refinement of operative techniques in aneurysm surgery. The application of microscope-integrated fluorescence-based videoangiography represents a recent milestone in this surgical evolution, enabling fast, accurate, and real-time intraoperative blood flow assessment.

CONCLUSION: The concepts of how best to treat intracranial aneurysms have evolved over many generations and will continue to do so as science and technology mature. However, as in the evolution of any type of surgery, innovations often arise from the criticism of currently available techniques.

INTRODUCTION

Technological advancement has facilitated cerebrovascular neurosurgeons to address the broad spectrum of vascular disorders affecting the central nervous system. The development of intracranial aneurysm surgery has benefited from these innovations. Modern aneurysm surgery may have transpired when the first silver clip was placed on the neck of an intracranial aneurysm in 1936.(1-3) However, the foundation upon which the techniques and principles of contemporary operative vascular neurosurgery were laid had been developed almost 200 years prior. This study examined the key historical landmarks that have shaped the way we practice intracranial aneurysm surgery in the modern era.

THE HUNTERIAN PRINCIPLE OF CAROTID ARTERY LIGATION

The first transformative concept in the surgical treatment of intracranial aneurysms was based on the Hunterian principle of proximal ligation of the feeding artery. John Hunter (1728-1793), the Scottish scientist and surgeon, first described this technique in 1748 when he induced thrombosis within the aneurysm in the peripheral arteries.(4, 5) When Astley Paston Cooper (1768-1841) of London applied this technique to treat a cervical aneurysm in 1805, the patient became hemiplegic and died a few weeks later.(6) In 1808, Cooper persisted on a second attempt and "successfully treated" a pulsating tumour at the angle of the jaw.(7) Table 1.1 summarizes the key milestones in the surgical evolution of intracranial aneurysms since this period to the present day.

Early reports of aneurysm exposure were only made through serendipitous discovery during the surgical approach for other intracranial pathologies. Victor Horsley (1857-1916) was among the first to report on these findings. In 1885, Horsley reported a giant internal carotid artery (ICA) aneurysm that was compressing the optic chiasm, which he treated using bilateral cervical carotid artery occlusion.(2, 8, 9) Horsley later performed a carotid ligation procedure in 1902 when he operated on a presumed middle fossa tumour that was in fact an ICA aneurysm upon surgical exposure.(10)

Despite the overall scepticism of many surgeons at the time, proximal carotid ligation gave the early cerebrovascular pioneers, for the first time, a treatment option for intracranial aneurysms. Carotid ligation also gained a wide spectrum of applications, including the use in the treatment of seizures, trigeminal neuralgia, and psychosis.(11) Over time, this technique was refined. In 1905, William Halsted (1852-1922) promoted the idea of fractional ligation, in

which “gradual” stricture of the carotid artery was performed in order to minimise surgical morbidity.(12) This gave rise to the invention of the Dott, Crutchfield, Selverstone, Kindt and Drake vascular clamps or tourniquets (among others), which enabled surgeons to place the clamp across the artery and to gradually ligate them over a period of days.(13-17). In 1911, Rudolph Matas (1860-1957) described the test that became known by the inventor in which the carotid artery was subjected to preoperative digital compression to assess the degree and efficacy of collateral circulation. The Matas test became routine for determining tolerance to carotid occlusion(18), thus enabling surgeons to minimise unfavourable operative outcomes.

Many surgeons, however, remained doubtful of the therapeutic value of proximal carotid ligation for cerebral aneurysms. In 1940, Schorstein reported on 60 cases of carotid ligature for the treatment of cerebral aneurysms. Twenty-seven were collected from the literature and 33 from the British experience. Eight patients died (13%) and 8 had hemiplegia (13%).(19) In a literature review of therapeutic outcomes for carotid artery ligations between 1933 and 1960, Tonnis and Walter reported 3 to 41% mortality and high surgical morbidity, the majority of which were related to infection and thrombosis.(20) The rate of aneurysm obliteration was low, with success often limited to ICA aneurysms.(19, 21, 22) In 1969, a larger series of 461 patients with carotid ligation was published by Sahs and Locksley(23), where they reported a 20.7% mortality rate and a 30% stroke rate. Winn’s report in 1977 established no difference in the rate of re-haemorrhage for those aneurysms that were treated by carotid ligation as compared to those that were conservatively managed.(24)

EXTENDING THE HUNTERIAN PRINCIPLE TO SURGICAL TRAPPING OF INTRACRANIAL ANEURYSMS

In 1932, Axel Herbert Olivecrona (1891-1980) performed the first successful unplanned surgical trapping and excision of a large posterior inferior cerebellar artery (PICA) aneurysm.(25, 26) Based on this principle, Walter Edward Dandy (1886-1946) successfully trapped a cavernous sinus aneurysm in 1936 by ligating the ICA within the neck and then intracranially.(27) Vertebral ligation and trapping was also used during this era for treatment of vertebral and basilar aneurysms because of the high morbidity resulting from direct surgery to posterior circulation aneurysms. Dandy was credited for performing the first vertebral artery ligation beneath the atlas to treat a vertebral aneurysm in 1944.(21) In 1948, Henry Schwartz described his experience with a direct surgical approach, to a large basilar artery aneurysm, and successfully trapped it using silver clips.(28) Further in 1956, Logue ligated

the proximal dominant anterior cerebral artery in patients with ruptured anterior communicating artery aneurysms.(29) Later, Tindall and Odom described the ligation of the contralateral internal carotid artery in the neck to assist in aneurysm thrombosis in patients with ruptured anterior communicating aneurysms.(30)

THE BEGINNING OF DIRECT SURGERY ON INTRACRANIAL ANEURYSM

The technology available in the 1930s made direct surgery on intracranial aneurysms a significant undertaking. Ligatures and silver clips were the only devices developed at the time that were available in the cerebrovascular neurosurgeon's armamentarium. The ability to maintain haemostasis in the event of aneurysm rupture was limited. Frustrated by the outcomes of Hunterian carotid ligation, Sir Norman McComish Dott (1897-1973) in 1931 planned and successfully treated a ruptured intracranial aneurysm by direct exposure and wrap reinforcement with muscle taken from the patient's thigh.(2, 31, 32) Dott was able to provide proof, through the publication of his seminal work, that direct operative exposure and application of muscle was feasible. Cohen-Gadol proposed that Dott might have acquired this technique from Harvey Williams Cushing (1869-1939) during his residency training in 1923 and 1924.(33) In a monograph published in 1925, Cushing had already reported the use of muscle to pack and wrap an intracranial aneurysm, combining this treatment with cervical carotid artery ligation during surgery for a suspected tumour in the region of the Gasserian ganglion.(34)

Despite his landmark report in 1931, Dott continued to recommend proximal ligation of the ICA whenever possible for the treatment of cerebral aneurysms. Between 1932 and 1939, Dott managed 57 patients with suspected or proven aneurysmal subarachnoid haemorrhages. Of these, he performed 13 carotid artery ligations and no muscle wrappings.(32) During this time, Dott had already recognized that most aneurysms were located at arterial junction points and associated with vessel wall weakness.(31, 35) He advocated for conservative treatment for many anterior circulation aneurysms because "it is felt that the patient's interests will be served best by relying on those chances of spontaneous healing rather than undergoing the risks incidental to direct operative exposure".(31) When the aneurysm was located proximal to the circle of Willis, Dott had recommended carotid artery ligation. When the aneurysm was distal to the circle of Willis, he had recommended the "direct operative exposure and application of muscle"(31, 35)

During this period, other surgeons had also established their experience with direct surgery on aneurysms using muscle wrap reinforcement techniques.(36-39) In 1934, Wilhelm Tonis (1898-1978) split the corpus callosum to cover the surface of an anterior communicating aneurysm with a piece of muscle.(36) Similarly, in Ireland in 1936, Adams McConnell (1884-1972) opened a subchiasmal ICA aneurysm and packed it with muscle.(37) The patient's vision was subsequently restored. Dutton and Selverstone introduced wrapping as a routine method for treating intracranial aneurysms that were difficult or impossible to clip.(38, 39)

THE BIRTH OF SURGICAL CLIP LIGATION OF INTRACRANIAL ANEURYSMS

In 1911, Harvey Cushing described the use of the silver clips to occlude when a ligature could not be made to encircle the vessel.(40) The silver clip revolutionised Cushing's ability to maintain haemostasis in tumour surgery, although he did not incorporate these clips for the occlusion of intracranial aneurysms. It was not until 1937 that Dandy made use of these clips to perform the first planned surgical neck ligation of a saccular intracranial aneurysm. On February 16, 1937, a 43 year-old patient presented to the John Hopkins Hospital with a painful right third cranial nerve palsy that had developed 6 days prior. Based on the clinical findings, Dandy diagnosed a cerebral aneurysm and proposed that the lesion would have most likely arisen from the right ICA or posterior communicating artery (PCoA). On March 23, 1937, Dandy performed a right-sided frontotemporal craniotomy ("hypophyseal approach") to expose a "pea-sized aneurysm" that originated from the ICA adjacent to the PCoA. Having identified the neck of the aneurysm, Dandy placed a Cushing-McKenzie silver clip across its neck and cauterized its dome.(27) He observed that the aneurysm pulsation ceased and it became softer after the clip was applied. This marked the beginning of modern aneurysm surgery.

In the years to follow, Dandy continued direct surgical clip ligation and collected a large patient series. In 1944, he published the first monograph describing aneurysm surgery, *Intracranial Arterial Aneurysms*(21), in which he described his surgical experience with 64 aneurysms found at operation. In 36 operations designed to treat the aneurysm, Dandy reported a 25% mortality with 55% of the patients he considered "cured".

The development of visualising the aneurysm prior to surgery through angiography, first developed by Egaz Moniz on a patient finally surviving the investigation in June 1927, was clearly a great motivator for further innovation in the planned management of aneurysms.(41)

By the 1950s and early 1960s, however, surgical morbidity associated with the direct treatment of intracranial aneurysms remained high. The operating microscope was yet to be introduced and many surgeons continued to favour the indirect methods of proximal vessel ligation. McKissock and colleagues performed the first randomized neurosurgical trial and demonstrated that the results of conservative treatment were better than that of direct attack on anterior communicating artery aneurysms.(42)

THE MICROSURGICAL ERA OF ANEURYSM TREATMENT

The next leap in the evolution of surgical treatment of intracranial aneurysm was the introduction of the operating microscope to neurosurgery. The application of microsurgical techniques in the late 1960s and their propagation in the 1970s, 1980s and 1990s greatly influenced the results of aneurysm surgery. The earliest series of microsurgery for intracranial aneurysms was reported by Kurze(43), Pool and Colton(44) and Rand and Jannetta(45). In 1969, following publications by Lougheed and Marshall(46) and Yasargil(47), "microsurgery" swept through the discipline of neurosurgery and quickly became standard for intracranial aneurysm surgery. Yasargil, a Turkish medical scientist and neurosurgeon, was the key figure in this evolution. His elegant microsurgical techniques helped to redefine the surgical approaches to aneurysms, emphasising the importance of understanding cisternal anatomy and microvascular anatomy in optimising surgical outcomes.(47-51)

For the first time, vascular neurosurgeons could effectively illuminate and see the aneurysm. Perhaps the greatest impact of the operating microscope was not just in enhancing the results of experienced aneurysm surgeons, but also in accelerating the learning curve of young neurosurgeons that enabled them to master microsurgical skills and achieve competitive results within a shorter period of time. Thus, a new generation of dedicated cerebrovascular neurosurgeons emerged and began implementing, and in many instances, improving their mentors' microsurgical techniques. This remarkable improvement, facilitated by both technological developments and improved understanding of the microsurgical anatomy, was welcomed by Drake(17), Sundt(52-55), Spetzler(56-59), Dolenc(60-62), Samson(63, 64), and Yasargil(47-51).

The approach to posterior circulation aneurysms lagged considerably behind that of the anterior circulation. The difficulty in achieving safe operative exposure and the relative low incidence of these lesions rendered few surgeons the opportunity to gain the necessary experience to manage them well. As late as 1968 Ken Jamieson, an accomplished

neurosurgeon with 28 cases of posterior circulation aneurysm surgeries, reported, “it is clear that the basilar bifurcation is no place for the faint of heart. Only time and greater experience will indicate whether it is a place for neurosurgeons at all.”(65)

Not long after, however, Charles George Drake (1920-1998) adopted the use of the operating microscope in 1971 and contributed greatly to the understanding of the complex anatomy of posterior circulation aneurysms and enhanced the surgical outcomes for these lesions. In 1996, Drake, Peerless and Hernesniemi published a monograph on the unprecedented and since unmatched series of 1,767 vertebrobasilar aneurysms, an astonishing experience amassed over a 40-year span.(17) Drake had set the standard for the surgical treatment of posterior circulation aneurysms.

THE DEVELOPMENT OF CRANIAL BASE APPROACHES TO INTRACRANIAL ANEURYSMS

An important technical advancement in aneurysm surgery was the gradual maturation of cranial base surgical approaches. Earlier, Norman Dott used a bicoronal scalp flap for a left subfrontal approach to a supraclinoid carotid aneurysm.(31) Dandy described the use of the frontolateral approach for aneurysms of the anterior circulation in 1944.(21) Several other approaches were introduced, including the bifrontal bone flap(66, 67) and unilateral frontal approach.(68) Yasargil and Fox popularized the pterional approach under the microscope for all proximal anterior circulation aneurysms in the late 1960s and this rapidly became the standard approach, marking the modern era of aneurysm surgery.(49)

Over the last 3 decades, the popularization of radical skull base techniques has unveiled important microsurgical corridors to access deep-sited and midline intracranial aneurysms. Key operative strategies encompassed the anterolateral transsylvian(50), lateral subtemporal(69, 70), and posterolateral suboccipital(71) approaches and their various modifications over the years.(60, 72-74) These techniques reduced the distance between the surgeon and the aneurysm, increased surgical manoeuvrability, and minimised retraction on neighbouring neurovascular structures to improve safe aneurysm clipping.

Midline transoral, transcervical and transfacial approaches were also attempted with varying degree of success for aneurysms in the retroclival region(75-77). However, anterior microsurgical approaches were quickly abandoned due to high postoperative risk of CSF leakage and meningitis(78-82).

As radical techniques continued to evolve, better options for brain protection during focal circulatory arrest (temporary clipping) were available. Furthermore, the selective use of deep hypothermia and global circulatory arrest, and extracranial-intracranial bypass for selected cases were also introduced.(52)

THE REFINEMENT OF ANEURYSM CLIP DESIGNS

The first aneurysm clip, as used by Dandy, was a V-shaped, malleable silver clip, initially developed by Cushing in 1911, and later modified by McKenzie.(27, 40) This clip could not be reopened after it was applied; the procedure was, therefore, unforgiving and required total precision and accuracy.

Recognizing this limitation, Norlen and Olivecrona modified the original silver clip design by adding winged blades, an innovation that allowed the clip to be reopened if placement was suboptimal.(2) It is the concept of "repositionable" clips that remains central to all modern aneurysm clip designs. These clips, however, could crush the aneurysm neck and provoke shearing and tearing.

Schwartz developed the cross-action alpha clip originally intended for use in temporary occlusion in the 1950s. Although excellent in concept, the Schwartz clip was difficult to use in the setting of intracranial aneurysm surgery.(83) The clip was large and the applicator was awkward to use. It wasn't until the early 1950s that Frank Mayfield provided subtle, but important, improvements in several aspects of clip technology. He and George Kees narrowed the shank as much as possible and produced clips of various lengths (from 6 to 26mm), angles (bayoneted, forward or lateral angle blades), and wider blade openings. Serrations were also added to the blades to increase their purchase and minimise the risk of slippage. The Mayfield-Kees clip became the most popular clip of the 1950s and 1960s, providing the neurovascular surgeon with greater flexibility during surgery.(83-85)

In treating many posterior circulation aneurysms, Drake recognised the need to develop a clip that would allow access to the neck of an aneurysm without compromising vessels that were in the way. As a result, Drake modified the Mayfield-Kees clip with his idea of a fenestrated aneurysm clip.(86) By developing the fenestration, the aneurysm clip could be safely placed along the neck of an aneurysm without displacing and potentially compromising other vessels in the field. Thoralf Sundt, Jr's (1930-1992) encircling clip-graft was another significant innovation in aneurysm clip technology that allowed for repair of vessel tears or small

irregularities that are untreatable by ordinary clipping methods.(55, 87) Dujovny introduced very sophisticated techniques to measure the closing force at different points along the blades of the clip, which allowed better design and quality control.(88)

Further modifications to the aneurysm clip were based on metallurgy and different design configurations. Yasargil, Sundt, and Sugita (among others) introduced a series of clips made of noncorrosive alloys and with predictable closing pressures.(48) Many of these clips included metals that were compatible with magnetic resonance imaging (as introduced by Spetzler)(89); thus, the modern standard of aneurysm surgery unfolded. Axel Perneczky (1945-2009), a renowned Hungarian neurosurgeon, modified the clip-applier relationship to allow the use of a slimmer clip applier profile, allowing the applier head to be on the inside of the clip handles.(90) Further development of size, shape and strength of closure were made by many neurosurgeons. Furthermore, clip on clip development, "Booster clips", by Kees, Sundt, Piepgras and Marsh enhanced the ability to treat giant aneurysms.(87)

CONTINUING MICROSURGICAL INNOVATIONS FOR INTRACRANIAL ANEURYSM SURGERY

In 2003, Andrea Raabe and the team at the Barrow Neurological Institute introduced the use of intraoperative near-infrared indocyanine green (ICG) videoangiography to vascular neurosurgery.(91) ICG dye is a near infrared (NIR) fluorescent tricarbocyanine dye, which has been widely used in ophthalmology for the assessment of retinal microcirculation. The application of this technique during intracranial aneurysm surgery enables real-time intraoperative assessment of the degree of aneurysm obliteration, exclude parent vessel compromise, and evaluate patency of perforators.(92-99) More importantly, it obviates the need for intraoperative catheter-based angiography in most cases.(99-101) Since its application to aneurysm surgery in 2005(100), numerous studies have demonstrated the safety and efficacy of this technique.(92-101)

ENDOSCOPIC ENDONASAL APPROACH AND SURGICAL TREATMENT OF INTRACRANIAL ANEURYSMS

The development and technological maturation of endoscopic surgery in recent years have emboldened neurosurgeons, who are already familiar with the transsphenoidal techniques, to consider expanded endonasal approaches for the treatment of more complex cranial base pathologies. The surgical relevance of an endoscopic transnasal access for the clip

reconstruction of intracranial aneurysms is a natural extension of the philosophy underlying this evolution. Kassam reported the first purely endoscopic endonasal clipping of a coiled vertebral artery aneurysm via the transclival approach.(102) Since then, six other case reports have been published demonstrating the feasibility of this technique on various aneurysm locations along the skull base.(103-108) However, the validity of such a technique has yet to be defined. The therapeutic value of this approach can be judged only when dedicated endonasal instruments have been developed, and a statistically meaningful number of clinical cases have been performed.

CONCLUSION

The success of the future is built upon the dedication and innovative thinking of the neurovascular neurosurgeon in order to overcome present challenges. Microsurgical treatment of intracranial aneurysms has reached a high level of sophistication, yet the need for surgical expertise and innovation in the management of aneurysms continues. As in the evolution of any type of surgery, innovations often arise from the criticism of currently available techniques. Neurosurgeons must therefore continue to maintain their role as innovators in aneurysm surgery, in order to take aneurysm repair to a new level.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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Table 1.1 Milestones in the surgical evolution of intracranial aneurysms

Year	Contributor	Event
1748	John Hunter (4)	Described the principle of proximal vessel ligation in the treatment of peripheral aneurysms.
1805	Astley Cooper (6)	Performed the first ligation of the CCA for a cervical artery aneurysm. The patient developed hemiplegia on the 8th postoperative day and died on the 21st day.
1808	Astley Cooper (7, 109)	Successfully performed a carotid artery ligation on a patient with a pulsating tumor at the angle of the jaw.
1885	Victor Horsley (110)	Exposed what he thought to be a middle fossa tumor and found it to be an aneurysm. He treated this patient by ligating the carotid artery in the neck.
1902	Victor Horsley (2, 8)	Reported treatment of a giant ICA aneurysm by bilateral cervical carotid artery ligation.
1905	William Halsted (12)	Promoted the concept of fractional ligation, in which "gradual" stricture of the carotid artery was performed in order to minimise surgical morbidity.
1911	Rudolph Matas (18)	Emphasized the importance of testing and increasing collateral vessels by temporary occlusion of the carotid artery preoperatively.
1927	Ega Moniz (41)	Successfully demonstrated the technique of cerebral angiography.
1928	Walter Dandy (111)	Ligated the carotid artery on a patient with a carotid aneurysm, producing sudden third nerve palsy. The patient died a few days later from infarction.
1931	Norman Dott (31)	Performed the first planned direct surgical exposure of an intracranial aneurysm and wrap reinforcement with muscle.
1932	Axel Olivecrona (112)	Performed the first successful unplanned surgical trapping and excision of a large PICA aneurysm.
1933	Ega Moniz (113)	Published an article demonstrating the use of cerebral angiography to identify intracranial aneurysms.
1933	Norman Dott (31)	Became the first to operate on an aneurysm previously demonstrated by carotid arteriography
1934	Wilhelm Tonnis (36)	Split the corpus callosum to cover the surface of an ACoA aneurysm with muscle.
1936	Walter Dandy (114)	Successfully trap a cavernous sinus aneurysm by ligating the ICA in the neck and intracranially.
1937	Walter Dandy (27)	Performed the first direct surgical clip ligation of the aneurysm neck with the modified Cushing-McKenzie silver clip.
1937	Adams McConnell (37)	Opened a subchiasmal aneurysm and packed it with a piece of muscle

1940	Joseph Schorstein (19)	Reported 60 cases of carotid ligation for the treatment of nontraumatic intracranial aneurysms: 33 were from the British experience and 27 were collected from the literature. He reported a 13% mortality and 13% morbidity rate.
1957	Theodore Kurze (43)	Became the first neurosurgeon to perform aneurysm surgery under the microscope.
1958	Charles Drake (115)	First operated on a man with a superior cerebellar artery aneurysm with good results. Drake subsequently made various advancements in treating posterior circulation aneurysms, which many others had considered impossible.
1960	Wylie McKissock (42)	Based on his randomized controlled study, he concluded that surgery was not better than conservative management.
1966	Lawrence Pool (44)	First publication about the use of the operating microscope for intracranial aneurysm surgery
1969	Mahmut Yasargil (47)	His contribution to early history of microneurosurgery and its application in the treatment of all intracranial aneurysms greatly improved the outcome of these operations.
1974	Fedor Serbinenko (116)	Introduced the use of detachable balloons for the treatment of intracranial aneurysms. He first used it in a patient with an extradural cavernous aneurysm.
1970s	Kenchiro Sugita (117)	Significantly contributed to the progress of neurosurgical techniques. He invented many surgical instruments including Sugita clips, the surgical microscope, operative chair and table..
1991	Guido Guglielmi (118, 119)	Invented the Guglielmi detachable coil (GDC), which has been a major step in the endovascular treatment of intracranial aneurysms. It was first used in March 1990 in a case of carotid cavernous fistula, and then for aneurysms in January 1991 at University of California, Los Angeles.
1996	Charles Drake (17)	Published his unprecedented and since unmatched surgical series of 1,767 vertebrobasilar artery aneurysms, setting a standard in aneurysm surgery.
2002	Andrew Molyneux (120)	Presented the results of the International Subarachnoid Aneurysm Trial that has greatly impacted on the changing paradigm of aneurysm treatment from predominantly microsurgery to endovascular therapy.
2003	Andrea Raabe (91)	Introduced the use of indocyanine green videoangiography (ICGVA) into cerebrovascular neurosurgery, enabling the real-time assessment of blood flow without the need of a catheter-based angiography.
2006	Amin Kassam (102)	Reported the first successful surgical treatment a of vertebral artery aneurysm using an endoscopic endonasal transclival access

CHAPTER 2

THE IMPACT OF CHANGING INTRACRANIAL ANEURYSM PRACTICE ON THE EDUCATION OF CEREBROVASCULAR NEUROSURGEONS

PREFACE TO CHAPTER 2

The success of endovascular therapy has challenged the existence of aneurysm surgery. This chapter examines the paradigm change in the management of intracranial aneurysms following the introduction of endovascular services into Australia. The impact of this change on the education of cerebrovascular neurosurgeons is discussed.

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Endovascular repair of intracranial aneurysms has transformed the practice of cerebrovascular surgery. The current study was performed to investigate what trends exist in Australia that may underscore the importance of reviewing how we train for, and maintain our competence in performing, aneurysm surgery.

METHODS: We reviewed the National Hospital Morbidity Database in Australia for the years 2000 to 2008 and investigated the changing trends of aneurysm practice. The implications of reduced numbers of surgically treated aneurysms were considered for the education of cerebrovascular neurosurgeons in Australia.

RESULTS: During the study period, 7,503 craniotomies for aneurysm repair and 7,863 endovascular coiling procedures were performed. The number of aneurysm procedures performed surgically reduced from 9 cases per neurosurgeon per year to 4.2 cases, a reduction of 53.3%. The number of endovascular treatments increased 2.1 fold, from 3.6 aneurysms per neurosurgeon in 2000 to 7.5 in 2008.

CONCLUSION: There has been a change in the practice of aneurysm treatment in Australia from 2000 to 2008. This carries implications for both the current and new generations of neurosurgeons who may wish to pursue cerebrovascular surgery as a subspecialty. In the treatment of cerebral aneurysms, guidelines for demonstrable competence (such as Fellowships in aneurysm surgery) and the maintenance of competence are urgently required.

INTRODUCTION

Endovascular therapy has changed the practice of cerebrovascular neurosurgery. After a novel invention by Guglielmi to treat intracranial aneurysms there has been increasing evidence that endovascular repair is an effective treatment (119). The trend favoring interventional neuroradiological management over surgical treatment is evident in many neurosurgical centers around the world (121-124).

The tendency to choose endovascular aneurysm repair continues despite the lack of evidence that patients benefit from this choice. Analysis of the outcome data from the International Subarachnoid Aneurysm Trial (ISAT) in 2009 and 2010 (125, 126) shows little difference between clipping and coiling in terms of death and morbidity and is far less convincing than the 2005 declaration that "updated results confirm that the changes in practice seen on the basis of the preliminary findings should have led to substantial reductions in death and dependency for patients with subarachnoid hemorrhage" (127). Studies in the United Kingdom (128), Canada (123), Finland (124), Italy (129) and the United States (130) have failed to demonstrate a benefit to patients with aneurysmal subarachnoid hemorrhage (aSAH) despite an increasing proportion of cases managed by endovascular coiling.

Although ISAT has often been credited with the change in aneurysm treatment, there is evidence to suggest that the trend existed prior to the results of the ISAT study. French centers declined to participate in ISAT with more than 85% of aSAH cases being treated by endovascular means prior to ISAT and a belief that such a trial was not needed (131). Lindsay (132) reported that for the seven months immediately prior to the trials completion of enrolment, 34% of patients underwent coil embolisation in the United Kingdom as compared with 54% during the four subsequent months. The trend towards coiling treatment predates the analysis of the ISAT results. This cannot be fully explained by the Data Monitoring Committee calling a premature halt to recruitment in April 2002. This trend was dramatically evident in the six highest recruiting centers in the trial with an increase in endovascular treatments from 49% immediately prior to the trial to 87% immediately after the trial.

The increase in endovascular treatment of vascular problems has not been confined to that of intracranial aneurysms. The use of stents in the management of coronary artery disease predates that of aneurysm management by coiling with a similar continuing trend (133). Similarly, the evidence of overall benefit to patient care is questionable (134).

Irrespective of what may be considered best practice in the management of patients with intracranial aneurysms, the drift towards endovascular procedures will likely continue. This will inevitably have a significant impact upon both the maintenance of competence in those already performing aneurysm surgeries on a regular basis as well as an impact upon the education that develops this competence during the formative years of a neurosurgeon's career.

The current study was performed to investigate what trends exist in Australia that may underscore the importance of reviewing how we train for, and maintain our competence in performing, aneurysm surgery.

METHODS

Data Source

Hospitalizations for microsurgical clipping and endovascular coiling of ruptured and unruptured intracranial aneurysms were identified from the National Hospital Morbidity Database (NHMD) for the years 2000 to 2008. The NHMD is a collection of records for hospital admitted patients from public and private hospitals in Australia, and is governed by the Australian Institute of Health and Welfare (AIHW) (135). Almost all hospitals in Australia are included in this database including public acute and Department of Veterans' Affairs hospitals, public psychiatric hospitals, private acute and psychiatric hospitals and private freestanding day hospital facilities. Detailed information on the design of the AIHW and the NHMD is available at www.aihw.gov.au. Diagnoses, procedures and external causes of injury are recorded using the International Statistical Classification of Diseases and related Health Problems, Tenth revision, Australian Modification (ICD-10-AM).

The NHMD contains clinical and non-clinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patient's admission and discharge status, demographic information and length of stay in hospital. The procedure for treatment of intracranial aneurysm was defined by the procedure codes for either direct surgical clipping (ICD 10 code 3980000) or endovascular coiling (ICD 10 codes 3980001, 3541200, 3532100, 3311600, 6000900 and 600090). For the period between 2000 and 2006, cerebral aneurysms treated by endovascular coiling in Australia did not have a specified procedural code. For this reason, coiling was assigned to aneurysms that were listed with the codes 3980001 for reinforcement of aneurysm sac, 3532100 for transcatheter

embolisation of blood vessel, 3311600 for endovascular repair of aneurysm, or 6000900 and 6000901 for Digital Subtraction Angiography (DSA) of head and neck with more than 10 runs with or without arch aortography that was performed in conjunction with a general anesthetic procedure. Endovascular coiling of cerebral aneurysms was formally assigned a procedural code of 3541200 after the Medical Services Advisory Committee (MSAC) for Australia recommended public funding for this procedure in 2006 (136).

Inclusion and Exclusion Criteria

Using the same data source and in the same study period, we also evaluated the case volume for resection of intracranial tumors and spinal fusion procedures. Procedures for removal of intracranial lesions included the cerebrum (3970900), brain stem (3970901), cerebellum (3970902), cerebral meninges (3971200), intraventricular lesion (3971203), cerebellopontine angle (4157500) and other intracranial lesion (3971204).

For spinal fusion procedures, we identified posterior spinal fusion one or two levels (4864200), posterior spinal fusion three or more levels (4864500), posterior spinal fusion with laminectomy one level (4865400), posterolateral spinal fusion with laminectomy one level (4865401), posterior spinal fusion with laminectomy two or more levels (4865700), posterolateral spinal fusion with laminectomy two or more levels (4865701), anterior spinal fusion one level (4866000), anterior spinal fusion two or more levels (4866900), odontoid screw fixation (4031600), simple internal fixation of spine (4867800), non-segmental internal fixation of spine (4868100), segmental internal fixation of spine one or two levels (4868400), segmental internal fixation of spine three or four levels (4868700) and segmental internal fixation of spine five or more levels (4869000).

In determining the Neurosurgery workforce in Australia, data was obtained from The Royal Australasian College of Surgeons (RACS) with regards to the number of neurosurgeons actively in the workforce in each year during the study period. Data on the number of neurosurgical trainees per year was obtained from the AIHW. Data on census population in Australia between the year 2000 and 2008 were obtained from the Australian Bureau of Statistics (ABS) at www.abs.gov.au.

Statistical Analysis

Case volumes performed by neurosurgeons were determined by dividing the total number of cases per year by the number of neurosurgeons in the Australian workforce. This was expressed as the average number of cases per neurosurgeon in each year of the study period. Case volumes performed by neurosurgical trainees were determined by dividing the total number of cases per year by the number of neurosurgical trainees actively registered in the training program in each year of the study period. Case volumes by the general population were determined by dividing the total number of cases per year by the census population per 100,000 persons.

RESULTS

Between the year 2000 and 2008, 7,503 craniotomies for intracranial aneurysms were performed and 7,863 endovascular coiling procedures performed. The number of aneurysm procedures managed surgically reduced from 9 cases per neurosurgeon in the year 2000 to 4.2 cases per neurosurgeon in 2008. This represented a 53.3% reduction in the number of aneurysms surgically clipped per neurosurgeon in Australia. At the same time, the proportion of aneurysms managed with endovascular coiling increased by almost 2.1 times, from 3.6 to 7.5 procedures per neurosurgeon. Figures for the numbers of aneurysm procedures performed by clipping or coiling per neurosurgeon, per neurosurgical trainee, and per 100,000 populations are summarized in Table 2.1.

Case volumes of surgically clipped aneurysms as performed by neurosurgical trainees reduced from 8.1 cases to 4.8 cases during this study period, as compared with a paradoxical increase in the number of coiled aneurysm cases from 2.9 to 9.1 cases per neurosurgical trainee per year.

From a population perspective, clipping was 2.5 times more prevalent as compared to endovascular coiling in the year 2000. Thus for patients presenting with an intracranial aneurysm during this time, they were at least twice more likely to be clipped than coiled. By 2008, this trend had reversed and endovascular coiling was 1.8 times more frequent as compared to surgical clipping. This change in trend of aneurysm practice in Australia is demonstrated graphically in Figure 2.1.

We identified 30,842 craniotomies for removal of intracranial tumor. The procedures performed per neurosurgeon per year are shown in Table 2.2. Overall the mean number of procedures performed per year is 25.1 cases per neurosurgeon (range 23.2-26.3). Meanwhile, there were 77,432 cases of spinal fusion surgeries performed. The average number of spinal fusion cases performed per neurosurgeon per year increased from 45.5 cases to 70.4 cases. These figures are graphically demonstrated in Figure 2.2.

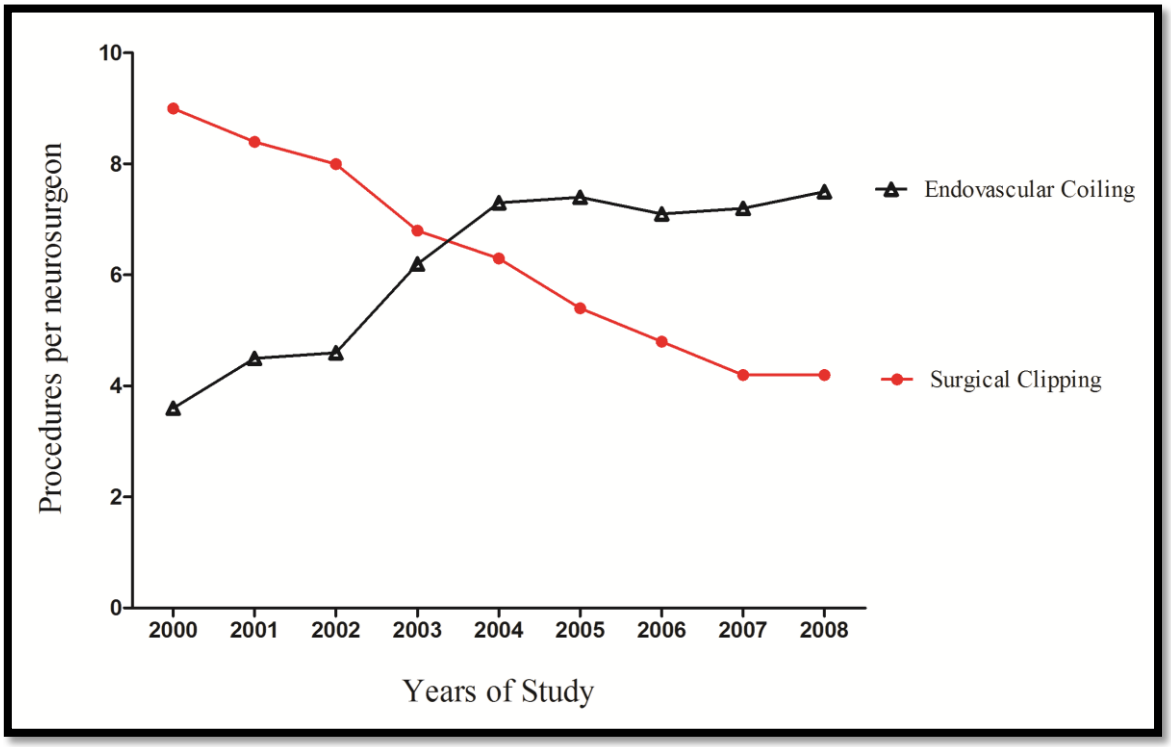

Figure 2.1 Case volumes of surgical clipping and endovascular coiling of intracranial aneurysms per neurosurgeon per year in Australia for the years 2000 to 2008

DISCUSSION

The changing trends of aneurysm surgery in Australia, with an increase in the proportion of these being treated by endovascular coiling, as demonstrated in this study, share similar experiences among other nations. In Canada, over a period from 2001 to 2004, data from large Toronto hospital revealed an increase in endovascular coiling from 18% to 35.6% at the expense of surgical clipping following the completion of ISAT (137). In the United Kingdom, similar findings show an increase in the rate of endovascular coiling from 35% of aneurysms in 2001 to 68% in 2003, while clipping reduced from 51% to 31% (138). A study in the United States using the National Inpatient Sample demonstrated an increase in endovascular

Table 2.1 Case volumes of surgical clipping and endovascular coiling of intracranial aneurysms in Australia per neurosurgeon, per neurosurgical trainee, and per 100,000 population for the years 2000 to 2008

Years of Study	Clip/surgeon	Coil/surgeon	Clip/trainee	Coil/trainee	Clip/100,000 population	Coil/100,000 population
2000	9.0	3.6	8.1	2.9	5.0	2.0
2001	8.4	4.5	6.9	3.5	4.9	2.6
2002	8.0	4.6	6.4	3.7	4.9	2.8
2003	6.8	6.2	5.9	5.6	4.4	4.0
2004	6.3	7.3	6.0	7.4	4.2	4.8
2005	5.4	7.4	5.0	7.2	3.7	5.1
2006	4.8	7.1	5.1	7.8	3.5	5.2
2007	4.2	7.2	4.2	8.0	3.3	5.7
2008	4.2	7.5	4.8	9.1	3.5	6.2

Table 2.2 Case volumes of intracranial tumor resections and spinal fusion procedures in Australia per neurosurgeon, per neurosurgical trainee, and per 100,000 population for the years 2000 to 2008

Years of Study	Tumors/surgeon	Spine Fusions/surgeon	Tumors/trainee	Spine Fusions/trainee	Tumors/100,000 population	Spine Fusions/100,000 population
2000	25.3	45.5	22.7	40.9	14.0	25.2
2001	25.6	46.3	21.2	38.1	14.9	26.9
2002	26.2	53.3	20.8	42.4	16.0	32.6
2003	26.3	59.7	22.9	52.0	17.0	38.5
2004	26.0	65.0	24.5	61.4	17.3	43.3
2005	25.1	64.2	23.5	60.0	17.5	44.7
2006	24.4	68.3	26.3	73.7	17.9	50.2
2007	23.8	70.4	23.9	70.9	18.8	55.6
2008	23.2	76.7	26.0	86.0	19.0	62.8

treatment of ruptured intracranial aneurysms from 3% to 17% between the years 2000 and 2006. In that same period, surgical clipping reduced from 31% to 23% (139). Since the publication of the ISAT (120), patients in Australia with SAH are mostly treated at tertiary centers with facilities and expertise of both endovascular intervention and microsurgery. Ideally, every patient should be managed according to their individual merits with careful considerations regarding the suitability for any particular modality and the expertise available. Surgical expertise in aneurysm treatment has been linked with both institutional and surgeon volumes (140, 141). Therefore, it is reasonable to propose that competence will decline unless measures are taken to actively change patterns of practice and education.

A survey of 106 practicing neurosurgeons, published in 2000 by the Australian Medical Workforce Advisory Committee showed the percentage of professional time they spent in different areas of neurosurgery (142). Spinal surgery took up the highest percentage with 41.2% of time worked; 20.5% of time was spent on tumor surgery and 11.5% on intracranial vascular surgery. Assuming the 9 cases of aneurysms managed per neurosurgeon equate to the 11.5% cerebrovascular practice, a decrease in case volume by 2008 would mean that the same group of neurosurgeons would be spending 5% of their practice time on cerebrovascular neurosurgery. In reality, by 2008 there were 176 neurosurgeons in the workforce and surgical case volume for aneurysms had reduced dramatically. Therefore, it is reasonable to assume that most neurosurgeons in the current Australian workforce spend less than 5% of their practice performing aneurysm surgery.

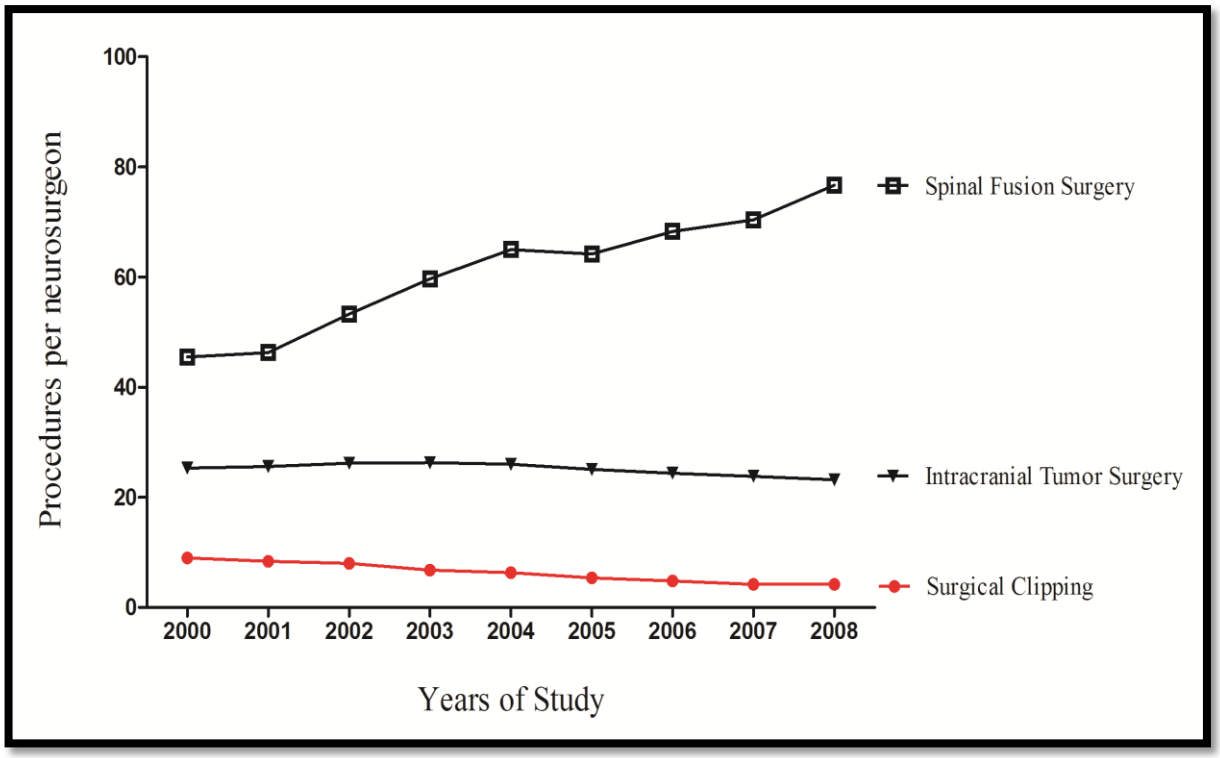

Figure 2.2 Surgical trends in intracranial tumor resection and spinal fusion procedures per neurosurgeon in Australia for the years 2000 to 2008

The decline in surgical aneurysm practice poses many more challenges than simply concentrating the performance of surgery amongst fewer neurosurgeons. The challenges that need to be met also include the changing complexity of the aneurysmal case mix, the volume that allows surgical innovation and the support education for aneurysm surgery. Although neurosurgeons are agglomerating into larger units, the average unit with 5 neurosurgeons would be performing 20 surgeries for aneurysms per year with the likelihood of this number diminishing. Such experience is likely to be insufficient for more complex aneurysms unable to be adequately managed by endovascular techniques. Such experience may be failing to prepare the next generation of aneurysm surgeons.

An advantage of high case volume per surgeon is that an audit of practice will allow performance that is considered below an acceptable standard to become evident. However, when volumes are low this safeguard for the Australian people is not possible. There is a need for specific demonstrable competence amongst neurosurgeons performing aneurysm surgery and a requirement for continuing demonstration that competence is maintained.

The three arguments against confining the practice of aneurysm surgery to fewer subspecialists relate to the requirement for emergency service, the usefulness that the skills of aneurysm surgery bring to tumor surgery training and the loss of a component of workload. While it has been argued that all neurosurgeons may need to evacuate an intracerebral hemorrhage from a ruptured aneurysm in an emergency, the volume of such cases is, in reality, very small. However there will always be a number of aneurysm cases that require the most competent surgeon that is reasonably accessible (although not immediately accessible). With regards to education, it can be argued that the skills that are learnt in treating aneurysm cases are important for those who wish to be competent in non-aneurysmal intracranial surgery. However, considering that the average neurosurgeon performs 25 cases of cranial resection for tumors per year, there should be enough scope for abandoning aneurysm surgery as a requirement for training to competently manage tumors. Finally, with the case-load for spinal fusion procedures increasing from 45 cases per neurosurgeon per year to almost 80 cases, many neurosurgeons will be able to sub-specialize in spine and neurooncology without concern for the loss of workload that results from withdrawing from the care of aneurysm patients.

LIMITATIONS OF STUDY

There are well known limitations to analyses of national hospital databases (143). There are errors in coding, potential limitations in sampling, and the susceptibility of selection bias in a retrospective study. Furthermore, administrative databases usually lack specific information about aneurysm morphology, long-term functional outcomes and other clinical characteristics that might have justified the changing trends in the selection of interventional treatments. Our study was also limited by the lack of accurate procedure codes for endovascular repair of intracranial aneurysms, which was only established after 2006. Therefore, the annual number of endovascular coiling procedures is at best a national estimate of the true incidence of endovascular procedures for aneurysms repair. Taken collectively, however, the data reveal interesting information concerning the trends in surgical and interventional procedures used to treat intracranial aneurysms in Australia.

CONCLUSION

There has been a change in the practice of aneurysm treatment in Australia from 2000 to 2008. This carries implications for both the current and new generations of neurosurgeons who may wish to pursue cerebrovascular surgery as a subspecialty. In the treatment of cerebral aneurysms, guidelines for demonstrable competence (such as subspecialty fellowships in aneurysm surgery) and the maintenance of competence are urgently required.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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CHAPTER 3

INCIDENCE OF SUBARACHNOID HEMORRHAGE: AN AUSTRALIAN NATIONAL HOSPITAL MORBIDITY DATABASE ANALYSIS

PREFACE TO CHAPTER 3

This chapter investigates the incidence of subarachnoid hemorrhage (SAH) in Australia for the years 1998 to 2008. The research presented here represents the first study that reports our nationwide SAH incidence. Following on the discussion of a changing aneurysm surgical practice in the previous chapter, the implications of an increasing elderly population and a declining cerebrovascular workforce are considered and discussed in this chapter.

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Incidences of subarachnoid hemorrhage (SAH) in Australia have been reported in a number of regional studies with variable rates. We investigated the national SAH rate and evaluate the trend over the ten years from 1998 to 2008.

METHODS: We reviewed the National Hospital Morbidity Database in Australia for the years 1998 to 2008 and investigated the incidence of SAH. The trends of annual SAH rates were evaluated.

RESULTS: The crude SAH incidence, not related to trauma or arteriovenous malformations, was estimated at 10.3 cases per 100,000 person-years [95% confidence interval (CI) 10.2-10.4]. Females have a higher SAH incidence (12.5 cases per 100,000; 95% CI 12.3-12.8) as compared to males (8.0 cases per 100,000; 95% CI 7.8-8.3), with age-adjusted incidence increases with increasing age for both sexes. Less than 10% of SAH occurred in the first three decades of life. The peak age groups to experience a SAH were between 45 and 64 years, accounting for almost 45% of the overall annual SAH admissions. Aneurysms located in the anterior circulation were a more common source of rupture as compared to those located in the posterior circulation (rate ratio 3.9; 95% CI: 3.6-4.2).

CONCLUSION: The crude SAH incidence in Australia was 10.3 per 100,000 person-years for the years 1998 to 2008. Contrary to contemporary observations in the literature, we did not observe a decline in the incidence of SAH during this study period.

INTRODUCTION

Subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysms continues to impose devastating consequences to patients despite increased efforts in recent years to identify and manage aneurysms prior to rupture (144). While accounting for only 5% of all strokes in general, the loss of productive life years due to SAH is as great as that for cerebral infarction because of its propensity to affect patients younger than 65 years of age (145). Each year in the United States, between 21,000 and 33,000 people experience a subarachnoid bleed (146, 147). In the United Kingdom, this figure is estimated to be around 5000 patients per year (148). Currently in Australia, it is estimated that 450,000 to 1.4 million people harbor unruptured cerebral aneurysms (136). Of these, over 2000 aneurysms bleed each year.

There have been a number of epidemiological studies in Australia that have focused on either stroke or SAH incidences. Previous reports on SAH rates vary according to the population characteristics; ethnicity and regional differences defined within the study groups. The Australasian Cooperative Research on Subarachnoid Hemorrhage Study examined the incidence of SAH in Australia and New Zealand from data in four population-based registers between 1995 and 1998 (149). Out of a total population in the four cities of 2.8 million, 436 cases of SAH were identified of which 330 (76%) were found to have a ruptured cerebral aneurysm. The mean age was 57 years (range: 16 - 94 years) and 62% were female. The crude annual incidences for Perth, Adelaide, and Hobart were 6.9, 7.7, and 11.1 per 100 000 person-years, respectively. Age-specific rates showed a continuous upward trend with age, although the shape and strength of this association differed between the sexes.

A separate study in Perth revealed 4% (322/7784) of hospital admissions for stroke between 1995 and 1998 were related to SAH (150). The mean age of these patients was 54.3 years (range 52.3 to 56.3) and 57.5% female. During the same period, the North East Melbourne Stroke Incidence Study (NEMESIS) reported incidence of stroke among a population of 133,816 residents of one area of Melbourne between 1996 and 1997 (151). The crude annual incidence of SAH was estimated at 9 per 100 000 [95% confidence interval (CI), 4-14] person-years with a higher incidence rate among females at 13 per 100 000 (95% CI, 5-22) compared to males at 3 per 100 000 (95% CI, 0-10) person-years.

The worldwide literature on crude SAH incidences share similar patterns of rate variations, depending on the criteria and level of investigation utilized to diagnose aneurysmal rupture as the etiology of SAH. Furthermore, many epidemiologic studies include other causes of non-traumatic SAH, such as arteriovenous malformations (AVM), which may give an imprecise

estimate of the true incidence of aneurysmal subarachnoid hemorrhage (aSAH) among populations in which differences in demographics and risk factors alone could not be responsible (152, 153). Rates have been reported to be as low as 2.2 per 100,000 persons per annum in China (154) and as high as 33 to 37 per 100,000 per annum in Finland (155, 156). In a 2007 systematic review (157), the worldwide average incidence of SAH was estimated at 9.1 (95% CI 8.8-9.5) per 100,000 person-years, based on 42 international studies.

Whereas much is known of the incidence of aSAH in Australia prior to 2000, there is reason to investigate current data given the suggestion that earlier detection of unruptured aneurysms, improved vascular health, and advances in imaging may impact upon the incidence of aSAH. The current study was performed to investigate the national incidence of subarachnoid hemorrhage in Australia for the year 1998 to 2008. The trends of annual SAH rates were evaluated. Implications of an increasing elderly population and a declining cerebrovascular neurosurgical workforce were considered and discussed.

METHODS

Data Source

We obtained data from the National Hospital Morbidity Database (NHMD) for all episodes related to subarachnoid hemorrhage (I60) as a principal diagnosis for the years 1998 to 2008. The NHMD is a collection of records for hospital admitted patients from public and private hospitals in Australia, and is governed by the Australian Institute of Health and Welfare (135). It contains clinical and non-clinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patient's admission and discharge status, demographic information and length of stay in hospital. Almost all hospitals in Australia are included in this database including; public acute and Department of Veterans' Affairs hospitals, public psychiatric hospitals, private acute and psychiatric hospitals and private freestanding day hospital facilities.

The source population data was obtained from the Australian Bureau of Statistics (www.abs.gov.au.) and compiled from the annual census data between 1998 and 2008, by gender, age, and region. The annual incidence rates were calculated by dividing the number of all events by person years, after direct standardization to the entire study period (1998-2008).

Inclusion and Exclusion Criteria

We identified all cases with a principal diagnosis of non-traumatic SAH admitted to Australian hospitals from 1998 to 2008, using the diagnostic codes I60.0 to I60.9 from the International Statistical Classification of Diseases, tenth edition, the Australian modification (ICD-10, AM) which is routinely used to classify diagnoses in Australian hospitals. I60.8 was excluded from the current study as it represents 'other subarachnoid hemorrhage', which incorporates meningeal hemorrhage, rupture of specified AVM (I60.80), SAH from coagulation disorder classified elsewhere (I60.81), SAH from primary intracerebral hemorrhage classified elsewhere (I60.82), SAH from ruptured mycotic aneurysm (I60.83), SAH from intracranial artery dissection (I60.84) and SAH due to tumor (I60.85).

The ICD-10 diagnostic codes I60.0 to I60.7 and I60.9 were included in the current study. These codes represent primary SAH not related to trauma, AVM or other non-aneurysmal causes related to I60.8. To identify ruptured cerebral aneurysms according to their locations along the circle of Willis, we utilized diagnostic codes from the *Application of the International Classification of Diseases to Neurology* (ICD-10, NA) (158). The diagnostic codes I60.0 to I60.3 represent ruptured anterior circulation aneurysms, while codes I60.4 to I60.6 represent posterior circulation aneurysms (Table 3.1). Codes I60.7 and I60.9 represent primary subarachnoid hemorrhage in which aneurysm location was not otherwise specified or a ruptured aneurysm could not be identified for the SAH admission.

Statistical Analysis

The annual incidence rates were calculated by dividing the number of all events by person years, after direct standardization to the entire study period (1998-2008). Incidence rates were age-standardized to the "world Standard Population" using 5-year age groups (159). Crude incidence, together with 95% CI, was calculated for each age, sex and aneurysm location. The effects of age and sex on the incidence were estimated with a Poisson regression model.

Table 3.1 Aneurysm location according to diagnostic codes [adapted from application of the International Classification of Diseases to Neurology 10th Edition **(158)**]

ICD 10 NA Codes	Explanation
I60.0	SAH from carotid siphon and bifurcation, incorporating - I60.00 – aneurysms at origin of ophthalmic artery - I60.01 – aneurysms at origin of anterior choroidal artery - I60.02 – aneurysm at origin of PCoA - I60.03 – aneurysm at bifurcation of ICA - I60.04 – carotid-cavernous aneurysm
I60.1	SAH from MCA, incorporating - I60.10 – proximal (M1-horizontal segment) MCA aneurysm - I60.11 – aneurysm at major bi- or trifurcation of MCA - I60.12 – Distal MCA aneurysm
I60.2	SAH from ACoA, incorporating - I60.20 ACoA aneurysm, - I60.21 – Proximal (A1-horizontal segment) ACA aneurysm - I60.22 Distal (A2-vertical segment) anterior cerebral artery aneurysm - I60.23 Pericallosal bifurcation artery aneurysm
I60.3	SAH from PCoA or distal PCoA aneurysms
I60.4	SAH from BA, incorporating - I60.40 proximal BA (vertebral artery confluence) - I60.41 mid-BA aneurysm - I60.42 top of BA aneurysm - I60.43 bifid BA aneurysm - I60.44 aneurysm at origin of SCA - I60.45 aneurysm at origin of AICA
I60.5	SAH from VA, incorporating - Aneurysm at origin of PICA - SAH from ruptured spinal artery aneurysm
I60.6	SAH from other intracranial arteries, incorporating - I60.60 distal SCA aneurysm - I60.61 distal AICA aneurysm - I60.62 distal PICA aneurysm - I60.63 Internal auditory artery aneurysm - I60.64 Proximal PCA aneurysm - I60.65 distal PCA aneurysm - I60.67 ruptured aneurysms of several intracranial arteries - I60.68 aneurysm of other specified intracranial arteries
I60.7	Ruptured (congenital) berry aneurysm, not otherwise specified; from - Cerebral artery, not otherwise specified - Communicating artery, not otherwise specified - Multiple cerebral arteries, not otherwise specified
I60.9	SAH unspecified, incorporating - I60.90 Ruptured (congenital) cerebral aneurysm not otherwise specified - I60.91 primary SAH (without aneurysm, AVM or other cause)

PCoA, posterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; BA, basilar artery; SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery; PCA, posterior cerebral artery; AVM, arteriovenous malformation.

RESULTS

Overall Incidences

During the 10-year period from 1998 to 2008, a total of 20,406 hospital admissions were identified for primary spontaneous SAH not related to trauma or AVM rupture. Among them, 12,502 were females (61.3%). The crude incidence rate of SAH was 10.3 per 100,000 person-years (95% CI: 10.1–10.4) when adjusted to the average Australian population. During this study period, we did not observe a reduction in the incidence of SAH presented to Australian hospitals. The absolute number of SAH admissions continued to rise steadily each year, with an increase of 274 (14.5%) cases per annum by the end of the 2008, reflecting on the overall increasing Australian population.

Gender

Female populations had a higher incidence of SAH at 12.5 per 100,000 (95% CI: 12.3–12.8) person-years compared to the male populations, which averaged at 8.0 per 100,000 (95% CI: 7.8 - 8.3) person-years. The overall rate ratio of female to male populations was calculated at 1.6 (95% CI: 1.5–1.6). In general, female populations account for 60% of SAH admissions to Australian hospitals during the study period. Table 3.2 shows the annual incidences and the absolute number of SAHs adjusted to sex. Figure 3.1 demonstrates the crude incidence of SAH and the gender-adjusted differences in these rates.

Age

Age-specific analysis demonstrated that the incidence of SAH increases with increasing age for both sexes, with the highest incidence rate found in the oldest age group for men and at 75-84 years age group for women. In populations with a mean age of 35 years or less, the calculated incidence was 1.9 per 100,000 person-years (95% CI: 1.8-2), accounting for less than 10% of the annual SAH admissions. This rapidly increased by 10-fold when populations reached 45 to 64 years to 19.1 per 100,000 person-years (95% CI: 18.7-19.5). Although the incidence of SAH in general increases with age when adjusted in age-specific analysis, most incidences of SAH occurred in patients between the ages of 45 to 64 years, representing almost 45% annual SAH admissions among Australian hospitals. Table 3.3 demonstrates the absolute and incidence rate of SAH adjusted to age groups.

The age-specific average annual incidence rates were higher among males than females in the younger age groups, until after the age 35 where the rates for females rise disproportionately compared to the male populations. Figure 3.1 shows the age-specific crude incidences of SAH according to sex. Female populations showed a continuously rising trend of incidence with age compared to the male populations (with a slightly lower incidence rise). These age-specific incidence curves are consistent with results obtained from the literature as well as the Australasian data from the ACROSS study.

Aneurysm Location

We identified 9,329 SAH admissions in which aneurysm locations were specified. Among these, anterior communicating and associated anterior cerebral arteries (I60.2) were the most common locations for aneurysmal rupture, accounting for 35.4% (overall incidence of 2.4 per 100,000 person-years). A total of 22.9% (1.6 per 100,000) of aneurysmal ruptures occurred in the middle cerebral artery (I60.1), 19.6% (1.4 per 100,000) in the vertebrobasilar system (I60.4, I60.5, and I60.6), 18% (1.3 per 100,000) in the posterior communicating artery (I60.3), and (4.1% 0.3 per 100,000) in the internal carotid artery (I60.0). Figure 3.2 illustrates the sex-adjusted percentage of ruptured cerebral aneurysm according to location.

When categorized into anterior and posterior circulation and adjusted for age groups (Table 3.4), we observed the incidences of aneurysmal rupture for both locations increase with age to a peak of 75 years to 84 years. Aneurysms located in the anterior circulation were a more common source of rupture in all age groups compared to those located in the posterior circulation. The overall rate ratio was 3.9 (95% CI: 3.6 to 4.2) for anterior circulation aneurysms.

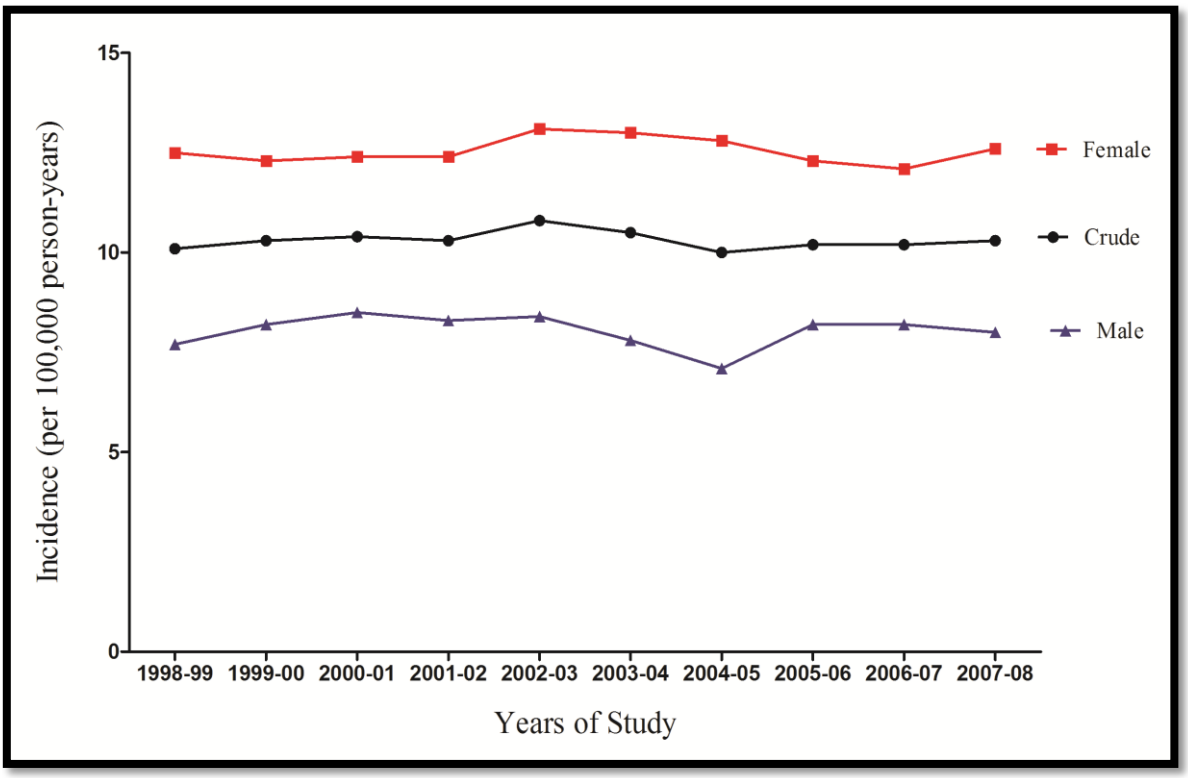

Figure 3.1 Crude incidences of SAH in Australia for the years 1998 to 2008, based on the female populations, the male populations, and the combined populations.

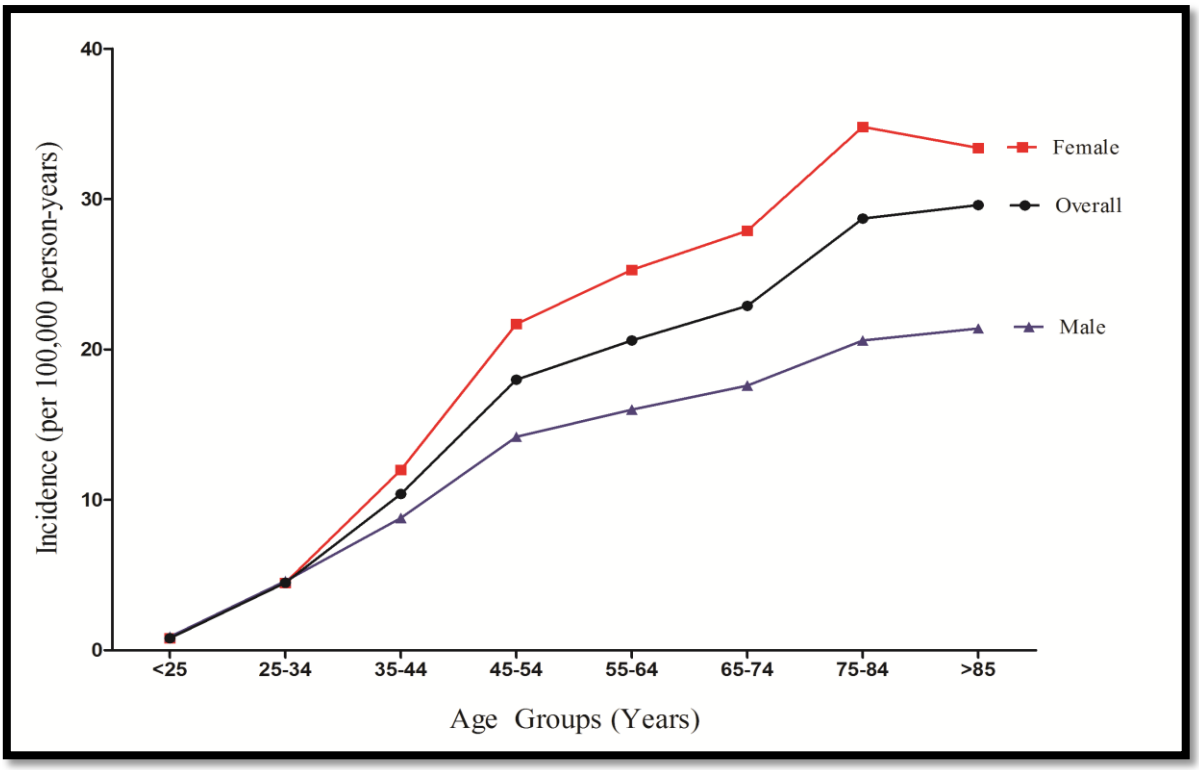

Figure 3.2 Crude incidences of SAH by age and gender, demonstrating that the rate for female populations rises disproportionately as compared to the male populations

Table 3.2 Incidences of SAH (per 100,000 person-years) in Australia for the years 1998 to 2008 based on data obtained from the Australian National Hospital Morbidity Database.

Year	Overall Incidences			Female			Male		
	n	Rate	(95% CI)	n	Rate	(95% CI)	n	Rate	(95% CI)
1998-99	1896	10.1	(9.7, 10.6)	1176	12.5	(11.8, 13.2)	720	7.7	(7.2, 8.3)
1999-00	1940	10.3	(9.8, 10.7)	1168	12.3	(11.6, 13.0)	772	8.2	(7.7, 8.8)
2000-01	1999	10.4	(10.0, 10.9)	1195	12.4	(11.7, 13.1)	804	8.5	(7.9, 9.1)
2001-02	2009	10.3	(9.9, 10.8)	1212	12.4	(11.7, 13.1)	797	8.3	(7.7, 8.9)
2002-03	2116	10.8	(10.3, 11.2)	1297	13.1	(12.4, 13.8)	819	8.4	(7.8, 9.0)
2003-04	2081	10.5	(10.0, 10.9)	1307	13.0	(12.4, 13.8)	774	7.8	(7.3, 8.4)
2004-05	2006	10.0	(9.5, 10.4)	1295	12.8	(12.1, 13.5)	711	7.1	(6.6, 7.7)
2005-06	2088	10.2	(9.8, 10.7)	1258	12.3	(11.6, 12.9)	830	8.2	(7.7, 8.8)
2006-07	2101	10.2	(9.7, 10.6)	1261	12.1	(11.5, 12.8)	840	8.2	(7.6, 8.7)
2007-08	2170	10.3	(9.9, 10.8)	1333	12.6	(12.0, 13.3)	837	8.0	(7.5, 8.6)

CI, confidence interval; n, absolute number of patients with subarachnoid hemorrhage; SAH, subarachnoid hemorrhage

Table 3.3 Age-adjusted incidences of SAH (per 100,000 person-years) in Australia for the years 1998 to 2008 based on data obtained from the Australian National Hospital Morbidity Database.

Age Groups (years)	Overall Incidences			Female			Male		
	n	Rate	(95% CI)	n	Rate	(95% CI)	n	Rate	(95% CI)
<25	557	0.8	(0.8, 0.9)	248	0.8	(0.7, 0.9)	309	0.9	(0.8, 1.0)
25-34	1303	4.5	(4.3, 4.8)	647	4.5	(4.1, 4.8)	656	4.6	(4.2, 4.9)
35-44	3118	10.4	(10.1, 10.8)	1810	12.0	(11.5, 12.6)	1308	8.8	(8.3, 9.3)
45-54	4851	18.0	(17.5, 18.5)	2942	21.7	(21.0, 22.5)	1909	14.2	(13.6, 14.8)
55-64	4072	20.6	(20.0, 21.3)	2479	25.3	(24.3, 26.3)	1593	16.0	(15.3, 16.8)
65-74	3101	22.9	(22.1, 23.7)	1948	27.9	(26.7, 29.2)	1153	17.6	(16.6, 18.6)
75-84	2527	28.7	(27.6, 29.9)	1757	34.8	(33.2, 36.4)	770	20.6	(19.2, 22.1)
>85	828	29.6	(27.6, 31.7)	640	33.4	(30.9, 36.0)	188	21.4	(18.5, 24.6)

CI, confidence interval; n, absolute number of patients with subarachnoid hemorrhage; SAH, subarachnoid hemorrhage

Table 3.4 Aneurysm location and age-adjusted incidences of SAH (per 100,000 person-years) in Australia for the years 1998 to 2008 based on data obtained from the Australian National Hospital Morbidity Database.

Age Groups (years)	Anterior Circulation			Posterior Circulation		
	n	Rate	(95% CI)	n	Rate	(95% CI)
<25	169	0.3	(0.2, 0.3)	51	0.1	(0.1, 0.1)
25-34	437	1.5	(1.4, 1.7)	120	0.4	(0.3, 0.5)
35-44	1247	4.2	(3.9, 4.4)	302	1.0	(0.9, 1.1)
45-54	1975	7.3	(7.0, 7.6)	483	1.8	(1.6, 2.0)
55-64	1593	8.1	(7.7, 8.5)	361	1.8	(1.6, 2.0)
65-74	1119	8.3	(7.8, 8.8)	275	2.0	(1.8, 2.3)
75-84	786	8.9	(8.3, 9.6)	194	2.2	(1.9, 2.5)
>85	171	6.1	(5.3, 7.1)	46	1.6	(1.2, 2.2)

CI, confidence interval; n, absolute number of patients with subarachnoid hemorrhage

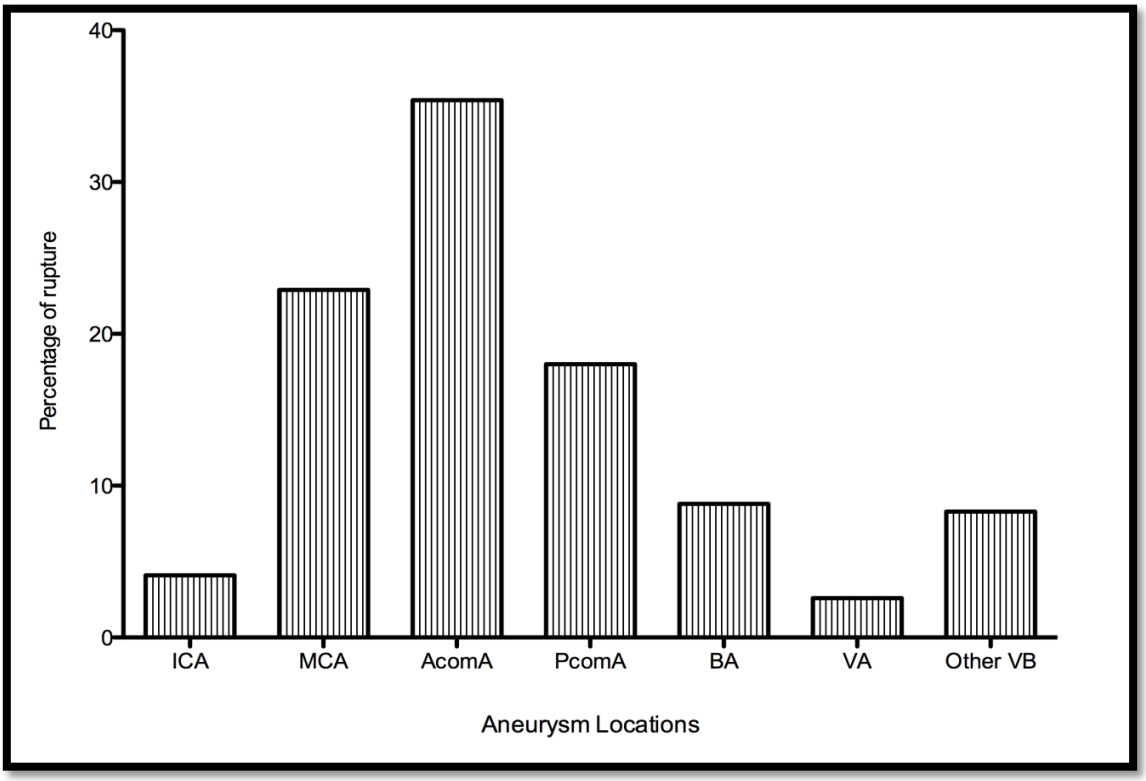

Figure 3.3 Distribution of ruptured intracranial aneurysms from aSAH in Australia for the years 1998 to 2008. ICA, internal carotid artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; BA, basilar artery; VA, vertebral artery; Other VB, other vertebrobasilar arteries; aSAH, aneurysmal subarachnoid hemorrhage

DISCUSSION

The crude incidence of subarachnoid hemorrhage in Australia was estimated at 10.3 per 100,000 person-years per annum. This is in keeping with most regional reports in the literature. In an earlier study on the incidence of SAH in Australia between 1978 and 1979, 27 patients with SAH were recorded in Melbourne. The incidence was reported at 11.8 per 100,000 person-years between 35 and 44 years of age, rising to 34.7 per 100,000 person-years per annum over the age of 65 years (160). Likewise, the ACROSS study estimated the crude annual incidence of 8.1 per 100,000 person-years over the four Australasian population groups (149). This is also similar to the 9 per 100,000 annual incidence reported by the NEMESIS study in 2001 (151).

In earlier literature, the annual incidence of SAH commonly ranged from 10 to 15 per 100,000 of the population (161). With the increasing availability of computed tomography (CT) where more rigorous diagnosis were possible, studies showed the rate as being closer to 6 per 100,000 of the population. Outcomes after aneurysmal subarachnoid hemorrhage are said to have improved slightly during the last few decades with the incidence of SAH reported

to be declining (162, 163) and the mean age of patients increased by 10 years (164). In the current report, we did not observe a decreasing trend in the annual incidence of SAH during our specified study period. Rates ranged from 10.0 to 10.8 per 100,000 person-years with no apparent decline in the last four years of the study from 2005. Patients within the age group of 45 to 64 years were at highest risk of SAH, accounting for almost 45% of the annual number of SAH admissions each year. The most common age of presentation was between 50 to 54 years.

Unlike other types of strokes, there is a female preponderance for spontaneous SAH. In almost all non-Finnish studies, female are at greater risk for SAH with incidence rates about 1.5 times greater than male. We found similar patterns among our female populations with an incidence of 12.5 per 100,000 compared to 8.0 per 100,000 for male populations, and an overall rate ratio of 1.6. On the basis of prospective stroke studies from Dijon, Tilburg, Perth, Malmo, and Oxford, a meta-analysis suggested annual incidences of 7.1 per 100,000 females (95% CI: 5.4 to 8.7) and 4.5 per 100,000 males (95% CI: 3.1 to 5.8) (165). Several series have further emphasized gender-specific differences in annual incidence rates among different geographic regions, including New Zealand (14.1 per 100,000 females and 8.4 per 100 000 males), Australasia (9.7 and 6.5), Denmark (5.4 and 3.8) (166), The Netherlands (6.8 and 5.2) (167) and Canada (11.2 and 8.0) (168). The reasons for the overall higher SAH incidence among female remains unclear, but hormonal factors (including use of hormone replacement therapy) have been postulated (169) as well as geometric differences in the Circle of Willis between the two sexes (170).

Contrary to the previous belief that SAH mainly affects the young and middle-aged people (171), the results of our study suggest that the incidence of SAH increases with increasing age and reaches a maximum in the oldest age groups. This trend has been repeatedly observed in a number of overseas and local studies (172-174). Whereas the elderly population are under-represented in most aneurysmal SAH management reports (175), active treatment has been suggested for these patients because of more favorable outcomes for those who were treated (176-180) compared to those who were managed conservatively (181, 182).

In general, endovascular management of aneurysmal SAH patients in the elderly population has been advocated as a feasible and safer treatment option (183, 184), although data from prospective randomized trials remain inconclusive (120, 127, 185, 186). Numerous authors have agreed that the key determinant for outcome after aneurysmal SAH in the elderly population is in the severity of the SAH at presentation and not so much the type of treatment

utilized (124, 187). Indeed, the integration of coil embolisation at individual institutions failed to show improved overall outcome of aneurysmal SAH in the elderly patients. Others reported increased hazard of death or subsequent readmission for aneurysmal SAH among patients who were coiled (123), challenging the generalizability of the International Subarachnoid Aneurysm Trial (ISAT) study to all ruptured aneurysms

At present, the number of subarachnoid hemorrhages managed in Australian hospitals amount to over 2000 cases annually. By 2020, with the projected Australian population to be above 23.8 million (188), case volume for subarachnoid hemorrhage is estimated to increase by at least 200 cases per year (based on an annual incidence of 10.3 per 100 000 person-years). With a concurrent increase in the proportion of elderly patients admitted with SAH, the role of aneurysm surgery becomes imperative as the trend towards microsurgical treatment of incompletely coiled or recurrent aneurysms grows (189-191). The concerning reality is the impending decline in cerebrovascular-neurosurgical workforce in Australia. For every ruptured cerebral aneurysm presented to Australian hospitals, patients are twice as likely to be treated by endovascular coiling than by microsurgical clipping (192). With a retiring generation of skilful cerebrovascular neurosurgeons exiting the workforce over the next 10 years, the challenges that need to be met by a younger generation of aneurysm surgeons will be considerable, given the changing complexity of aneurysm case mix and volume.

LIMITATIONS OF STUDY

There are sell known limitations to analyses of national hospital databases (143). There are errors in coding, potential limitations in sampling, and the susceptibility of selection bias in a retrospective study. Furthermore, administrative databases usually lack specific information with regard to aneurysm morphology, inpatient progress and other long-term functional outcomes. Our study was limited by the lack of specified aneurysm location within the diagnostic codes I60.7 and I60.9 that account for a large portion of SAH admissions in the analysis. Whilst every attempt was made to eliminate confounders of non-aneurysmal subarachnoid hemorrhages, there remains a large subset of patients within our analysis diagnosed with peri-mesencephalic SAH, whom we cannot separate due to the limitations of codes from our database. In the literature peri-mesencephalic SAH accounts for approximately 10% of all non-traumatic SAH and 21% and 68% of patients with angiogram-negative SAH (193). Assuming 10% of our SAH admissions were related to peri-mesencephalic bleed, the re-adjusted incidence of SAH is estimated at 9.3 per 100,000

person-years (95% CI: 9.1 to 9.4), reflecting primary SAH not related to trauma, AVM rupture, peri-mesencephalic bleed or other non-aneurysmal confounders defined by our exclusion criteria. This estimate of aneurysmal SAH incidence is even closer to current worldwide average incidence and is also in keeping with previous Australian reports.

CONCLUSION

We report a 10.3 per 100,000 person-years crude SAH incidence in Australia for the ten years between 1998 and 2008. Females were more prone to aneurysmal rupture than males, and the incidence increased with increasing age for both sexes. Contrary to current observation in the literature, we did not observe a decline in the incidence of SAH during this period.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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CHAPTER 4

PREDICTORS OF IN-HOSPITAL SHUNT-DEPENDENT HYDROCEPHALUS FOLLOWING RUPTURE OF CEREBRAL ANEURYSMS: A NATIONWIDE ANALYSIS OF 10,807 ANEURYSMAL SUBARACHNOID HEMORRHAGE PATIENTS

PREFACE TO CHAPTER 4

This chapter investigates the incidence and predictors of shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhages in a large nationwide administrative dataset.

This chapter has been peer reviewed and published:

Lai, L. and Morgan, KM., Predictors of in-hospital shunt-dependent hydrocephalus following rupture of cerebral aneurysms: a nationwide analysis of 10,807 aneurysmal subarachnoid hemorrhage patients. Journal of Clinical Neuroscience, 2013. 20 (8): p. 1134-1138.

AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: The development of shunt-dependent hydrocephalus is a well-recognised complication after aneurysmal subarachnoid hemorrhage and negatively impacts on outcomes among survivors. This study aimed to identify early predictors of shunt dependency in a large administrative dataset of aneurysmal subarachnoid hemorrhage patients.

METHODS: We reviewed the National Hospital Morbidity Database in Australia for the years 1998 to 2008 and investigated the incidence of ventricular shunt placement following aneurysmal subarachnoid hemorrhage (aSAH) admissions. Putative risk factors were evaluated with univariate and multivariate logistic regression analysis to identify independent predictors of outcome. The following variables were considered: poor admission neurological grade, aneurysm location, intracerebral hemorrhage, intraventricular hemorrhage, acute hydrocephalus requiring the insertion of an external ventricular drain, surgical clipping, endovascular coiling, meningitis and prolonged period of external ventricular drainage.

RESULTS: A total of 10,807 hospitalisations for aSAH were identified. Among them, 701 [6.5%; 95% confidence interval (CI), 6.04-6.97] required a permanent CSF diversion procedure during the same admission as the aSAH. On multivariate analysis, poor admission neurological grade, acute hydrocephalus, the presence of intraventricular hemorrhage, ruptured vertebral artery aneurysm, surgical clipping, endovascular coiling, meningitis, and prolonged period of external ventricular drainage were significant predictors of shunt dependency. A patient with a ruptured middle cerebral artery aneurysm was unlikely to develop shunt dependency (OR 0.58; 95% CI 0.46-0.73; $p<0.001$).

CONCLUSION: The development of shunt-dependent hydrocephalus following SAH appears to be multi-factorial. Indications for ventricular shunt placement must take into account various predisposing factors along the course of patients' SAH admission.

INTRODUCTION

The incidences of ventricular shunt placement following ruptured cerebral aneurysms vary substantially among institutions with rates reported between 4% and 64% (194-213). This variation may be explained in part by differences in institutional definitions of hydrocephalus, disparity in protocols and timing of evaluation. In clinical practice, the prediction of shunt dependency is often difficult. Over the years, numerous predisposing factors such as female sex (202, 204, 206, 209, 210, 214, 215), increasing age (203, 204, 206-209, 211, 215-219), poor admission neurological grade (196-199, 201-206, 208-214, 217, 218, 220, 221), intraventricular hemorrhage (196, 198, 201-206, 208-211, 213, 222-225), acute hydrocephalus (197, 199, 201, 203-205, 207-210, 213, 215, 217, 221, 226-229), meningitis (203-205, 210), vasospasm (196, 206, 209, 212, 217, 230), aneurysm locations (198, 202, 204, 206, 207, 209, 211, 214) and endovascular treatment (196, 197, 201, 209) have been recognised as important contributors to the development of chronic hydrocephalus. Few studies, however, have considered the association between risk factors and shunt dependency in a large administrative database of subarachnoid hemorrhage (SAH) patients, nor have many covered a long period of time. We analysed the nationwide incidence of shunt-dependent hydrocephalus in patients with aneurysmal SAH between the years 1998 and 2008, and sought to identify early predictors of a chronic hydrocephalic outcome. We hypothesised that several clinical and radiological variables on admission and during the patient clinical course could potentially predict the need for a permanent shunt placement.

METHODS

Data Source, Selection Criteria and Definition of End Points

We conducted our analysis using the Australian National Hospital Morbidity Database (NHMD) for the years 1998 through to 2008. The NHMD is a collection of records for hospital admitted patients from public and private hospitals in Australia, and has been used previously to study outcomes of patients treated for ruptured and unruptured cerebral aneurysms (192, 231). It contains clinical and non-clinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patient's admission and discharge status, demographics and length of hospital stay. Almost all hospitals in Australia are included in this database including; public acute and Department of

Veterans' Affairs hospitals, public psychiatric hospitals, private acute and psychiatric hospitals and private freestanding day hospital facilities.

All patients who presented with primary SAH not related to trauma or arteriovenous malformation were identified by the diagnostic codes I600 to I607, using the International Classification of Diseases and related Health Problems, Tenth revision, Australian Modification (ICD-10-AM). We excluded patient admissions with codes I60.8 and I60.9 as these represented SAH episodes where a ruptured aneurysm was neither identified nor found to be the cause of their presentation.

Chronic shunt-dependent hydrocephalus was defined by the occurrence of any procedures involving permanent CSF diversion. These include the insertion of ventriculo-peritoneal shunts (4000302), ventriculo-pleural (4000301), ventriculo-atrial (4000300) or other variants such as ventricular shunt to other extracranial sites (4000303) and lumbo-peritoneal shunts (4001800).

A number of related diagnoses were identified to assess for their prognostic value in predicting shunt dependency during patients' admission episode. These were considered for factors related to the patient's admission status, ruptured aneurysm location and in-hospital variables.

Admission Status Risk Factors

Poor admission neurological grade was considered for those patients who required intubation and admission into intensive care unit (ICU) for ventilator support (1388201, 1387900). In addition, the presence of intraventricular hemorrhage (I615), intracerebral hemorrhage (I610, I611, I612, I613, I614, I616, I618, I619, I629), and acute hydrocephalus requiring an external ventricular drain (EVD) placement (39015) were investigated.

Ruptured Aneurysm Locations

Ruptured aneurysm locations were identified by the diagnostic codes I60.0 to I60.7. Codes I60.0, I601, I602 and I60.3 represented ruptured anterior circulation aneurysms related to the internal carotid artery, middle cerebral artery (MCA), anterior communicating artery (ACoA) and posterior communicating artery, respectively. Codes I60.4, I60.5 and I60.6 represented

posterior circulation aneurysms characterised by the basilar artery, vertebral artery and other vertebrobasilar arteries, which incorporated the posterior cerebral artery, posterior inferior cerebellar artery and anterior inferior cerebellar artery.

In-hospital Related Variables

A number of in-hospital related variables were considered in the analysis. These included therapeutic interventions by surgical clipping (3980000, 3980600) or endovascular coiling (3980001, 3541200, 3532100, 3311600, 6000900, and 6000901). To establish the true impact of treatment modality on the development of shunt-dependent hydrocephalus, only patients who were treated exclusively by clip ligation or coil embolisation were considered. Those patients in whom both procedures were performed during the same admission were excluded from the analysis. In addition, the diagnosis of nosocomial meningitis (G000 to G003, G008, G009, G030 to G032, G038, and G039) and prolonged duration of CSF drainage (defined as two or more insertions of EVDs per patient per admission) were also investigated.

Statistical Analysis

All data were converted into categorical variables, either dichotomisation or stratification. To establish the relationship between variables and the chronic shunt dependency, statistical analyses were conducted using the Statistical Package for the Social Sciences software (SPSS version 19; Chicago, IL, USA). The Pearson chi-square test (Fisher's exact test) or student T-test was first used, where appropriate, significance was set to a probability value of 0.05. Univariate logistic regression analysis was used to determine variables that may be associated with the likelihood of chronic hydrocephalus. Multivariate logistic regression analysis was performed to identify independent predictors for shunt dependency based on the result of univariate analysis. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Between 1998 and 2008, we identified 10,807 aneurysmal SAH admissions. Acute hydrocephalus requiring the insertion of an EVD occurred in 2,842 patients (26.3%). Chronic hydrocephalus, defined as the occurrence of a ventricular shunt placement procedure during the same admission as that for the aneurysmal subarachnoid hemorrhage, developed in 701 patients (6.5%). Table 4.1 summarises the investigated variables related to patient admission episode.

Admission Status Risk Factors

Based on our definition of poor admission neurological grade, 1,958 patients required admission to ICU for ventilator support. Among them, 245 (12.5%) needed a permanent shunt placement procedure (OR 2.63; 95% CI 2.24-3.10; p=0.00). The incidence of shunt dependency among the 288 patients identified with intraventricular hemorrhages was 14.9% (OR 2.63; 95% CI 1.89-3.67; p=0.00) and 7.3% among the 313 patients with intracerebral hemorrhages (OR 1.15; 95% CI 0.75-1.77; p=0.53). Of the 2,842 patients with acute hydrocephalus requiring the insertion of an EVD, 464 (16.3%) patients developed chronic shunt dependency (OR 6.36; 95% CI 5.41-7.49; p=0.00).

Ruptured Aneurysm Locations

Anterior communicating artery aneurysms (3,679 patients) and middle cerebral artery aneurysms (2,327 patients) were the most common sources of subarachnoid bleeding, accounting for over 50% of the total number of ruptured aneurysms. The incidence of permanent shunt placement among the ruptured ACoA aneurysms was 8.2% (OR 1.49; 95% CI 1.28-1.74; p=0.00) and 4.2% for the MCA aneurysms (OR 0.57; 95% CI 0.46-0.72; p=0.00).

Posterior circulation aneurysms were recognised in a total of 2,019 patients. Among them, ruptured vertebral artery aneurysm accounted for the highest incidence of shunt dependency (10.7%; OR 1.76; 95%CI 1.19-2.61; p=0.00).

In-hospital Related Variables

Of the 4,255 aneurysms that underwent surgical treatment, 9.6% developed hydrocephalus requiring the placement of a permanent CSF shunt diversion (OR 2.27; 95% CI 1.94-2.65; p=0.00) as compared with 9.8% of the 1,670 aneurysms treated by coil embolisation (OR 1.73; 95% CI 1.44-2.08; p=0.00). The incidence of shunt-dependency was highest among those patients with meningitis (32.1%; OR 7.19; 95%CI 4.96-10.42; p=0.00) and those who required prolonged period of CSF drainage (28.6%; OR 7.41; 95% CI 6.10-9.00; p=0.00).

Multivariate Logistic Regression Analysis

When the considered variables were adjusted in a multivariate analysis, a number of independent factors were identified as significant independent predictors of chronic shunt dependency (Table 4.2). These included: poor neurological admission grade requiring ICU admission (OR 1.53; 95% CI 1.28-1.83; p <0.001), acute hydrocephalus requiring EVD insertion (OR 3.42; 95% CI 2.83-4.13; p <0.001), the presence of IVH (OR 1.45; 95% CI 1.01-2.09; p <0.05), surgical clipping (OR 2.84; 95% CI 2.30-3.52; p <0.001), endovascular coiling (OR 2.26; 95% CI 1.76-2.91; p <0.001), meningitis (OR 2.92; 95% CI 1.94-4.39; p <0.001), prolonged CSF drainage (OR 2.44; 95% CI 1.96-3.05; p <0.001), and ruptured vertebral artery aneurysms (OR 1.62; 95% CI 1.06-2.49; p <0.05). Ruptured MCA aneurysms negatively predicted the likelihood of a shunt requirement (OR 0.64; 95% CI 0.51-0.81; p <0.001).

Table 4.1 Admission status, aneurysm location, and inpatient clinical characteristics for the 10,807 ruptured intracranial aneurysms

	No. of patients	No. Shunted (%)	*p* value	OR (95% CI)
Total SAH admissions	10,807	701 (6.5%)	-	-
Admission Status				
Required ventilation in ICU	1958	245 (12.5%)	0.00	2.63 (2.24-3.10)
Intraventricular hemorrhage	288	43 (14.9%)	0.00	2.63 (1.89-3.67)
Intracerebral hemorrhage	313	23 (7.3%)	0.53	1.15 (0.75-1.77)
Insertion of EVD	2842	464 (16.3%)	0.00	6.36 (5.41-7.49)
Aneurysm Location				
Internal Carotid Artery	453	25 (5.5%)	0.39	0.84 (0.56-1.26)
Middle Cerebral Artery	2327	98 (4.2%)	0.00	0.57 (0.46-0.72)
Anterior Communicating Artery	3679	300 (8.2%)	0.00	1.49 (1.28-1.74)
Posterior Communicating Artery	1877	139 (7.4%)	0.08	1.19 (0.98-1.44)
Basilar Artery	895	52 (5.8%)	0.39	0.88 (0.66-1.18)
Vertebral Artery	271	29 (10.7%)	0.00	1.76 (1.19-2.61)
Other Vertebrobasilar Arteries	853	50 (5.9%)	0.44	0.89 (0.66-1.20)
In-Hospital Events				
Surgical Clip Only	4255	408 (9.6%)	0.00	2.27 (1.94-2.65)
Endovascular Coil Only	1670	163 (9.8%)	0.00	1.73 (1.44-2.08)
Meningitis	134	43 (32.1%)	0.00	7.19 (4.96-10.42)
Prolonged CSF drainage (Multiple EVDs)	622	178 (28.6%)	0.00	7.41 (6.10-9.00)

**ICU, Intensive care unit; EVD, external ventricular drain*

DISCUSSION

Chronic shunt-dependent hydrocephalus, defined as ventricular shunt placement, occurred in 6.5% of our patients. This estimate is in keeping with institutional reports in the literature (195-199, 201-207, 209-212, 232, 233). Based on the results of our analysis, a number of factors were identified as significant early predictors of chronic hydrocephalus following aneurysmal SAH.

If the risk of shunt dependency were assessed exclusively based on aneurysm location, we established that ruptured aneurysms along the anterior communicating artery and the vertebral artery imposed the greatest clinical impact. This may be related to the different patterns and amount of bleeding into the subarachnoid space and the ventricles. Vertebral artery and anterior communicating artery aneurysm rupture often leads to a large volume of blood in the basal cisterns, since the subarachnoid space around them is wide and offers little resistance to extravasations (198, 204, 206, 211). However, when adjusted to other variables in a multivariate analysis, only ruptured vertebral artery aneurysms maintained statistical significance. In contrast, the narrow Sylvian cistern is a more restricted subarachnoid corridor. This may explain those patients who presented with rupture of middle cerebral artery aneurysms in the current study were not as likely to require shunt placements.

Several studies have identified the level of consciousness at admission as a risk factor for the later development of hydrocephalus (196-199, 201-213). This study also observed a similar finding, which supports that a patient with a poorer SAH admission neurological status would be more likely to require permanent ventricular shunt surgery. This was based on our assumption that those aneurysmal SAH patients who required ICU admission for ventilator support were of a poorer grade. However, Hunt-Hess grade V patients whom may not require ventricular shunt surgery because of their low long-term survival rate can influence these results.

The effect of intraventricular hemorrhage on the development of hydrocephalus has been well established (196, 198, 201-206, 209-211, 213, 230). The presence of IVH is implicated to increase CSF viscosity and lead to early CSF circulation disturbances. Our study showed results comparable to those found in these previous studies (198, 201, 202, 206, 211, 213, 234). Of the 288 patients with evidence of IVH at the time of admission, 43 (14.9%) became shunt dependent. On the contrary, the presence of intracerebral hemorrhage has not been implicated to have an influence on the risk of shunt dependency (205, 208). However, this was found in our analysis.

Table 4.2 Factors significantly associated with ventricular shunt placement

	Odds ratio	95% CI	p value
Positive Predictors			
Surgical Clip Only	2.84	2.30-3.52	<0.001
Endovascular Coil Only	2.26	1.76-2.91	<0.001
Intraventricular hemorrhage	1.45	1.01-2.09	<0.05
Insertion of EVD	3.42	2.83-4.13	<0.001
Prolonged CSF drainage (Multiple EVDs)	2.44	1.96-3.05	<0.001
Required ventilation in ICU	1.53	1.28-1.83	<0.001
Meningitis	2.92	1.94-4.39	<0.001
Vertebral Artery Aneurysms	1.62	1.06-2.49	<0.05
Negative Predictors	Odds ratio	95% CI lower	p value
Middle Cerebral Artery Aneurysms	0.64	0.51-0.81	<0.001

**ICU, Intensive care unit; EVD, external ventricular drain*

Whereas the presence of acute hydrocephalus has been implicated to be a significant predictor of outcome, a number of studies have indicated that this factor may not necessarily lead to the development of shunt dependency (210, 215, 229). In the current study, the placement of an EVD for the treatment of acute hydrocephalus was associated with the onset of shunt-dependent hydrocephalus. Among the 2,842 patients that were recognised with an EVD placement procedure, 464 (16.3%) required a permanent ventricular shunt surgery. The early placement of an EVD independently predicted the likelihood of a shunt-dependent state (OR 3.42; 95% CI 2.83-4.13; p<0.001). The mechanisms that explain this association, however, remain unclear.

The duration of CSF drainage from EVDs has been advocated to additionally contribute to the development of shunt dependency (212, 218). Patients requiring prolonged external ventricular drainage have a significantly higher risk of chronic hydrocephalus after SAH. Although direct measurement of the duration of drainage was not possible, our study indicated multiple EVD placements were associated with a similarly increased risk. The use

of multiple EVDs implies an increased drainage period or an increase in rate of blockage (presumably related to the volume of blood within the ventricles).

Drain replacement may additionally indicate infection, which has been demonstrated to be a potential contributor to shunt dependency in this study. While it has been suggested that nosocomial meningitis is associated with a prolonged duration of CSF drainage from EVDs (203, 221, 235, 236), the results of this study showed that these two factors were independent predictors of a shunt outcome.

Finally, it has been postulated that surgery allows irrigation and early evacuation of subarachnoid clots as compared with endovascular coiling and thereby reduces the probability of chronic hydrocephalus. However, the influence of treatment modality on shunt dependency remains controversial. In a retrospective review of 839 patients with SAH, Nam et al. showed that the treatment modality for cerebral aneurysms did not independently affect the rate of shunt placement (208). When adjusted for Fisher grade, endovascular coiling was associated with a lower incidence of shunt dependency for Fisher grade 2 patients (2% in coiling versus 13% in clipping, p=0.043), while surgical clipping was associated with lower shunt dependency for Fisher grade 4 patients (44% in coiling versus 23% in clipping, p=0.004). Similarly, Sethi et al. showed no statistical significance in clipped versus coiled patients with aneurysmal SAH; their study, however, was limited to anterior circulation aneurysms (200). In contrast, several studies suggest that endovascular treatment is independently associated with shunt dependency in SAH patients (197, 201, 209). A recent meta-analysis which included a total of 1,718 patients (1,336 clipped aneurysms, 382 coiled aneurysms) from five studies (196-198, 201, 209) found a significantly lower risk of ventricular shunt placement in patients treated with surgical clipping (RR 0.74, 95% CI 0.58-0.94, p=0.01) as compared with endovascular coiling (196). In our series, the incidences of ventricular shunt requirements were similar for both the surgical (9.6%) and endovascular (9.8%) groups. The development of shunt-dependent hydrocephalus was equally affected by surgery (OR 2.84; 95% CI 2.30-3.52; p<0.001) or endovascular embolisation (OR 2.26; 95% CI 1.76-2.91; p<0.001).

LIMITATIONS OF STUDY

The interpretation of our results may be limited by the use of an administrative database for clinical research. Other than the possible errors in coding, and potential limitations in sampling, the utilisation of surrogates to estimate clinical outcomes will not be as refined as in clinical studies (143, 237). A procedure to place a ventricular shunt is an appropriate

assumption for chronic hydrocephalic state, signifying hydrocephalus of sufficient severity to warrant intervention. However, there remains a degree of subjectivity in this approach, as the threshold for shunt placement will vary among neurosurgeons. In our endeavor to analyse a number of clinical variables, assumptions were made with regards to poor admission neurological grade, acute hydrocephalus, and prolonged drainage of CSF. It is possible that these definitions may not apply to all the patients that were included in the analysis. Furthermore, endovascular coiling is a new and evolving procedure, and as such endovascular codes may be underrepresented in this study.

A final limitation of this study is that the NHMD only contains data on index hospitalisation. It was not possible to identify or follow up patients once they have been discharged from the acute hospital, and the data does not allow for patients to be tracked longitudinally. Therefore, the NHMD has inherent selection bias for cases of hydrocephalus in which a permanent ventricular shunt placement was performed during the same admission as the aneurysmal SAH. Patients with delayed or chronic hydrocephalus who present with symptoms at a later date were not captured in this study.

CONCLUSION

The development of shunt-dependent hydrocephalus following SAH appears to be multi-factorial. Indications for ventricular shunt placement must take into account various predisposing factors along the course of patients' SAH admission.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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CHAPTER 5

THE RISK OF SEIZURES DURING THE IN-HOSPITAL ADMISSION FOR SURGICAL OR ENDOVASCULAR TREATMENT OF UNRUPTURED INTRACRANIAL ANEURYSMS

PREFACE TO CHAPTER 5

This chapter investigates the peri-procedural risk of seizures following surgical clipping or endovascular coiling of unruptured intracranial aneurysms. The issue of return to driving following elective treatments for unruptured intracranial aneurysms is discussed.

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Ms O'Donnell aided in the discussion with regards to current official guidelines for return to driving following neurosurgery. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Few studies detail the risk of in-hospital seizures following elective surgical or endovascular treatment of unruptured intracranial aneurysms (UIAs). We compared the peri-procedural seizure incidence for clipping and coiling of UIAs in a nationally representative discharge database.

METHODS: A retrospective cohort study using the Australian National Hospital Morbidity Database for the years 1998 to 2008 was conducted. Treatment modalities were compared for the combined primary end point related to seizure. Putative risk factors were investigated with univariate and multivariate logistic regression analysis to identify independent predictors of outcome.

RESULTS: A total of 5,922 hospitalisations for UIAs (3,098 clipping, 2,824 coiling) were identified. Overall, surgery was associated with a 2.7% (95% CI 2.2-3.4) incidence of peri-operative seizures, compared to a 0.6% (95% CI 0.4-1.0) incidence following endovascular treatment (adjusted OR: 4.40; 95% CI 2.64-7.33; $p<0.001$). The incidences of seizures declined over the 11 years study period in both treatment groups, from 4.2% to 2.0% for surgery and 2.8% to 0.3% for endovascular. Hemorrhagic complication with intracerebral hemorrhage predicted the occurrence of a seizure (OR 3.41; 95% CI 1.20-9.66; $p=0.021$), whereas treatment by endovascular coiling was associated with a better seizure outcome (OR 0.23; 95% CI 0.14-0.39; $p<0.001$).

CONCLUSION: Elective surgical treatment of UIAs is associated with a higher risk of seizure occurrence as compared to endovascular coiling. Contrary to conventional thinking, the risk of seizures following endovascular treatment is not entirely absent. Consideration must be given to current recommendations related to the issue of driving after elective intracranial aneurysm treatment.

INTRODUCTION

The effect of seizures on employment prospects and the suitability of return to driving following treatment for unruptured intracranial aneurysms (UIAs) is an important consideration (238, 239). A perceived advantage of endovascular therapy over an elective craniotomy in the treatment of UIAs relates to the risk of seizure (240, 241). However, the risk of seizures following endovascular treatment varies substantially among published reports, and has been estimated to range from 0.01% to 6.2% (242-244).

The accurate prediction of seizure outcomes following endovascular or surgical treatments remains difficult to establish because of the heterogeneity of reported data (127, 245-249). This makes precise annual risk calculation based on treatment modality difficult to determine. In-hospital seizures predict the potential for an ongoing seizure disorder (240, 250-252). Therefore, the in-hospital seizure rate may reflect the long-term risk of seizure events following elective treatment of intracranial aneurysms. Using population data derived from administrative databases, we compared the in-hospital seizure incidence for surgery with that of endovascular treatment of UIAs for the years 1998 to 2008. The primary objective of this study was to report the frequency of in-hospital seizure following surgical clipping or endovascular coiling of UIAs and to examine the annual trends in seizure outcomes during the study period. The secondary objective of this study was to identify putative risk factors that predict the likelihood of an in-hospital seizure occurrence.

METHODS

Data Source, Selection Criteria and Definition of End Points

The unruptured intracranial aneurysm admission dataset was obtained from the Australian National Hospital Morbidity Database (NHMD) for the years 1998 through to 2008. The NHMD is a collection of records for hospital admitted patients from public and private hospitals in Australia, and has been used previously to study outcomes of patients treated for ruptured and unruptured cerebral aneurysms (192, 231). It contains clinical and non-clinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patient's admission and discharge status, demographics and length of hospital stay. Almost all hospitals in Australia are included in this database including; public acute and Department of Veterans' Affairs hospitals, public psychiatric hospitals, private acute and psychiatric hospitals and private freestanding day hospital facilities.

Unruptured intracranial aneurysms (UIAs) were identified by the diagnostic codes I672 using the International Classification of Diseases and related Health Problems, Tenth revision, Australian Modification (ICD-10-AM). Data were analysed only when UIA was recognised as the primary diagnosis for the admission episode. Therapeutic modalities for UIAs were identified by procedure codes for surgical clipping (3980000 and 3980600) or endovascular coiling (3980001, 3541200, 3532100, 3311600, 6000900, and 600090). To establish the true effect of treatment-related outcomes for seizure, only patients who were treated exclusively by clip ligation or coil embolisation were considered. Those patients in whom both procedures were performed during the same admission were excluded from the analysis.

Defining the Risk of Seizures Based on Treatment Modalities

Clipping and coiling of UIAs were compared for the combined primary end point related to seizure. These were considered for the occurrence of simple partial seizures (G401), complex partial seizure (G402), generalised tonic-clonic seizures (G406), petit mal seizure (G407), epileptic convulsions, fits or seizures not otherwise specified (G409), other and unspecified convulsions (R568), and status epilepticus of variable types including grand mal (G410), petit mal (G411), complex partial (G412), other and unspecified status epilepticus (G418, G419).

Defining Predictive Factors for Seizures

Various in-hospital related diagnoses and procedures were identified and included in the analysis to evaluate their predictive value for a seizure outcome. These included hemorrhagic complications related to intraventricular hemorrhage (IVH) involving the lateral, third, fourth or multiple ventricles (I615); intracerebral hemorrhages (ICH) involving the cortical (I611, I612), sub-cortical (I610), and posterior fossa components (I613, I614); and subdural hemorrhages (SDH) not related to trauma (I620). In-hospital interventional procedures including surgical clipping, endovascular coiling or the insertion of an external ventricular drain (EVD; 3901500) were also examined.

Establishing a Difference in Complication Rates for Clipping and Coiling

To assess how treatment modality affects outcomes for seizure, we investigated the differences in complication rates associated with clipping and coiling of UIAs. These were considered for the presence of hemorrhagic complications such as an intraventricular (IVH), intracerebral (ICH), or subdural hemorrhage (SDH) and the requirement of an EVD insertion.

Statistical Analysis

All data were converted into categorical variables, either as dichotomisation or stratification. To establish the relationship between variables and the seizure outcome, statistical analyzes were conducted using the Statistical Package for the Social Sciences software (SPSS version 19; Chicago, IL, USA). The chi-square test (Fisher's exact test) or student T-test was first used, where appropriate, significance was set to a probability value of 0.05. Annual risk of seizures was expressed as a percentage based on the number of patients reported with seizures over the total number treated for the respective year. Multivariate logistic regression analysis was used to determine factors that best predicted the occurrence of seizures. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Risk of seizures following surgical clipping or endovascular coiling of UIAs

A total of 5,922 hospitalisations for UIAs (3,098 exclusively clipped, 2,824 exclusively coiled) were identified during the 11 years study period. The overall in-hospital incidence of seizure following surgery was 2.7% (85 out of 3098 patients) and 0.6% for endovascular coiling (18 out 2,824 patients; X^2 =38.4, p <0.001). Table 5.1 outlines the incidence of seizure for each year of the database based upon the treatment modality for UIAs. The proportion developing seizures decreased over time across both treatment modalities, from 4.2% to 2.0% for surgery and 2.8% to 0.3% for endovascular coiling.

Table 5.1 Annual risk of seizure by treatment modality for unruptured intracranial aneurysms

	Surgical Clipping		Endovascular Coiling	
Year	No. of Procedures	No. Seizures (%)	No. of Procedures	No. Seizures (%)
1998	212	9 (4.2)	36	1 (2.8)
1999	273	11 (4.0)	80	1 (1.3)
2000	313	15 (4.8)	142	1 (0.7)
2001	314	5 (1.6)	150	0 (0.0)
2002	280	9 (3.2)	228	0 (0.0)
2003	289	7 (2.4)	299	1 (0.3)
2004	250	6 (2.4)	355	4 (1.1)
2005	270	6 (2.2)	348	4 (1.1)
2006	289	4 (1.4)	427	3 (0.7)
2007	311	7 (2.3)	463	2 (0.4)
2008	297	6 (2.0)	296	1 (0.3)

Predictors of in-hospital seizures

The following factors were considered for their predictive value of a seizure outcome: Surgical clipping; endovascular coiling; intraventricular hemorrhage, intracerebral hemorrhage; subdural hemorrhage; and insertion of ventricular drain. The case number and odds ratio for each of these variables are provided in Table 5.2.

Based on univariate analysis, surgical clipping (OR 4.40, 95%CI 2.64-7.33; $p<0.001$), the presence of an intracerebral hemorrhage (OR 4.48, 95%CI 1.59-12.63; $p<0.01$), and subdural hemorrhage (OR 4.13, 95%CI 1.26-13.54; $p<0.02$) were associated with the risk of developing in-hospital seizures following elective treatment of UIAs. Endovascular coil embolisation of intracranial aneurysms was less likely to have resulted in the occurrence of seizures (OR 0.23, 95%CI 0.14-0.38; $p<0.001$). The adjusted odds ratio for the occurrence of seizures following surgical clipping as compared with endovascular coiling was 4.40 (95% CI 2.64-7.33; $p<0.001$). The placement of an external ventricular drain was not a statistically significant predictor of seizure outcome.

When adjusted to other variables in a multivariate analysis, the presence of an ICH predicted the likelihood of a seizure event (OR 3.41; 95%CI 1.20-9.66; p = 0.021), whereas treatment by endovascular coiling was associated with a reduced risk of seizure occurrences (OR 0.23; 95% CI 0.14-0.39; p = 0.000).

Complications associated with surgical clipping and endovascular coiling of UIAs

The presence of hemorrhagic complications (e.g. ICH, IVH, and SDH) and the need for EVD placements were considered as complicating events in the setting of elective treatment of UIAs. Overall, surgery was associated with a higher risk of complications (Table 3). Hemorrhagic events related to ICH and SDH occurred more frequently in the surgical group (ICH 44 cases, 1.4%; SDH 41 cases, 1.3%) as compared to the endovascular group (ICH 12 cases, 0.4%; SDH 4 cases, 0.1%). Seizure occurred more commonly among those surgical cases with a hemorrhagic complication: 4 of the 44 patients (9.1%) with ICH and 3 of the 41 patients (7.3%) with SDH in the surgical group experienced an in-hospital seizure. The placement for EVDs was also noted to be more frequent for the surgical cohort (3.3%) as compared to the endovascular cohort (0.8%).

DISCUSSION

In the years following the completion of the International Subarachnoid Aneurysm Trial (ISAT)(247), technical morbidity related to intracranial aneurysm surgery has been subjected to careful scrutiny. One such important focus was the higher incidence of seizures associated with microsurgical repair as compared with endovascular coil embolisation. Among the 2,143 subarachnoid hemorrhage (SAH) patients enrolled into the ISAT, the rates of seizures following surgery at treatment, 1 year and 5 years were 3%, 5.2% and 9.6% respectively, as compared to 1.4%, 3.3% and 6.4%, respectively in the endovascular group.(127, 253) Although the results of the ISAT study do not directly apply to the UIAs cohort, there are important lessons to be learnt from this trial with regards to the importance of tissue handling and the issue of unnecessary brain retraction during aneurysm surgery in order to minimise the risk of seizures (254, 255).

Whereas a correlation between early and late seizures is not well defined for UIAs, in-hospital seizures have been shown to predict the potential for an ongoing seizure disorder in ruptured

aneurysms.(240, 250-252) Numerous predisposing factors such as: poor neurological admission status; prolonged loss of consciousness at presentation; higher cisternal clot burden; the presence of intracerebral haematomas; middle cerebral artery location; occurrence of hydrocephalus; and cerebral ischemia have been recognised as important contributors to the development of chronic seizures.(245, 246, 249, 250, 253, 256-263) Therefore, the frequency of in-hospital seizure may reflect the long-term risk of seizure events following elective treatment of intracranial aneurysms.

For unruptured intracranial aneurysms, the incidence of seizures following surgical treatment is reported to be between 0.1% and 9.2% and that following endovascular repair 0.01% and 6.2%.(242-244) This difference was further underscored in a recent study, utilising the National Inpatient Sample (NIS) database in the United States, which demonstrated a higher incidence of seizures in the elective surgical clipping group for unruptured aneurysms compared with endovascular coiling (9.2% versus 6.2%, respectively)(244). In the current study, surgery was associated with a greater incidence of in-hospital seizures (2.7%) as compared with endovascular treatment (0.6%). This difference may be explained by a higher incidence of peri-operative ICH and SDH associated with surgical treatment. Among the 3,098 electively clipped UIAs, 44 (1.4%) had ICH and 41 (1.3%) had SDH, compared to 12 (0.4%) and 4 (0.1%) among the 2,824 coiled aneurysms, respectively. Furthermore, hemorrhagic complication with an intracerebral hemorrhage predicted the occurrence of a seizure (OR 3.405; 95%CI 1.200-9.663; p = 0.021).

During the study period, the incidence of in-hospital reported seizures associated with microsurgery reduced from 4.2% in 1998 to 2.0% in 2008. The improvement may be related to accuracy of reporting, changes in patient selection, and improved surgical technique. Furthermore, sub-specialisation in aneurysm surgery in the years following the completion of the ISAT trial may also play a role (192). At the present time, most aneurysms can be clipped effectively and expeditiously while preserving normal anatomy. Aneurysm surgery is now performed by the specialised few. Unnecessary brain retraction can be avoided with improved skull base techniques. Furthermore, novel intra-operative blood flow evaluation with microscope-integrated indocyanine green (ICG) fluorescence angiography can be applied safely and efficiently to provide real-time information on the degree of aneurysm occlusion and vascular flow in the perforating branches.(92, 94, 100, 264, 265)

A fundamental question that has arisen in recent years, in part related to the increasing trend towards endovascular treatment of UIAs, is whether electively coiled patients are safe for

return to driving immediately following this type of procedure. In Australia, the current official guidelines for driving of vehicles as granted by the Austroads and Australian Transport Council publication (266) do not provide clear and robust recommendation with regards to this matter. This is likely due to the absence of robust data that would inform recommendations. Each state and territory of Australia has a driver licensing authority and all refer to the Austroads publication for clinical guidelines. There is variation in the medical report procedures of each authority. At present, driving restriction applies only to those patients "following supra-tentorial surgery or retraction of the hemispheres", regardless of the presence of a post-operative seizure. For private vehicle drivers, this restriction is applicable for up to 6 months in the post-treatment period. For commercial vehicle drivers, this period is 12 months. However, when an in-hospital seizure event had occurred following elective treatment of UIAs, the restrictions on driving apply to all patients regardless of the treatment modality (clipping or coiling). Based on the current recommendations, restriction is applicable for 6 months for a private vehicle driver and 10 years for a commercial vehicle driver. Contrary to conventional thinking, the peri-procedural seizure outcomes following endovascular repair of UIAs although minimal (0.6%) is not entirely absent and needs to be taken into account in the treatment recommendation process.

LIMITATIONS OF STUDY

There are well known limitations to analyses of national administrative databases.(143, 237) There are errors in coding, potential limitations in sampling, and the susceptibility of selection bias in a retrospective study. Furthermore, administrative databases usually lack specific information with regards to aneurysm morphology, inpatient progress and other long-term functional outcomes. A potentially important concern is whether the seizures considered in this study were a pre-existing condition or new in the peri-operative period. It was not possible to identify the pre-operative seizure status from the current dataset. Furthermore, data in the literature regarding the incidence of pre-existing seizures for UIAs are conflicting. It is known that giant aneurysms or aneurysms that are anatomically related to the temporal-medial region (such as the MCA or posterior communicating artery) tend to present with seizures,(267, 268) but seizure or epilepsy as the initial clinical manifestation of UIAs is rare(269). Interestingly, the incidence of pre-treatment seizures has been reported to be comparable for both clipping (4.4%) and coiling (4.0%) cohorts in the International Study of Unruptured Intracranial Aneurysm.(243)

Another important limitation of this database is the lack of information on the timing of seizures and the prophylactic use of antiepileptic medications. Whereas the current data only captured seizure events that had occurred during the inpatient episode, the occurrence of delayed seizures is not accounted for in this study. Furthermore, the use of prophylactic antiepileptic medications was not considered in the current analysis.

CONCLUSION

Elective surgical clipping of unruptured intracranial aneurysms is associated with a higher risk of seizures as compared to endovascular coiling. The risk of seizure following an endovascular procedure, although minimal, is not completely absent. This calls for a re-evaluation of the current driving recommendations from both the clinician and driving authorities for all patients undergoing elective aneurysm treatments.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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Table 5.2 Predictors of seizures for the 5,922 electively treated unruptured intracranial aneurysms between 1999 and 2009

	No. Seizures (%)	Odds Ratio	95% CI	*P* Value
Univariate Analysis				
Surgical Clipping (n=3,098)	85 (2.7)	4.40	2.64-7.33	<0.001
Endovascular Coiling (n=2,824)	18 (0.6)	0.23	0.14-0.38	<0.001
Intraventricular Hemorrhage (n=10)	0 (0)	NA	NA	NA
Intracerebral Hemorrhage (n=56)	4 (7.1)	4.48	1.59-12.63	<0.01
Subdural Hemorrhage (n=45)	3 (6.7)	4.13	1.26-13.54	<0.02
Insertion of EVD (n=127)	4 (3.1)	1.87	0.68-5.17	0.23
Multivariate Analysis (Forward LR)				
Intracerebral Hemorrhage		3.41	1.20-9.66	<0.03
Endovascular Coiling		0.23	0.14-0.39	<0.001

**n*, the number of patients *; EVD*, external ventricular drainage; *LR*, likelihood ratio; *CI*, confidence interval

Table 5.3 Complications associated with the 3,098 surgically clipped and 2,284 endovascular coiled unruptured intracranial aneurysms

	Surgical Clipping		Endovascular Coiling		*p* value
	Patients (%)	**Seizure (%)**	**Patients (%)**	**Seizure (%)**	
Overall	3,098	85 (2.7)	2,824	18 (0.6)	<0.01
Intraventricular hemorrhage	4 (0.1)	0 (0)	6 (0.2)	0 (0)	0.74
Intracerebral hemorrhage	44 (1.4)	4 (9.1)	12 (0.4)	0 (0)	<0.01
Subdural hemorrhage	41 (1.3)	3 (7.3)	4 (0.1)	0 (0)	<0.02
Insertion of external ventricular drainage	103 (3.3)	3 (2.9)	24 (0.8)	1 (4.2)	0.36

CHAPTER 6

OUTCOMES FOR A CASE SERIES OF UNRUPTURED OPHTHALMIC SEGMENT ANEURYSM SURGERY

PREFACE TO CHAPTER 6

This chapter examines the surgical outcomes following repair of unruptured ophthalmic segment aneurysm surgery and considers the role of microsurgery in contemporary endovascular era. The data presented here is based on the senior author's (MKM) extensive surgical experience in treating unruptured intracranial aneurysms. This study was approved by the Macquarie University Human Ethics Committee, and was conducted in accordance with institutional ethics committee guidelines (ethics reference number: HE26SEP2008-R06107)

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE**:** Ophthalmic segment aneurysms present unique technical challenges because of their proximity to the optic nerve and the anterior clinoid process. The current study was performed to examine whether surgery for unruptured ophthalmic segment aneurysms is an effective treatment modality with acceptable complication rates.

METHODS**:** A consecutive case series (prospectively collected data) was retrospective reviewed for the period between April 1992 and August 2012. Putative risk factors including patient's age, aneurysm size, aneurysm morphology, presence of calcification, the use of temporary clipping, and the implementation of a contralateral operative approach were investigated using regression analyses. Clinical results, operative complications, angiographic outcomes and prognostic factors associated with surgery are presented.

RESULTS: Of the 169 patients with 182 unruptured ophthalmic segment aneurysms that were surgically repaired, 11 (6.4%) experienced a new permanent neurological deficits, including 6 instances of complete visual loss. There was one postoperative death (0.6%) related to a middle cerebral artery infarction. Transient morbidity occurred in 18 cases (10.4%), including cerebrospinal fluid rhinorhea (10 cases), oculomotor nerve palsy (4 cases) and transient dysphasia (4 cases). A total of 142 aneurysms (78.0%) had documented postoperative angiography. Surgical treatment resulted in 135 (95.1%) complete obliterations and 7 (4.9%) neck remnants. Retreatment was performed in 3 cases (1.7%). Logistic regression analysis of risk factors revealed that age ($p<0.02$), aneurysm size ($p<0.01$) and the use of temporary clipping ($p<0.01$) were significant negative predictors of outcome.

CONCLUSION: The risk associated with surgical repairs for unruptured ophthalmic segment aneurysms is no greater than aneurysms in other locations (6.4% morbidity; 0.6% mortality) and no more hazardous than outcomes achieved by alternative therapies. The robustness of aneurysm repair achieved by open microsurgery is an important consideration.

INTRODUCTION

When intervention is deemed appropriate, understanding the risk for aneurysm repair is confounded by the choice between an endovascular option and a microsurgical option. The management of unruptured ophthalmic segment aneurysms remains at the forefront of this controversy. Audits, such as The International Study of Unruptured Intracranial Aneurysms (ISUIA) (243) and the California unruptured aneurysm database (270) have provided evidence that endovascular therapy may be safer than open microsurgical clipping for many patients with unruptured aneurysms. Such large multi-center studies can offer statistical power and evidence-based robustness. However, as these studies are audits, the decision biasing the selection of treatments has not been eliminated. Factors influencing the recommendation for a selection of treatment option may also impact upon the risks of this treatment (such as larger size favoring a recommendation to treat by microsurgery rather than endovascular therapy). Contextually important information may well explain the differences between modes of treatment, but are often difficult to extract from such multi-centered audits where contexts are subjected to a Gaussian blur. Therefore, treatment recommendations for unruptured intracranial aneurysms cannot be based solely on the results presented in de-contextualised audits because the aneurysms selected for microsurgical or endovascular treatment may differ. There remains an important place to combine information from larger audits with case series where contextual richness is preserved (271-273).

We present our experiences with surgical repairs of unruptured ophthalmic segment aneurysms over a 20-years period in an institution that continues to provide microsurgery as a primary treatment modality. Clinical results, complications and prognostic factors for surgical outcomes are presented.

METHODS

Clinical Material

This study was approved by the Macquarie University Human Ethics Committee and performed in accordance with institutional Ethics Committee guidelines. All patients who underwent treatment of unruptured ophthalmic segment aneurysms by the senior author (MKM) between April 1992 and August 2012 were eligible for review. Data were collected prospectively in a specifically designed database that includes patient demographic, clinical presentation, radiological features, aneurysm size and morphology, presence of irregularities

(secondary “bubbles” or “blebs”), presence of thrombi or calcifications of the aneurysm on computed tomography (CT) and treatment-related information. All patients underwent digital subtraction angiography (DSA) or computed tomography angiography (CTA) prior to treatment. We defined ophthalmic segment aneurysms as those that arise from the internal carotid artery segment between the distal dural ring and the origin of the posterior communicating artery. Mycotic, traumatic and dissecting aneurysms or those that arise from the cavernous or the clinoidal segments of the internal carotid artery were excluded. To minimise the confounding effects of multiple aneurysm surgery, patients whose ophthalmic segment aneurysm was treated in conjunction with other aneurysms during the same operative session were also excluded. The size of the aneurysm dome was categorized according to the ISUIA study criteria into <7mm (small), 7-12mm (medium), 13-24mm (large), and ≥25mm (giant) (243).

Technical Consideration

Surgical approach to the aneurysm consisted of an orbito-pterional exposure, incorporating the removal of the lateral roof and superior lateral wall of the orbit and an extradural removal of the anterior clinoid process. The lateral edge of the falciform ligament overlying the optic nerve is opened to gain access to the distal dural ring that is variably resected depending upon the needs of the aneurysm repair. Early decompression of the optic nerve through the opening of the falciform ligament and de-roofing of the optic canal were performed for all cases. Surgical techniques, complexity of surgery, and the use and duration of temporary clipping were noted. The arterial reconstructions varied and were classified as: simple clipping; suture repair of aneurysm supplemented with clipping; trap with bypass surgery; or wrap reinforcement with Teflon (DuPont, Wilmington, DE, USA). Because of the greater difficulty with proximal temporary clip placement in this location (in comparison with most other aneurysm locations) it was not routinely employed and only utilized when necessary (e.g. intraoperative rupture). A contralateral surgical approach was implemented in patients with bilateral ophthalmic segment aneurysms during the same operation from a single craniotomy. For contralateral ophthalmic segment aneurysms, no removal of the anterior clinoid process or un-roofing of the optic nerve occurred. In patients in whom a saphenous vein extracranial-intracranial (EC-IC) bypass was performed, mild hypothermia and barbiturate therapy were used during the temporary occlusion time.

Outcome Assessment

Clinic visits were routinely scheduled at 6 weeks and at 1 year following surgery. Typically, patients underwent a postoperative CTA or DSA within the first 6 weeks postoperative period or at 1 year following surgery. It is not our routine practice to perform intraoperative angiography. The modified Rankin Score (mRS) of individual patients was assessed preoperatively, at 6 weeks following surgery, and at the final clinical review. For patients to be considered to have a surgical complication, they required to have both a new permanent neurological deficit attributed to surgery or angiography remaining present at the 6 weeks postoperative visit and a mRS greater than 1 at the last postoperative visit. If a neurological deficit related to surgery had been determined at the 6-week review, the mRS of the last review was used as the basis for this report. Non-fatal complications that did not produce a neurological deficit, as well as mRS downgrades with causes other than ophthalmic segment aneurysm treatment were not considered. We used the risk of surgical complication per operation rather than per individual aneurysm or patient. This decision was based on an attempt to incorporate cases of multiple aneurysms and multiple surgeries.

Statistical Analysis

The Pearson correlation test was used to analyse correlations between variables studied. Univariate logistic regression analysis was used to determine which of the many factors should be entered into the multivariate analysis. Multivariate logistic regression analysis was performed to identify independent predictors for surgical outcome. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations. A p value of less than 0.05 was considered statistically significant. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

From April 1992 to August 2012, 198 patients with 217 ophthalmic segment aneurysms were surgically treated by the senior author (MKM). Twenty-nine patients with 35 aneurysms were excluded from the current study, including acute subarachnoid hemorrhages in 16 patients, multiple aneurysms treated in the same operative session (nine patients), fusiform aneurysm

(one patient), dissecting aneurysm (one patient) and traumatic aneurysms (two patients). This resulted in a total of 169 patients with 182 unruptured ophthalmic segment aneurysms included for review in the study. Patient demographics, clinical presentation, aneurysm size, and multiplicity are presented in Table 6.1.

Table 6.1 Patients and aneurysm characteristics for unruptured ophthalmic segment artery aneurysms

No. of Patients, n (%)	169
Female/male (ratio)	147/22 (6.7:1)
Age, mean ± SD (range), years	50.6 ± 12.1 (13-82)
Family history of intracranial aneurysms	34 (20.1)
Multiple aneurysms	54 (32.0)
Clinical presentations, n (%)	
Incidental	67 (39.6)
Headache	39 (23.1)
Visual symptoms	28 (16.6)
Family history screening	17 (10.1)
Residual from previous coiling	8 (4.7)
Associated with arteriovenous malformation	7 (4.1)
Transient ischemic attack	3 (1.8)
No. of Aneurysms, n (%)	182
Left/right (ratio)	117/65 (1.8:1)
Size, mean ± SD (range), mm (%)	9.0 ± 6.9 (1.5-25.5)
<7mm	106 (58.2)
7-12mm	31 (17.0)
13-24mm	31 (17.0)
≥25mm	14 (7.7)
Calcium on CT	9 (4.9)
Bubbles or blebs on CT	51 (28.0)
Previous Guglielmi Detachable Coil treatment	8 (4.4)

SD, standard deviation; CT, computed tomography

Surgical Procedures

One hundred seventy-three craniotomies were performed, including 156 procedures (90.2%) for simple surgical clipping (Table 6.2). Suture repair supplemented with clipping was used in two cases of giant aneurysms and unexpectedly in one patient following an intraoperative rupture. There were four aneurysms of 1 to 2mm diameter that were operated on concurrently with other larger ophthalmic segment aneurysms, three of which were treated with wrap reinforcement using Teflon (DuPont). A total of 11 surgical trapping procedures was performed, of which nine (six giant and three large aneurysms) were supplemented with a planned saphenous vein extracranial-intracranial (EC-IC) bypass. The remaining two surgical trap ligations were performed as a planned procedure in one case and as an emergency in one case.

In 29 operations, temporary clipping was required (16.8%). The proximal temporary clip was placed either on the exposed cervical ICA, the ICA in the petrous segment of the carotid canal (extradural drilling for exposure) or in the pre-distal dural ring segment of ICA. Temporary clipping duration was for less than 10 minutes in 13 (7.5%) patients, 10-20 minutes in 5 (2.9%) patients, and greater than 20 minutes in 11 (6.4%) of cases. Contralateral surgical approach was implemented in 11 patients with bilateral ophthalmic segment aneurysms, of which one patient (9.1%) suffered a postoperative complication.

Intraoperative Complications

Intraoperative aneurysm rupture was encountered in five of the 173 procedures (2.9%). In three cases, the arterial reconstruction was possible with repair by direct surgical clipping. In the remaining two patients, prolonged temporary clamp duration was required for suture repair of the aneurysm supplemented with clipping (one patient) and surgical trapping (one patient). This resulted in a new permanent neurological deficit in two patients (Table 6.2).

Transient Morbidity

Cerebrospinal fluid (CSF) rhinorhea was recognised in 10 patients (5.8%), which were surgically repaired at a mean 9.7 days following the initial craniotomy (range 6 - 24 days). The causes of the CSF leak were related to ethmoid sinus entry during the extradural anterior clinoidectomy. No cases of meningitis occurred. Four patients suffered from transient

oculomotor nerve palsy and another four from transient dysphasia following surgery. All acute neurological episodes improved by the 6 week postoperative review.

Table 6.2 Surgical procedures and outcomes for unruptured ophthalmic segment artery aneurysms

	Total	Morbidity, n (%)	Mortality, n (%)
No. Of Procedures, n	173	11 (6.4)	1 (0.6)
Clipping	156	7 (4.5)	0
Clip and suture	3	1 (33.3)	0
Trap	2	1 (50.0)	1 (50.0)
Trap and bypass	9	2 (22.2)	0
Wrap reinforcement	3	0	0
Intra-operative Factors, n			
Use of temporary clipping	29	6 (20.7)	1 (3.5)
<10 minutes duration	13	2 (15.4)	1 (7.8)
10-20 minutes duration	5	2 (40.0)	0
>20 minutes duration	11	2 (18.2)	0
Contralateral approach	11	1 (9.1)	0
Complications			
CSF rhinorrhoea	10	0	0
Third nerve palsy	4	0	0
Transient dysphasia	4	0	0
Intraoperative aneurysm rupture	5	2 (40.0)	0
Complete visual loss	6	6 (100%)	0
Ischemia/Infarction	6	4 (66.7)	1 (16.7)

CSF, cerebrospinal fluid

Permanent Morbidity and Mortality

Combined permanent morbidity and mortality occurred in 12 operations (7.0%; 95% CI, 3.9-11.8; Table 6.2), including 11 new permanent postoperative neurological deficits and one death. The one case of mortality occurred in a 55-year-old woman with a giant aneurysm that was electively trapped without bypass, following a satisfactory balloon test occlusion. This patient developed significant middle cerebral artery infarction from a propagated thrombus in the ICA. Six operations were complicated by complete loss of vision in the postoperative period, including two patients who presented with preoperative visual field defect, one patient with reduced visual acuity and three patients with normal preoperative visual function. Vessel occlusions leading to cerebral infarction were recognised in four patients (embolic in 1 patient; perforator infarct in two patients; EC-IC bypass graft thrombosis in one patient). Table 6.3 outlines the 12 patients with surgical morbidity and mortality encountered in this series.

There was one patient with delayed onset of infarction (occurring >1week following surgery) as a result of vasospasm. This occurred in a patient with multiple aneurysms underwent a contralateral craniotomy for repair of a middle cerebral artery and a superior cerebellar artery aneurysm 1 week prior to her ophthalmic segment aneurysm surgery, She developed postoperative vasospasm following her ophthalmic aneurysm surgery, which necessitated balloon angioplasty. During this procedure, her left middle cerebral artery was perforated, resulting in a left temporal ischemic infarct.

Visual Outcomes

Twenty-eight patients presented with visual symptoms, including diplopia (five patients), visual field defect (five patients), reduced visual acuity (8 patients) and complete loss of vision (ten patients; Table 6.4). The aneurysm size distribution in these patients were <7mm (n = 5), 7-12mm (n = 5), 13-24mm (n = 10) and ≥25mm (n = 8). In 14 patients, temporary clipping was required secondary to large and giant aneurysm sizes. Of the 28 patients who presented with preoperative visual symptoms, visual function remained unchanged in nine patients, improved in 16 and was made worse by surgery in three patients. Three patients who presented with normal preoperative visual function experienced a complete loss of vision following surgery.

Angiographic and Clinical Outcomes

One hundred forty-two (78.0%) aneurysms had documented postoperative angiography with a mean follow up of 24.7 months (range, 1.6-195.9 months). Surgical repairs resulted in 135 (95.1%) aneurysms with complete obliterations and seven (4.9%) with residual neck remnants. Three of these aneurysms were re-operated to re-clip residual necks. Four patients with small neck remnants were monitored without further intervention. It was possible to follow up the surgical outcome in 95.0% of the patients at 6 weeks, and 51.5% of the patients at ≥ 12 months. In the mean clinical follow up of 30.3 months (range, 1.6-236.7 months), no aneurysm recurrence or acute subarachnoid hemorrhage was noted in 426 person years of follow-up.

Prognostic predictors of surgical outcomes

Table 6.5 outlines the results of regression analysis of various preoperative and intraoperative predictors of surgical outcomes.

Age

The risk of surgery increased with age. Surgical complications occurred in 1.2% (1/83) of patients age ≤50 years of age, as compared with 12.8% (11/86) for patients age >50 years. The odds ratios (OR) of surgical downgrade for patients age ≤50 years and >50 years were 0.09 (95% CI 0.01-0.67; $p<0.02$) and 11.81 (95% CI 1.49-93.47; $p<0.02$), respectively.

Size

The risk of surgery increased with size. For aneurysms of size <7, 7-12, 13-24, and >25mm, the risks of surgical complications were 3.8%, 3.2%, 12.9% and 21.4%, respectively. When size was dichotomized to ≤15mm and >15mm, poor outcome was more likely to occur for larger size aneurysms (17.1%; OR 5.60; 95% CI 1.67-18.74; $p<0.01$) as compared to those with sizes ≤15mm (3.6%).

Table 6.3 Surgical morbidity and mortality in patients with unruptured ophthalmic segment artery aneurysms

Sex/Age, y	Size, mm	Side	Procedure and temporary clipping time, min	Postop mRS	Complication
F/53	18	L	Clip, 5-10	2	Postoperative CSF leak repaired; delayed loss of vision left eye
F/60	>25	L	Clip, 5-10	3	Lenticulostriate infarction resulting in mild hemiparesis
F/55	8	L	Clip, 0	2	Loss of vision left eye
F/56	6	L	Trap only, 10-20	1	Intraoperative rupture necessitating prolonged temporary clipping; EC-IC bypass attempted but no veins; complete loss of vision left eye postoperatively.
F/50	6	L	Clip, 0	3	Postoperative vasospasm despite no intraoperative rupture. MCA ruptured during balloon angioplasty for postoperative vasospasm, resulting in left temporal ischemic infarct
F/60	>25	L	Suture and clip, 15-20	4	Ruptured intraoperatively requiring prolonged temporary clipping; postoperatively developed ischemia and dense right hemiparesis.
F/76	17	R	Clip, 0	1	Loss of vision right eye
F/55	16	L	Trap and bypass (planned), >30	1	CCA to ICA bypass graft thrombosed resulting in cortical ischemia. Clinically, patient developed expressive dysphasia.
F/68	4	L	Clip, 0	1	Loss of vision left eye
F/55	16	L	Trap and bypass (planned)	1	Thrombosed EC-IC bypass graft resulting in cortical infarct 48 hours following surgery
F/59	4	R	Clip, 0	1	Delayed loss of vision right eye, 24 hours following surgery
F/55	>25	L	Trap only, 5-10	6	Died. MCA infarct from ICA occlusion

mRS, modified Rankin Score; MCA, middle cerebral artery; ICA, internal carotid artery; CCA, common carotid artery; CSF, cerebrospinal fluid; postop, postoperative

Table 6.4 Visual outcomes of patients presented with preoperative and postoperative visual deficits for unruptured ophthalmic segment artery aneurysms

	Postoperative Visual Outcomes		
	Unchanged	Improved	Worse
Preoperative Visual Outcomes			
Diplopia (n=5)	1	4	0
Visual field defect (n=5)	2	1	2
Reduced visual acuity (n=8)	0	7	1
Complete loss of vision (n=10)	6	4	0
TOTAL	9	16	3

Table 6.5 Logistic regression analyses of prognostic factors based on 173 operations for the management of unruptured ophthalmic segment artery aneurysms

	Odds Ratio	95% CI	*p V*alue
Univariate analysis			
Age > 50 years	11.81	1.49-93.47	<0.02
Size > 15mm	5.60	1.67-18.74	<0.01
Left sided aneurysms	2.94	0.63-13.87	0.17
Bubbles or 'Blebs' on CT	1.31	0.38-4.55	0.67
Calcium on CT	4.66	0.85-25.40	0.08
Temporary clipping	9.42	2.75-32.28	<0.01
Contralateral approach	0.82	0.10-6.73	0.85
Direct clipping	0.22	0.06-0.75	<0.02
Multivariate analysis			
Age > 50 years	10.85	1.33-88.75	<0.03
Temporary clipping	8.70	2.42-31.27	<0.01

CT, computed tomography

Calcification, Thrombus, and Irregularities of the Aneurysms on CT scans

Two of the nine operations with calcified aneurysms that were identified on preoperative imaging, and one of the 45 operations with irregularly shaped aneurysms had postoperative

complications. The OR was not significant to predict surgical downgrades based on the CT appearance of aneurysm shape, calcification or the presence of thrombus.

Surgical Procedures

Seven of the 156 direct clipping procedures had surgical downgrades (6.4%), compared to five of the 14 (35.7%) non-direct clipping procedures. Surgical complications did not occur in the three patients that were treated by wrap reinforcement of the aneurysm. When direct clipping was possible, the OR was 0.22 (95%CI 0.06-0.75; $p<0.02$) as compared with 12.78 (95%CI 3.38-48.29; $p<0.01$) for procedures other than direct simple clipping.

Temporary Clipping

The use of temporary clipping was associated with a poor outcome in seven patients (24.1%; 95% CI 12.0-42.4). For aneurysm repair in which no temporary clipping were required, poor outcomes occurred in five of 144 operations (3.5%; 95% CI 1.3-8.1). The odds ratio of poor outcome in association with the use of temporary clipping was 9.42 (95% CI 2.75-32.28; $p<0.01$) as compared with 0.11 (95% CI 0.03-0.36; $p<0.01$) when no temporary clipping was used. However, it should be noted that temporary clipping was selectively used usually in crisis situations (e.g. where unexpected intraoperative rupture occurred).

Specific Subgroup of Patients with Surgical Complications

When patient age and aneurysm size were combined and compared for the primary end point of a poor surgical outcome, the following subgroups of patients were considered: group 1 (age ≤50, aneurysm ≤15mm), the risk of surgical downgrade was 1.4% (1/71); group 2 (age ≤50, aneurysm >15mm), the risk of surgical downgrade was 0% (0/18); group 3 (age>50, aneurysm ≤15mm), the risk of surgical downgrade was 5.7% (4/70); and group 4 (age >50, aneurysm >15mm), the risk of surgical downgrade was 30.4% (7/23).

Logistic Regression Analysis of Prognostic Factors

Univariate analysis revealed that age (>50years), aneurysm size (>15mm) and the use of temporary clipping were associated with an unfavorable surgical outcome (Table 6.5). When aneurysms could be directly clipped without the use of sutures repairs, trapping or a bypass, the odds of surgical complications were 0.22 (95% CI 0.06-0.75; p<0.02). Aneurysms located on the left side, the presence of bubbles or blebs on CT, the identification of calcification on preoperative imaging, and the implementation of a contralateral surgical approach were not statistically significant predictors. When the variables were adjusted in a multivariate analysis, advanced age (OR 10.85; 95% CI 1.33-88.75; p<0.03) and the use of temporary clipping (OR 8.70; 95% CI 2.42-31.27; p<0.01) maintained their statistical significance.

DISCUSSION

In the current study, we analysed 169 patients with 182 unruptured ophthalmic segment aneurysms of the internal carotid artery surgically treated in 173 operations by a single surgeon. Our results revealed a procedure-related 6.4% permanent new neurological deficit, 10.4% transient morbidity and 0.6% mortality. Factors that were associated with poor surgical outcomes were recognised for advanced age (>50 years), larger aneurysm size (>15mm), and when temporary clipping was necessary. When direct surgical clipping could be performed without the use of alternative methods such as trapping, suture techniques or a bypass procedure, the risk of surgical complications was low.

The recent debate over whether all unruptured aneurysms should be considered for intervention is in part based on the controversial low rupture rates reported in the ISUIA. The ISUIA proposed that the 5-year cumulative rupture risk for unruptured anterior circulation aneurysms was 0%(243), and therefore “it would be difficult to improve on the natural history of these lesions”. However, we believe that the more accurate conclusion is that it was a reflection of good clinical judgment by the clinicians who enrolled their patients with small untreated aneurysms into the study. As for those aneurysms that were treated, no conclusion can be drawn with regards to their natural history. As surgeons were not naïve to morphological features that may increase the risk of surgery prior to the audit’s commencement date (274-277), there is reason to believe that those aneurysms treated during the audit period were different from those that were left untreated.

There is evidence to suggest that small aneurysms can and do rupture.(278-281) In a multicenter prospective study of small unruptured intracranial aneurysms, Sonobe et al. followed 448 unruptured aneurysms less than 5mm in size (374 patients) over a mean period of 41.0 months (278). They reported an overall annual rupture rate of 0.54% for lesions less than 5mm. This risk was higher for patients less than 50 years of age (HR 5.23; 95% CI 1.03-26.52; p = 0.046), aneurysm diameter of 4mm or greater (HR 5.86; 95% CI 1.27-26.95; p = 0.023), hypertension (HR 7.93; 95% CI 1.33-47.42; p = 0.023), and aneurysm multiplicity (HR 4.87; 95% CI 1.62-14.65; p = 0.0048). Similarly, Chmayssani et al. identified 51 patients with 64 aneurysms of sizes less than 7mm in a systematic review that aimed to assess the rupture risk in small aneurysms (282). Over a 6-years follow up period (range 6months to 20 years), 30 of the 64 aneurysms had ruptured (282). Eighty-nine per cent of the ruptured aneurysms were located in the anterior circulation and the overall mean aneurysm size of 3.9 ± 2.3mm in the ruptured group. Likewise, in familial intracranial aneurysms (FIAs) studies, both retrospective and prospective series continue to emphasise a higher rupture risk in these lesions compared to sporadic aneurysms, and a tendency for FIAs to rupture at smaller sizes (<6mm) (279, 283-285). Based on our institutional experience, at least 50% of the unruptured ophthalmic segment aneurysms treated was less than 7mm in diameter. For many of these patients, surgery was performed because of a young age at presentation, a familial history of intracranial aneurysms, or an irregular aneurysm morphology, which do not conform to the same natural history as that proposed by the ISUIA. In a number of selected cases, surgery was also performed for psychosocial reasons.

At present, there is no uniform recommendation for the management of asymptomatic unruptured paraclinoid aneurysms. Kumon et al. recommended treatment for all asymptomatic unruptured carotid-ophthalmic artery aneurysms in order to prevent a fatal subarachnoid hemorrhage (286). In contrast, Iihara advocated treatment should only be instigated for aneurysms >5mm based on their experience with 111 unruptured paraclinoid aneurysms (287). De Jesus et al. proposed treatment for all aneurysms >4mm that extend into the subarachnoid space provided the patient was in good medical condition with at least a 10 years life expectancy (288). In our opinion, the decision to treat should be simple. Ophthalmic segment aneurysms that require intervention are judged on the same basis as aneurysms in other locations (289). Small aneurysms should be considered for surgery for younger patients (particularly with long standing smoking history or hypertension) or in patients with familial intracranial aneurysms.

Over the years, cumulative endovascular experiences for ophthalmic segment artery aneurysms have demonstrated low incidences of morbidity and mortality (272, 273, 290-292) (although the risk of retinal artery occlusion may be more common to this particular approach) (293, 294). However, treatment efficacy remains a key limitation for the endovascular repair of aneurysms in the paraclinoid region. In a study of 170 unruptured carotid-ophthalmic aneurysms, Yadla et al. reported 1.4% morbidity and 0% mortality (271). Total aneurysm occlusion was achieved in 71 (48.3%) of the 147 endovascular procedures performed. Eighteen cases required further retreatment (12.2%). Even with modern day advancement in endovascular technology, Colby et al. reported a 15.5% and 41.5% rate of aneurysm recurrences for stent-assisted and non-stent assisted coiling of 90 paraophthalmic aneurysms, respectively. Initial complete aneurysm occlusion was achieved in 43.3% of the stented patients and in 31.7% of the non-stented patients (295). Similarly, Iihara et al. reported 6.5% morbidity and 0% mortality in their treatment of 77 unruptured paraclinoid aneurysms by endovascular coil embolisation (287). However, complete occlusion was achieved in 66.2% of aneurysms. Retreatment was needed in 4% of cases. We shared similar operative outcomes to the above studies (6.4% morbidity, 0.6% mortality). The robustness of aneurysm repair by microsurgery was demonstrated by a 95.1% complete aneurysm obliteration rate and a 1.7% incidence of retreatment. Based on a mean angiographic follow up of 24.7 months (range, 1.6-195.9 months), no aneurysm recurrence or acute subarachnoid hemorrhages were observed.

Visual morbidity was encountered in six patients (3.5%) in this series, all because of monocular blindness. Previous studies have suggested the role of heat injury to the optic nerve during drilling of the optic canal, optic pathway ischemia, or the effect of manipulation or direct compression by the aneurysm clip onto the optic nerve (296-300). In our practice, we routinely decompress the optic nerve in the early parts of the surgery by opening the falciform ligament and de-roofing the optic canal. This relieves the pressure and distortion from the aneurysm, and improves the nerve's tolerance to manipulation. The loss of vision in each of our cases was believed to be optic nerve damage in the region of the aneurysm rather than retinal ischemia.

Some aspects of our surgical technique may be controversial. First, the routine use of an orbital osteotomy may be considered by some surgeons to be unnecessary, particularly for patients with small ophthalmic or superior hypophyseal aneurysms (301-303). In our hands, the addition of the orbital osteotomy does not add significant operative time, with no increase in postoperative morbidity in regards to deficits or the length of hospital stay. More

importantly, this additional maneuver provides a widened operative corridor, which improves illumination and eliminates the need for fixed brain retraction. Second, we believe that an extradural anterior clinoidectomy allows for greater exposure of the ICA proximal to the aneurysm. The main complication related to this approach is CSF rhinorhea through opening the ethmoid sinus, as evident by a 5.8% leak rate in this series.

Third, neck exposure of the cervical internal carotid artery for proximal vascular control is no longer routinely performed in our practice. In the early surgical experience of the senior author, the neck was regularly prepared in the event that proximal control was required. In the latter years, this manoeuvre was not routinely performed given the speed with which proximal control can be obtained intradurally if required. Unlike aneurysm repair elsewhere, however, the use of temporary clipping is considered complex in this location as it was rarely performed unless there was surgical difficulty. This differs significantly in other locations where the preparation for proximal control by temporary clipping is far simpler.

LIMITATIONS OF STUDY

The current study is subjected to a number of limitations. First, while this is a large series of ophthalmic segment artery aneurysms, the results presented in this study reflect a single surgeon's operative experience over a 20 year period. Examining outcomes over an extended period of time may be difficult to account for changes in operative techniques and technology that may impact on patient care. Microsurgical techniques and neuroanaesthesia has evolved significantly during this period of time. Second, a substantial number of aneurysms in the current series did not have documented postoperative angiography (21.4%; 39/182). While the inherent difficulty in obtaining follow-up images following surgical clipping is noted by some authors (304), the results regarding the clinical course of aneurysm remnant in this series must be interpreted with reservations.

CONCLUSION

Based on our institutional experience, surgical repairs of unruptured ophthalmic segment aneurysms were associated with 6.4% permanent morbidity and 0.6% mortality. The age of the patient (>50 years) and the need for temporary clipping during surgery were associated with a poor outcome. The robustness of aneurysm repair as achieved by open microsurgical

repair is an important consideration. For patients with aneurysms less than 15 mm diameter and who are less than 50 years of age the permanent morbidity (mRS>1) and mortality was 1.4%.

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CHAPTER 7

OUTCOMES FOR A CASE SERIES OF UNRUPTURED ANTERIOR COMMUNICATING ARTERY ANEURYSM SURGERY

PREFACE TO CHAPTER 7

This chapter examines the surgical outcomes following repair of unruptured anterior communicating artery aneurysm surgery and considers the role of microsurgical repair in contemporary endovascular era. The data presented here is based on the senior author's (MKM) extensive surgical experience in treating unruptured intracranial aneurysms. This study was approved by the Macquarie University Human Ethics Committee, and was conducted in accordance with institutional ethics committee guidelines (ethics reference number: HE26SEP2008-R06107)

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Dr Gragnaniello assisted in part of the discussion and literature review for the manuscript. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Surgical outcomes following repair of unruptured anterior communicating artery (ACoA) aneurysms has not been adequately addressed in the literature. The objective of the current study was to report the procedure-related morbidity and angiographic outcomes associated with repairs in these patients.

METHODS: We present our operative experiences in a consecutive series of 103 patients with 115 unruptured ACoA aneurysms that were surgically treated between November 1992 and August 2012. Clinical results, operative complications, angiographic outcomes and prognostic factors associated with surgery are presented.

RESULTS: Of the 115 aneurysm repairs attempted, 114 were treated by clipping or excision and suture. One aneurysm, less than 2mm, was wrapped. Six patients (5.8%; 95% confidence interval [CI], 2.5 to 12.4) experienced a new permanent neurological deficit. There was no postoperative mortality. Transient morbidity occurred in 11 cases (10.7%; 95% CI, 5.9 to 18.3), including transient anosmia (4 cases), acute postoperative confusion and memory disturbances (4 cases), extradural haematoma requiring surgery (2 cases) and CSF rhinorhea (1 case). Of the 84 aneurysms (73.0%) that had documented postoperative angiography, 82 (97.6%) had complete obliteration of the aneurysm and 2 (2.4%) had neck remnants (mean angiographic follow-up 28.0 months; range, 1.6-146.4 months). Retreatment was performed in 1 case (1.0%). Logistic regression analysis of risk factors revealed that aneurysm size ($p<0.01$) was a significant predictor of outcome. There was no incidence of subarachnoid hemorrhage in the 272 person years of follow-up.

CONCLUSION: In the current study, surgical treatment of unruptured ACoA aneurysms resulted in 5.8% morbidity and no mortality. The robustness of aneurysm repair achieved by open microsurgery is an important consideration when considering the option between endovascular and microsurgical treatment for unruptured ACoA aneurysms.

INTRODUCTION

Of all intracranial aneurysms, the anterior communicating artery (ACoA) aneurysm is the most frequent, and represents an increased risk of rupture as compared to aneurysms in other locations (120, 305-311). Surgical treatment can be a significant undertaking because of the deep and midline location, along with multiple perforators and the frequent anatomical variations that are inherent to this communicating arterial segment of the anterior circulation (308, 312, 313). The application of endovascular techniques in recent years have provided a less invasive alternative to the management of ACoA aneurysms, but have led to a reduction in the robustness of aneurysm repair and an increased need for retreatment (314-318). Increasingly, aneurysms are being preferentially treated by endovascular techniques in Australia (192). However, such trends have occurred in the absence of evidence of the superiority of endovascular repair over that of microsurgical repair of unruptured aneurysms. The purpose of this study was to ascertain the efficacy and safety of surgical repair of unruptured ACoA aneurysms. We present our experience of surgical management in a consecutive series of patients with unruptured ACoA aneurysms. Clinical results, operative complications, angiographic outcomes and prognostic factors associated with surgery are presented.

METHODS

Clinical Material

This study was approved by the Macquarie University Human Ethics Committee and was performed in accordance with institutional ethics committee guidelines. All patients who underwent surgical repair of unruptured ACoA aneurysms by the senior author (MKM) between November 1992 and August 2012 were eligible for review. Data were collected prospectively in a specifically designed aneurysm database that included demographic, clinical, radiological and treatment-related information. All aneurysms were diagnosed through magnetic resonance angiography (MRA), high-resolution three-dimensional computed tomography (CT) angiography, or digital subtraction angiography (DSA). We defined ACoA aneurysms as lesions that arise from the arterial segment between the left and right anterior cerebral arteries (ACAs). Mycotic, traumatic and dissecting aneurysms were excluded from the analysis. To minimise the confounding effects of multiple aneurysm surgery, patients who were treated in conjunction with aneurysms at locations other than

ACoA during the same operative session were also excluded. The size of the aneurysm dome was categorized according to the ISUIA study criteria into <7mm (small), 7-12mm (medium), 13-24mm (large), and ≥25mm (giant) (243).

Technical Consideration

Surgical approach to the aneurysm was generally performed through a one piece orbitozygomatic exposure, incorporating the removal of both the lateral roof and superior lateral wall of the orbit and a Sylvian fissure dissection. This enables an angle that usually negates the need for a fixed brain retraction, obviates the need for gyrus rectus resection and provides ready access to both the proximal anterior cerebral arteries (A1s). The side of the operative approach was usually from the side opposite to the direction of the aneurysm dome projection, from the right where there is no projection into the frontal lobe or, from the side best suited for the treatment of other aneurysms where one surgery can be performed for multiple aneurysms. Fenestration of the lamina terminalis is often performed to facilitate brain relaxation by CSF drainage. In general, we avoid gyrus rectus resection to provide additional exposure. Surgical techniques, complexity of surgery, and the use and duration of temporary clipping were noted. The arterial reconstructions varied and were classified as: simple clipping; suture repair of aneurysm supplemented with clipping; or wrap reinforcement with Teflon (Dupont, Wilmington, DE, USA).

Outcome Assessment

Clinic visits were routinely scheduled at 6 weeks and at 1 year following surgery. Typically, patients underwent a postoperative CTA or DSA within the 6 weeks postoperative period or at 1 year follow up. It is not our routine practice to perform intraoperative angiography. The modified Rankin Score (mRS) of individual patients was assessed preoperatively, at 6 weeks following surgery, and at the final clinical review. For patients to be considered to have an unfavorable surgical outcome, they were required to have both a new permanent neurological deficit attributed to surgery or angiography remaining present at the 6 weeks postoperative visit and a mRS greater than 1 at the last postoperative visit. If a neurological deficit related to surgery had been determined at the 6-week review, the mRS of the last review was used as the basis for this report. We excluded patients with a mRS of 1, as all patients have scalp paraesthesia and a substantial number have some degree of temporalis muscle wasting that

would result in a mRS of 1. We used the risk of surgical complication per operation rather than per individual aneurysm or patient. This decision was based on an attempt to incorporate cases of multiple aneurysms and multiple surgeries.

Statistical Analysis

The Pearson correlation test was used to analyse correlations between variables studied. Univariate logistic regression analysis was used to determine which of the many factors should be entered into the multivariate analysis. Variables associated with an unfavorable surgical outcome in univariate analyses ($P<0.20$) were included in a forward, stepwise, multivariate logistic regression. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations. A *p* value of less than 0.05 was considered statistically significant. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Between November 1992 and August 2012, 286 patients with 310 ACoA aneurysms were surgically treated by the senior author (MKM). One hundred eighty-three patients with 195 aneurysms were excluded due to acute subarachnoid hemorrhages (144 patients) and multiple aneurysm surgeries (39 patients). This resulted in a total of 103 patients with 115 unruptured ACoA aneurysms included for review in the current study. Patient and aneurysm characteristics have been detailed in Table 7.1.

Surgical Procedures

One hundred three craniotomies were performed, including 99 procedures (96.1%) for simple surgical clipping (Table 7.2). Suture repair supplemented with clipping was planned in the 3 cases of large and giant aneurysms. One aneurysm of 1 to 2mm diameter was treated with wrap reinforcement using Teflon. In 56 operations, temporary clipping was required (54.4%). The proximal temporary clips were placed on both the ipsilateral and contralateral A1. Temporary clipping duration was less than 10 minutes in 44 cases, 10-20 minutes in 7 cases,

and greater than 20 minutes in 5 cases. Intraoperative aneurysm rupture occurred in one of the 103 procedures (1.0%), but did not lead to a postoperative morbidity.

Table 7.1 Patients and aneurysm characteristics for unruptured ACoA aneurysms

Characteristics	Value
No. of Patients, n (%)	103
Female/male (ratio)	62/41 (1.5:1)
Age, mean ± SD (range), years	54.6 ± 12.8 (25-79)
Clinical presentations, n (%)	
Incidental	48 (46.6)
Headache	13 (12.6)
Previous SAH	13 (12.6)
Family history screening	10 (9.7)
Residual from previous coiling	8 (7.8)
Seizures	6 (5.8)
Visual symptoms	5 (4.9)
No. of Aneurysms, n (%)	115
Size, mean ± SD (range), mm (%)	8.0 ± 5.4 (1.5-25.5)
<7mm	59 (51.3)
7-12mm	42 (36.5)
13-24mm	9 (7.8)
≥25mm	5 (4.3)
Calcium on CT	5 (4.3)
Bubbles or blebs on CT	42 (36.5)
Previous Guglielmi Detachable Coil treatment	8 (7.0)

SD, standard deviation; CT, computed tomography; ACoA, anterior communicating artery

Morbidity

There was no mortality in this series (upper 95% CI 4.32%). Morbidity is tabulated in Table 7.2 and permanent morbidity detailed by case in Table 7.3. Transient morbidity following surgery occurred in 11 patients (10.7%; 95% CI, 5.9 to 18.3). The two patients with

postoperative extradural haematoma required prompt return to theatre for urgent evacuation. No permanent neurological deficits occurred in these two patients. CSF rhinorhea was recognised in 1 patient, which was surgically repaired on day 13 following the initial craniotomy. No cases of meningitis had occurred. One of the cases of acute short-term memory disturbances following surgery returned to normal preoperative cognitive function by the 6 weeks review at clinic.

Permanent neurological deficit following surgery was encountered in 6 patients (5.8%; 95% CI, 2.5-12.4) as a result of vessel occlusions leading to cerebral infarction (medial striate artery injury in 2 cases; perforator occlusion leading to hypothalamic infarct in 1 case; ACA territory infarct in 3 cases). Among them, 2 patients also suffered severe loss of memory, which persisted beyond the 6 weeks postoperative review. Table 7.3 summarises the cases contributing to surgical morbidity in this series. No postoperative seizures occurred in this series of patients.

Angiographic and Long-term Outcomes

Eighty-four (73.0%) aneurysms had documented postoperative angiography with a mean follow up of last angiographic study of 28.0 months (range, 1.6-146.4 months). Of these cases, angiography confirmed 82 (97.6%) aneurysms had complete obliteration and 2 (2.4%) had residual neck remnants. One aneurysm required further surgery to re-clip the residual neck. One case was monitored without further intervention.

In the current series, 27 patients with 31 aneurysms (27%) did not have documented postoperative angiography. Among them, 12 patients with 16 aneurysms were treated for sizes less than 6mm and were thought to be confidently repaired at the time of surgery; 5 patients were older than 70 years of age and were thought not likely to benefit from further surgery if a small residual were to be detected; two patients had neurological deficits that were thought not likely to recover from and were sufficiently profound to believe further surgery would be unwarranted even with the presence of a small residual; and 8 patients were followed up at another institution.

It was possible to follow up the clinical outcome in 95.0% of the patients at 6 weeks, and 60.2% of the patients at ≥ 12 months. In the mean clinical follow up of 31.7 months (range, 1.6-146.4 months), no aneurysm recurrence or acute subarachnoid hemorrhage was noted in 272 person years of follow-up.

Table 7.2 Surgical procedures and outcomes for unruptured ACoA aneurysms

	Total	Permanent Morbidity, n (%, 95%CI)
No. Of Procedures, n	103	6 (5.8, 2.5-12.4)
Clipping	99	4 (4.0, 1.3-10.3)
Clip and suture	3	2 (66.7, 20.2-94.4)
Wrap reinforcement	1	0
Use of temporary clipping	56	5 (8.9, 3.5-19.7)
<10 minutes duration	44	2 (4.6, 0.4-16.0)
10-20 minutes duration	7	1 (14.3, 0.5-53.4)
>20 minutes duration	5	2 (40.0, 11.6-77.1)
Complications		
Acute confusion	3	0
Acute memory loss	1	0
Extradural haematoma	2	0
Anosmia	4	0
CSF rhinorhea	1	0
Intraoperative aneurysm rupture	1	0
Ischemia/Infarction and permanent memory loss	6	6 (75.0, 40.1-93.7)

ACoA, anterior communicating artery

Specific Subgroup of Patients with Surgical Complications

When patient age and aneurysm size were combined and compared for the primary end point of procedure-related permanent morbidity, the following subgroups of patients and their results were considered: group 1 (age ≤50, aneurysm ≤15mm), 0% (0/29); group 2 (age ≤50, aneurysm >15mm), 25.0% (1/4); group 3 (age>50, aneurysm ≤15mm), 3.3% (2/61); and group 4 (age >50, aneurysm >15mm), 33.3% (3/9). For aneurysm sizes ≤15mm, the risk of an unfavorable surgical result was 2.2% (95%CI 0.1-8.2). When aneurysm sizes were >15mm, surgical morbidity was 38.0% (95%CI 12.4-58.0).

Prognostic predictors of surgical outcomes

By univariate analysis (Table 7.4), prognostic factors affecting treatment outcomes included aneurysm size ($p<0.01$), male gender ($p<0.04$), calcification seen on preoperative CT imaging ($p<0.01$), and when surgical treatment other than direct clipping was required ($p<0.01$). In multivariate analysis, aneurysm size ($p<0.01$) was the only clinical factor identified as an independent predictor of outcome.

DISCUSSION

Specific treatment outcomes following surgery for unruptured ACoA aneurysms were difficult to establish from the literature as most series combined the results of both ruptured and unruptured pathologies (308, 319-323). In their series of 75 ACoA cases, Andaluz et al. reported 12 unruptured ACoA aneurysms of which surgical repairs achieved a good outcome in all patients (mRS 0 to 2) (319). Nussbaum et al. treated 76 ACoA aneurysms (46 small, 29 large and 1 giant) in their surgical experience with 450 unruptured intracranial aneurysms (324). The overall results at 6 months follow up showed 98.7% of the patients having a GOS of 1. Only one patient died because of a complication of the repair of a 6 mm ACoA aneurysm related to systemic thromboembolism. Mori reported a series of 10 patients with unruptured ACoA aneurysm treated by the lateral supraorbital keyhole approach. Based on their preliminary experience, transient morbidity occurred in 3 patients (meningitis 1 case, frontalis palsy 1 case, chronic subdural haematoma 1 case) (325). There was no permanent neurological deficit, memory disturbances, or death reported in this study.

In the current study, we analysed the surgical outcomes of 103 patients with 115 unruptured ACoA aneurysms managed over a 20-year period. Our results support the continuing role of microsurgery in treating unruptured ACoA aneurysms. In keeping with previous reports (318, 326, 327), the superior durability of microsurgical treatment as compared with endovascular coiling was demonstrated by 97.5% complete occlusion of aneurysms in the mean 28.0 months angiographic follow-up period and the absence of subarachnoid hemorrhage or late interventions in 272 person-years of follow-up. Transient procedure-related morbidity was 9.7%. There was no death in this series. Overall, new permanent neurological deficits occurred in 5.8% of the 103 patient cohorts. We found that aneurysms that were 15mm or smaller were associated with favorable surgical outcomes (2.2%), irrespective of the age of the patient. When aneurysm sizes were larger than 15mm, the risk of surgical morbidity

increased significantly (38%). The only factor that predicted a surgical outcome was related to the size of the aneurysm ($p<0.01$), with increasing aneurysm size correspondingly increases the risk of surgical morbidity.

The risk of postsurgical personality and memory disturbances ("ACoA Syndrome") following surgery for ACoA aneurysms has been previously described in a number of studies (322, 328-333). The true influence of surgery on memory functions, however, remains difficult to establish because of the confounding effect of the subarachnoid hemorrhages in these studies. To date, there has been only one study that directly compared the cognitive functioning of patients with ruptured ACoA aneurysms treated either by microsurgery (9 patients) or endovascular coiling (9 patients) (334). The findings of this study showed that patients treated with coil embolisation showed significantly fewer severe cognitive deficits as compared to those who had undergone surgical clip ligation. In our experience with repair of 115 unruptured ACoA aneurysms, the risk of causing permanent memory disturbances appears to be low [2 patients; 1.9% (95% CI 0.1-7.2)]. Therefore, the results of our study may better reflect the true effect of surgery on the cognitive function following ACoA aneurysm surgery.

At present, many ACoA aneurysms can be treated safely with endovascular coiling. However, direct comparison of outcomes between endovascular and microsurgical treatment outcomes is difficult because of the heterogeneity in study designs, patient cohorts and clinician bias (318, 335-337). Endovascular techniques remains limited for a large number of ACoA aneurysm cases because of the inherent unfavorable vascular morphology (small dome, wide neck, and multiple perforators). Table 7.5 summarises the clinical and angiographic outcomes of combined ruptured and unruptured ACoA aneurysms treated by endovascular techniques. (314, 338) What is apparent is the attempt at endovascular treatment does not reliably lead to occlusion, recurrence occurred in approximately one in four aneurysms treated and approximately half of these were deemed appropriate for retreatment. Microsurgery appears to offer a significant advantage over endovascular repairs with regards to complete occlusion at the primary procedure, reduction in retreatment and the number of residual aneurysms requiring monitoring.

LIMITATIONS OF STUDY

The current study is subjected to a number of limitations. While this being a large series of ACoA aneurysms, the results presented in this study reflects a single surgeon's operative experience over a 20-year period. Examining outcomes over an extended period of time may

be difficult to account for changes in operative techniques and technology that may impact on patient care. Microsurgical techniques and neuroanaesthesia has evolved significantly during this period of time.

Second, the lack of morphological features of aneurysm dome projection undermines the complex technical decision-making process that is involved in the management of ACoA aneurysms. Prognostic predictors and risk analysis in this study were therefore limited to aneurysm size and other related morphology.

Third, a substantial number of aneurysms in the current series did not have documented routine postoperative angiography (27%, 31/115). The reason for this was due to the assessment that the patient was unlikely to benefit from re-operation for a small residual (e.g. age greater than 70 or poor neurological outcome from surgery), the small size of the aneurysm (<6mm) at surgery allowed for great confidence that repair was successful (particularly with the advent of ICG) or follow-up by other institutions. While the inherent difficulty in obtaining follow-up images following surgical clipping is noted (304, 339) the results regarding the clinical course of aneurysm remnant in this series must be interpreted with reservations.

CONCLUSION

Surgical repairs of unruptured anterior communicating artery aneurysms resulted in 5.8% morbidity and 0% mortality. The superior durability of surgical clip ligation as compared with alternative treatment methods is an important consideration. For patients with aneurysms less than 15mm diameter, the permanent morbidity related to surgical repairs was 2.2%. Microsurgical repair of unruptured ACoA aneurysms is a reasonable option when treatment is deemed appropriate. Because of the continuing evolving techniques and change of aneurysm practice, a randomized control study would be very difficult. However, a registry of aneurysm outcomes and action research on such a registry would enhance our understanding of the wise choice of aneurysm treatments.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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Table 7.3 Surgical morbidity in patients with unruptured ACoA aneurysms

Sex/Age, y	Size, mm	Procedure and temporary clipping time, min	Postoperative mRS	Complication
F/50	17.5	Clip, 5-10	3	Left recurrent artery of Heubner infarction resulting in aphasia and right hemiparesis
M/64	25.5	Suture and clip, >20	3	Right anterior cerebral artery infarction
M/79	11.5	Clip, 5-10	3	Severe memory loss from presumed hypothalamic infarction
M/60	17.5	Clip, 0	3	Right anterior cerebral artery infarction
M66	21.5	Suture and clip, >20	4	Right recurrent artery of Heubner infarction
M/74	9.5	Clip, 10-20	3	Severe memory loss and Right ACA infarction

mRS, modified Rankin Score; ACoA, anterior communicating artery; MCA, middle cerebral artery; ICA, internal carotid artery; CCA, common carotid artery; CSF, cerebrospinal fluid

Table 7.4 Logistic regression analyses of prognostic factors based on surgical treatment of 115 unruptured ACoA aneurysms

	Odds Ratio	95% CI	*p* Value
Univariate analysis			
Age > 50 years	3.39	0.38-29.97	0.27
Size <10mm	0.04	0.01-0.34	<0.01
Size 10-20mm	7.39	1.35-40.50	<0.03
Size >20mm	13.13	1.83-94.05	<0.01
Male	10.14	1.14-90.04	<0.04
Bubbles or 'Blebs' on CT	1.80	0.35-9.32	0.49
Calcium on CT	17.67	2.28-137.08	<0.01
Temporary clipping	5.69	0.64-50.29	0.12
Direct clipping	0.30	0.05-1.76	0.18
Non-direct clipping	26.75	2.97-241.29	<0.01
Multivariate analysis			
Size <10mm	0.04	0.01-0.37	<0.01

CT, computed tomography; ACoA, anterior communicating artery

Table 7.5 Literature review on endovascular outcomes of ACoA aneurysm series that incorporate unruptured aneurysms

Author & year	No. of aneurysms	No. of unruptured aneurysms (%)	Uncoilable (%)*	Procedure-related permanent morbidity (%)*	Procedure-related mortality (%)*	Complete occlusion (%)*	Recurrence (%)*	Retreatment (%)*
Moret et al., 1996	36	16.7	19.4	3.4	0.0	79.3	na	na
Birknes et al., 2006	123	8.1	9.8	0.9	0.0	91.9**	33.3	na
Finitsis et al., 2009	282	14.6	4.3	7.0	4.4	29.5	25.2	11.5
Guglielmi et al., 2009	306	22.9	3.9	3.6	1.0	45.4	23.2	23.2

*Outcomes reported are combined ruptured and unruptured aneurysms of the entire series; **defined complete as >95% aneurysm dome occlusion; na, data not available; ACoA, anterior communicating artery.

CHAPTER 8

THE IMPORTANCE OF ANTERIOR CHOROIDAL ARTERY PRESERVATION DURING THE SURGICAL CLIP RECONSTRUCTION FOR UNRUPTURED POSTERIOR COMMUNICATING ARTERY ANEURYSMS

PREFACE TO CHAPTER 8

This chapter examines the surgical outcomes following repair of unruptured posterior communicating artery aneurysm surgery and considers the importance of preserving the anterior choroidal artery in the elective treatment of these types of aneurysms. The data presented here is based on the senior author's (MKM) extensive surgical experience in treating unruptured intracranial aneurysms. This study was approved by the Macquarie University Human Ethics Committee, and was conducted in accordance with institutional ethics committee guidelines (ethics reference number: HE26SEP2008-R06107)

This chapter will be submitted for publication.

AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: The morbidity of anterior choroidal artery (AChA) injury following surgical treatment of posterior communicating artery (PCoA) aneurysms is well recognised. We defined the risks of AChA injury in a contemporary surgical series with unruptured PCoA aneurysms and discussed operative strategies that may overcome this challenge.

METHODS: A consecutive case series of unruptured PCoA aneurysms (prospectively collected data) was retrospectively analysed for the period between May 1992 and September 2012. Clinical results, operative complications, angiographic outcomes and prognostic factors associated with surgery are presented.

RESULTS: Of the 121 patients with 128 unruptured PCoA aneurysms that were surgically repaired in 122 procedures, 9 [7.4%; 95% confidence interval (CI), 3.8 to 13.6] experienced a new permanent adverse outcome. Seven of these patients were related to anterior choroidal artery infarction (incidence 5.7%; 95%CI 2.6-11.6). There was no postoperative mortality. Transient morbidity occurred in 10 patients (8.2%; 95% CI, 4.4 to 14.6). Oculomotor nerve recovery was observed in 12 patients (92.3%; 95% CI, 64.6-100.7). Of the 97 aneurysms (75.8%) that had documented postoperative angiography, 96 (99.0%) had complete aneurysm occlusion and 1 (1.0%) had neck remnant (mean angiographic follow-up 27.2 months; range, 1.6-210.3 months). There was no incidence of subarachnoid hemorrhage in the 296 person years of follow-up. Multivariate regression analysis of risk factors revealed that simple aneurysms (size $\leq$ 15mm, no calcification) when repaired by direct surgical clip reconstruction were associated with a favorable outcome (3.0% permanent morbidity; 95% CI, 0.6-8.7%).

CONCLUSION: Surgery remains an effective and robust treatment option. Great vigilance is required to preserve the AChA during the surgical clip reconstruction of unruptured PCoA aneurysms. The robustness of open aneurysm clip reconstruction is an important consideration when considering the option between endovascular and microsurgical treatment of unruptured posterior communicating artery (PCoA) aneurysms.

INTRODUCTION

The anterior choroidal artery (AChA) is the most important branch associated with the posterior communicating artery (PCoA) aneurysm, lying adjacent to its distal neck. The AChA provides critical blood flow to the optic tract, lateral thalamus, the genu and posterior limb of the internal capsule. Injury to this critical vessel can render the patients with devastating postoperative neurological deficits including hemiparesis, hemisensory loss and hemianopia.

The drift towards endovascular treatment in recent years has inherently changed the complexity and profiles of aneurysms that are presently referred for surgical repair. For PCoA aneurysms, this equate to larger size aneurysms, presence of calcification, presence of coils, and unfavorable morphology. The consequences of AChA injury can be devastating and great vigilance must be given to the preservation of this vessel during the surgical clip reconstruction of PCoA aneurysms. In the present study, we examined the surgical and angiographic outcomes in a consecutive series of unruptured PCoA aneurysms. The purpose of this investigation was to identify the risk of permanent adverse outcome due to AChA infarction and to offer operative strategies that may overcome this challenge.

METHODS

Clinical Material

This study was approved by the Macquarie University Human Ethics Committee and was conducted in accordance with institutional ethics committee guidelines. All patients who underwent surgical repair of unruptured PCoA aneurysms by the senior author (MKM) between May 1992 and September 2012 were eligible for review. Data were collected prospectively in a specifically designed aneurysm database that included demographic, clinical, radiological and treatment-related information. All aneurysms were diagnosed through magnetic resonance angiography (MRA), high-resolution three-dimensional computed tomography (CT) angiography, or digital subtraction angiography (DSA). We defined PCoA aneurysms as lesions that arise from the internal carotid artery (ICA) segment between the origin of the ophthalmic artery and the anterior choroidal artery (AChA). Mycotic, traumatic and dissecting aneurysms were excluded from the analysis. To minimise the confounding effects of multiple aneurysm surgery, patients who were treated in conjunction with aneurysms at locations other than PCoA during the same operative session

were also excluded. The size of the aneurysm dome was categorized according to the ISUIA study criteria into <7mm (small), 7-12mm (medium), 13-24mm (large), and ≥25mm (giant) (243).

Technical Consideration

Surgical approach to the aneurysms was generally performed through a one-piece orbitozygomatic exposure, incorporating the removal of both the lateral roof and superior lateral wall of the orbit. This enables an angle that usually negates the need for a fixed brain retraction. The chiasmatic cistern is opened and fenestration of the lamina terminalis is often performed to facilitate brain relaxation by CSF drainage. In most cases, a wide Sylvian fissure dissection is performed to separate the frontal and temporal lobes. This allows for the visualisation of the communicating segment of the ICA and proximal M1 segment of the middle cerebral artery (MCA). Proximal control of the aneurysm was gained by opening the apex of the optic-carotid triangle, and when required, opening of the falciform ligament to widen the interval between the ICA and the optic nerve. Surgical techniques, complexity of surgery, and the use and duration of temporary clipping were noted. The arterial reconstructions varied and were classified as: simple clipping; suture repair of aneurysm supplemented with clipping; or wrap reinforcement with Teflon.

Aneurysms were considered simple when they incorporate the following combined features: (1) size 15mm or less; (2) there was no associated calcification in the aneurysm dome; and (3) repair was achieved by direct clipping without the need for temporary clip occlusion. Aneurysms were considered complex when they contain any of the following characteristics: (1) size more than 15mm; (2) previous treatment with endovascular coils; (3) calcifications at the aneurysm neck or in the parent vessel; (4) at least 10 minutes of temporary occlusion time was required; or (5) when treatment other than direct clipping (such as surgical trapping, suturing of the aneurysm or bypass graft reconstruction) was required.

Outcome Assessment

Clinic visits were routinely scheduled at 6 weeks and at 1 year following surgery. It is not our routine practice to perform intraoperative angiography. Typically, patients underwent a postoperative CTA or DSA within the 6 weeks postoperative period or at 1 year follow up.

Aneurysm occlusion was classified as complete, minimal residual aneurysm (small neck remnant or dog-ear) or incomplete (less than 95% aneurysm dome occlusion).

The modified Rankin Score (mRS) of individual patients was assessed preoperatively, at 6 weeks following surgery, and at the final clinical review. For patients to be considered to have an unfavorable surgical outcome, they were required to have both a new permanent neurological deficit attributed to surgery or angiography remaining present at the 6 weeks postoperative visit and a mRS greater than 1 at the last postoperative visit. If a neurological deficit related to surgery had been determined at the 6-week review, the mRS of the last review was used as the basis for this report. We excluded patients with a mRS of 1, as all patients have scalp paraesthesia and a substantial number have some degree of temporalis muscle wasting that would result in a mRS of 1. We used the risk of surgical complication per operation rather than per individual aneurysm or patient. This decision was based on an attempt to incorporate cases of multiple aneurysms and multiple surgeries.

Statistical Analysis

The Pearson correlation test was used to analyse correlations between variables studied. Univariate logistic regression analysis was used to determine which of the many factors should be entered into the multivariate analysis. Variables associated with an unfavorable surgical outcome in univariate analyses ($P<0.20$) were included in a forward, stepwise, multivariate logistic regression. Odds ratios (ORs) were calculated with a 95% confidence interval (CI). The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations. A *p* value of less than 0.05 was considered statistically significant. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Between May 1992 and September 2012, the senior author (MKM) has surgically treated 225 patients with 247 PCoA aneurysms. One hundred four patients with 119 aneurysms were excluded due to acute subarachnoid hemorrhages (86 patients) and multiple aneurysms surgeries (18 patients). This resulted in a total of 121 patients with 128 unruptured PCoA

aneurysms included for review in the current study. Patient and aneurysm characteristics have been detailed in Table 8.1.

Surgical Procedures

One hundred twenty-two craniotomies were performed, including 118 procedures (96.7%) for direct surgical clipping. Details of the surgery and outcomes are summarised in Table 8.2. Suture repair supplemented with clipping was performed in a case of a giant aneurysm. Two patients required surgical trapping procedures supplemented with a planned saphenous vein extracranial-intracranial (EC-IC) bypass. One aneurysm of 1 to 2mm diameter was treated with wrap reinforcement using Teflon. Temporary clipping was performed in 29 operations (23.8%). Temporary clipping duration was less than 10 minutes in 21 patients, 10-20 minutes in 6 patients, and greater than 20 minutes in 2 patients. Intraoperative aneurysm rupture occurred in 1 of the 122 procedures (0.8%), but did not lead to a postoperative morbidity.

Morbidity

There was no mortality in this series (upper 95% CI 3.7%). Morbidity is tabulated in Table 9.2 and permanent morbidity detailed by case in Table 8.3. Transient morbidity following surgery occurred in 10 patients (8.2%; 95% CI, 4.4 to 14.6). The two patients with postoperative extradural haematoma required prompt return to theatre for urgent evacuation. No permanent neurological deficits occurred in these two patients. CSF rhinorrhoea was recognised in 1 patient, which was surgically repaired on day 12 following the initial craniotomy. No cases of meningitis had occurred. One patient developed new partial oculomotor nerve palsy postoperatively, which spontaneously resolved by the 6 weeks review at clinic. Acute hydrocephalus not requiring a permanent ventriculoperitoneal shunt placement occurred in one case. Asymptomatic postoperative ischemic complications occurred in 4 patients. No postoperative seizures occurred in this series of patients.

Permanent neurological deficit following surgery was encountered in 9 patients (7.4%; 95%CI, 3.8-13.6) as a result of vessel occlusions leading to cerebral infarctions (anterior choroidal artery territory infarct in 7 patients; posterior cerebral artery territory infarct in 1 case) and hydrocephalus requiring the placement of ventriculoperitoneal shunts (2 cases).

Oculomotor Nerve Palsy

Fifteen patients presented with oculomotor nerve palsy (14 complete and 1 partial paralyses). At a mean clinical follow-up of 23.7 months (range, 2.4-159.6 months) following surgery, 9 patients (69.2%) had complete resolution of their cranial nerve palsy. Three patients had partial recovery (23.1%) and 1 patient (7.7%) with initial complete oculomotor nerve palsy remained unaffected by surgery. There were 2 patients that were lost to follow up due to poor neurological recovery requiring nursing home admission (1 patient) and age older than 80 years (1 patient).

Angiographic and Long-term Outcomes

Ninety-seven (75.8%) aneurysms had documented postoperative angiography with a mean follow up of last angiographic study of 27.2 months (range, 1.6-210.3 months). Of these cases, angiography confirmed 96 (99.0%) aneurysms with complete obliteration and 1 (1.0%) with a small residual neck remnant. This case was monitored without further intervention.

In the current series, 29 patients with 31 aneurysms (24.2%) did not have documented postoperative angiography. Among them, 17 patients with 19 aneurysms were treated for sizes less than 6mm and were thought to be confidently repaired at the time of surgery; 2 patients were older than 70 years of age and were thought not likely to benefit from further surgery if a small residual were to be detected; 2 patients had neurological deficits that were thought not likely to recover from and were sufficiently profound to believe further surgery would be unwarranted even with the presence of a small residual; and 8 patients were followed up at another institution.

It was possible to follow up the clinical outcome in 95.0% of the patients at 6 weeks, and 61.2% of the patients at ≥ 12 months. In the mean clinical follow up of 29.3 months (range, 1.6-210.3 months), no aneurysm recurrence or acute subarachnoid hemorrhage was noted in 296 person years of follow-up.

Specific Subgroup of Patients with Surgical Complications

When various patient and aneurysm characteristics were combined and compared for the primary end point of procedure-related permanent morbidity (Table 8.4), the following

subgroups and their results were: simple aneurysms 3.0% (3/101); complex aneurysms, 16.7% (6/36); age 50 years or less with simple aneurysms, 2.8% (1/36); age more than 50 years with simple aneurysms, 3.5% (2/58); age 50 years or less with complex aneurysms, 9.1% (1/11); and age more than 50 years with complex aneurysms, 20.8% (5/24). Among these factors, only simple aneurysms maintained statistical significance when adjusted in a multivariate analysis ($p<0.01$).

DISCUSSION

Increasingly, unruptured intracranial aneurysms (UIAs) are being preferentially treated by endovascular techniques despite a lack of direct and robust evidence to support this change (121, 192, 270, 340, 341). Although the International Subarachnoid Aneurysm Trial (ISAT) and the Barrow Ruptured Aneurysm Trial (BRAT) were carried out to examine the efficacy of coiling versus clipping for ruptured intracranial aneurysms (125, 247, 342), the results have been extrapolated to justify the endovascular treatment for unruptured lesions. In recent years, data have been collated and examined in systematic reviews to investigate the immediate and long-term outcomes of endovascular treatment of UIAs (336, 343, 344). From these efforts, evidences reinforced an inferior durability of repair as achieved by coil embolisation, with the risk of bleeding following treatment remains relatively unaltered as compared to the original unruptured natural history (344).

In the current study, we analysed the surgical outcomes of 121 patients with 128 unruptured PCoA aneurysms managed over a 20-year period. Our results support the continuing role of microsurgery in treating unruptured PCoA aneurysms. In keeping with previous reports (318, 326, 327), the superior durability of microsurgical treatment as compared with endovascular coiling was demonstrated by 99% complete occlusion of aneurysms in the mean 27 months angiographic follow-up period and the absence of subarachnoid hemorrhage or late interventions in 296 person-years of follow-up. Transient procedure-related morbidity was 8.2%. There was no death in this series. Overall, new permanent neurological deficits occurred in 7.4% of the 121 patient cohorts. We found that when simple aneurysms were reconstructed with simple direct clipping, surgical outcomes were favorable (3%). As aneurysms became complex, the risk of permanent morbidity following surgical repair increased substantially (17%). The influence of patient's age, however, did not seem to affect the outcomes of surgery.

Of the 9 cases with permanent postoperative neurological deficit, 7 were related to an anterior choroidal artery territory infarction. Dense adhesions and thin aneurysm wall can make for difficult and risky dissection of the AChA from the aneurysm dome. This is particularly so when the dome is large or giant in size. Of the 7 cases of AChA territory infarctions encountered in this study, 5 (71%) were at least 15mm in diameter. Temporary clipping to soften the aneurysm and facilitate dissection, however, were not judiciously used in these cases. These complications underscore the importance of definitive dissection of the AChA from the aneurysm dome and the liberal use of temporal clip occlusion prior to definitive application of the clip.

Basic microsurgical techniques, however, are inadequate to treat complex PCoA aneurysms. Complex clipping techniques, bypass and reconstruction of the terminal ICA and direct PCoA to AChA end-to-end anastomosis have been utilized in our experience. Wherever possible, direct clip reconstruction with the aim to preserve flow in the AChA should be attempted first. This may require the use of multiple clips or fenestrated clips, but the emphasis should be in the inflow angle of the AChA. Care is taken not to bend the angle so that it kinks off.

For large or giant aneurysms, we recommend trapping of the PCoA segment and using a bypass reconstruction to turn the terminal ICA in a way that has the AChA as the end artery.

Finally, the PCoA and AChA may be directly joined together via an end-to-end anastomosis.

The development of oculomotor nerve palsy in a patient with unruptured PCoA aneurysm represents the possibility of aneurysm expansion demanding prompt intervention (345). Open surgical clip reconstruction offers the option of cranial nerve decompression and evacuation of the aneurysmal mass effect (346-354). Endovascular coiling may not alleviate the effect of a space-occupying lesion, but may eliminate aneurysmal pulsation as one possible cause of the oculomotor paresis (347, 352, 355-357). While both surgical and endovascular treatments have been associated with the recovery of the oculomotor nerve palsy, surgery seems to provide in a greater chance of recovery (358). In keeping the reports in the literature, we observed a 92% incidence of oculomotor paresis recovery following surgical treatment. One new case of transient partial oculomotor nerve palsy was observed in the present study as a result of intraoperative manipulation.

Although the current study did not address the issue of patient selection, it demonstrated the benefits of surgery for small to moderate size aneurysms with a better robustness of repair as compared to endovascular treatment.

LIMITATIONS OF STUDY

The current study is subjected to the limitation of a single-surgeon, single-center, retrospective review of surgical results. Examining outcomes over an extended period of time may be difficult to account for changes in operative techniques and technology that may impact on patient care. The potential confounding in a retrospective analysis of a case series is not fully compensated by the use of multivariate analysis. Microsurgical techniques and neuroanaesthesia has evolved significantly during this period of time.

Second, the lack of morphological features of aneurysm dome projection undermines the complex technical decision-making process that is involved in the management of ACoA aneurysms. Prognostic predictors and risk analysis in this study were therefore limited to aneurysm size and other related morphology.

However, this information is lacking in the current study, which undermines the complexity that would have been involved during surgery.

Third, a substantial number of aneurysms in the current series did not have documented routine postoperative angiography (27%). The reason for this was due to the assessment that the patient was unlikely to benefit from re-operation for a small residual (e.g. age greater than 70 or poor neurological outcome from surgery), the small size of the aneurysm (<6mm) at surgery allowed for great confidence that repair was successful (particularly with the advent of ICG) or follow-up by other institutions. While the inherent difficulty in obtaining follow-up images following surgical clipping is noted by some authors (304, 339) the results regarding the clinical course of aneurysm remnant in this series must be interpreted with reservations.

CONCLUSION

The robustness of aneurysm repair achieved by open microsurgery is an important consideration when considering the option between endovascular and microsurgical treatment for unruptured PCoA aneurysms. In particular, for younger age patients with small to moderate size aneurysms, surgery should remain the treatment of choice.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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Table 8.1 Patient and aneurysm characteristics for unruptured PCoA aneurysms

Characteristics	Value
No. of Patients, n (%)	121
Female/male (ratio)	100/21 (4.8:1)
Age, mean ± SD (range), years	55.9 ± 12.3 (27-85)
Multiple PCoA aneurysms	6 (5.0)
Clinical presentations, n (%)	
Incidental	56 (46.3)
Headache	19 (15.7)
Oculomotor nerve palsy	15 (12.4)
Previous SAH	9 (7.4)
Family history screening	11 (9.1)
Residual from previous coiling	6 (5.0)
Seizures	2 (1.7)
Visual field loss	3 (2.5)
No. of Aneurysms, n (%)	128
Size, mean ± SD (range), mm (%)	7.7 ± 5.6 (1.5-25.5)
<7mm	81 (63.3)
7-12mm	24 (18.8)
13-24mm	20 (15.6)
≥25mm	3 (2.3)
Left/Right	57/71
Presence of calcium	9 (7.0)
Presence of bubbles or blebs	45 (35.2)
Previous Guglielmi Detachable Coil treatment	8 (6.3)

PCoA, posterior communicating artery; SD, standard deviation; CT, computed tomography

Table 8.2 Surgical procedures and outcomes for unruptured PCoA aneurysms

	Total	Permanent Morbidity, n (%, 95%CI)
No. Of Procedures, n	122	9 (7.4, 3.8-13.6)
Clipping	118	8 (6.8, 3.3-13.0)
Clip and suture	1	1 (100, 16.8-103.9)
Clip and bypass	2	0
Wrap reinforcement	1	0
Use of temporary clipping	29	3 (10.3, 2.8-27.2)
<10 minutes duration	21	2 (9.5, 1.5-30.1)
10-20 minutes duration	6	1 (16.7, 1.1-58.2)
>20 minutes duration	2	0
Use of a contralateral approach	5	0
Complications		
Intraoperative aneurysm rupture	1	0
CSF rhinorrhoea	1	0
Extradural haematoma	2	0
New postoperative oculomotor nerve palsy	1	0
Hydrocephalus	3	2 (66.7, 20.2-94.4)
Ischemia/Infarction	11	7 (46.7, 24.8-69.9)

PCoA, posterior communicating artery

Table 8.3 Surgical morbidity in patients with unruptured PCoA aneurysms

Sex/Age, y	Size, mm	Procedure and temporary clipping time, min	Year of Surgery	Postoperative mRS	Complication
F/76	5.5	Clip, 10-20	1993	3	Posterior cerebral artery territory infarction and hydrocephalus
M/58	15.5	Clip, 0	1994	2	Anterior choroidal artery territory infarction
M/40	25.5	Suture & clip, 10-15	1994	2	Anterior choroidal artery territory infarction
F/67	19.5	Clip, 5-10	1995	3	Anterior choroidal artery territory infarction
F/59	9.5	Clip, 0	1999	3	Anterior choroidal artery territory infarction
F/71	15.5	Clip, 0	2001	2	Anterior choroidal artery territory infarction
F/64	7.5	Clip, 0	2002	2	Shunt dependent Hydrocephalus
F/38	9.5	Clip, 5-10	2003	3	Anterior choroidal artery territory infarction
F/70	15.5	Clip, 0	2006	3	Anterior choroidal artery territory infarction

mRS, modified Rankin Score; PCoA, posterior communicating artery

Table 8.4 Logistic regression analyses of prognostic factors based on 122 operations for the management of unruptured PCoA aneurysms

	Permanent Morbidity, n (%, 95%CI)	OR (95%CI)	*p* value
Univariate analysis			
Simple aneurysms	3 (3.0, 0.6-8.7)	0.11 (0.03-0.46)	<0.01
Complex aneurysms	6 (16.7, 7.5-32.3)	5.93 (1.40-25.20)	0.02
Age≤50, simple aneurysms	1 (2.8, 0-15.4)	0.30 (0.04-2.49)	0.27
Age>50, simple aneurysms	2 (3.5, 0.3-12.4)	0.32 (0.06-1.61)	0.17
Age≤50, complex aneurysms	1 (9.1, 0-39.9)	1.36 (0.15-12.02)	0.78
Age>50, complex aneurysms	5 (20.8, 8.8-40.9)	6.58 (1.62-26.77)	0.01
Multivariate analysis			
Simple aneurysms	2 (2.3, 0.1-8.6)	0.11 (0.03-0.60)	<0.01

PCoA, posterior communicating artery

CHAPTER 9

SMOKING INCREASES THE RISK OF DE NOVO INTRACRANIAL ANEURYSMS

PREFACE TO CHAPTER 9

This chapter examines the risk for the development of de novo intracranial aneurysms after surgical treatment when surveillance angiography (by CT scan or MRI) was routinely performed at intervals of two to five years. A history of smoking increases the risk of de novo aneurysm detection. The current study underscores the importance of routine surveillance angiography following aneurysm treatment for the detection of de novo aneurysms for the appropriate treatments to be implemented.

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AUTHOR'S CONTRIBUTION

Dr Lai and Professor Morgan conceived and designed the study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai and Professor Morgan. Dr Patel assisted in the literature review during the conception of this manuscript. The manuscript was written and revised by Dr Lai and Professor Morgan. Dr Lai, Professor Morgan and Dr Patel approved the final version for publication.

ABSTRACT

OBJECTIVES: Case series have identified that de novo intracranial aneurysms occur. However, the risk for this occurrence has not been established. We examined the risk for the de novo intracranial aneurysm detection in a consecutive surgical case series.

METHODS: A prospectively collected surgical database of intracranial aneurysms was retrospectively examined. Patients were analysed if they were followed for more than 6 months post-operatively with angiography. Kaplan-Meier curve analysis of de novo aneurysms detection included comparing: smoking versus never smoked; those with and without a family history; single versus multiple aneurysms at initial presentation; and original presentation with rupture versus non-rupture.

RESULTS: Of the 1,366 surgically treated patients (1,942 aneurysms), 472 patients (702 aneurysms) were followed with angiography for more than 6 months (average 54 months). Thirty-three patients (6.99%) were detected to have de novo aneurysms. Multivariate analysis found a smoking history significantly increases the likelihood of de novo aneurysm detection. Kaplan-Meier analysis found the five and ten-year de novo aneurysm detection rate to be 4.21% (95% CI 3.86-12.8) and 15% (95% CI 10-16) respectively. A smoking history increases the five and ten-year detection rate to 5.81% and 17% (HR 2.58; 95% CI 1.13-5.90) respectively. No increased risk was present for an initial presentation that included multiple aneurysms, a family history, or rupture.

CONCLUSION: There is a ten-year de novo aneurysm detection rate of between 10% and 16% following surgery. Smoking increases the risk of de novo aneurysm detection. Consideration needs to be given to surveillance angiography following aneurysm treatment.

INTRODUCTION

The potential for the development of de novo aneurysms after successful repair of intracranial aneurysms is well reported (90, 125, 304, 359-372). However, the risk for this development is not reliably known and therefore, there are no generally accepted recommendations for surveillance protocols with regards to the detection of de novo aneurysms. Establishing such a protocol is appropriate if: the risk for de novo aneurysms formation were known; de novo aneurysms present a risk of rupture; there was an opportunity to identify de novo aneurysms before rupture; and treatment of de novo aneurysms can be proven to be successful. At present, from case series (that allow a calculation of the incidence of de novo aneurysms and period followed from initial treatment) it is possible to estimate a crude risk of de novo aneurysm development that ranges from less than 0.3% risk per year (90, 125, 361, 364-368, 371, 372) to greater than 1% risk per year (360, 362). However, none of these studies utilized Kaplan-Meier techniques, few have a rigorous protocol of surveillance after treatment and many only detected rupture de novo rates. There is no population-based study that looks at the risk of de novo aneurysm formation. Therefore, there is little evidence to support any particular surveillance protocol from the current state of the literature.

The present study was performed to determine the risk of de novo aneurysm development after surgical treatment of an aneurysm. We examined both the literature and a prospectively collected database of a case series where a protocol was in place recommending patients have angiography [with computed tomography angiography (CTA) or magnetic resonance angiography (MRA)] at two to five year intervals following surgery. This research has the limitation of case series in that it is very context specific. As much as possible, we have provided additional information that will permit the identification of the patient that this data most appropriately applies.

METHODS

Literature Review

A combined Medline and EMBASE search was conducted to identify studies reporting outcomes on de novo intracranial aneurysm formation following surgery, endovascular intervention or observation. The following key words as MESH terms and text words were used in Medline: “intracranial aneurysm” in combination with “AND” “additional”, “new” and “novo” and in “OR” combinations. Results were narrowed to studies in which: (1) the

annual risk of de novo aneurysm formation can be determined; (2) there was a large sample size (>40 patients); (3) there was a long-term angiographic follow up (>12 months); and (4) the articles were written in English. Case reports or literature review of case reports were excluded from this review. A parallel search was run in the EMBASE, where journal coverage is slightly different. The abstracts of all papers meeting the aforementioned criteria were considered and the full text of relevant papers was evaluated for inclusion in this report. Bibliographies and cited references of key studies were also retrieved and relevant full texts were examined for possible inclusion.

Patient Population

This study was approved by the Macquarie University Human Ethics Committee and was performed in accordance with institutional ethics committee guidelines. A prospectively collected database of the senior author (MKM) containing consecutive patients was retrospectively analysed for the years 1991 to 2012. The database contained demographic, clinical, radiological and treatment-related information. Supplemental information was obtained from patient charts, operative notes, and radiological reports.

All patients had digital subtraction angiography (DSA) or CTA prior to treatment. The postoperative management protocol includes a CTA or DSA within the first six weeks and a CTA at one year. Follow-up imaging beyond one year was dependent upon the clinical status and preference of the patient as well as the recommendation of the surgeon but was recommended to be every two years for those considered at higher risk (including family history, multiple aneurysms or a history of smoking) or at five years for those without a perceived increased risk. Older patients were less likely to be routinely followed with radiological investigations because of the perceived lower likelihood of benefit of the diagnosis of an unruptured aneurysm. To be considered a de novo aneurysm, the aneurysm had to be located at a site remote from the original aneurysm and not identified on the original preoperative and immediate postoperative angiograms. In this study, we focused on patients with imaging beyond six months following surgery.

Patients were excluded if they: (1) did not have radiological studies (DSA, CTA or MRA) at six months or beyond; (2) had a mRS of >2 at last follow-up; (3) had aneurysm(s) other than saccular at their original presentation; and (4) were followed up elsewhere. The baseline

selected variables of each of these four excluded groups were compared with those of the cohort studied.

Statistical Analysis

From the literature review, where possible, a de novo aneurysm rate was recalculated from the data. The recalculated annual risk of bleeding (using the methodology of many the papers identified) was calculated (or recalculated) by dividing the number of de novo cases by the product of the mean follow-up in years and the number of cases. The modified Wald method was used to calculate the 95% confidence interval (CI) for a proportion (www.graphpad.com/quickcalcs/) for the recalculated annual risk of de novo aneurysm formation.

Kaplan-Meier curves were generated for those postoperative aneurysm cases followed for six months or more with radiological investigations for detecting first de novo aneurysms, comparing: (a) a history of cigarette smoking (at any time) with never smoked; (b) those with and without an original presentation with multiple aneurysms; (c) those with and without a family history; and (d) those with and without an original ruptured aneurysm presentation. The log-rank (Mantel-Cox) test was used to examine the difference between the curves. Cox regression was used to calculate the hazard ratio for a history of smoking and 95% CI. Analyses were carried out in Prism 5 for Mac OS X (GraphPad Software, Inc).

Comparisons unrelated to the Kaplan-Meier curves and Cox regression utilized Chi square test or two-tailed Student's unpaired t-test. Where appropriate, significance was set to a probability value of 0.05.

Univariate logistic regression analysis was used to determine which of the many factors should be entered into the multivariate analysis. Multivariate logistic regression analysis was performed to identify independent predictors for the development of de novo intracranial aneurysms. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations other than Kaplan-Meier curve generation.

RESULTS

Literature Review of de novo Aneurysm detection

Seventeen studies were found meeting the criteria of the literature search. In seven of these studies, each de novo aneurysm was diagnosed without presentation with rupture. Three of these seven studies were conducted on a mixture of both ruptured and unruptured initial presentations. There were significant differences amongst the reports for the risk for de novo aneurysms (Table 9.1; X^2 = 338.9; p<0.001). The recalculated annual risk of de novo aneurysm formation ranged from 0.02% to 1.81% (90, 125, 304, 359-372). Risk factors for new aneurysm formation were assessed in 4 studies. Smoking was a predictor for de novo aneurysm formation in 2 studies (361, 366). For the study of Juvela et al. smoking was significantly related to de novo aneurysm formation in a cohort of Finnish patients (362). For the study of Wermer et al., smoking was significantly related to de novo aneurysms or aneurysm growth in cases of aneurysmal subarachnoid hemorrhage (366). Other significant predisposing factors associated with the formation of de novo intracranial aneurysms were claimed for female gender (361), multiple aneurysms (304, 366), and follow up duration of more than 9 years (363).

Clinical Case Series

Between 1991 and August 2012, the senior author (MKM) has surgically treated 1,366 patients with 1,942 intracranial aneurysms. There were 922 (67.5%) females and 444 (32.5%) males (mean age 52.0 years; range 0.2-93 years). Four Hundred thirty nine (32.1%) patients with 462 aneurysms presented with acute subarachnoid hemorrhage.

The analysis was performed for 472 patients with 702 aneurysms. Table 9.2 provides selected baseline variables of the four excluded groups and the cohort included in the analysis. Comparisons were made between the cohorts analysed in this study with each of the groups excluded from analysis. The variables compared were: gender distribution; age of initial presentation; distribution between anterior and posterior locations; presentation with rupture; and aneurysm size. There were significant differences for each of these variables in each of the excluded groups as compared with the cohort analysed with the exception of aneurysm size in those who were followed clinically but did not have angiographic follow-up beyond 6 months.

Thirty-three patients (6.99% of the cohort studied) with 46 de novo intracranial aneurysms were identified (baseline characteristics reported in Table 9.3). Thirty patients were detected as unruptured lesions on routine follow-up imaging (CTA, MRA or DSA). Three patients presented with rupture of a de novo aneurysm.

A search for predisposing factors suggested that a history of smoking (p=0.03), and presentation with rupture (p=0.04) at initial presentation were associated with de novo aneurysm formation (Table 9.3). When the risk factors were adjusted in a multivariate analysis, a history of having smoked was the only variable that maintained statistical significance (p=0.03).

The five and ten year recurrence rates by Kaplan Meier analysis were respectively 4.21% (95% CI 3.86-12.8) and 15% (95% CI 10-16) (Table 9.4). Four Kaplan Meier comparisons were made (Figure 9.1): smoking versus never smoked; those with and without a family history; single versus multiple aneurysms at initial presentation; and original presentation with rupture versus non-rupture. The number of cases where data was omitted can be deduced from the number at risk. A smoking history was associated with a five and ten year de novo aneurysm detection rate of 5.81% and 17% (Hazard ratio 2.58; 95% CI 1.13-5.90) respectively. An absence of smoking history had a five and ten year de novo aneurysm detection rate to be 3% and 13% respectively. No increased risk was present for an initial presentation that included multiple aneurysms, a family history, or rupture.

DISCUSSION

The importance of performing investigations for the purpose of discovering de novo aneurysms rests on the following premise that: the risk for de novo aneurysms formation is significant; de novo aneurysms present a risk of rupture; there is an opportunity to identify de novo aneurysms before rupture; and treatment of de novo aneurysms can be proven to be successful. The reported incidence for de novo aneurysm formation averaged 1.7% of the analysed case series (90, 125, 304, 359-372).

The great variability in this incidence (from less than 0.3% to 20%) cannot be fully explained on the duration of follow-up, but rather is reflective of not capturing enough patients in follow up with surveillance. Therefore, the reported detection rate likely under reports the true incidence of de novo aneurysms. The annual rates of de novo detection for these case series are at such great variance that little reliance can be placed on the calculated average. Our

results correlate closely to that of Juvela et al. conducted in a Finnish population (361) and Kemp et al. (371). However, no case series has reported analysis with Kaplan-Meier techniques. Our results utilising Kaplan-Meier techniques suggest that there is a significant risk for de novo aneurysm development of 15% in the 10 years following initial aneurysm treatment.

A de novo aneurysm does present a risk of rupture. In the previous published series, 40% of de novo cases presented with rupture (Table 9.1). In our own series, three of the 33 cases presented with rupture. Given the small number of cases that rupture in any series, it is impossible to speculate as to whether these aneurysms when discovered are safe to manage conservatively.

De novo aneurysms can be diagnosed before rupture. Although several series only detected de novo aneurysms after rupture, more series reported unruptured de novo aneurysm. With a regimen of surveillance CTA or MRA at intervals of two to five years, we detected de novo aneurysms without rupture in 90% of all the de novo aneurysm cases. It will remain to be seen how changes to surveillance intervals impact upon the unruptured detection rate. That aneurysms can rupture soon after their formation may not make a reduction in the surveillance intervals more productive in the yield of unruptured aneurysms.

Treatment of de novo aneurysms can be successful. In our series of 46 de novo aneurysms, 45 were successfully treated by surgery and reviewed with post-operative angiography. Of the 33 cases undergoing surgery there was one case with new permanent neurological deficits leading to a mRS of two. Quite clearly the small number of cases makes definitive conclusions limited. However, that most of the aneurysms found are small, suggests that good outcomes may be the general experience for treatment of de novo aneurysms.

Our study is the first analysis of a prospectively enrolled database of a case series of aneurysms in which de novo aneurysms are identified by routine delayed radiological investigations. The analysis by the Kaplan-Meier method found that the five and ten year de novo aneurysm rate following surgical treatment of aneurysms is 4% and 15% respectively. A history of smoking significantly increased the risk of de novo aneurysm formation. However, the absence of a smoking history still had a five and ten year de novo formation rate following surgical treatment of aneurysms of 3% and 13% respectively. The data does not allow further differentiation for pack years smoked or those that discontinued smoking after the original aneurysm treatment. Family history, original presentation with rupture and

original presentation with multiple aneurysms did not appear to influence the risk of developing de novo aneurysms in this case series.

A protocol used in this case series, of routine angiographic surveillance every two years for those considered at higher risk and five years for those considered at low risk for the development of de novo aneurysms, was able to identify the majority of de novo aneurysms prior to their rupture. Furthermore, for these cases, surgical repair was safe.

LIMITATIONS OF STUDY

Interpretation of this data needs to take into consideration the large number of cases that failed to undergo progress angiography. Although the characteristics and reasons for exclusion have been included, the selection bias for the cohort not studied was significantly weighted to those unlikely to benefit from the knowledge that they harbored a new aneurysm. This included those with poor outcomes from the initial rupture or management, and older patients. Furthermore, no analysis of the volume of cigarette smoking history or current smoking status was performed.

CONCLUSION

The data supports surveillance angiography (especially MRA and CTA) for the detection of de novo aneurysms after treatment of aneurysms. Future analysis will focus on whether discontinuing smoking will reduce the risk for the development of de novo aneurysms. Although the performance of a study that may take 10 years to complete would be difficult, the establishment of the risk for de novo aneurysms is of importance and such a study should be performed.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

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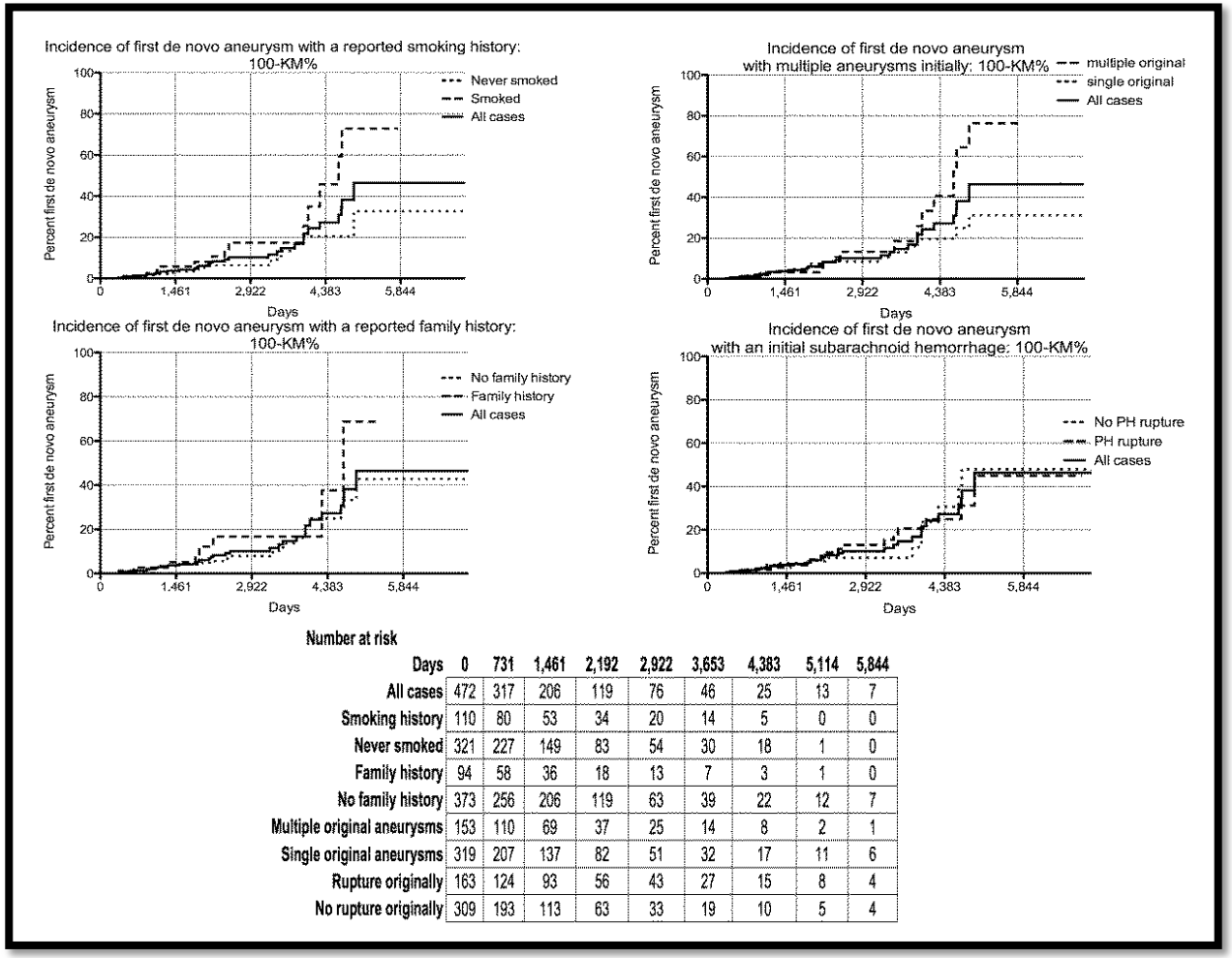

Number at risk

Days	0	731	1,461	2,192	2,922	3,653	4,383	5,114	5,844
All cases	472	317	206	119	76	46	25	13	7
Smoking history	110	80	53	34	20	14	5	0	0
Never smoked	321	227	149	83	54	30	18	1	0
Family history	94	58	36	18	13	7	3	1	0
No family history	373	256	206	119	63	39	22	12	7
Multiple original aneurysms	153	110	69	37	25	14	8	2	1
Single original aneurysms	319	207	137	82	51	32	17	11	6
Rupture originally	163	124	93	56	43	27	15	8	4
No rupture originally	309	193	113	63	33	19	10	5	4

Figure 9.1 Kaplan Meier curve analyses for de novo intracranial aneurysm detection. Four Kaplan Meier curve comparisons were made for: (1) smoking versus never smoked; (2) those with and without a family history; (3) single versus multiple aneurysms at initial presentation; and (4) original presentation with rupture versus non-rupture. Only smoking versus never smoked was significant with a Hazard ratio of 2.58 (95% CI 1.13-5.90).

Table 9.1 Literature review for series of greater than 40 cases reporting de novo intracranial aneurysms

Author & Year	No. of patients	Presentation of cases studied	Mean Follow up, yr (Range)	No. of de novo aneurysms	No. of de novo presenting with rupture	Recalculated Annual risk denovo aneurysm formation (%)
Miller et al., 1985	620	Ruptured and unruptured	16.0 (3.0-30.0)	10	10	0.10
Rinne et al., 1993	1150	Ruptured and unruptured	15.5 (5.0-34.0)	15	na	0.08
Sasaki et al., 1993	986	Ruptured	5.7 (4-7.5)	9	9	0.16
David et al., 1999	102	Ruptured and unruptured	4.4 (2.6-9.7)	8	0	1.81
Juvela et al., 2001	94	Ruptured and unruptured	18.9 (1.2-38.9)	19	7	1.06
Tsutsumi et al., 2001	112	Ruptured and unruptured	9.0 (3.0-21.0)	9	4	0.89
Akuyz et al., 2004	136	Ruptured	3.9 (3.0-7.1)	2	0	0.38
Yoneoka et al., 2004	483	Ruptured	10.7 (2.6-23.8)	12	12	0.23
van der Schaaf et al., 2005	495	Ruptured	8.1 (4.0-14.0)	19	0	0.47
Wermer et al., 2005	610	Ruptured	9.1 (4.4-13.7)	19	0	0.34
Edner et al., 2007	43	Ruptured	19.8 (19.3-20.3)	8	0	0.93
Kim et al., 2007	2887	Ruptured and unruptured	8.9 (1.0-16.7)	12	12	0.05
Molyneux et al., 2009	2143	Ruptured	7.8 (6.0-14.0)	6	6	0.04
Sprengers et al., 2009	65	Ruptured and unruptured	5.1 (4.9-5.3)	1	0	0.30
Ferns et al., 2011	276	Ruptured and unruptured	5.0	2	0	0.14
Plowman et al., 2011	570	Ruptured and unruptured	6.1 (0.5-15.9)	1	1	0.02
Kemp et al., 2012	611	Ruptured and unruptured	na	42	10	0.97

Table 9.2 Baseline characteristics of those excluded and included in the analysis

	Total treated by surgery	Excluded due to fusiform, dissecting or mycotic aneurysms	Excluded due to postoperative mRS>2	Excluded due to clinical F/U >6 months and angiographic F/U <6 months	Excluded due to followed elsewhere	Cohort included in the final analysis
Number of patients	1,366	57	174	142	521	472
Number female (%)	922 (67.5)	26 (46)	116 (66.7)	94 (66.2)	335 (64.3)	357 (75.6)
[X^2; p value]		[8.86; p=0.003]	[49.54; p<0.001]	[37.81; p<0.001]	[371.79; p<0.001]	
Mean age ± SD (years)	52.0 ± 23.2	46.9 ± 15.7	56.5 ± 12.5	54.0± 12.0	53.3 ± 13.4	49.1 ± 11.6
[p value]		[p=0.14]	[p<0.001]	[p<0.001]	[p<0.001]	
Original presentation with rupture (% of patients)	439 (32%)	16 (28%)	109 (62.6%)	35 (24.6%)	143 (27.4%)	137 (29.0%)
[X^2; p value]		[18.36; p<0.001]	[30.83; p<0.001]	[56.59; P<0.001]	[287.01; p<0.001]	
Aneurysm data						
Number of aneurysms	1,942	64	237	217	722	702
Posterior circulation (%)	311 (22.8%)	24 (42%)	55 (31.6%)	30 (21.1%)	97 (18.6%)	103 (21.8%)
[X^2; p value]		[7.29; p=0.007]	[42.25; p<0.001]	[21.71; p<0.001]	[140.83; p<0.001]	
Mean aneurysm size ± SD (mm)	8.4 ± 6.4	13.7 ± 8.2	10.6 ± 7.5	7.0 ± 5.6	8.5 ± 6.3	7.8 ± 5.9
[X^2; p value]		[p<0.001]	[p<0.001]	[p=0.12]	[p=0.02]	
Mean angiographic follow-up months ± SD (range)						54 ± 46 (6-237)

mRS, modified Rankin Score; F/U, follow up; SD, standard deviation

Table 9.3 Characteristics of 33 patients who developed 46 de novo intracranial aneurysms

Characteristics	Value (%)
Sex	
Female	27 (81.8)
Male	6 (18.2)
Presentation	
Discovered on angiographic follow up	30 (90.9)
Subarachnoid hemorrhage	3 (9.1)
Angiographic Follow up (years)	6.8 ± 4.2, (1.0-13.5)
Age at diagnosis of de novo aneurysms, mean ± SD, range (years)	49.3 ± 11.3, (23.6-73.5)
Size of de novo aneurysms at diagnosis, mean ± SD, range (mm)	4.4± 3.6, (1.5-25.5)
Location of aneurysms	
Anterior circulation	37 (80.4)
ICA Paraclinoid	8 (17.4)
ICA Posterior Communicating	4 (8.7)
ICA Anterior Choroidal Artery	1 (2.2)
ICA Bifurcation	2 (4.3)
Middle cerebral artery	13 (28.3)
Anterior communicating artery	9 (19.6)
Posterior circulation	9 (19.6)
Basilar bifurcation	6 (13.0)
Basilar trunk	2 (4.3)
Vertebral artery	1 (2.2)
Surgical Procedures	
No. of aneurysms surgically repaired by clip	46 (100)
No. of aneurysms deemed completely occluded on angiography	45 (97.8)
Surgical outcomes*	
No. of patients with postoperative mRS >1 as a consequence of surgery	1 (3.0)
No. of patients with postoperative mRS >2 as a consequence of surgery	0 (0)

SD, standard deviation; mRS, modified Rankin Score; *outcomes based on number of patient

Table 9.4 Logistic regression analysis, log-rank (Mental-Cox) test and Cox regression of risk factors for first de novo intracranial aneurysms

			Kaplan Meier			Cox regression	Univariate Analysis	
Risk factor		**Number of first de novo cases (%)**	**Percent de novo at 5 years (95%CI)**	**Percent de novo at 10 years (95% CI)**	**P (log rank)**	**Hazard ratio (95% CI)**	**OR (95% CI)**	***p* value**
Smoking	Never smoked	17 (5.48)	2.77	13	0.03	2.58 (1.13-5.90)	2.40 (1.12-5.11)	0.03
	Smoked	13 (11.8)	5.81	17				
Family history	Nil	24 (6.43)	4.02	14	0.15		1.35 (0.59-3.12)	0.48
	Present	8 (8.5)	4.21	17				
Original aneurysm number	Single	19 (5.96)	4.67	13	0.16		1.59 (0.78-3.26)	0.21
	Multiple	14 (9.15)	3.24	19				
Original presentation	Unruptured	16 (5.18)	4.49	7.1	0.85		2.13 (1.05-4.34	0.04
	Ruptured	17 (10.4)	3.67	21				
All cases		33 (6.99)	4.21 (3.86-12.8)	15 (10-16)				
							Multivariate Analysis	
Smoking							2.40 (1.12-5.11)	0.03

Family History, first degree relative of parents or parents' siblings; CI, confidence interval; OR, odds ratio

CHAPTER 10

THE USE OF INDOCYANINE GREEN VIDEOANGIOGRAPHY DURING INTRACRANIAL ANEURYSM SURGERY REDUCES THE INCIDENCE OF POSTOPERATIVE ISCHEMIC COMPLICATIONS: A RETROSPECTIVE MATCHED-PAIR COMPARISON WITH HISTORIC CONTROL

PREFACE TO CHAPTER 10

This chapter investigates the role of Indocyanine Green (ICG) videoangiography in reducing the risk of postoperative ischemic complications following aneurysm surgery. The data presented here represents a prospective study conducted by Dr Lai over a two-year period, in which patients were recruited into the ICGVA cohort. This study was approved by the Macquarie University Human Ethics Committee, and was performed in accordance with institutional ethics committee guidelines (ethics reference number: 5201000813)

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Dr Lai. Professor Morgan and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Microscope-integrated near-infrared indocyanine green videoangiography (ICGVA) has been shown to be a useful adjunct for intracranial aneurysm surgery. That the routine application of this technique reduces the risk of postoperative ischemic complication, however, has not been reported.

METHODS: We present a retrospective match-pair comparison of ICGVA guided aneurysm surgery versus historic control surgical cohort treated by the same author. Index patients and controls were matched for aneurysm size, location, patient demographics, risk factors, co-morbidities, and surgical treatments.

RESULTS: Ninety-one eligible patients with 100 intracranial aneurysms were treated using ICGVA assistance. There were no statistically significant differences between the two groups in terms of patient age, gender, risk factors, co-morbidities and aneurysm characteristics. Of the 100 aneurysms in the ICGVA group, 107 investigations of ICGVA were performed. In 79 aneurysms (79.0%), ICGVA was considered useful but did not affect surgical management. In 6 cases (6.0%), ICGVA led to crucial change of intraoperative strategies. In 9 cases (9.0%), it was considered critical in assuring patency of small perforators. ICGVA was of no benefit in 4 cases (4.0%) and was misleading in two (2.0%). Postoperative ischemic complications occurred in 3 cases (3.3%) in the ICGVA group as compared with 7 cases (7.7%) in the control group ($p<0.001$).

CONCLUSION: Our study supports the use of ICGVA in aneurysm surgery as a safe and effective modality of intraoperative blood flow assessment. With all limitations of a retrospective matched-pair comparison, the use of ICGVA during routine aneurysm surgery reduces the incidence of postoperative ischemic complications.

INTRODUCTION

Microscope-integrated near-infrared indocyanine green videoangiography (ICGVA) is a recent innovation in vascular neurosurgery. It enables real-time intraoperative assessment of blood flow and is routinely utilized in intracranial aneurysm surgery to assess the degree of aneurysm obliteration, exclude parent vessel compromise, and evaluate patency of perforators. The application of ICGVA is rapid and reliable, and in many instances, obviates the need for intraoperative catheter-based angiography (99-101). Since its application to vascular neurosurgery in 2005 (100), numerous studies have demonstrated the safety and efficacy of ICGVA in aneurysm surgery (92-101). However, objective assessments as to whether the use of ICGVA reduces ischemic complications have not been adequately addressed in the literature. The purpose of this investigation was to examine whether the routine use of ICGVA during intracranial aneurysm surgery at our institution have led to a reduction in the incidence of postoperative ischemic events as compared with the prior standard of care.

METHODS

Clinical Material

This study was approved by the Macquarie University Human Ethics Committee and performed in accordance with institutional Ethics Committee guidelines. The ICGVA-integrated microscope (OPMI Pentero Flow800, Carl Zeiss Co.) was available at our institution as of December 2010, and since then, we have maintained a prospective database with information regarding patient demographics, aneurysm characteristics, the number and dosages of ICG used, treatment related outcomes, and complications directly associated with the use of the ICG dye. During the study period in which ICGVA was available, all patients who underwent surgical repair of intracranial aneurysms by the senior author (MKM) were eligible for review. All aneurysms were diagnosed through magnetic resonance angiography (MRA), high-resolution three-dimensional computed tomography (CT) angiography, or digital subtraction angiography (DSA). Mycotic, traumatic and dissecting aneurysms were excluded from the current study. In addition to our standard protocol for intracranial aneurysm surgery, a history of iodine allergy, pregnancy, and previous anaphylactic reactions to contrast media or dye injection was acquired either from the patients or their relatives

depending on the clinical condition. Written informed consent was obtained prior to enrolling patients into the study.

Eligible patients treated with ICGVA assistance were matched with historic control patients with aneurysms of similar characteristics (size, location and rupture status), general demographics (age, gender, risk factors and co-morbidities) and treatment related profiles (types of procedures and the use and duration of temporary occlusion). Information regarding the control aneurysms was obtained from our database of aneurysms surgically treated by the senior author (MKM) between December 1995 and October 2010. Patients treated prior to 1995 were not selected as this period was considered to be a learning curve in the senior authors surgical experience with intracranial aneurysms.(373) Index cases and control were compared for the combined primary end point related to ischemic complication.

Outcome Assessment

Clinic visits were routinely scheduled at 6 weeks and at 1 year following surgery. The modified Rankin Score (mRS) of individual patients was assessed preoperatively, at 6 weeks following surgery, and at the final clinical review. A postoperative CTA or DSA within the first 6 weeks postoperative period or at 1 year was also performed. It is not our routine practice to perform intraoperative angiography. The postoperative CT scans were compared with preoperative images. We defined the presence of an ischemic complication when an infarct has occurred following surgery in which a new hypodensity appeared in the area supplied by of a branch artery or a perforating artery that usually arises from the parent vessel of the treated aneurysm. Non-fatal complications that did not produce a neurological deficit, as well as postoperative morbidity with causes other than aneurysm treatment was not considered. We used the risk of surgical complication per patient rather per individual aneurysm or operation.

Surgical Management

All patients underwent surgery with a standard pterional or orbitozygomatic approaches, except for those with aneurysms located at the vertebral or posterior inferior cerebellar arteries, which were treated by a far lateral approach. The arterial reconstructions varied and were classified as: simple clipping; suture repair of aneurysm supplemented with clipping;

surgical trapping only; or surgical trapping supplemented with bypass surgery. Intraoperative ICGVA was performed following a complete dissection of the aneurysm complex, its parent vessels, and branches. The decision to perform ICGVA before or after clip application or both was based on the individual case and morphological complexity of the aneurysm.

Principles of ICG Videoangiography

ICG dye is a near infrared (NIR) fluorescent tricarbocyanine dye, which has been widely used in ophthalmology for the assessment of retinal microcirculation. The application of fluorescein sodium to evaluate brain surface microcirculation has been utilized since 1967,(374-376) although the specific use of this method to assess the macro-circulation during aneurysm surgery has only been recently introduced.(91, 100) When administrated intravascularly, the dye binds to alpha-1 lipoproteins and has a plasma half-life of 3 to 4 minutes. The dye remains intravascular for at least 10 minutes until the fluorescein is excreted in the urine or glucoronized in the liver. Vessel fluorescence remains active for at least 10 minutes; at which point the ICG injections may be repeated to reassess blood flow (maximum daily dose of 5mg/kg). The fluorescence of the dye (range 780-950nm) can be induced by a NIR-illuminated field (range 700-850nm) and recorded by a non-intensified video camera to be replayed for the surgeon. The ICG dye can be administered rapidly (25mg in 5ml of saline) by the anesthetist via a central line at the request of the surgeon. The videoangiography can be reviewed within minutes, and an aneurysm clip can be repositioned before ischemia can occur (Figure 10.1 and 10.2).

Statistical Analysis

Continuous data are presented as mean ± standard deviation (SD). Categorical data were compared with the Chi Square or Fisher exact test. Where appropriate, significance was set to a probability value of 0.05. The Wilcoxon rank sum test and the Student t test (two-tailed) were used to compare continuous data between two-level categorical variables. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations.

RESULTS

Between December 2010 and November 2012, 91 eligible patients with 100 intracranial aneurysms were treated with ICGVA assistance. This was matched with a historic patient cohort treated by the senior author (MKM) in the period prior to the introduction fluorescence-based intraoperative angiography at our institution during December 1995 to October 2010. Patient and aneurysm characteristics are outlined in Table 10.1. There were no significant differences between the 2 groups in terms of patient age, gender, risk factors and co-morbidities. The majority of the aneurysms were unruptured (95.0%) and the locations of the aneurysms were matched accordingly.

There were no significant differences with regards to the types of surgical procedures performed between these 2 study periods. The use of temporary clip occlusion was more prevalent in the control group as compared to the ICGVA group, although the duration of arterial occlusion was similar in both groups (Table 10.2). Overall, the incidence of ischemic complications as a direct consequence of aneurysm surgery has reduced from 7.7% in the period prior to the routine use of ICGVA to 3.3% in period after ($p<0.001$). Table 10.3 outlines the case summaries of these ischemic morbidities.

In the current study, 107 investigations of ICGVA were performed for the 100 intracranial aneurysms treated in the period in which ICGVA was available at our institution (Table 10.4). ICGVA was performed before clip application in three patients, and after clip application in 104 patients. The time required for ICGVA from the injection to image generation was less than 2 minutes (range 1-10 minutes). The maximum number of ICG applications for a patient was three. There was one case of adverse drug reaction with transient de-saturation of oxygenation (1.1%) intraoperatively. This episode lasted less than 1 minute and resolved spontaneously. No other intraoperative or postoperative complications were encountered. The image quality and spatial resolution were excellent in 103 applications, allowing real-time assessment of the vascular patency.

In the majority of patients (79%), ICGVA was considered useful but did not influence surgical management. In nine patients (9%), ICGVA was considered critical in demonstrating the presence of blood flow in the perforators following surgical treatment of basilar tip and anterior communicating artery aneurysms. In four patients, ICGVA was not useful due to the deep-sited aneurysms and significant vessel calcifications. In all but two patients, the ICGVA findings intraoperatively were comparable with those based on postoperative angiography. This resulted in a false negative rate of 2% for ICGVA in the current study.

Following intraoperative ICGVA, abnormal findings were encountered in six patients that led to crucial intraoperative surgical changes. These cases are summarised in Table 10.5. In four of these patients, ICGVA demonstrated compromised flow in either the parent vessel or a perforator artery arising adjacent to the aneurysm following clipping. After clip adjustment, a repeat ICG angiography confirmed restoration of flow in all four patients. In the remaining two patients, ICGVA demonstrated compromised perfusion secondary to suboptimal clip placements. In these cases, an arterial bypass graft was performed in one and a suture repair supplemented with clip placement in another.

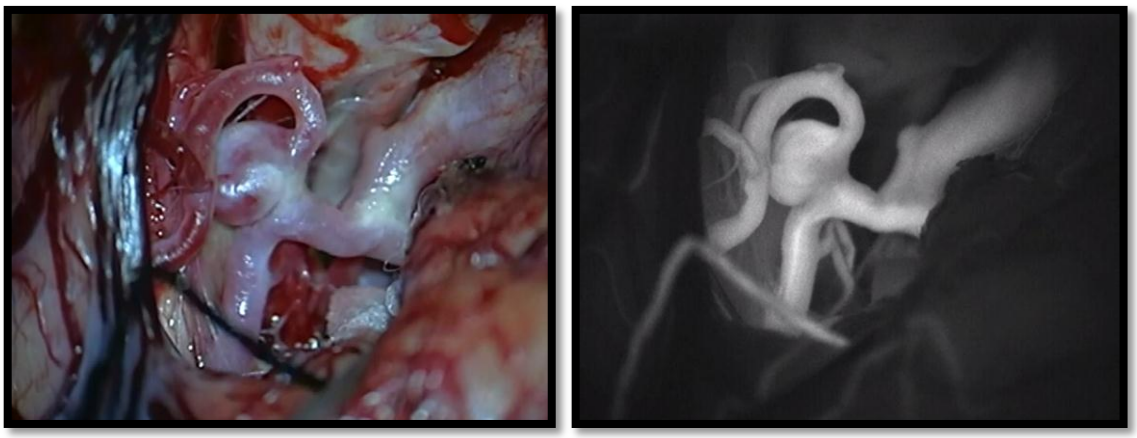

Figure 10.1 The use of ICGVA to visualise blood flow prior to surgical clipping in a middle cerebral artery aneurysm (microscopic and infrared view).

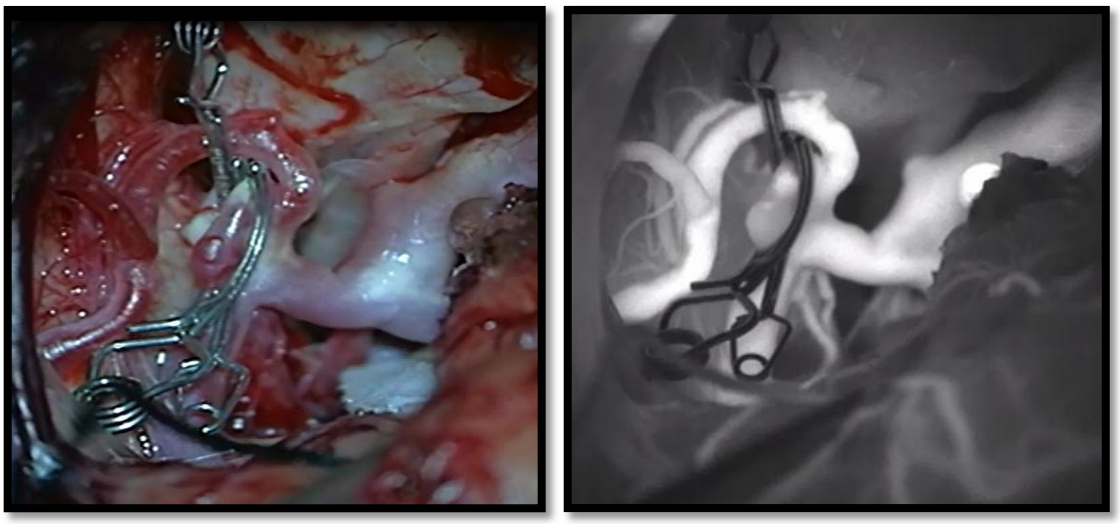

Figure 10.2 The use of ICGVA to visualise blood flow following surgical clipping in a middle cerebral artery aneurysm (microscopic and infrared view).

Table 10.1 Comparison of patient and aneurysm characteristics for historic versus ICGVA cohort

	Control	ICGVA	*p* value
Time Period	1995-2010	2010-2012	
No. of patients, n (%)	91	91	
Mean age ± SD (range) (year)	54.1±11.6 (25-78)	54.1±12.0 (27-76)	1.0
Female	66 (72.5)	67 (73.6)	1.0
Hypertension	29 (31.9)	34 (37.4)	0.36
Smoking History	21 (23.1)	20 (22.0)	0.69
Family History of Intracranial Aneurysms	18 (19.8)	30 (33.0)	0.23
Previous SAH	0	8 (8.8)	na
Previous GDC Treatment	4 (4.4)	3 (3.3)	0.70
No. of aneurysms, n (%)	100	100	
Mean size ± SD (mm)	6.7±5.0	6.6±4.9	1.0
Small (<7mm)	75 (75.0)	77 (77.0)	
Medium (7-12mm)	18 (18.0)	16 (16.0)	
Large (13-24mm)	2 (2.0)	3 (3.0)	
Giant (≥25mm)	5 (5.0)	4 (4.0)	
Unruptured	95 (95.0)	95 (95.0)	1.0
Anterior circulation aneurysms, n	86	86	
Cavernous segment of internal carotid artery	2	2	
Paraclinoid segment of internal carotid artery	20	20	
Posterior communicating artery	10	10	
Anterior choroidal artery	5	5	
Internal carotid artery bifurcation	5	5	
Anterior Communicating Artery	10	10	
Distal anterior cerebral artery	6	6	
Middle Cerebral Artery	28	28	
Posterior circulation aneurysms, n	14	14	
Basilar Bifurcation	6	6	
Posterior Cerebral Artery	2	2	
Superior Cerebellar Artery	1	1	

Posterior Inferior Cerebellar Artery	1	1
Vertebral Artery	4	4

Table 10.2 Comparison of procedures characteristics and ischemic outcomes for historic versus ICGVA cohort

	Control	ICGVA	*p* value
No. of procedures performed, n	92	92	
Clip	84	83	
Clip and Suture	2	3	
Trap	1	0	
Trap and Bypass	5	6	
Use of Temporary Clipping, n	32	24	<0.001
Mean duration ± SD (minutes)	17.1 ± 9.8	16.6 ± 11.0	0.79
Ischemic Complications	7 (7.7%)	3 (3.3%)	<0.001

DISCUSSION

The improper placement of aneurysm clip may be associated with compromised blood flow and the subsequent development of delayed neurological deficit or death. Despite attempts to preserve the patency of the important vessels, direct visualisation is insufficient to reveal arterial compromise or satisfactory dome occlusion. Over the years, various intraoperative vascular imaging modalities have been employed to optimise surgical outcomes (377-384). These efforts underscored the importance of complete dome obliteration and the preservation of parent and branch vessels during aneurysm surgery. When aneurysms were inadequately treated, the risk of subsequent rebleeding has been reported to range from 3.7% to 47% of cases (304, 385-388). When arterial compromise has occurred in the parent or branch vessels, the risk of disabling postoperative stroke can range from 16% to 50%(389, 390). At present, intraoperative catheter-based angiography remains the gold standard for the assessment of vessel patency and degree of dome occlusion. However, this technique is expensive, time-

consuming, requires logistical support and carries a procedure-related complication rate of 0.4% to 2.6% (378, 379, 391-395). The application of ICGVA during aneurysm surgery represents a novel intraoperative vascular assessment that allows real-time visualisation of blood flow and brain perfusion. The principal advantage of ICGVA relies on the simplicity and speed with which the procedure can be accomplished.

In this retrospective matched-pair analysis, we found a significant reduction in the occurrence of postoperative ischemic morbidities in patients treated with ICGVA assistance as compared with similar aneurysms that were matched for size and location treated prior to the availability of ICGVA at our institution. Overall, there was a reduction in 4.4% risk of postoperative ischemia. These results suggest strongly that the use of ICGVA during aneurysm surgery improve operative morbidity by reducing the incidence of ischemic complications in the postoperative period. In keeping with other studies (92-98, 100), our results support the safety and efficacy of ICGVA. In 6% of the cases, intraoperative ICGVA had led to crucial intraoperative surgical changes that would have otherwise resulted in poor surgical outcomes. There were two false-negative outcomes in this series (2%) in which discordance existed between the postoperative angiographic and intraoperative ICGVA findings. In 80% of patients, ICGVA was considered helpful to the aneurysm surgery but did not impact on the overall surgical management strategy. In these patients, ICGVA was useful in confirming aneurysm obliteration and in assuring patency and flow in the parent and distal vessels. In nine patients (9%), ICGVA was considered critical in demonstrating the presence of blood flow in the perforator vessels, which is of significant importance in achieving good outcome following aneurysm surgery. At present, ICGVA is the only intraoperative vascular imaging modality that can establish patency in these small vessels. Alternative methods such as intraoperative catheter-based angiography and micro-Doppler are suitable assessment tools for large arteries, but are less reliable when used to evaluate smaller perforators.

The usefulness and safety profile of ICGVA are well reported in the literature (92-101). Table 10.6 presents a summary of these findings. When the results were combined, there is an overall false negative outcome of 5.8%. In at least 7% of cases, ICGVA influenced the surgical management and led to a readjustment of the clip or a change in the surgical strategy. In most studies, ICGVA correlated in at least 90% of cases with the postoperative DSA. ICG dye is also safe to use in angiography and can be repeated multiple times intraoperatively. Adverse drug reaction, when occurred, has been insignificant. In the literature, only one case (0.1%) of mild skin rash was reported out of the 844 patients in the review (97).

The main limitation of ICGVA relates to the NIR views, which are restricted to the field of the operating microscope. Vessels that are covered by blood clots, brain tissue, or aneurysm clips may not be reliably visualised. Similarly, calcifications, thick-walled vessels, or aneurysmal thrombosis can affect ICG fluorescence. For this reason, ICGVA cannot replace catheter-based angiography, but can be used as an adjunct to intraoperative angiography or as an alternative when this procedure is not readily available.

LIMITATIONS OF STUDY

The current study is subjected to a number of limitations. First, this was not a randomized, controlled trial comparing ischemic outcomes of patients who were treated with the assistance of fluorescence-based angiography during intracranial aneurysm surgery as compared to those without. The results are therefore subjected to the bias of a single-surgeon, single-center, retrospective review of surgical results.

Second, patients in the ICGVA cohort were treated during the past 2 years, while controls had been treated across a longer and earlier interval. Examining outcomes over an extended period of time may be difficult to account for changes in operative techniques and technology that may impact on patient care. Microsurgical techniques and neuroanaesthesia has evolved significantly during this period of time.

Finally, increased experience may have accounted for some of the improved surgical outcomes seen in the ICGVA group. However, on reviewing the senior author's experience with surgical treatment of intracranial aneurysms in the past 20 years (373), the risk of postoperative adverse events were not significantly different for those patients that were treated since 1994. Although experience can still confound the improved ischemic events presented in this study, the routine use of ICGVA during intracranial aneurysm surgery remains an important prognostic factor. These limitations notwithstanding, our study is the first to establish the role of ICGVA guided aneurysm surgery in reducing ischemic complications.

CONCLUSION

Microscope-integrated ICG videoangiography is a simple, fast, and reliable modality of providing real-time data on blood flow during aneurysm surgery. Visualisation of small perforators is one of the most important advantages of ICGVA. Based on a matched-pair comparison in the present study, the routine use of ICGVA during intracranial aneurysm surgery reduces the risks of postoperative ischemic events.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

Dr Lai is supported by a scholarship funded by Carl Zeiss Co. The authors declare that they have no further financial or other conflicts of interest in relation to this research and its publication.

Table 10.3 Summary of cases with postoperative ischemic complications encountered in this study

Case	Cohort	Year of Surgery	Age/Sex	Size/Location	Procedure	Postop Event
1	ICGVA	2011	71/M	22 mm/MCA	Clip	Superior division of middle cerebral artery territory infarction
2	ICGVA	2012	56/F	25mm/ICA	Trap & bypass	Anterior choroidal artery territory infarction
3	ICGVA	2012	45/F	10mm/PCoA	Clip	Anterior choroidal artery territory infarction
4	Control	2001	70/M	6mm/MCA	Clip	Middle cerebral artery territory infarction
5	Control	2003	56/F	26mm/Cavernous	Trap & bypass	Thrombosed graft; hemiparesis
6	Control	2003	53/M	26mm/ICA	Trap & bypass	Thrombosed bypass graft; died
7	Control	2005	55/M	26mm/VA	Clip	Pontomedullary infarction
8	Control	2005	66/M	24mm/MCA	Suture & Clip	Middle cerebral artery territory infarction
9	Control	2007	64/F	3mm/MCA	Clip	Patchy embolic infarctions in the parietal, frontal and para-ventricular regions
10	Control	2008	74/M	10mm/ACoA	Clip	Proximal anterior cerebral artery territory infarction with memory problems

ICA, internal carotid artery; MCA, middle cerebral artery, ACoA, anterior communicating artery; PCoA, posterior communicating artery; ICGVA, indocyanine green videoangiography

Table 10.4 ICG characteristics for the 100 aneurysms analysed in the ICGVA cohort

	Value (%)
No. of ICG injections	107
Pre-clipping	3
Post-clipping	104
Mean per aneurysm	1.1
Range	1-3
Time (minutes)	
Mean per aneurysm	2.0
Range	1-10
Adverse Reaction	1 (1.1%)
Grading of ICGVA in Aneurysm Surgery	
1 (Falsely reassuring)	2 (2.0%)
2 (Not helpful)	4 (4.0%)
3 (Helpful, does not influence surgery)	79 (79.0%)
4 (Helpful, influences surgery)	6 (6.0%)
5 (Critical to case)	9 (9.0%)

Table 10.5 Surgical aneurysm cases influenced by ICGVA intraoperatively

Case	Age/Sex	Size/Location	Calcification	Procedure	ICGVA Findings
1	63/F	7mm/paraclinoid	no	Clip	Kinking ophthalmic artery; clip repositioned
2	60/F	4mm/MCA	no	Clip	Stasis at level of clip. Clip replaced from 5mini to 3mini - then showed good parent flow.
3	48/M	5mm/vertebral	no	Clip and wrap	First injection vertebral artery did not fill; clip repositioned and then vertebral artery filled - confirmed patency of PICA.
4	72/F	3.5mm/AChA	yes	Clip	Showed slow filling of AChA. Clip repositioned
5	55/F	6.5mm/MCA	yes	Bypass	No flow through frontal branch; confirmed also with Doppler; bypass performed.
6	53/F	10mm/SCA	yes	Suture	SCA not filling; clip repositioned, not ideal; opted for suture repair

Table 10.6 Summary of published series on the use of ICGVA during intracranial aneurysm surgery

Author, year	No. of Patients	No. of Aneurysms	No. of SAH patients	No. of ICG injections	False Negative Outcome	ICGVA Influenced Surgery	Correlation of ICGVA and DSA	ADRs
Raabe et al., 2005	114	124	50	187	6/60	10/114	45/50	0
de Oliveira et al., 2007	60	64	30	93	2/36	1/36	34/36	0
Imizu et al., 2008	13	13	2	13	na	5/13	na	0
Dashti et al., 2009	190	239	112	457	29/239	na	210/239	0
Li et al., 2009	120	148	84	208	6/108	10/208	102/108	0
Ma et al., 2009	45	45	na	89	1/43	8/45	42/43	0
Jing et al., 2010	42	42	40	na	0/42	5/42	42/42	1
Khurana et al., 2010	27	27	13	na	0/27	6/27	27/27	0
Gruber et al., 2011	104	123	29	198	3/123	8/123	120/123	0
Wang et al., 2011	129	152	110	276	1/145	3/145	144/145	0
				1.7 p/a	**5.8%**	**7.4%**	**94.2%**	**0.1%**
				(1521/908)	**(48/823)**	**(56/753)**	**(766/813)**	**(1/844)**

p/a, per aneurysm; ADRs, adverse drug reaction; DSA, digital subtraction angiography; ICG, indocyanine green; na, not available

CHAPTER 11

A CADAVERIC STUDY OF THE ENDOSCOPIC TRANSCLIVAL APPROACH TO THE BASILAR ARTERY

PREFACE TO CHAPTER 11

This chapter examines the surgical relevance of the endoscopic endonasal transclival approach to the basilar artery aneurysms. The data presented here represented work performed by Dr Lai to explore the feasibility, limitations and potential clinical application of a novel approach. This study was approved by the local institutional review board and was conducted in accordance with ethics committee guidelines for the use of human anatomical specimens (license number H11/5683-2).

This chapter has been peer reviewed and published:

Lai, L., Morgan, KM., Chin, D., Snidvongs, K., Huang, J., Malek, J., Lam, M., McLachlan, R., Harvey, RJ. A cadaveric study of the endoscopic transclival approach to the basilar artery. Journal of Clinical Neuroscience 2013; 20 (4), p 587-592.

AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan and Professor Harvey provided advice and supervision during the conception and design of the study. Doctors Chin, Snidvongs, Huang, and Malek along with Mr. Lam and Mr. McLachlan assisted in preparing the endonasal accesses during the cadaveric dissections. All endoscopic transcranial works were performed by Dr Lai and Dr Chin. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan, Professor Harvey and Dr Lai. Professor Morgan, Professor Harvey and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: The anterior transclival route to basilar artery aneurysms is not widely performed. The objective of this study was to carry out feasibility assessment of the transclival approach to basilar aneurysms with advanced endonasal techniques.

METHODS*:* Eleven cadaver heads were studied. Clival dura was exposed from sella to the foramen magnum between the paraclival segments of the internal carotid arteries laterally. An inverted dural 'U' flap was reflected inferiorly to expose the basilar artery. The maximal dimensions from operative measurements were recorded. Surgical maneuverability of multiple instruments and the proficiency to place proximal and distal vascular clips were evaluated.

RESULTS: The mean (± standard deviation) operative depth, measured from the anterior choanae to the basilar artery, was 110 ± 6 mm. The lateral corridors were limited distally by the medial pterygoid (mean width 21 ± 2 mm) and paraclival internal carotid arteries (mean width 20 ± 2 mm). The mean transclival craniectomy dimensions were 19 ± 2 mm (width) and 23 ± 4 mm (height). Exposure of the basilar-anterior inferior cerebellar artery junction, superior cerebellar artery, and the basilar caput were possible in 100%, 91%, and 64%, respectively. Placements of proximal and distal aneurysm clips were achieved in all cases.

CONCLUSION: The transclival endoscopic endonasal surgery approach provides excellent visualisation of the basilar artery. Clip application and maneuverability of instruments was considered adequate for basilar aneurysm surgery. Surgical skills and instrumentation to control significant hemorrhage can potentially limit the clinical applicability of this technique.

INTRODUCTION

Since the 1960's, innovations in skull base techniques have unveiled important microsurgical corridors to access midline posterior circulation aneurysms in the retroclival region. Key operative strategies encompassing the anterolateral transsylvian (50), lateral subtemporal (69, 70), and posterolateral suboccipital (71) approaches have been implemented and modified (60, 72-74) in attempts to optimise aneurysm exposure. From a skull base perspective, the anterior transclival approach offers several key advantages. It provides a direct line of sight for a midline basilar artery aneurysm, and capitalises on bony resection close to the target. Upon dural opening, direct exposure to the aneurysm and parent vessels is possible that facilitates early proximal and distal vascular control, while brain retraction and cranial nerve manipulation can be minimised. However, early efforts to gain direct ventral surgical access to basilar artery aneurysms failed to gain popularity on the basis of poor operative exposure, an inability to achieve watertight dural closure and an increased risk of postoperative cerebrospinal fluid (CSF) leaks and meningitis (396-398)

The development of expanded endoscopic endonasal surgery enables access and visualisation through the narrowest practical corridor with minimal disruption to normal tissue (399-403). Maximum effective action at the target lesion can be achieved through wider and closer vision of the surgical field. Skull base defects can now be reliably repaired endoscopically using vascularised or free grafts with good long-term prevention of CSF leaks and intracranial infection (404-406). Based on these innovations, the current study was performed to re-explore the practicality of the anterior transclival route to basilar artery aneurysms using an expanded endoscopic endonasal technique. The objectives of this study were to define the dimensions of the endonasal corridor and to establish the degree of vascular exposure attainable by maximal endoscopic dissection to the basilar artery.

METHODS

This study was approved by the local institutional review board and was performed in accordance with ethics committee guidelines for the use of human anatomical specimens. Bi-nasal endoscopic endonasal skull base (EESB) surgery through the clivus was performed on fresh adult cadaver heads. Key measured parameters were the depths of the operative fields, the lateral limits of the endonasal corridor and the size of the transclival opening that could be achieved using the anterior endoscopic approach. Surgical maneuverability was assessed

using a selection of instruments via both ipsilateral and contralateral nostrils. The degree of vascular exposure and the ability to place proximal and distal clip application at various points of the basilar artery were also examined.

Specimens

Eleven adult fresh frozen cadaver heads were used. The heads were placed in the supine position slightly flexed and turned 10 to 15 degrees toward the right in the horizontal plane. Zero degree endoscopes (Karl Storz and Co, Tuttlingen, Germany) that were 4mm in diameter and 18cm in length were used. The endoscope was connected to a light source via a fiber-optic cable and to a camera fitted with 3 charge-coupled device (CCD) sensors. The video camera was connected to a 21-inch monitor supporting the high resolution of the 3 CCD technologies.

Surgical dissection

The inferior turbinate was out fractured. The middle turbinate was lateralised or the lower half of the middle turbinate removed to facilitate visualisation of the entire sphenoid anterior wall. Bilateral sphenoidotomies were performed and combined with a 2cm posterior nasal septectomy.

The full width of the sphenoid from lateral opticocarotid recess (OCR) to the contralateral OCR was exposed. The pterygoid canal with its Vidian nerve was the lateral boundary on the approach. This nerve enters the pterygopalatine fossa, which is bounded medially by the medial pterygoid plate and corresponded, to the lateral boundary of this surgical corridor in the upper third of the clivus. The soft tissue of the nasopharynx was removed with Coblation Procise EZ wand (Arthrocare, Sweden) as this is the surgical device used clinically. The vomer and sphenoidal floor were completely drilled out, creating a wide communication between the sphenoid and nasopharyngeal parts of the clivus.

The clivus bone was removed with a 5-mm course diamond burr drill and 2-mm Kerrison rongeur, from the sella floor to the foramen magnum. In the upper and middle third clivus, dissection extended laterally until the paraclival segments of the ICA were reached. In the lower third, this lateral restriction was the anterior occipital condyles.

The clival dura was exposed from the sella to the foramen magnum, and laterally between the paraclival ICAs. An inverted dural 'U' flap was created and reflected inferiorly to expose the basilar artery and its associated VB vessels. The arachnoid bands forming the prepontine and medullary cisterns were opened using sharp dissection, upon which the posterior circulation vasculature was systematically identified. The following parameters were assessed intraoperatively:

Dimensions of the surgical field and craniotomy

The depth of the operative field, measured from the anterior choanae to the basilar artery (mm), was recorded. The lateral limits of the endonasal corridor, defined proximally by the margins of the alar rims, and more distally by the distance between the medial pterygoid and the paraclival ICAs (mm) were determined. Other measurements included the extents of the transclival and dural opening (mm).

Exposure of the posterior circulation arteries

The degree of basilar arteries exposure within the confines of the transclival and dural openings were recorded as dichotomous outcomes of "accessible" or "unsuccessful". These included six sites; the basilar bifurcation (BB), posterior cerebral artery (PCA), superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA), vertebrobasilar junction (VBJ) and both left and right vertebral arteries (VA) as one location.

Instrument access and clip application

Instrument access and surgical maneuverability were measured by evaluating the ability of surgical instruments to access each corner of the transclival opening (defined dichotomously for superior right & left and inferior right & left). Three attempts were made before a decision was agreed upon. This was performed for endoscopic scissor, knife and suction instruments at each of the four corners of the transclival opening. The ability to place proximal and distal vascular clips was evaluated in each specimen (recorded as dichotomous as successful or unsuccessful). Temporary clips were placed along the BA/SCA junction, BA/AICA junction, the VBJ and the left and right VAs.

Statistical analysis

Descriptive data was presented as percentage and mean ± SD. Paired T-test (two-tailed) was used for comparisons of paired parametric data. 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

Eleven cadaver heads were dissected (mean age 77 ± 12, range 58-93 years, 91% female). Endoscopic endonasal transclival exposure of the basilar system was successful in all specimens.

Dimensions of the surgical field and craniotomy

The mean operative depth, measured from the anterior choanae to the basilar artery, was 110 ± 6 mm (range 100-130mm) (Table 11.1). The mean width of the endonasal corridors, defined proximally by the alar rim openings, was 25 ± 2 mm (range 20-28mm). Further distally, the widths were defined by the distance between the medial pterygoid (mean 21 ± 2 mm, range 16-25mm) and the paraclival ICA (mean 20 ± 2 mm, range 17-23mm) (Figure 11.1).

Overall, the mean width and height of the transclival craniectomy were 19 ± 2 mm (range 15-25mm) and 23 ± 4 mm (range 16-30mm), respectively (Figure 11.2). Dural opening via an inverted 'U' flap was achieved, with a mean width of 17 ± 4 mm (range 10-24mm) and height of 19 ± 4 mm, range (12-27mm) (Table 11.1).

Exposure of the posterior circulation arteries

Exposure of the distal basilar complex (basilar bifurcation, PCA and SCA) was possible in 64% of instances (Table 11.2). The AICA was present and exposed in all specimens (100%). Further inferiorly, the VBJ and both distal VAs were exposed in 36% and 18%, respectively.

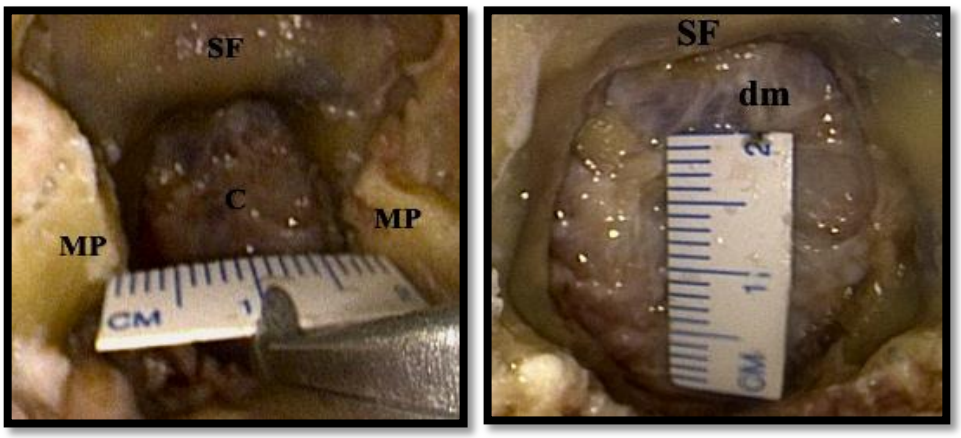

Figure 11.1 & 11.2 Measuring the dimensions of the endonasal surgical field and transclival craniotomy. C, clivus; dm, dura mater; MP, medial pterygoids; SF, sella floor

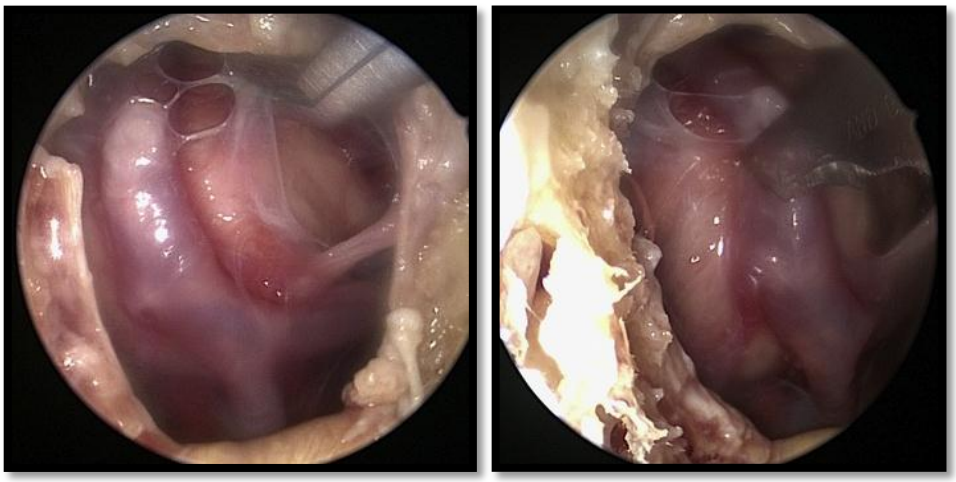

Figure 11.3 & 11.4 Dissection of arachnoid membrane using endoscopic scissor and knife following a transclival craniotomy and dural opening

Instrument access and clip application (Table 11.2)

Surgical accesses through both ipsilateral and contralateral nostrils for clip placement were possible in all specimens (Figure 11.3 & 11.4). Accesses to superior right and left corners of the transclival opening were achieved in all specimens. Accesses to the inferior right and left corners were 55% and 73%, respectively.

Proximal and distal aneurysm clips were placed in 91% and 100% of cases at the BA/SCA junction and the BA/AICA junction, respectively (Figure 11.5 & 11.6). Inferiorly, clip placements were possible in 36% of cases at the VBJ, and 18% for both left and right distal VA (Figure 11.7 & 11.8).

Table 11.1 Dimension of the surgical field and craniotomy for the endoscopic endonasal transclival approach

	Mean Distance ± SD (range) (mm)
Endonasal Corridor Dimensions	
Operative Field Depth	110 ± 6 (100-130)
Lateral Limits of endonasal corridor	
Between alar rims	25 ± 2 (20-28)
Between medial pterygoids	21 ± 2 (16-25)
Between paraclival ICAs	20 ± 2 (17-23)
Transclival opening	
Height	23 ± 4 (16-30)
Width	19 ± 2 (15-25)
Dural opening	
Height	19 ± 4 (12-27)
Width	17 ± 3 (10-24)

ICA, internal carotid artery; SD, standard deviation

DISCUSSION

Sano et al. first reported the anterior approach to a basilar trunk aneurysm via the transpharyngeal-transclival route in 1966 (75). Since that time, various authors have utilized the anterior strategy to tackle midline posterior fossa aneurysms through the transoral, transcervical, and transfacial approaches (76, 77). Further attempts at using this route were discouraged as reported rates of postoperative CSF leak and meningitis were unacceptably high (78-82). A review of the literature in the last five decades yielded 45 published cases of midline posterior fossa aneurysms treated via the anterior transclival route (Table 11.3) (70, 76-79, 81, 82, 398, 407-419). Forty-three patients (95.6%) presented with acute subarachnoid hemorrhage. Overall, operative mortality rate was 25%, with 50% risk of postoperative CSF leaks and 45% meningitis

In recent years, the application of EES to midline cranial base pathologies has been established through various cadaveric and clinical studies (420-428). The deliberate transclival approach to the ventral skull has also been described for a variety of extradural and intradural pathologies (423, 429-432). Kassam reported the first purely endoscopic endonasal

clipping of a coiled vertebral artery aneurysm via the transclival approach (102). Since then, six other case reports have been published demonstrating the feasibility of this technique on various aneurysm locations along the skull base (103-108) (Table 11.4).

For midline aneurysms located in the posterior circulation, the development of EES as a minimally invasive approach may reopen a surgical route long considered too risky by many. We determined that the anterior endonasal corridor assumes the longest operative depth (mean distance 110 ± 6mm) compared to conventional transcranial routes. The skull base approaches afforded by microsurgical dissection provide access corridors that are shallow and wide, and can be considered as conical shapes. This allows for maximal proximal surgical maneuverability while further distally enabling more precise and controlled fine motor movements at the target lesion. On the other hand, the endoscopic trajectory provides a long and narrow cylindrical corridor, which may limit the operative maneuverability particularly at the distal surgical field. In the current study, it was possible to pass multiple instruments, while using bimanual techniques with two operators during the extradural and intradural aspects of the procedure. The panoramic view, offered by the endoscope, provides superior visualisation of the basilar artery and is an advantage that may compensate partially for this narrow corridor (Figure 11.9). In addition, the use of multiple clips along the basilar artery was possible without compromising the endoscopic view of the posterior fossa vasculature.

An adequate transclival opening was achieved in all specimens with direct visualisation of the basilar trunk and distal basilar complex in 100% and 64% of cases respectively. The proficiency to place proximal and distal vascular clips along the basilar artery was possible in all cases for a potential mid basilar trunk aneurysm. The lateral extents of the transclival opening, bracketed by the paraclival ICAs, bear no limitations on the degree of vascular exposure afforded by this technique. The basilar artery and its associated branches remained in the midline location in all 11 specimens. On the other hand, the longitudinal exposure of the basilar artery (from VBJ to the bifurcation) was limited, depending on the anatomical variation of the basilar artery relative to the clivus.

Table 11.2 Degree of vascular exposure, instrument access and clip placement within the confines of the endonasal corridor

Vascular Exposure	
Basilar Bifurcation	64%
PCA	64%
SCA	64%
AICA	100%
VBJ	36%
VA (left and right)	18%
Instrumental Access for endoscopic scissor, knife and suction tip (through both nostrils)	
Superior Right	100%
Superior Left	100%
Inferior Right	55%
Inferior Left	73%
Clip Placements	
BA/SCA Junction	91%
BA/AICA Junction	100%
VBJ	36%
VA (left and right)	18%

PCA, posterior cerebral artery; SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; VBJ, vertebrobasilar junction; VA, vertebral artery.

Minimalistic approaches undoubtedly impact on the neurosurgeon's ability to secure hemostasis. This is particularly important in the endonasal approach to aneurysms in which bleeding from venous plexus or arteries can profoundly impair visualisation of the operative field. While the technical challenges of a true intraoperative aneurysmal rupture cannot be determined from the current study, the importance of the ability to tackle arterial bleeding and familiarity with haemostatic techniques cannot be overemphasized. Endovascular techniques may be used to close the vascular wall defect by either occluding the parent vessel or aim to maintain vascular flow (433). Alternatively, in a recent review of the literature, Valentine et al. described various endonasal packing materials such as surgical gauze, Teflon and methyl methacrylate patch, Syvek marine polymer, muscle patch, fibrin glue, gel foam and

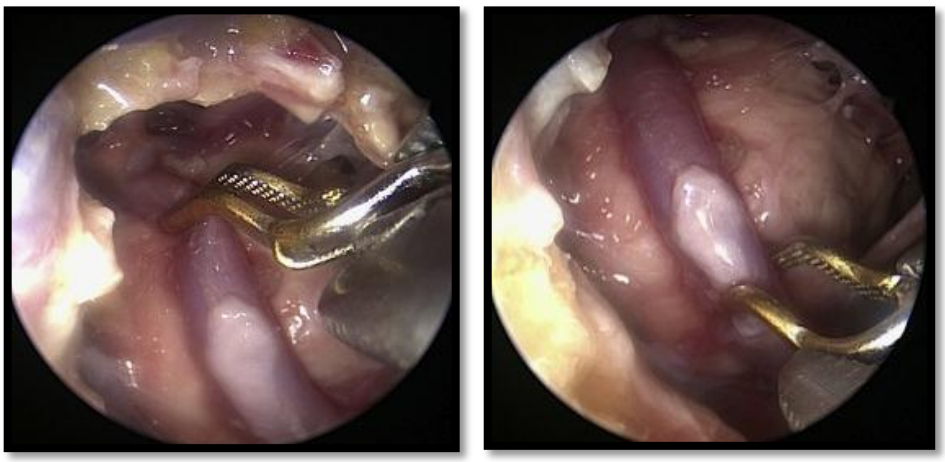

Figure 11.5 & 11.6 Endoscopic clip placements on the distal and proximal basilar artery

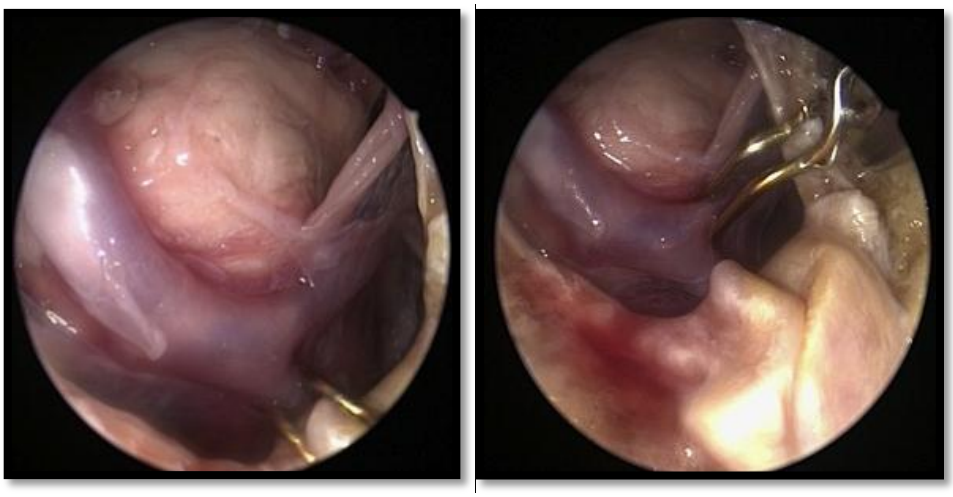

Figure 11.7 & 11.8 Endoscopic clip placements on the right and left vertebral artery

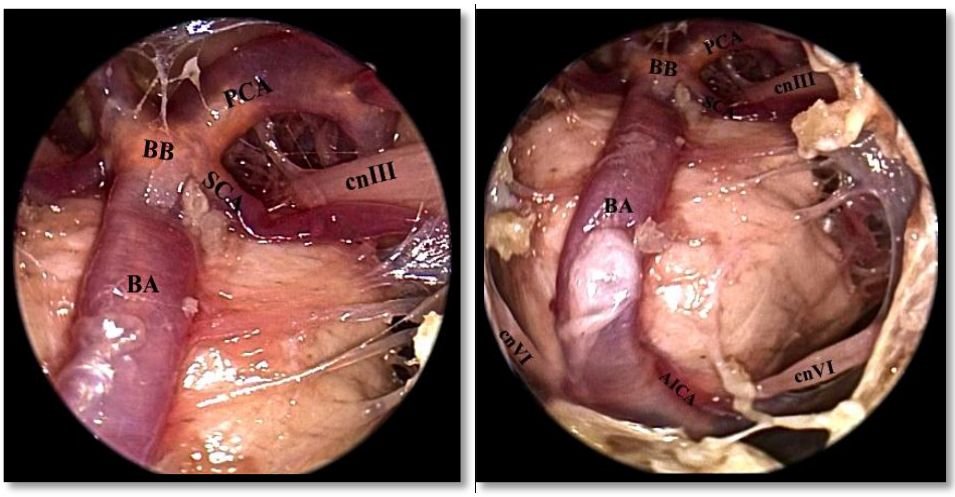

Figure 11.9 & 11.10 Endoscopic endonasal transclival view of the distal basilar complex, and endoscopic view of the entire basilar artery and the associated structures as seen in this approach. AICA, anterior inferior cerebellar artery; BA, basilar artery; BB, basilar bifurcation; PCA, posterior cerebral artery; SCA, superior cerebellar artery; cnIII, oculomotor nerve; cnVI, abducen nerve.

oxidised cellulose packing, thrombin-gelatin matrix, Oxygel and glue, and muslin gauze (434-436) that could be used to effectively control acute bleeding. Based on their studies in animal research, the authors demonstrated the superiority of crushed muscle as a haemostatic agent. Other salvage options include direct vascular repair using endoscopic U clip closure (if training and equipment exist), endoscopic vascular clamps (Medtronic Wormald Endovascular Clamp Set), conversion to an open pterional approach or the option of lateral rhinotomy or mid face degloving approach by an experienced ENT surgeon (437), which would enable quick open access to the ventral skull base.

The principles of multilayer reconstructions and the routine use of vascularised flaps in expanded endonasal surgery have drastically decreased the risk of postoperative CSF complications and meningitis, previously concerned by many (406, 438). In a recent systematic review evaluating the risk of post EES CSF leaks, the reported incidence was 6.7% (439). Vascularised skull base reconstructions for large dural defects had a clear and significant advantage over free grafting in the prevention of postoperative CSF leaks. The rate of meningitis following EES remains to be defined in the literature, although recent studies have reported rates of 0 to 14.3% (440, 441).

Another important technical limitation to EES in managing vascular lesions at present is the lack of instrumentation designed specifically for endoscopic transnasal approaches. Although smaller cranial approaches represent important innovations in cerebrovascular neurosurgery (442), microsurgical dissectors, clip applicators, and similar instruments are designed for larger craniotomies where the instruments can be introduced at a wider angle to their target than that possible in the endoscopic approach. Endoscopic cranial base surgery requires the development of specific instruments for vascular purposes. As an example, the possibility that clip handles may protrude into the sphenoid sinus could make the closure challenging. Furthermore, endoscopic surgery is a very specific skill set that requires gradual transition from simple to complex skull base pathologies (443) . The treatment of vascular lesions via the endonasal route necessitates advanced familiarity with endoscopic surgery, and the application of which should be reserved for experienced dedicated endonasal skull base and cerebrovascular teams. (443-445) (443-445) (444-446) (388-390) (450-452)

CONCLUSION

The transclival endoscopic endonasal approach provides excellent visualisation of the basilar artery. Both clip application and maneuverability of instruments was considered adequate for basilar aneurysm surgery. This may represent a potential treatment alternative for selected midline basilar trunk aneurysm. Surgical skills acquisition and instrumentation development will be needed to occur for the clinical applicability of this technique.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

Dr Lai is supported by a scholarship funded by Carl Zeiss Co.

Professor Richard J Harvey has served on an advisory board for Schering Plough, NeilMed Pharmceuticals and Glaxo-Smith-Kline. He has also acted as a consultant for Olympus and Medtronic, and speakers' bureau for Merek Sharp Dolme, Glaxo-Smith-Kline and Arthrocare. In addition, Professor Harvey has received grant support from NeilMed Pharmaceuticals.

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The authors declare that they have no further financial or other conflicts of interest in relation to this research and its publication.

Table 11.3 A literature review for the anterior transclival approaches to the posterior circulation aneurysms for the years 1960 to 2000

	Studies	Patients	SAH (%)	Mortality (%)	Morbidity (%)	CSF Leak (%)	Meningitis (%)
1960-69	4	5	100 (5/5)	40 (2/5)	80 (4/5)	40 (2/5)	20 (1/5)
1970-79	6	10	80 (8/10)	20 (2/10)	90 (9/10)	50 (5/10)	30 (3/10)
1980-89	7	13	100 (13/13)	23.1 (3/13)	53.8 (7/13)	46.2 (6/13)	46.2 (6/13)
1990-99	4	17	100 (17/17)	5.9 (1/17)	52.9 (9/17)	29.4 (5/17)	41.2 (7/17)
TOTAL	21	45	95.6 (43/45)	17.8 (8/45)	64.4 (29/45)	40.0 (18/45)	37.8 (17/45)

Table 11.4 A Literature review for the endoscopic endonasal clipping of intracranial aneurysms

Author and year	**Location**	**Size (mm)**	**Presentation**	**Approach**	**Complication**	**Outcome**
Kassam et al., 2006	Vertebral	11	Previously coiled	Transclival	CSF leak	Independent
Kassam et al., 2007	SHA	5	Unruptured	Transplanum	Nil	Independent
Germanwala et al., 2011	Paraclinoid	10	Ruptured	Transplanum	Nil	Independent
Froelich et al., 2011	ACoA	7	Unruptured	Transplanum	Nil	Independent
Ensenat et al., 2011	Vertebral-PICA	1.2	Ruptured	Transclival	CSF leak	Independent
Drazin et al., 2011	SCA	4	Ruptured	Transclival	Nil	Independent

CHAPTER 12

A CADAVERIC STUDY OF THE ENDOSCOPIC ENDONASAL TRANSPLANUM APPROACH TO THE PARACLINOID INTERNAL CAROTID ARTERY

PREFACE TO CHAPTER 12

This chapter examines the surgical relevance of the endoscopic endonasal transplanum approach to the treatment of paraclinoid internal carotid artery aneurysms. The data presented here represented work performed by Dr Lai to explore the feasibility, limitations and potential clinical application of a novel approach. This study was approved by the local institutional review board and was conducted in accordance with ethics committee guidelines for the use of human anatomical specimens (license number H11/5683-2).

This chapter has been peer reviewed and published:

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan and Professor Harvey provided advice and supervision during the design of the study. Doctors Chin and Snidvongs assisted in preparing the endonasal accesses during the cadaveric dissections. All endoscopic transcranial works were performed by Dr Lai and Dr Chin. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan, Professor Harvey, Professor Sacks and Dr Lai. Professor Morgan, Professor Harvey and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: The anterior transplanum approach to paraclinoid internal carotid artery aneurysms is not widely performed. The current study was carried out to investigate the relevance of an endoscopic transnasal approach to the surgical treatment of paraophthalmic aneurysms.

METHODS: Bi-nasal endoscopic transplanum surgery was carried out on 7 cadaver heads. The key outcome measures included 1) dimensions of the endonasal corridor, including the operative field depth; lateral limits, and size of the transplanum craniotomy. 2) the degree of vascular exposure, and 3) surgical maneuverability and success for clip placements via left and right nostrils.

RESULTS: The mean operative depth was 90 ± 4 mm. The lateral corridors were limited proximally by the alar rim openings (29 ± 4 mm), and distally by the distance between the optico-carotid recesses (19 ± 2 mm). The mean postero-anterior distance and width of the transplanum craniotomy were 19 ± 2 mm and 17 ± 3 mm, respectively. Vascular exposure was achieved in 100% of cases for the clinoidal ICA, ophthalmic artery, superior hypophyseal artery, and the proximal Ophthalmic ICA. Surgical access and clip placement was achieved in 97.6% of cases for vessels located anterior to the pituitary stalk (OR 73.8; 95% CI 7.66-710.8; $p = 0.00$).

CONCLUSION: The endoscopic transnasal approach provides excellent visualisation of the paraclinoid region vasculature and offers potential surgical alternative for paraclinoid aneurysms.

INTRODUCTION

Paraophthalmic aneurysms arise from the segment of the internal carotid artery (ICA) between the distal dural ring and the origin of the posterior communicating artery (PCoA) (297, 446, 447). They represent a unique subset of anterior circulation aneurysms because of their proximity to the optic nerve and the anterior clinoid process (ACP), demanding familiarity with a cranial base surgical approach. The challenges in dealing with paraophthalmic region aneurysms relates to the ability to adequately expose and obtain proximal control, entailing resection of the ACP, opening of the falciform ligament, un-roofing of the optic canal, and mobilisation of the distal dural ring (299, 448-452). For these reasons, surgical obliteration of paraophthalmic aneurysms can be a significant undertaking and the inherent risks associated with microsurgery have been well documented in the literature (453-456).

From a skull base perspective, the anterior transplanum approach via an endoscopic endonasal corridor offers several important technical advantages (103, 104, 106, 405, 406, 439, 457, 458). These include: providing direct line of sight for medially projecting aneurysms; avoiding the need to open the optic canal and resect the ACP; utilising optic nerve manipulation; and readily achieving proximal control of the ICA (103, 106, 458). The current study was performed to evaluate the feasibility of endoscopic skull base approaches to the surgical treatment of paraophthalmic aneurysms.

METHODS

This study was approved by the local institutional review board and was performed in accordance with ethics committee guidelines for the use of human anatomical specimens. Expanded endoscopic endonasal surgery via the planum sphenoidale was performed on fresh adult cadaver heads. Key measured parameters included the depths of the operative fields, the lateral limits of the endonasal corridor and the size of the transplanum craniotomy. Surgical maneuverability was assessed for clip placements via both ipsilateral and contralateral nostrils. The degree of vascular exposure and the capacity for temporary clip placements were also examined.

Specimens

Adult fresh frozen cadaver heads were used. The heads were placed in the supine position slightly extended and turned 10 to 15 degrees toward the right in the horizontal plane. Zero degree endoscopes (Karl Storz and Co, Tuttlingen, Germany) that were 4mm in diameter and 18cm in length were used. The endoscope was connected to a light source via a fiber-optic cable and to a camera fitted with 3 charge-coupled device (CCD) sensors. The video camera was connected to a 21-inch monitor supporting the high resolution of the 3 CCD technologies.

Surgical dissection

The middle turbinate was lateralised or the lower half of the middle turbinate removed to facilitate visualisation of the entire sphenoid anterior wall. The sphenoid sinus was opened widely, exposing the para-sella segment of the ICA, sella and planum sphenoidale. The full width of the sphenoid from lateral optico-carotid recess (OCR) to the contralateral OCR was exposed. A 20mm posterior nasal septectomy was performed to allow for an expanded endonasal technique.

The anterior sella bone, tuberculum sella, and planum sphenoidale were removed. The bone opening of the planum was extended in the postero-anterior direction for approximately 20mm. From this point, the assistant held the endoscope to allow the use of both hands for the surgeon. The dura mater was opened and resected maximally along the margins of the transplanum opening. The arachnoid bands forming the optico-carotid cisterns under the optic chiasm were opened using sharp dissection, upon which the paraclinoid vasculature was systematically identified (Figure 12.1 & 12.2).

Dimensions of the surgical field, craniotomy, and the infra-chiasmal window

The surgical corridor was defined by three dimensions: 1) the depth of the operative field, which was measured from the anterior choanae to the pituitary stalk, 2) the lateral limits of the endonasal corridor, defined proximally by the margins of the alar rims and more distally by the distance between the left and right optico-carotid recesses, and 3) the dimensions of the infra-chiasmal window, with its height (defined by the distance between the optic chiasm superiorly and the diaphragma sella inferiorly) and width (defined by the distance between the left and right proximal ICAs) recorded in millimeters. Other operative measurements included

the extent of the transplanum and dural opening (mm), measured in lateral dimension from optic nerve to optic nerve, and postero-anterior dimension from tuberculum sellae to the proximal cribiform plate. Three attempts were made before a decision was agreed upon, following which the average measurement was recorded.

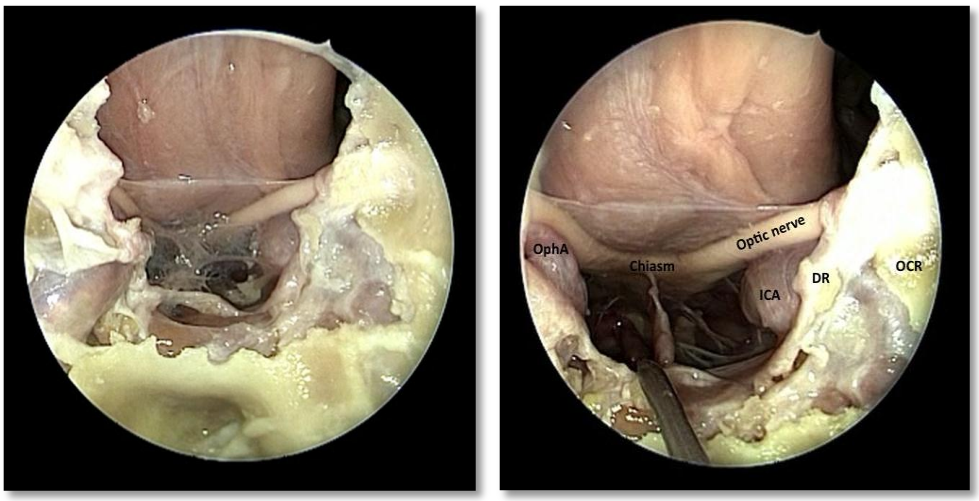

Figure 12.1 & 12.2 Endoscopic endonasal transplanum view of the infrachiasmal window before the removal of the arachnoid bands. Endoscopic endonasal transplanum view of the infrachiasmal window after the removal of the arachnoid bands, demonstrating the paraclinoid region vascular anatomy. OphA, ophthalmic artery; DR, distal dural ring; OCR, optico-carotid recess; ICA, internal carotid artery.

Exposure of the clinoidal ICA segment and proximal vascular control

A 10mm window at the prominence of the ICA was drilled to expose a segment of the clinoidal ICA on each side. We used the Vidian canal as the inferior limit of this exposure, which anatomically represents the anterior genu of the petrous ICA (459). Temporary aneurysm clip placement was applied to evaluate the ability for proximal vascular control using the endoscopic approach (defined dichotomously as successful or unsuccessful of three attempts).

Exposure of the paraclinoid region vasculature

The degree of paraclinoid region vasculature that was exposed within the confines of the transplanum and dural openings were recorded as dichotomous outcomes as accessible or not. These included 10 sites incorporating the left and the right 1) Clinoidal ICA segment, 2) proximal Ophthalmic ICA segment, 3) ophthalmic artery (OA), 4) superior hypophyseal artery (SHA), and 5) origin of the PCoA.

Instrument access and clip application

Instrument access and surgical maneuverability were measured by assessing the ability of surgical instruments to access and manipulate each of the following vessels: clinoidal ICA, paraophthalmic ICA, OA, SHA and PCoA (recorded dichotomously as successful or unsuccessful). An angled endoscopic vascular clamp (Wormald Endovascular Clamp Set, Medtronic, MN, USA) and a variety of Codman aneurysm clips were used for assessment.

Predictors of surgical access and vascular clip placement

A number of technical variables were assessed for their prognostic value in predicting surgical access and clip applicability of the following vessels: clinoidal ICA, paraophthalmic ICA, OA, SHA and PCoA. These were considered for the following surgical point of references: 1) Vascular structures anterior to the Pituitary stalk; 2) Vascular structures posterior to the pituitary stalk; 3) the left nostril access and 4) the right nostril access.

Statistical Analysis

Descriptive data were presented as percentage and mean ± SD. Paired T-test (two-tailed) was used for comparisons of paired parametric data. Student's T-test (two-tailed) was used for comparisons of unrelated groups of parametric data. Logistic regression analysis was used to determine which of the measured parameters independently predict the success of surgical access and clip placement. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations. A p value of less than 0.05 was considered statistically significant. The modified Wald method was used to calculate the 95%

confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Seven cadaver heads were dissected (mean age 77 ± 12, range 58-93 years, 43% female). Endoscopic endonasal transplanum exposure of the paraclinoid region vasculature was successful in all specimens.

Dimensions of the surgical field, craniotomy, and the infra-chiasmal window (Table 12.1)

The mean operative depth was 90 ± 4 mm (range 85-95mm). The mean width of the endonasal corridors, proximally alar, was 29 ± 4 mm (range 25-35mm), and distally by the distance between the left and right optico-carotid recesses was 19 ± 2 mm (range 15-20mm).

The mean postero-anterior distance and width of the transplanum craniotomy were 19 ± 2 mm (range 15-20mm) and 17 ± 3 mm (range 15-20mm), respectively. Dural opening was performed in all specimens with a mean width of 16 ± 3 mm (range 12-20mm) and a postero-anterior distance of 15 ± 3 mm (range10-18mm).

The overall width and height of the infra-chiasmal window were 11 ± 1 mm (range 10-13mm) and 5 ± 1 mm (range 4-8mm), respectively (Figure 12.2).

Exposure of the clinoidal ICA segment for proximal vascular control

A 10mm length along the clinoidal segment of the ICA was exposed in all specimens (100%). Temporary clip placement for proximal vascular control was achieved in 100% of cases for both left and right nostril approach (Figure 12.3).

Exposure of the paraclinoid region vasculature (Table 12.2)

Exposure of the vasculature in the paraclinoid region was possible in all specimens (100%) along the clinoidal segments of the ICA, the OA, the SHA, and the proximal paraophthalmic

artery segments. The left and right PCoA origin was only exposed in 14% and 57% of cases, respectively.

Instrument access and clip application (Table 12.2)

Surgical accesses through both ipsilateral and contralateral nostrils for clip placement were possible in 100% of cases for the clinoidal ICA segments and the SHAs. Clip placement for the ophthalmic artery and proximal Ophthalmic ICA segment just distal to the ophthalmic artery origin was successful in 86% of cases. Accesses to and clip ligation of the left and right PCoA were achieved in 0% and 29% of cases, respectively.

Table 12.1 Dimensions of the surgical field, craniotomy, and the infrachiasmal window

	Mean Distance ± SD (range) (mm)
Endonasal Corridor Dimensions	
Operative Field Depth	90 ± 4 (85-95)
Lateral Limits of endonasal corridor	
Between alar rims	29 ± 4 (25-35)
Between left and right optico-carotid recesses	19 ± 2 (15-20)
Transplanum Craniotomy	
Postero-anterior length (from tuberculum sellae to proximal cribiform plate)	17 ± 3 (15-20)
Width (between left and right optic nerves)	19 ± 2 (15-20)
Dural opening	
Postero-anterior length	15 ± 3 (10-18)
Width	16 ± 3 (12-20)
Infra-chiasmal window	
Height	5 ± 1 (4-8)
Width	11 ± 1 (10-13)

Predictors of surgical access and vascular clip placement

The pituitary stalk provides a good surgical point of reference for which vascular access and clip placement may be defined. For those vessels that are located anterior to the stalk, surgical access and clip placements were achieved in 97.6% of cases (OR 73.8; 95% CI 7.66-710.8; $p<0.001$). For those vessels located posterior to the stalk, access and clip placements were possible in 35.7% of cases (OR 73.80; 95% CI 7.66-710.78; $p<0.001$). Surgical accesses and clip placements were achieved in 95.2% and 94.7% of cases for the left and right nostril approach, respectively (Table 12.3). When the considered variables were adjusted in a multivariate analysis, only those vessels that were located anterior to the pituitary stalk maintained statistical significance (OR 73.80; 95% CI 7.66-710.78; $p<0.001$).

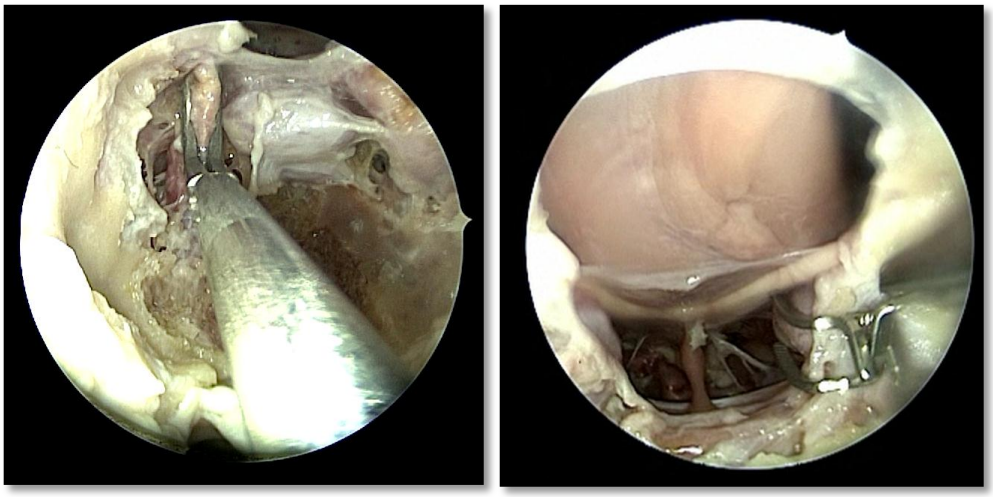

Figure 15.3 & 15.4 Application of an endoscopic vascular clamp for proximal control over the right clinoidal ICA segment. Endoscopic endonasal clip application to vessels within the infrachiasmal window.

DISCUSSION

Evolution in the approach to aneurysm management has been driven by the need to overcome significant disadvantages with existing practice (192, 458, 460). Skull base approaches facilitated the need to reduce the amount of retraction used but came at the expense of a greater amount of time and technical expertise in bone removal (460). Endovascular therapies eliminated the need for skull removal but led to a reduction in robustness of aneurysm repair (139, 271, 292, 295, 318, 344). An endoscopic endonasal approach offers the potential for minimal bone disruption and robust aneurysm repair.

The development of endoscopic endonasal surgery has the potential to offer optimal surgical control at the target through wider and closer vision of the surgical field, whilst the basic tenets of cerebrovascular surgery can still be strictly followed. The deliberate endonasal approach for clip ligation of aneurysms along the cranial base has been attempted in recent years, unveiling for the most part, a feasible operative strategy in well-selected lesions along the midline corridors (102-107, 457).

In the current study, we investigated the relevance of the endoscopic strategy to the surgical treatment of paraophthalmic aneurysms. Our findings suggest that the overall depth of the operative field was approximately 90mm, with the lateral limits of this corridor being 29mm proximally (alar rims) and 19mm further distally (between the optico-carotid recesses). Intracranially, the optico-carotid recess corresponds to the optic strut of the anterior clinoid process. Above this recess, the bone opening can be widened over the planum sphenoidale. The panoramic view, offered by the endoscope, enables greater appreciation of the neuro-anatomical complexity within this region. Such visualisation from a craniotomy would have required brain retraction, extensive drilling of the ACP and manipulation of the optic nerve. Surgical access and clip placement was considered adequate for the clinoidal ICA, the ophthalmic artery and the SHA. The infra-chiasmic window, bounded by the optic chiasm superiorly, the optico-carotid recesses laterally and the diaphragma sella inferiorly, serves as an important surgical framework for which aneurysms arising inside this confine may be treated by an endoscopic endonasal approach with adequate vascular visualisation and access. The overall width and height of the infrachiasmic window were 11 ± 1 mm (range 10-13mm) and 5 ± 1 mm (range 4-8mm), respectively. However, operative access beyond the origin of the PCoA was perceived to be difficult because of the deep location of these vessels behind the pituitary stalk, requiring retraction of the optic chiasm and tract for visualisation. Based on the results of this study, it would be feasible to consider an endoscopic transnasal access to paraophthalmic aneurysms in which the domes are located anterior to and projected medially towards the pituitary stalk (Figure 12.4). For those lesions projecting superiorly under the optic nerve or laterally beyond the boundaries of the infrachiasmic window, the application of this approach for aneurysm clip ligation would appear insufficient in terms access and clip placement.

Table 12.2 The percentage of success of vascular exposure, instrument access, and clip placements by site in the seven cadaver heads

	Vascular exposure, n (%; 95% CI)		Access and Clip Placements, n (%; 95% CI)	
	Right	Left	Right	Left
Clinoidal ICA segments	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)
Proximal Paraophthalmic ICA segments	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	6 (85.7; 46.7-99.5)
Ophthalmic artery	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	6 (85.7; 46.7-99.5)
Superior hypophyseal artery	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)	7 (100; 59.6-150.0)
Posterior communicating artery (origin)	1 (14.3; 0.5-53.4)	4 (57.1; 25.0-84.3)	0 (0; 0-40.4)	2 (28.6; 7.6-64.8)

ICA, internal carotid artery

Table 12.3 Predictors of surgical access and clip placements

Univariate Analysis	Access achieved (%)	OR	95% CI	p value
Anterior to pituitary stalk	97.6	73.80	7.66-710.78	<0.001
Posterior to pituitary stalk	35.7	0.01	0.00-0.13	<0.001
Left nostril access	95.2	26.67	4.54-156.75	<0.05
Right nostril access	94.7	14.40	2.63-78.87	<0.001
Multivariate Analysis (Forward LR*)				
Anterior to pituitary stalk		73.80	7.66-710.78	<0.001

* LR, likelihood ratio; OR, odds ratio

A potential technical advantage of the anterior endoscopic access relates to the ability for acquiring proximal vascular control via the same operative corridor. The ipsilateral clinoidal ICA segment may be exposed and temporarily clipped for proximal vascular control, thereby surpassing the morbidity of a separate neck dissection to access the cervical ICA. Although the clinoidal ICA may serve to be a better site of proximal control because of its proximity to the target lesion, the challenge with this approach relates to the need to enter the cavernous sinus before the carotid artery can be clamped. The associated venous bleeding may profoundly impair visualisation of the operative field. Thus, requiring additional time for haemostatic control, and taking away time from when the aneurysm would need to be managed while temporary arterial occlusion is in place.

Minimalistic approaches, such as an endonasal corridor, undoubtedly impact on the neurosurgeon's ability to secure hemostasis. Although the technical challenges of a true intraoperative aneurysmal rupture cannot be determined from the current study, the importance of the ability to tackle arterial bleeding and familiarity with haemostatic techniques cannot be overemphasized (434-436).

In recent years, the application of multilayer reconstructions and the routine use of vascularised flaps in expanded endonasal surgery have drastically decreased the risk of postoperative CSF complications and meningitis, previously concerned by many (406, 438). At present, the risk of postoperative CSF leak following vascularised endonasal reconstruction for expanded endoscopic skull base surgery is estimated at 6.7% (439). The rate of meningitis, however, remains to be defined in the literature, although recent studies have suggested rates of 0 to 14.3% (440, 441, 461). Furthermore, the minimal brain retraction

that occurs in ventral endonasal surgery may limit the risk of post-operative seizure. In a recent systematic analysis, the incidence of post-treatment seizure following an expanded endoscopic endonasal approach was estimated at <1% (462).

In the current study, technical limitations for the anterior transnasal access were recognised in a number of instances. First, bimanual dissection using microsurgical principles demands the assistance of a relatively experienced endoscopic surgeon. With two surgeons working within the confined space provided by the nostrils, ergonomic freedom can be limited. For open microsurgical approaches, access corridors are shallow and wide and can be considered as conical shapes. This allows for maximal proximal surgical maneuverability while further distally enabling more precise and controlled fine motor movements at the target. For the endoscopic transnasal access, the operative corridor is a long and narrow tunnel. This translates into a loss of surgical "wrist action" at the target lesion, thereby hampering the ability to manipulate blood vessels and modulate clip angles.

Second, visual depth perception is essential when operating on critical intracranial neurovascular structures, particularly when working in a deep and confined corridor. The 2-dimensional visualisation provided by single-channel optical systems in current endoscopes lack the depth perception of three-dimension provided by the binocular optical systems used in standard microsurgery.

Third, consideration must be given to the issue of lack of appropriate instrumentation designed specifically for the endoscopic transnasal vascular surgery. As an example, the possibility that clip handles may protrude into the sphenoid sinus could make the closure challenging. Furthermore, recurrent or residual aneurysms following treatment in this location may stand to be a technical challenge in the reoperation because of the limited surgical field, poor instrumentation and non-specifically designed vascular clips.

Finally, endoscopic surgery is a very specific skill set that requires gradual transition from simple to complex skull base pathologies (441, 443). The application of endoscopic endonasal treatment for arterial lesions such as paraclinoid aneurysms should be reserved for experienced dedicated endonasal skull base and cerebrovascular teams. Such a technique necessitates advanced familiarity with endoscopic surgery and adequate training in endoscopic arterial lesion management. The establishment of these skill sets should be a pre-requisite before such surgeries should be considered.

CONCLUSION

The transplanum endoscopic endonasal approach provides excellent visualisation of the vasculature in the paraclinoid region. Both surgical access and clip application was considered adequate for a potential ophthalmic and superior hypophyseal artery aneurysm that projects medially and anterior relative to the pituitary stalk. Further development is required to improve operative maneuverability and dedicated endonasal instrumentation for treatment of vascular pathology in the endoscopic endonasal approach.

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Professor Richard J Harvey has served on an advisory board for Schering Plough, NeilMed Pharmceuticals and Glaxo-Smith-Kline. He has also acted as a consultant for Olympus and Medtronic, and speakers' bureau for Merek Sharp Dolme, Glaxo-Smith-Kline and Arthrocare. In addition, Professor Harvey has received grant support from NeilMed Pharmaceuticals.

Dr Lai would like to acknowledge Professor Harvey and the team at the St Vincent Hospital Anatomy Laboratory (Sydney, Australia) for providing the cadaver heads and endoscopic equipment to carry out this research.

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CHAPTER 13

A CADAVERIC STUDY OF THE ENDOSCOPIC ENDONASAL TRANSTUBERCULAR APPROACH TO THE ANTERIOR COMMUNICATING ARTERY COMPLEX

PREFACE TO CHAPTER 13

This chapter examines the surgical relevance of the endoscopic endonasal transtubercular approach to the anterior communicating artery aneurysms. The data presented here represented work performed by Dr Lai to explore the feasibility, limitations and potential clinical application of a novel approach. This study was approved by the local institutional review board and was conducted in accordance with ethics committee guidelines for the use of human anatomical specimens (license number H11/5683-2).

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and acquired the data for this study. Professor Morgan and Professor Harvey provided advice and supervision during the conception and design of the study. Doctor Dalgorf, Ms Sacks, and Mr. Bokhari assisted in preparing the endonasal accesses during the cadaveric dissections. All endoscopic transcranial works were performed by Dr Lai and Dr Dalgorf. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan, Professor Harvey, Professor Sacks and Dr Lai. Professor Morgan, Professor Harvey and Dr Lai approved the final version for publication.

ABSTRACT

OBJECT: Endoscopic transnasal approach to the anterior communicating artery (ACoA) complex is not widely performed. The purpose of this cadaveric study was to investigate the relevance of the ventral endoscopic approach to the surgical treatment of ACoA aneurysms.

METHODS: Bi-nasal endoscopic transtubercular surgery was carried out on fresh adult cadavers. Primary outcomes were: dimensions of the endonasal corridor (operative field depth; lateral limits, size of the transplanum craniotomy and dural opening), vascular exposure [proximal and distal anterior cerebral arteries (ACAs), ACoA, clinoidal internal carotid artery (ICA) segment] and surgical maneuverability defined by clip placements (ipsilateral and contralateral).

RESULTS: Eight cadaver heads were used (mean age 84 ± 7, range 76-94 years; 75% female). Mean operative depth was 97 ± 4mm. The lateral corridors were limited proximally by the alar rim openings (31 ± 2mm), and distally by the optic nerves (22 ± 6mm). The endonasal craniotomy dimensions were 21 ± 5 mm anteroposterior and 22 ± 4mm laterally. Vascular exposure was achieved in 100% of cases for the ACoA segment and the ACA segments proximal to the ACoA (A1). The ACA segments distal to the ACoA (A2) were accessible only in 40% of cases. Endonasal clip placement across the ACoA segment, clinoidal ICA, A1s and A2s were 100%, 90%, 90%, and 30%, respectively.

CONCLUSION: The ventral endoscopic endonasal approach to the ACoA complex provides excellent vascular visualisation without brain retraction and gyrus rectus resection. However, the limitation in access to the A2s for temporary clip placement may prove to be a significant limitation of this approach.

INTRODUCTION

Of all cerebral aneurysms, the anterior communicating artery (ACoA) aneurysm is the most frequent and represents an increased risk of rupture as compared to aneurysms in other locations (120, 305-311). Transcranial clip ligation (via the pterional transsylvian, supraorbital or interhemispheric corridors) presents significant technical challenges because of the deep and midline location of these lesions. Infrequently, surgical morbidity arises from frontal lobe retraction or partial gyrectomy that are necessary to facilitate aneurysm exposure (308, 322, 331, 333). The application of endovascular techniques in recent years have provided a less invasive alternative to the management of ACoA aneurysms, but have led to an inferior durability of aneurysm repair and an increased risks for retreatment (314-318). Cranial base approaches with clip obliteration maintain treatment robustness but came at the expense of a greater amount of bone removal and extracranial tissue morbidity.

The concept of an anterior transnasal approach to the ACoA complex is not new. Previously, the microscopic transsphenoidal approach for treatment of aneurysms around the circle of Willis has been described.(ref) However, early efforts to gain direct ventral surgical access have been hindered by poor operative exposure, an inability to achieve watertight dural closure and an increased risk of postoperative cerebrospinal fluid (CSF) leaks and meningitis.

The emergence and expansion of endonasal surgery as a ventral corridor to the cranial base has brought new surgical relevance to the ACoA complex that may provide a more direct access route and minimal brain retraction. In this anatomical study, the relevance of an endoscopic transnasal access to the ACoA vasculature was investigated on the basis of 3 outcome measures: (1) the depth and lateral limitations of the endonasal corridor; (2) the degree of vascular exposure; and (3) the degree of surgical freedom and clip placement permissible within the constraints of the endonasal corridor.

METHODS

This study was approved by the local institutional review board and was performed in accordance with ethics committee guidelines for the use of human anatomical specimens. Adult fresh frozen cadaver heads were used. The cadaver heads were placed in the supine position slightly extended and turned 10 to 15 degrees toward the right in the horizontal plane. Zero degree endoscopes (Karl Storz and Co, Tuttlingen, Germany) that were 4mm in diameter and 18cm in length were used. The endoscope was connected to a light source via a fiber-

optic cable and to a camera fitted with 3 charge-coupled device (CCD) sensors. The video camera was connected to a 21-inch monitor supporting the high resolution of the 3 CCD technologies.

Surgical dissection

Expanded endoscopic endonasal surgery through the planum sphenoidale and tuberculum sella was performed. The middle turbinate was lateralised or the lower half of the middle turbinate removed to facilitate visualisation of the entire sphenoid anterior wall. The sphenoid sinus was opened widely, exposing the para-sella segment of the ICA, sella and planum sphenoidale. The full width of the sphenoid from lateral optico-carotid recess (OCR) to the contralateral OCR was exposed. A 20mm posterior nasal septectomy was performed to allow for a binasal expanded endonasal technique.

The anterior sella bone, tuberculum sella, and planum sphenoidale were removed. The bone opening of the planum was extended in the postero-anterior direction for approximately 20mm and laterally to the optic canals. From this point, the assistant held the endoscope to allow the use of both hands for the surgeon. The dura mater was opened and resected maximally along the margins of the transplanum opening. The arachnoid bands forming the chiasmatic cisterns above the optic chiasm were opened using sharp dissection, upon which the anterior communicating complex vasculature was systematically identified.

Defining the Endonasal Dimensions

The endonasal corridor was defined in millimeters (mm) by: 1) the depth of the operative field, which was measured from the anterior choanae to the ACoA segment, and 2) the lateral limits, as defined proximally by the margins of the alar rims and more distally by the divergent margins of the optic nerves. Because the distance between the optic nerves was variable, measurement was taken at an arbitrary line that passes through the centre of the craniotomy. The extents of the transplanum and transtubercular craniotomy and dural opening (mm) were measured and recorded. Three attempts were made before a decision was agreed upon, following which the average measurement was recorded.

Exposure of the ACoA complex

The degree of vascular exposure in the ACoA region above the optic chiasm was recorded as dichotomous outcomes as accessible or not. These included 4 sites of the left and the right proximal (A1) and distal (A2) anterior cerebral arteries (ACA). The ACoA segment itself was assessed separately and categorically divided into 4 surfaces (anterior, posterior, superior and inferior). These surfaces represent the hypothetical aneurysm dome projections, in which access and maneuverability of clip placement was later evaluated.

Feasibility assessment of instrument access and clip placement

Instrument access and surgical maneuverability were measured by assessing the ability of surgical instruments to access and manipulate the proximal and distal ACAs and the ACoA segment (recorded dichotomously as successful or unsuccessful of 3 attempts). An angled endoscopic vascular clamp (Wormald Endovascular Clamp Set, Medtronic, MN, USA) and a variety of Codman aneurysm clips were used. To assess for the ability of temporary clip placements, a 10mm window over the parasellar prominence of the ICA was drilled to expose clinoidal ICA on each side. The Vidian canal was used as the inferior limit of this exposure, which anatomically represents the anterior genu of the petrous ICA. Temporary clip placement was assessed at multiple sites, including the clinoidal ICA, proximal and distal ACAs (Figure 16.1-16.3). Finally, the ACoA segment was evaluated for the ability of the clip to "open and close" over the anterior, posterior, superior and inferior surfaces. This represented the ability for clip placement for the different types of aneurysm dome projections at this region.

Statistical analysis

Descriptive data were presented as percentage and mean ± SD. Paired T-test (two-tailed) was used for comparisons of paired parametric data. Student's T-test (two-tailed) was used for comparisons of unrelated groups of parametric data. The Statistical Package for the Social Sciences software (SPSS v 19.0, Chicago, IL, USA) was used for statistical calculations. A p value of less than 0.05 was considered statistically significant. The modified Wald method was used to calculate the 95% confidence intervals for a proportion (GraphPad Software, La Jolla, CA, USA; www.graphpad.com/quickcalcs).

RESULTS

Endoscopic endonasal transtubercular exposure of the ACoA complex was performed on 8 adult cadaver heads (mean age 84 ± 7, range 76-94 years; 75% female). One specimen had an ACoA aneurysm. Transnasal and dura exposure was possible on all specimens.

Endonasal Dimensions

Table 13.1 outlines the endonasal dimensions and cranial opening as achieved by the ventral endoscopic approach. The operative depth was 97 ± 4 mm (range 90-105mm). The proximal width of the endonasal corridors (between the alar rims) was 31 ± 2 mm (range 28-35mm). The distal lateral limits, as defined by the divergent margins of the optic nerves, were 22 ± 6mm (range 15-32mm). The postero-anterior distance and width of the endonasal craniotomy were 21 ± 5 mm (range 15-30mm) and 22 ± 4 mm (range 17-30mm), respectively. Dural opening was performed in all specimens with a mean width of 23 ± 4 mm (range 17-30mm) and a postero-anterior distance of 21 ± 5 mm (range 15-30mm).

Table 13.1 Dimensions of the surgical field and craniotomy in the endoscopic endonasal transtubercular approach

	Mean Distance ± SD (range) (mm)
Endonasal Corridor Dimensions	
Operative Field Depth	97 ± 4 (90-105)
Lateral Limits of endonasal corridor	
Between alar rims	31 ± 2 (28-35)
Between divergent optic nerves	15-32
Transplanum Craniotomy	
Postero-anterior length (from tuberculum sellae to proximal cribiform plate)	21 ± 5 (15-30)
Width (between left and right optic nerves)	22 ± 4 (17-30)
Dural opening	
Postero-anterior length	21 ± 5 (15-30)
Width	23 ± 4 (17-30)

Exposure of the ACoA complex

Exposure of the left and right proximal ACA (A1) and the ACoA was achieved in all specimens (100%; 95% confidence interval [CI], 77-103). Particular to the communicating segment, it was possible to expose and visualise the anterior, superior and inferior surfaces in all cases (Table 13.2). However, visualisation of the posterior surface was not possible with a 0 degree endoscope. In 3 out of the 8 cases, the distal ACAs (A2) were exposed and visualised (38%; 95% CI, 14-70).

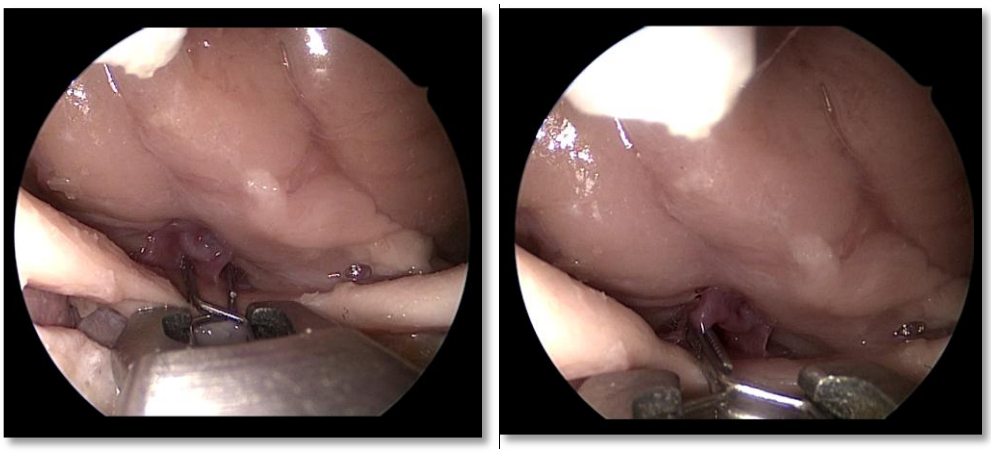

Figure 13.1 & 13.2 Endoscopic endonasal transtubercular access and clipping of the left and right A1s (via a left nostril approach).

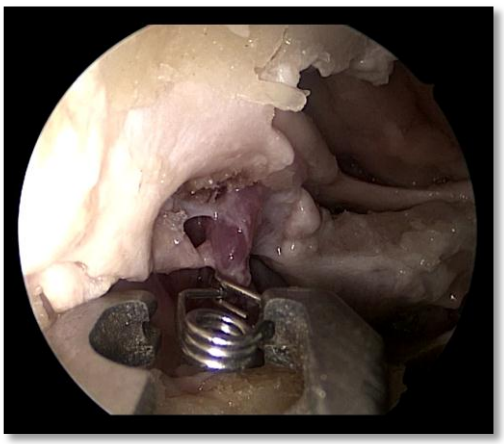

Figure 13.3 Endoscopic endonasal clip application of the right clinoidal internal carotid segment for proximal control.

Feasibility assessment of instrument access and clip placement

Endoscopic temporary clip placement over the clinoidal ICA segment was achieved in 90% (95%CI, 60-100%) of cases for both the left and right nostril approach (Table 13.2). Endoscopic access and temporary clip placement for the distal A1 and proximal A2 were achieved in 90% (95% CI, 60-100%) and 30% (95%CI, 10-50%) of cases, respectively. Surgical accesses through both ipsilateral and contralateral nostrils for clip placement were possible in 100% (95% CI, 80-100%) of cases for the superior, anterior and inferior surfaces of the ACoA segment. Clip placement was not possible in all cases for the posterior surface of the ACoA 0% (9%CI, 0-20%).

DISCUSSION

The development and advancement of endoscopic surgery have emboldened neurosurgeons, who are already familiar with the transsphenoidal techniques, to consider expanded cranial base approaches for treatment of more complex suprasellar lesions such as tuberculum sellae meningioma and craniopharyngioma.(463, 464) A purely endoscopic endonasal approach for the surgical treatment of ventrally located intracranial aneurysms is a natural extension of the philosophy underlying this evolution. Vascular lesions, however, present different challenges.

In the current study, we investigated the technical feasibility and limitations of the endoscopic strategy to the surgical treatment of ACoA aneurysms. Similar to the findings in our previously published work,(458) the results of this study suggests that the endonasal corridor is long (10cm) and narrow (3cm lateral limits) with a variable distal lateral margin as permitted by the distance between the optic nerves. Although surgical access, visualisation and clip placement over the distal A1s were achieved in all specimens, the relationship between the aneurysm and the optic chiasm remains difficult to define because of the small sample size in the present study. The relationship between the communicating arterial segment and the chiasm is an important determining factor to the success of the ventral endoscopic approach, as more posteriorly positioned vascular complex relative to the optic chiasm (postfixed) may hinder full visualisation of the A1 vessels for proximal occlusion.

Dissection of the proximal ACA around the optic chiasm and temporary clipping can be achieved in almost 90% of cases. The proximal A2, however, was visualised in relatively

fewer cases (38%) with temporary clipping only possible in 30% of cases. It is anticipated that in the presence of a large ACoA aneurysm that is anteriorly or superiorly projecting, the dome of the aneurysm will conceal the distal ACA, which presents a risk for premature bleeding.

Based on our findings, the endoscopic endonasal approach provides ready access and visualisation to all surfaces of this vessel, except for the posterior surface. Although the technical challenges of a true ACoA aneurysm and its projection could not readily be studied in the present investigation, clip placement by opening and closing of the blades were achievable in all cases for the superior, anterior and inferior surfaces. By serendipity, one of the cadaver specimens was found to have an ACoA aneurysm (Figure 13.4 & 13.5). Using this to our advantage, we assessed the various aneurysm dome projections and tested the ability of the endoscopic clip placement. In this instance, endoscopic endonasal clip placement was achievable for a dome that projects in the superior, anterior or inferior direction.

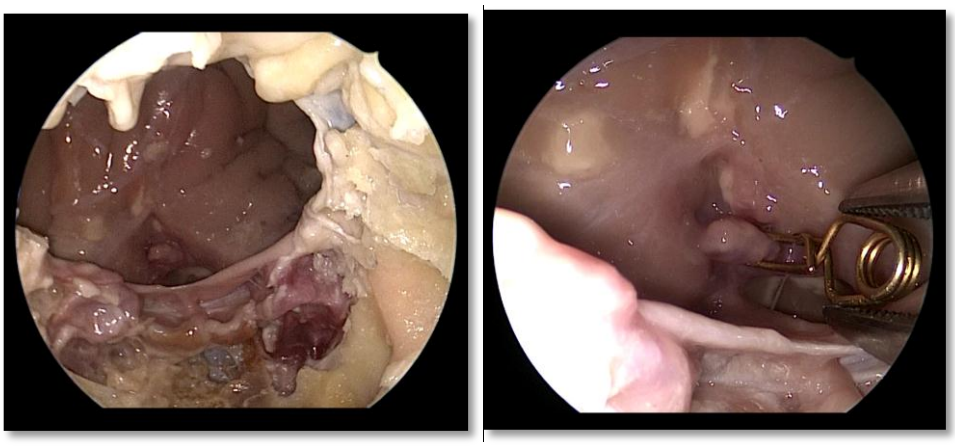

Figure 13.4 & 13.5 Endoscopic endonasal transtubercular exposure and clipping of a serendipitous ACoA aneurysm (via a left nostril approach).

Microsurgical approaches using cranial base access creates a shallow and wide operative window, optimising the degree of freedom of surgical movement. The ventral endoscopic access, on the other hand, is hindered by the intradural neural and vascular structures, which cannot be easily manipulated, thereby limiting the operative maneuverability in this field. In the current study, it was possible to pass multiple instruments, while using bimanual techniques with 2 operators during the extradural and intradural aspects of the procedure. The advantage of the endonasal technique is that it obviates the need for extensive dissection of the Sylvian fissure and frontal lobe retraction in order to access the ACoA complex. The

endoscope also moves the lens and light source much closer to the vascular junction than conventional operative microscopy, providing superior visibility, with the ability to assess adequacy of dome occlusion and direct visualisation of small perforator vessels. A further potential technical advantage of the anterior endoscopic access relates to the ability for acquiring proximal vascular control at multiple points via the same operative corridor. The ipsilateral clinoidal ICA segment may be exposed and temporarily clipped for proximal vascular control. Similarly, the proximal ACAs may be exposed and placed with temporary clip occlusions. However, the inability to be confident of A2 temporary clip placement, a possible pre-condition of safe ACoA aneurysm surgery, may prove to be the limitation of this approach.

In recent years, sporadic case reports have been published demonstrating the feasibility of the endonasal endoscopic clip ligation on various aneurysm locations along the cranial base (102-108). Table 11.4 summarises the findings in these studies. Specific to the ACoA segment, the use of an anterior transnasal approach has been described in 2 case reports describing the endoscopic endonasal technique (108) for a superiorly projecting aneurysm and the microsurgical transphenoidal technique (104) for an anteriorly projecting aneurysm. These cases and the findings in this study demonstrate that it is technically possible to treat an ACoA aneurysm using the endoscopic transtubercular route. However, whether the ventral endonasal route should be utilized for intracranial aneurysm surgery remains controversial and poses ethical concerns. At present, many ACoA aneurysms can be treated safely with microsurgical or endovascular techniques.(318, 335-337) Microsurgery are well established, enabling prompt vascular control in the case of intraoperative rupture and are associated with limited morbidity in experienced hands. The present study reports the feasibility assessment of the ventral endoscopic access to surgical treatment of ACoA aneurysm. However, its value and place in cerebrovascular neurosurgery will be defined only when improved dedicated endonasal instruments are employed and a statistically meaningful number of clinical cases have been performed.

CONCLUSION

The endoscopic endonasal transtubercular approach to the ACoA complex has the potential to provide a less invasive surgical alternative as compared to conventional transcranial approach, and a more robust aneurysm repair as compared with endovascular coiling. Further

development is required to improve operative maneuverability and refinement of endonasal instrumentation before clinical application should be considered.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

Dr Lai is supported by a scholarship funded by Carl Zeiss Co.

Professor Richard J Harvey has served on an advisory board for Schering Plough, NeilMed Pharmceuticals and Glaxo-Smith-Kline. He has also acted as a consultant for Olympus and Medtronic, and speakers' bureau for Merek Sharp Dolme, Glaxo-Smith-Kline and Arthrocare. In addition, Professor Harvey has received grant support from NeilMed Pharmaceuticals.

Dr Lai would like to acknowledge Professor Harvey and the team at the St Vincent Hospital Anatomy Laboratory (Sydney, Australia) for providing the cadaver heads and endoscopic equipments to carry out this research.

The authors declare that they have no further financial or other conflicts of interest in relation to this research and its publication.

Table 13.2. The percentage of success of vascular exposure, instrumental access, and clip placements by site in the eight cadaver heads

	Vascular exposure, n (%; 95% CI)		Access and Clip Placements, n (%; 95% CI)	
	Right	Left	Right	Left
Clinoidal ICA segments	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	7 (87.5, 50.8-99.9)
Anterior Cerebral Artery (A1 Segment)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	7 (87.5, 50.8-99.9)	7 (87.5, 50.8-99.9)
Anterior Communicating Artery Segment				
Anterior surface	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)
Posterior surface	0 (0)	0 (0)	0 (0)	0 (0)
Superior surface	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)
Inferior surface	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)	8 (100; 62.8-104.8)
Anterior Cerebral Artery (A2 Segment)	3 (37.5, 13.5-69.6)	3 (37.5, 13.5-69.6)	2 (25.0; 6.3-59.9)	2 (25.0; 6.3-59.9)

ICA, internal carotid artery; A1, proximal anterior cerebral artery; A2, distal anterior cerebral artery

CHAPTER 14

EXPANDED ENDOSCOPIC ENDONASAL SKULL BASE SURGERY AND THE RISK OF POSTOPERATIVE SEIZURE: A SYSTEMATIC REVIEW OF PUBLISHED EVIDENCE

PREFACE TO CHAPTER 14

With the increased applications of endoscopic endonasal procedures that are currently performed for a variety of cranial base pathologies, it becomes relevant to know the risk of postoperative seizures following these types of surgeries. This chapter investigates the incidence of postoperative seizure following expanded endoscopic endonasal skull base surgery.

This chapter has been peer reviewed and published:

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AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and performed the literature review for this study. Dr Lai and Mr. Trooboff acquired the data. Professor Morgan and Professor Harvey provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Professor Harvey, and Dr Lai. Professor Morgan, Professor Harvey and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Although postoperative seizure is an acknowledged risk following transcranial surgery, the incidence of seizure after removal of intradural pathology via an expanded endoscopic endonasal approach is not well defined. The current study was performed to systematically review the risk of seizure in patients under- going endoscopic endonasal skull base (EESB) surgery.

METHODS: Embase (1980 to 9 March 2012) and Medline (1950 to 9 March 2012) were searched using a search strategy designed to include any studies that report the perioperative outcomes following EESB surgery. Outcomes of patients undergoing a simple closure of cerebrospinal fluid fistulae or encephaloceles and transellar approaches for pituitary or intrasellar lesions were excluded because this review is focused on large skull base defects. A title search selected those articles relevant to clinical series on expanded endoscopic approaches. A subsequent search of abstracts selected for manuscripts of any report that documented the presence or absence of postoperative seizure.

RESULTS: A total of 2234 manuscripts were selected initially and full text analysis produced 67 studies with extractable data regarding the perioperative outcomes for EESB surgery. Of these manuscripts, seven reported the incidence of seizure following EESB procedures. Two of these studies were excluded due to duplication of authorship and institutional data. The overall risk of postoperative seizure following EESB surgery was estimated at 1.1% (six of 530). Subgroup analyses of data revealed that the risk of seizure following an endoscopic endonasal to the anterior cranial base was 2.3% (one patient of 43). For a posterior cranial base approach, the risk of seizure was indeterminate due to deficiency of reporting in the current literature.

CONCLUSION: We concluded that the risk of seizure following an EESB procedure appears to be low (1%). However, the lack of reporting on the incidence of seizures or the use of antiepileptic pro- phylaxis following EESB procedure is a key limitation. Future EESB studies will need to include seizure as an outcome to accurately define this risk.

INTRODUCTION

In neurosurgical centers in recent years there has been an ongoing trend to consider endoscopic endonasal surgery as the preferred option when managing both benign and malignant diseases of the cranial base (439, 465). The advantages offered by this technique over conventional trans-cranial or trans-facial surgery is in part related to minimal disruption of normal tissue, superior visualisation at the target, and the avoidance of brain and cranial nerve retraction. Moreover, the extent of tumor resection afforded by the endoscopic ventral approaches is considered comparable to traditional microsurgical skull base series (466-468).

As the clinical indications for EESB surgery continues to expand, few studies have defined the risk of postoperative seizures following this type of surgery. The aim of this study was to critically and systematically review the data available on the perioperative outcomes of published case series, cohorts and case control studies on EESB surgeries of various cranial base lesions. The primary outcome measure was to define the overall incidence of seizure following an expanded EESB surgery. The secondary outcome measure was to establish if a difference exists in the seizure rates for anterior skull base approach compared to a posterior skull base approach.

METHODS

A systematic review of published literature was performed for the primary outcome of postoperative seizure following endoscopic skull base surgery. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org) style was adhered to where possible but quality assessment was not performed, as the target study type was case series and cohorts.

Eligibility criteria

Published manuscripts in English were eligible. All manuscripts reporting original data on patients undergoing endoscopic endonasal trans-cranial surgery were eligible, including those with any intervention for the treatment of specific pathologies, such as meningioma, craniopharyngioma, skull base metastasis, chordoma and chondrosarcoma where a trans-cranial transdural approach would be anticipated. Because this review is of large skull base defects, outcomes of patients undergoing simple closure of CSF fistulae or encephaloceles and transellar approaches for pituitary or intrasellar lesions were excluded due to the vast

majority of these defects being relatively small. Only the studies where an endonasal craniotomy was created as part of a procedure were included. Trials included subjects of any age, with any co-morbidity, and with varied duration of follow-up were included. Local and regional flap reconstructions of endonasal skull base surgery series were included. Case series, case-control studies, cohort studies and randomized controlled trials were included.

Search criteria

The Medline database was searched from 1950 to March 09, 2012, and the EMBASE database was searched from 1980 to March 09, 2011. The Cochrane Collaboration database and the NHS Evidence Health Information Resources website were also searched. The bibliographies of identified manuscripts were also reviewed and used as an additional data source. No unpublished trials were included. We designed a search strategy to include manuscripts relevant to any aspect of endoscopic skull base surgery and skull base reconstruction. The search strategy used for EMBASE and MEDLINE databases is shown in Table 14.1.

Two authors (LTL and ST) selected the studies in an un-blinded standardised manner once the searches were completed. The publications extracted were grouped by title and obvious duplicates were excluded. The abstracts were then reviewed to ascertain whether they met the inclusion and exclusion criteria.

Data extraction

Standardised data sheets were used for each study. The primary outcomes were recorded as the presence or absence of reporting for postoperative seizures as well as the use of peri-operative anti-epileptic drugs (AEDs). Secondary analysis of this outcome focused on the dichotomisation of data for anterior skull base (via a transcribiform or a transplanum route) and posterior skull base surgeries (via a transclival route) to establish if a difference exists in the seizure rates following these two types of endonasal approaches. For each group, the number of patients, the type of approach, pathology, and peri-operative morbidity relevant to the skull base surgery was recorded. The large range of methods, study aims, and pathologies were reported qualitatively in the data. Studies were deemed suitable for inclusion only if they document the presence or absence of postoperative seizure following EESB surgery.

Statistical analysis

Statistical assessments were performed primarily with descriptive data. Case by case analysis was performed for summary data. Assessment of different pathologies was performed as nominal data and analysed using SPSS software version 17 (Statistical software for social sciences, SPSS Inc. Chicago, IL).

RESULTS

Literature Review Results

The search of EMBASE and Medline produced a total of 2211 studies written in English. Additional records identified through bibliographic and referencing resources yielded further 23 studies that were included in the analysis, thus a total of 2234 studies. After exclusion of duplicates, 1805 studies remained. A title search found 278 articles on skull base surgery. Those studies captured in the search that described simple CSF leak repairs (n=47; 16.9%), repairs for encephaloceles (n=6; 2.2%), and microscopic skull base series (n=59; 21.2%) were excluded from the analysis. The selection process is outlined in Figure 14.1.

The remaining 166 articles describing solely EESB surgery were subjected to full-text assessment. Of these, 43 (25.9%) were reviews of endoscopic or endonasal techniques, 19 (11.4%) were pituitary series utilising the transellar approach, 15 (9.0%) were simple case reports and 22 (13.2%) had no extractable data. These studies were further excluded.

Primary Outcome Measure: Overall Risk of Seizure following Expanded Endoscopic Endonasal Skull Base Surgery

The full-text analysis produced 67 studies with extractable data regarding endoscopic endonasal trans-cranial surgery for various pathologies of the skull base (427, 440, 463, 464, 469-531). Among them, seven studies (10.4%) commented on the postoperative seizure status following EESB surgery (464, 469, 481, 494, 519, 520, 526). The other 60 studies did not. Two of the seven studies were excluded from the analysis due to duplicity in reporting by the same author and institutional database (464, 520). One study was excluded because the reported seizure event was related to a transellar approach for a non-functioning pituitary

macro-adenoma (481). None of the 67 full-text articles commented on the use of antiepileptic medications, either prophylactically or therapeutically.

The remaining four studies were included in the quantitative analysis to determine the overall risk of postoperative seizure following EESB surgery (469, 494, 519, 526) (Table 17.2). In all, there were a total of 859 patients, of which only 530 were considered to have undergone EESB surgery. All patients with pituitary adenomas in which a transellar approach was used were excluded from the analysis. The mean age was 54.1 years (range 3-96 years). The overall incidence of postoperative seizure following endoscopic skull base surgery was estimated at 1.1% (6/530). One case occurred following resection of a sinonasal malignant tumor that extended into the anterior cranial base (526). The remaining five patients were reported in a large review from the University of Pittsburgh's endoscopic skull base surgical experience (519). The types of trans-cranial corridors in these five patients, however, were not specified.

Secondary Outcome Measure: Subgroup Analysis for Risk of Seizure Following Expanded Endoscopic Endonasal Anterior Skull Base and Posterior Skull base Surgeries.

Twenty studies described the endoscopic endonasal transcribiform or transplanum approach to various lesions of the anterior skull base (440, 469, 471, 473, 475, 483, 490, 494, 495, 497, 499, 502, 505, 507, 509, 517, 518, 523, 525, 526). Among them, only three studies commented on the postoperative seizure status of patients (469, 494, 526) (Table 14.3). Quantitative analyses of these three articles revealed a total of 43 patients with a mean age of 55.7 years (range 19 to 91 years) followed up over a mean 19.1 months (range 3-62 months). Forty-two of the 43 patients (97.7%) had various sinonasal malignancies with trans-cranial extension and one patient (2.3%) suffered from an anterior cranial base metastasis requiring extended endoscopic endonasal resection. Overall, one patient experienced a seizure 3 weeks after being released from hospital (2.3%). Brain Computed Tomography (CT) scans showed moderate subdural haematoma, which was treated conservatively. Peri-operative use of AED was not mentioned in this case.

Ten studies described the endonasal transclival approach to the posterior cranial fossa in 116 patients with a mean age of 46.4 years (range 4-87 years) (470, 482, 484, 491, 501, 504, 508, 510, 516, 522) (Table 14.4). There were 48 females (41.4%) and the mean follow up was 15.4 months (range 0.2-54 months). The majority of pathologies were due to chordoma (n=95),

chondrosarcoma (n=3), Meningioma (n=2) and metastasis (n=2). Neither seizures nor the prophylactic use of AED were reported in any of these 10 studies.

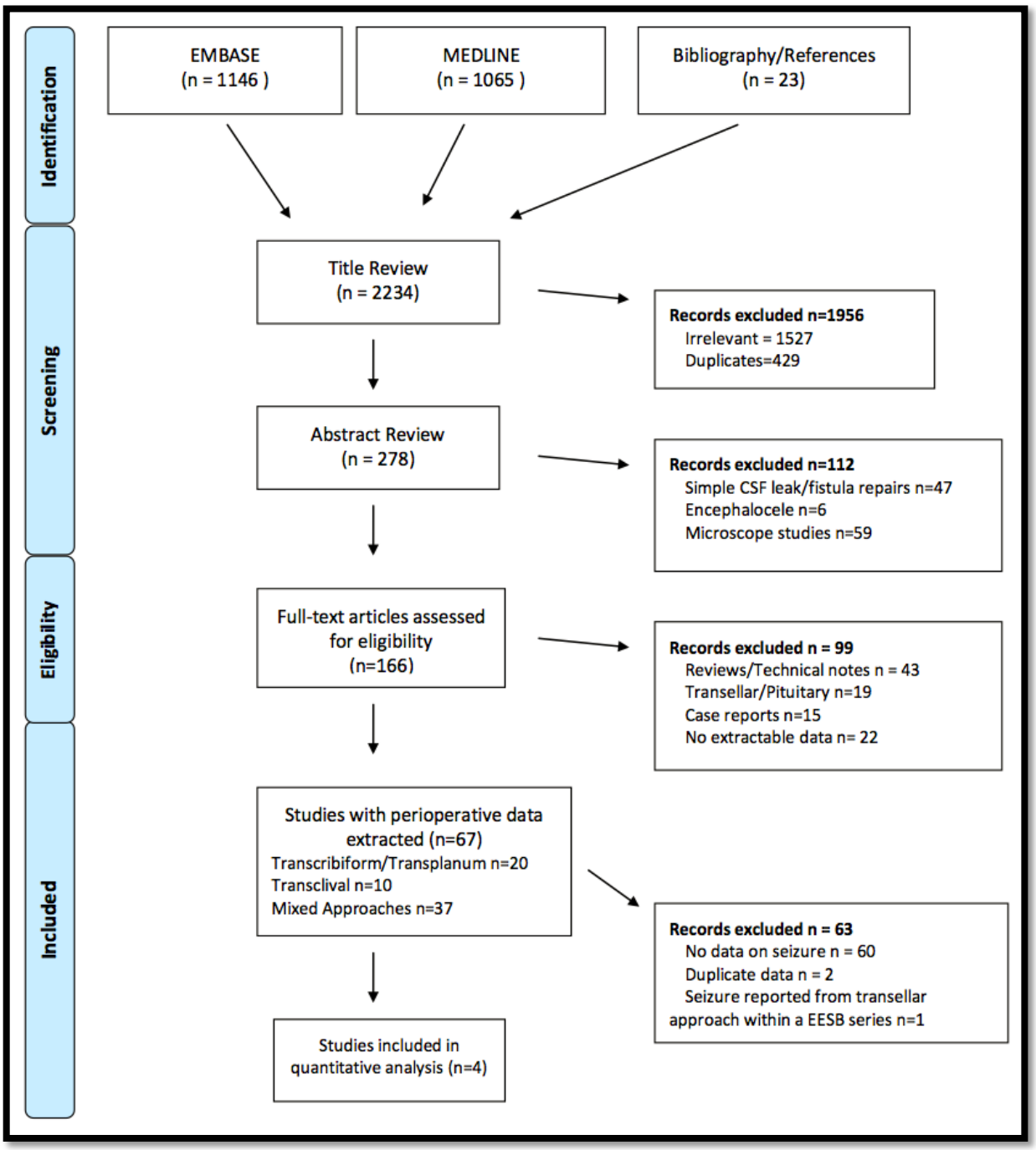

Figure 14.1 Article selection process from EMBASE and Medline database searches

DISCUSSION

The risk of postoperative seizure following intracranial surgery is well recognised. Its true incidence, however, remains variable depending on the types of pathology and the surgical approaches utilized. For supratentorial craniotomies, the overall incidence of postoperative seizures was reported at 17 per cent in a retrospective study of 1000 patients (241). With variability in pathologies, this risk may differ for aneurysms (range 3%-42.1%) (240, 241), arteriovenous malformations (range 5.9-50.0%) (532, 533) and supratentorial meningioma (range 6.3%-22.9%) (534, 535). For surgeries in the posterior fossa, the development of postoperative seizures is less well known but is clearly likely to be less of a problem as compared with supratentorial surgery, and incidences have been reported to range from 1.8% to 5.9% (536, 537).

Table 14.1 Medline search strategy (similar modified version used in EMBASE)

1. exp Cranial Fossa, Anterior/in, pa, su [Pathology, Surgery] or anterior cranial fossa.mp.
2. exp Cranial Fossa, Middle/in, pa, su [Pathology, Surgery] or middle cranial fossa.mp.
3. exp Cranial Fossa, Posterior/in, pa, su [Pathology, Surgery] or posterior cranial fossa.mp.
4. exp Sella Turcica/in, pa, su [Pathology, Surgery] or Sella Turcica.mp.
5. exp Skull Base Neoplasms/co, pa, su [Complications, Pathology, Surgery] or skull base neoplasm$.mp
6. exp Skull Base/in, pa, su [Pathology, Surgery] or skull base.mp.
7. or 1-6
8. exp Endoscopy/ae, co [Adverse Effects, Complications] or endoscop$.mp.
9. exp Neuroendoscopy/ae [Adverse Effects] or neuroendoscop$.mp.
10. (transethm$ or transsphen$ or transcliv$ or transplan$).mp.
11. (trans-ethm$ or trans-sphen$ or trans-cliv$ or trans-plan$).mp.
12. (transnas$ or trans-nas$ or endonas$ or endosin$).mp.
13. (endoscopic endonas$ or expanded endoscopic endonas$).mp
14. exp Craniotomy/ae, su [Adverse Effects, Surgery] or craniotomy.mp.
15. craniectomy.mp.
16. exp Dura Mater/su [Surgery]
17. exp Surgical Procedures, Minimally Invasive/ae [Adverse Effects] or Surgical Procedures, Minimally Invasive.mp.
18. or 8-17
19. exp Seizure/co, su [Complications, Surgery]or seizur$.mp.
20. exp Epilepsy/co, su [Complications, Surgery] or epileps$.mp.
21. convulsion.mp.
22. exp treatment outcome/ or treatment outcome.mp.
23. exp postoperative complication/ or postoperative complication$.mp.
24. or 19-23
25. 7 and 18 and 24
26. Limit 25 to English language

Seizures following microsurgical resection of skull base lesions are thought to occur less commonly. In a retrospective study involving 136 consecutive patients after open skull base surgery, Jenssen et al. reported zero incidences of clinical seizures (538). Of the 17 patients who had electroencephalogram assessment, 11 demonstrated sharp waves on the side of the surgery, the significance of which was unclear. In another study, Al-Melfty et al. described the occurrence of postoperative non-convulsive encephalopathy status in seven patients following surgical resection for skull base tumors (539). Clinical manifestation included postoperative delayed and progressive decline in the level of consciousness to deep coma that is time-limited to several days with abrupt awakening. However, the incidence of postoperative seizure was not determined in this study.

Because of the need to determine the role for prophylactic AEDs and the timing to return to driving following surgery, defining the postoperative seizure risk is important following endoscopic endonasal approaches to various skull base pathologies. In the current study, we performed a systematic analysis of the literature to establish the risk of seizure following expanded endoscopic endonasal skull base surgery. Our results indicated an overall 1.1% risk of seizures following EESB surgery. Cases that involved endoscopic pituitary resection were excluded because simple transellar approach with no arachnoid dissection was not considered to be extensive skull base surgery. However, in our review, one case of postoperative seizure occurred in a 40-year old male following total resection of an intrasellar non-functioning pituitary macroadenoma. This patient developed generalised tonic-clinic seizures a few hours after the surgical procedure. It was thought that the large amount of intraoperative CSF loss and consequent pneumocephalus had triggered the seizure event (464).

A subgroup analysis of the available data indicated that the risk of seizures following an expanded EESB surgery to the anterior cranial fossa was 2.3%. However, for an endonasal approach to the posterior skull base, the incidence of seizure was indeterminate due to deficiency of reporting in the current literature.

The development of seizures following surgical resection may be associated with a number of important factors. First, the intrinsic nature of the lesion, particular for those located in the temporal or parietal lobes may be more epileptogenic than those located in the skull base (540). Secondly, retraction injury and circulatory compromise during surgery could also increase the risk of seizures. In a study that investigated the risk of seizure relative to surgical approach and localisation of lesion in patients with acoustic neuromas, Cabral et al. reported epilepsy only with the combined translabyrinthine/transtentorial approach in 22 per cent of

the cases compared with 0 per cent of those in whom the standard translabyrinthine route was used(541). Thomsen et al. demonstrated new onset and persistent epileptiform activity in EEG after surgery when using a middle fossa approach as compared to translabyrinthine approach (542). More importantly, postsurgical complications such as subdural haematoma, infection or oedema may further contribute to the risk of seizure development. In a study of 16 patients undergoing endoscopic skull base resection for ethmoid adenocarcinoma and olfactory neuroblastoma, Carta et al. described a case of seizures that occurred in a patient three weeks after being discharged from hospital. CT demonstrated moderate amount of subdural haematoma, which was treated conservatively (526). Among the five patients reported with postoperative seizures following EESB surgery in the Pittsburgh's surgical experience, one case of status epilepticus occurred in a patient with postoperative meningitis (519).

LIMITATIONS OF STUDY

The interpretation of our results is limited, in part, by the lack of uniform reporting for peri-operative outcomes following EESB surgeries. Seizures and the use of antiepileptic medications were not frequently reported. This limited the ability to robustly stratify seizure risks following anterior versus posterior skull base approaches, or in establishing the significance of meningitis or subdural haematoma to predict seizure development. More importantly, the issues of prophylactic antiepileptic medication use and return to driving following EESB surgery could not be addressed based on information currently available in the endoscopic skull base literature.

CONCLUSION

Our systematic analysis suggests that the overall risk of seizure following an EESB procedure may be low (1%). For an anterior cranial base surgery, this risk was 2.3%. However, the lack of reports on the incidence of seizures or the use of antiepileptic prophylaxis following EESB procedure is a key limitation. Future studies reporting therapeutic results for EESB surgeries will need to include seizure as an outcome measure in order to accurately define this risk.

DECLARATION OF INTEREST AND ACKNOWLEDGEMENTS

Dr Lai is supported by a scholarship funded by Carl Zeiss Co. The authors declare that they have no further financial or other conflicts of interest in relation to this research and its publication.

Table 14.2 Endoscopic endonasal skull base surgery and reported seizure incidence: characteristics of included studies

Author & Year	Total Patients	EESB Patients	Mean Age (yrs)	Sinonasal origin	Intracranial origin	Seizures	AEDs	Details of Seizures
Batra et al., 2005	9	9	55.0	9	0	0	NR	
Cohen et al., 2009	18	18	53.0	17	1	0	NR	
Kassam et al., 2011	487	487	49.2	85	402	5	NR	1 status epilepticus occurred from a patient with meningitis following EESB surgery.
Carta et al., 2011	16	16	59.0	16	0	1	NR	1 seizure occurred 3 weeks post discharge - CT showed moderate SDH.

*EESB patients were defined by true intracranial surgery with dural resection. EESB; endoscopic endonasal skull base ; AED: antiepileptic drug use. SDH: Subdural Haematoma; CT, computed tomography; NR: not reported.

Table 14.3 Endoscopic endonasal transcribiform/transplanum approach to the anterior skull base and reported seizure incidences*

Author & Year	Total Patients	EESB Patients	Mean Age (yrs)	Sinonasal origin	Intracranial origin	Mean FU (Mths)	Seizure	AEDs
Batra et al., 2005	25	9	55.0	9	0	24.0	0	NR
Carrau et al., 2006	20	20	NR	19	1	22.0	NR	NR
Leong et al., 2006	14	10	57.4	10	1	18.0	NR	NR
Dave et al., 2007	19	19	61.6	18	1	34.3	NR	NR
Divitiis et al., 2008	11	11	55.3	0	11	20.6	NR	NR
Nicolai et al., 2008	184	134	58.7	134	0	36.6	NR	NR
Stamm et al., 2008	7	7	23.4	0	7	36.2	NR	NR
Cavallo et al., 2009	22	22	49.4	0	22	28.6	NR	NR
Cohen et al., 2009	18	18	53.0	17	1	14.2	0	NR
Eloy et al., 2009	18	18	61.2	15	3	26.0	NR	NR
Folbe et al., 2009	23	16	56.6	16	0	45.2	NR	NR
Liu et al., 2009	10	10	38.4	4	3	NR	NR	NR
Vergez et al., 2009	17	17	68.0	17	0	35.5	NR	NR
Batra et al., 2010	31	31	57.5	30	1	31.7	NR	NR
Greenfield et al., 2010	44	43	55.4	11	7	29.0	NR	NR
Villaret et al., 2010	62	62	61.7	62	0	NR	NR	NR
Gallia et al., 2011	8	8	56.9	8	0	27.3	NR	NR
Muscatello et al., 2011	13	9	65.6	9	0	20.2	NR	NR

Van Gompel et al., 2011	13	13	62.0	0	13	14.9	NR	NR
Carta et al., 2011	16	16	59.0	16	0	NR	1	NR

* EESB patients were defined by true intracranial surgery with dural resection. AED: antiepileptic drug use. FU: follow up. NR: not reported.

Table 14.4 Endoscopic endonasal transclival approach to the posterior skull base surgery and reported seizure incidences*

Author & Year	Total Patients	EESB Patients	Mean Age (yrs)	Sinonasal origin	Intracranial origin	Mean FU (Mths)	Seizure	AEDs
Solares et al., 2005	6	6	50.0	1	4	13.0	NR	NR
Carraba et al., 2008	17	17	48.0	0	13	16	NR	NR
Dehdashti et al., 2008	12	12	49.4	0	12	16.0	NR	NR
Zhang et al., 2008	9	9	35.0	0	9	21.4	NR	NR
Hong et al., 2009	12	12	39.3	0	12	20.8	NR	NR
Stippler et al., 2009	20	20	44.4	0	20	12.5	NR	NR
Fraser et al., 2010	17	17	52.4	0	12	8.5	NR	NR
Holzmann et al., 2010	13	13	45.5	0	13	17.5	NR	NR
Prevedello et al., 2010	2	2	44.5	0	0	13.5	NR	NR
Mundi et al., 2011	8	8	55.0	0	8	15.0	NR	NR

*EESB patients were defined by true intracranial surgery with dural resection. AED: antiepileptic drug use. FU: follow up. NR: not reported.

CHAPTER 15

THE RISK OF MENINGITIS FOLLOWING EXPANDED ENDOSCOPIC ENDONASAL SKULL BASE SURGERY: A SYSTEMATIC REVIEW

PREFACE TO CHAPTER 15

With the rapid expansion of endoscopic endonasal skull base (EESB) surgeries for the treatment of cranial base pathologies, there remains an inherent concern among neurosurgeons with regards to the risk of postoperative CSF leak and meningitis. Through a systematic analysis of the published evidence in the literature, this chapter investigates the incidence of postoperative meningitis and CSF leak following EESB surgery

This chapter has been peer reviewed and published:

Lai, L., Morgan, KM., Trooboff, S., Harvey, RJ. The risk of meningitis following expanded endoscopic endonasal skull base surgery: A systematic review. Journal of Neurological Surgery, Part B: Skull Base, 2014; 75(1), 18-26.

AUTHOR'S CONTRIBUTION

Dr Lai conceived, designed and performed the literature review for this study. Dr Lai and Mr. Trooboff acquired the data. Professor Morgan and Professor Harvey provided advice and supervision during the conception and design of the study. Analysis and interpretation of the data was performed by Dr Lai. The manuscript was written by Dr Lai, and revised by Professor Morgan and Professor Harvey, and Dr Lai. Professor Morgan, Professor Harvey and Dr Lai approved the final version for publication.

ABSTRACT

OBJECTIVE: Meningitis in the postoperative period following an expanded endoscopic endonasal skull base (EESB) procedure is a significant surgical morbidity. These cases are uncommon and published clinical experience is often limited to small groups. The current study was performed to systematically review the reported incidence of meningitis from EESB surgery.

METHODS: A systematic analysis of publications identified through searches of the electronic databases from EMBASE (1980-July 17, 2012), Medline (1950-July 17, 2012) and references of review articles. Simple pituitary tumor studies were not included. All publications reporting on peri-operative complications and morbidity related to EESB surgery were included. Data were extracted and appraised independently and in duplicate, using standardised forms.

RESULTS: 2,444 manuscripts were selected initially and full text analysis produced 67 studies with extractable data regarding the peri-operative outcomes for EESB surgery. Fifty-two contained data regarding the frequency of postoperative meningitis. The overall risk of postoperative meningitis following EESB surgery was 1.8% (36/2005). For those reporting a CSF leak, meningitis occurred in 13.0% (35/269). For those not reporting a CSF leak, meningitis occurred in 0.1% (1/1736). The odds ratio for the development of meningitis in the presence of a postoperative CSF leak following an EESB procedure was 91.99 (95%CI 11.72-721.88; $p < 0.01$). There was no difference in reported incidence of meningitis or CSF leak between anterior and posterior cranial fossa surgery. There was one reported case of meningitis-related mortality following EESB surgery.

CONCLUSION: The evidence in skull base surgery is limited. This study demonstrates a low incidence of meningitis (1.8%) following EESB procedures. The incidence of meningitis from EESB surgery without an associated CSF leak is uncommon.

INTRODUCTION

Advancements in endoscopic endonasal skull base (EESB) surgery continue to evolve with increasing surgical complexity (439, 458, 465, 472, 484, 496, 543-546). The establishment of the endonasal route enables access and visualisation to the ventral cranial base through the narrowest practical corridor with minimal trauma to surrounding tissue. Within anatomical limitations, the degree of tumor resection and vascular manipulation is often considered comparable to conventional microsurgical skull base techniques (102, 103, 105-108, 458, 466-468, 546-548).

Major concerns following EESB surgery, however, are the risk of cerebrospinal fluid (CSF) rhinorhea and meningitis. Much improvement has been made with the development of vascularised mucosal flaps to aid in the reconstruction of the skull base after EESB surgery (439, 549, 550). These endoscopic reconstructions not only provide a reliable separation of the cranial and sinonasal cavity but are robust over time (551). A recent systematic review demonstrated that the rate of CSF leak after true intradural EESB was 15.6% (representing 51 out of 326 patients) with free graft techniques and 6.7% with vascularised flap reconstructions (representing 19 out of 283 patients) (439). This is comparable with open craniofacial surgery (552) but questions still arise due to the inability to formally provide a sterile field and connection with the upper aero-digestive tract.

Skull base pathologies are uncommon and thus the published evidence base is limited to centers with small numbers. Establishing the frequency of complications from small populations is challenging. The aim of this study was to review critically and systematically the data available on the peri-operative outcomes of published case series, cohorts and case control studies for endoscopic endonasal approaches to various cranial base pathologies. The primary outcome measure was to identify the incidence of meningitis following an intradural EESB procedure and to correlate this with the reported incidence of postoperative CSF leak rates. The secondary outcome measure was to establish if a difference in the risk of meningitis exists following EESB surgery to the anterior cranial fossa (ACF) versus a posterior cranial fossa (PCF) approach.

METHODS

A systematic review of published literature was performed for the primary outcome of postoperative meningitis following endoscopic skull base surgery. A Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA; www.prisma-statement.org) style was adhered to where possible but quality assessment was not performed, as the target study type was case series and cohorts.

Eligibility Criteria

Published manuscripts in English were eligible. Case series, case-control studies, cohort studies and randomized controlled trials were included. Only manuscripts reporting original data on patients undergoing endoscopic endonasal transcranial surgery were eligible, including those with any intervention for the treatment of specific pathologies, such as meningioma, craniopharyngioma, skull base metastasis, chordoma and chondrosarcoma where a transcranial transdural approach would be required. Because this review is of large skull base defects, outcomes of patients undergoing simple closure of CSF fistulae or encephaloceles and transellar approaches for pituitary or intrasellar lesions were excluded due to the vast majority of these defects being relatively small. Only studies where an endonasal craniotomy was created as part of a procedure were included. Trials included subjects of any age, with any co-morbidity, and with varied duration of follow-up were included. Local and regional flap reconstructions of endonasal skull base surgery series were included.

Search Criteria

The Medline database was searched from 1950 to July 17, 2012, and the EMBASE database was searched from 1980 to July 17, 2012. The Cochrane Collaboration database and the NHS Evidence Health Information Resources website were also searched. The bibliographies of identified manuscripts were reviewed for additional data sources. No unpublished trials were included. We designed a search strategy to include manuscripts relevant to any aspect of endoscopic skull base surgery and skull base reconstruction. The search strategy used for EMBASE and Medline databases is shown in Table 15.1.

Two authors (LTL and ST) selected the studies in an un-blinded standardised manner once the searches were completed. The publications extracted were grouped by title and duplicates were excluded. The abstracts were then reviewed to ascertain whether they met the inclusion and exclusion criteria as described above.

Data Extraction

Standardised data sheets were used for each study. The primary outcomes were recorded as the presence or absence of reporting on postoperative CSF leak and meningitis events. Secondary analysis of this outcome focused on the dichotomisation of data for anterior cranial fossa (via a transcribiform or a transplanum route) and posterior cranial fossa surgeries (via a transclival route) to establish if a difference exists in the rate of meningitis following these 2 types of endonasal approaches. For each group, the number of patients, the type of approach, pathology, and peri-operative morbidity relevant to the skull base surgery was recorded. The large range of methods, study aims, and pathologies were reported qualitatively in the data. Studies were deemed suitable for inclusion only if they document the presence or absence of postoperative meningitis following EESB surgery or explicitly stated that patients had no further adverse events other than that reported. Where duplicate publication was anticipated from centers re-publishing updated reports on their EESB experience over time (470, 471, 488, 516, 531, 553-556) the most recent or largest published data was included for analysis in the current study.

Statistical Analysis

Statistical assessments were performed primarily with descriptive data. Case by case analysis was performed for summary data. Comparison of proportions for small numbers was performed with a Fisher's exact test, where appropriate, significance was set to a probability value of 0.05. Logistic regression analysis was used to calculate the odds ratio in predicting the likelihood of meningitis. Assessment of different pathologies was performed as nominal data and analysed using SPSS software version 19 (Statistical software for social sciences, SPSS Inc. Chicago, IL).

RESULTS

Literature Review Results

The search of EMBASE and Medline produced a total of 2429 studies written in English. Additional records identified through bibliographic and referencing resources yielded a further 15 studies that were included in the analysis, totaling to 2444 studies. After exclusion of duplicates, 1985 studies remained. A title search found 293 articles on skull base surgery.

Those studies captured in the search that described simple CSF leak repairs (n=49; 16.7%), repairs for encephaloceles (n=14; 4.8%), and microscopic skull base series (n=59; 20.1%) were excluded from the analysis. This selection process is outlined in Figure 15.1.

The remaining 171 articles describing EESB surgery were subjected to full-text assessment. Of these, 56 (32.7%) were reviews of endoscopic or endonasal techniques, 33 (19.3%) were pituitary series utilising the transellar approach, and 15 (8.8%) were simple case reports. These simple case report studies were excluded due to strong publication bias.

Table 15.1 Medline search strategy (similar modified version used in EMBASE)

1. exp Cranial Fossa, Anterior/in, pa, su [Pathology, Surgery] or anterior cranial fossa.mp.
2. exp Cranial Fossa, Middle/in, pa, su [Pathology, Surgery] or middle cranial fossa.mp.
3. exp Cranial Fossa, Posterior/in, pa, su [Pathology, Surgery] or posterior cranial fossa.mp.
4. exp Sella Turcica/in, pa, su [Pathology, Surgery] or Sella Turcica.mp.
5. exp Skull Base Neoplasms/co, pa, su [Complications, Pathology, Surgery] or skull base neoplasm$.mp
6. exp Skull Base/in, pa, su [Pathology, Surgery] or skull base.mp.
7. or 1-6
8. exp Endoscopy/ae, co [Adverse Effects, Complications] or endoscop$.mp.
9. exp Neuroendoscopy/ae [Adverse Effects] or neuroendoscop$.mp.
10. (transethm$ or transsphen$ or transcliv$ or transplan$).mp.
11. (trans-ethm$ or trans-sphen$ or trans-cliv$ or trans-plan$).mp.
12. (transnas$ or trans-nas$ or endonas$ or endosin$).mp.
13. (endoscopic endonas$ or expanded endoscopic endonas$).mp
14. exp Craniotomy/ae, su [Adverse Effects, Surgery] or craniotomy.mp.
15. craniectomy.mp.
16. exp Dura Mater/su [Surgery]
17. exp Surgical Procedures, Minimally Invasive/ae [Adverse Effects] or Surgical Procedures, Minimally Invasive.mp.
18. or 8-17
19. exp Meningitis/co, su [Complications, Surgery] or meningitis.mp.
20. exp Cerebrospinal Fluid Rhinorrhoea/co, su [Complications, Surgery] or cerebrospinal fluid rhinorrhea.mp.
21. exp postoperative complication/
22. exp Treatment Outcome/ or treatment outcome.mp.
23. or 19-22
24. 7 and 18 and 23
25. Limit 24 to English language

Peri-operative outcomes were recorded for 67 EESB studies. An additional 15 studies were excluded due to duplicity of data (n=2) and non-extractable outcomes for meningitis (n=13). Fifty-two studies with reports of post-treatment meningitis were included in the final analysis (Table 15.2).

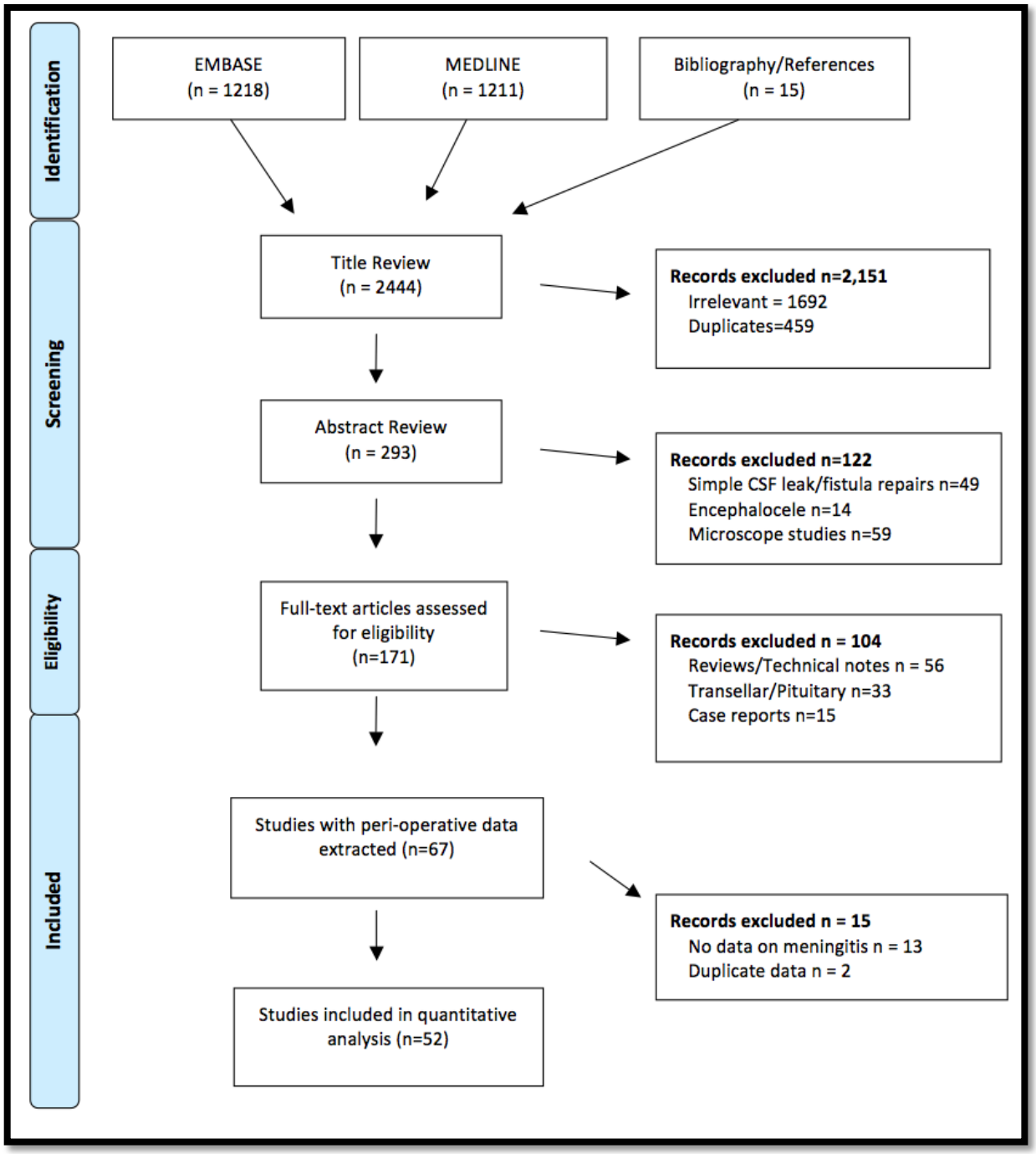

Figure 15.1 Article selection process from EMBASE and Medline database searches

Primary Outcome: Overall Risk of Meningitis following Expanded EESB Surgery

Quantitative analysis revealed a total of 2363 patients, of which 2005 were considered to have undergone an expanded EESB surgery. An attempt was made to exclude all patients with pituitary adenomas in which a transellar approach was used from the analysis. The mean age was 49.8 years (range 3- 91 years) and the mean follow up was 21.8 months (range 0.2-152 months). Of the studies that report on gender, females accounted for 49.8% of cases (943/1893).

The overall incidence of postoperative meningitis following EESB surgery was 1.8% (36/2005). Of the total population, 269 experienced a postoperative CSF leak (Table 15.3). This was represented as a 13.0% (35/269) risk of meningitis for those patients with CSF leak compared to 0.1% (1/1736) for non-CSF leak cases (X^2 = 221.64; p<0.01). Overall, the odds of developing meningitis in the presence of a postoperative CSF leak following an EESB procedure were 91.99 (95% CI 11.72-721.88; p < 0.01).

One death related to postoperative meningitis was reported in a 42 year-old male following an endoscopic transsphenoidal supra-diaphragmatic resection of a hypothalamic astrocytoma.(543) This patient underwent an uneventful subtotal resection of the tumor but experienced postoperative meningitis and died 2 weeks following surgery.

Secondary Outcome: Subgroup Analysis for Risk of Meningitis following Expanded EESB surgeries to the Anterior Cranial versus Posterior Cranial Fossae.

Thirty-two studies described the endoscopic endonasal transcribiform or transplanum approach to the anterior skull base (440, 464, 471-473, 477, 485-487, 490, 495, 531, 544, 557-561)(494, 496, 502, 511, 514, 526, 562-569). Of these 32 studies, 664 patients were considered to have undergone expanded EESB surgery of the ACF. The mean age was 51.9 years (range 4 to 91 years) and the mean follow up was 26.3 months (range 0.8 to 152 months). Sinonasal malignancies with transcranial extension was accounted for in 409 cases (61.6%), craniopharyngioma in 112 cases (16.9%), meningioma in 66 cases (9.9%), Rathke's cleft cyst in 43 cases (6.5%), chordoma in 7 cases (1.1%), metastasis in 5 cases (0.8%), glioma in 1 case (0.2%) and chondrosarcoma in 1 case (0.2%).

The risk of postoperative meningitis following EESB surgery to the ACF was 1.7% (11/664) and an 11.3% (75/664) CSF leak rate. The odds of developing postoperative meningitis

among the ACF cases with a postoperative CSF leak were 90.46 (95%CI 11.40-717.99; p<0.01). In contrast, only 1 patient experienced meningitis (0.2%) among the 589 patients with no postoperative CSF leak.

Nine studies described the endonasal transclival approach to the PCF in 97 patients with a mean age of 48.6 years (range 4 to 87 years).(427, 470, 478, 482, 484, 516, 556, 570, 571) There were 39 females (40.2%) and the mean follow up was 14.9 months (range 0.2 to 69 months). Chordoma was accounted for in 73 cases (75.3%), chondrosarcoma in 5 cases (5.2%), metastasis in 2 cases (2.1%), meningioma in 2 cases (2.1%), Sinonasal malignancy with posterior cranial fossa extension in 1 case (1.3%) and vascular in 1 case (1.3%).

The risk of meningitis following an EESB approach to the PCF was 1.0% (1/97) and a 16.5% (16/97) CSF leak rate. There were no reported meningitis cases in the 81 patients with no postoperative CSF leak and therefore no odds ratio was calculated. However, the presence of a postoperative CSF leak was significantly associated with the development of meningitis (X^2 = 5.12; p=0.02).

Overall, no differences between ACF and PCF outcomes were seen. The incidences of meningitis following an expanded EESB surgery to the ACF and PCF were similar, 1.7% (1/97) and 1.0% (1/97), respectively (X^2 = 0.21; p=0.64). The incidences of postoperative CSF leak following an EESB surgery to the ACF was 11.3% (75/664) and 16.5% (16/97) to the PCF, (X^2 = 2.17; p=0.14).

DISCUSSION

In the past decade, the application of EESB surgery to midline cranial base pathologies has been established through various cadaveric and clinical studies.(106, 420, 421, 458, 510, 546) The rapid expansion of this technique, however, carries with it a particular concern for the infectious ramifications of operating through the "clean-contaminated" field of the sinonasal cavities.(572) Problems with closure of the dura mater and prevention of CSF leaks remain a challenge and a significant source of postoperative morbidity following an endoscopic transnasal craniotomy.

In the current study, a systematic analysis of the literature was performed to establish the incidence of meningitis following expanded EESB surgery. Our results indicated an overall 1.8% risk of postoperative meningitis. The risk, however, was not substantially different for

an endoscopic endonasal approach to the anterior cranial base (1.7%) or a posterior cranial base (1.0%) (p=0.64). These rates are comparable to conventional transcranial or transfacial surgical approaches, which harbor a reported infectious risk ranging from 0.9 to 2.5%.(573, 574). Mortality related to meningitis was reported in one patient among the 36 reported cases of postoperative meningitis following an EESB procedure (543).

As expected, the presence of postoperative CSF leak as an association to subsequent meningitis (OR 91.99; 95% CI 11.72-721.88; $p < 0.01$). In a large retrospective series of 1000 endoscopic skull base patients treated at the University of Pittsburgh, Kono et al. identified a number of risk factors for subsequent meningitis (572). Included amongst the factors that were recognised to predispose to meningitis were: male gender; a history of prior craniotomy or endonasal surgery; the presence of ventriculo-peritoneal (VP) shunt or an external ventricular drain (EVD) at time of surgery; and higher-complexity intradural surgeries. The presence of postoperative CSF leak was, not surprisingly, considered by many an important factor in predisposing to the subsequent development of meningitis. The incidence of meningitis without an associated CSF, as demonstrated in this study, was very low (0.1%; 1/1736).

Although it is considered that endonasal surgery to the PCF is associated with a higher risk of both CSF leak and meningitis, the data presented in this study demonstrates no difference across 761 patients in which a comparison of approach could be made. Over the past few years, the application of multilayer reconstructions and the routine use of vascularised mucosal flaps in expanded endonasal surgery have drastically decreased the risk of postoperative CSF complications and meningitis (406, 438). Harvey et al. reported a 0.9% risk of subsequent intracranial complication with a delayed CSF leak rate of 1.9% in 106 endoscopic skull base repairs over a 5 year period (549). In a systematic review of endoscopic skull base reconstruction of large dural defects, postoperative CSF leak following vascularised endonasal reconstruction for expanded endoscopic skull base surgery was estimated to be 6.7% (439). The dramatic effect of vascularised dural closure techniques for EESB procedures have also been emphasized in a number of studies (439, 486, 549). In particular, Kono et al. observed a fivefold reduction in postoperative infections among intradural EESB patients from 11.5% to 2.4% following the introduction of vascularised endonasal flap reconstruction (572).

LIMITATIONS OF STUDY

EESB surgery is an evolving field and the risk of postoperative CSF and infectious complications may vary through time. In the current analysis, study heterogeneity was considerable, as investigations from various centers presented different study designs, methodologies, management paradigms, and patient populations. Most of the studies presented in this systematic review were retrospective non-adjudicated case series and the potential confounding in a non-randomized setting is not fully compensated by the use of multivariate analysis. The inherent publication bias, differences in patient demographic and clinical characteristics, variations in outcome definition and potential duplication of patients need to be taken into account.

In the current review, there is an over representation of the 2005 published cases by one group (520, 572)(520, 572). The University of Pittsburgh Medical Center (UPMC) data accounts for 1000 of the total 2005 (49.9%) included cases. However, in a sub-analysis the meningitis rate was similar for the UPMC experience 1.8% (18/1000) as compared to the remaining publications 1.8% (18/1005). The bias of a single large center publishing report does not appear to significantly alter the published reports for other centers.

Furthermore, our assumption of EESB patients were those who underwent endonasal surgery for pathologies other than simple pituitary adenomas, repair of CSF leakages or fistulas and encephaloceles repairs. Tumors such as chordoma and chondrosarcoma may not often involve a full thickness dural defect, and a transcranial approach in such cases would not be necessary. However, this is difficult to establish in the reported case series. Attempts were made to exclude such cases but some contamination in studies may occur.

CONCLUSION

Skull base pathologies are uncommon and the evidence base is mostly limited to small case series. Current evidence in this systematic review suggests that the risk of meningitis following expanded EESB surgery is low (1.8%). There was no difference in reported incidence of meningitis or CSF leak between anterior and posterior cranial fossa surgery. The incidence of meningitis from EESB surgery without an associated CSF is uncommon. Progress in EESB techniques that have reduced the incidence of subsequent CSF leaks will allow an expansion of indications of this direct approach to midline lesions.

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Table 15.2 Characteristics of included studies

Author, Year	Study Period	EESB Cases	Age, year (SD or range)	Female (%)	CSF Leak (%)	Meningitis (%)	Mortality related to meningitis (%)
Batra et al., 2005 (544)	1995-2003	9	55 (26-77)	33	11	0	0
Solares et al., 2005 (470)	2000-2004	6	50 (29-66)	33	0	0	0
Carrau et al., 2006 (471)	NR	20	NR	55	15	5	0
Frank et al., 2006 (427)	1998-2005	11	59.4 (32-76)	55	0	0	0
Frank et al., 2006 (472)	1998-2005	10	41.5 (11-61)	60	30	10	0
Leong et al., 2006 (473)	2000-2005	10	57.4 (26-84)	60	0	20	0
Cavallo et al., 2007 (557)	2004-2006	16	NR	NR	13	0	0
Dave et al., 2007 (558)	1997-2006	19	61.6 (39-81)	42	0	0	0
de Divitiis et al., 2007 (464)	2005-2006	6	56.1 (44-77)	50	17	0	0
de Santos et al., 2007 (477)	2001-2005	8	47.6 (9-79)	NR	25	25	0
Fortes et al., 2007 (478)	NR	3	54 (51-57)	67	67	0	0
Kassam et al, 2007 (575)	2000-2005	18	13.5 (3-18)	72	6	0	0
Laufer et al., 2007 (559)	NR	10	54 (38-73)	NR	10	0	0
Cappabianca et al., 2008 (576)	2004-2006	24	47.3	83	13	4	0
Carraba et al., 2008 (482)	2005-2008	17	48.0	41	24	0	0
de Divitiis et al., 2008 (560)	1983-2006	7	NR	NR	29	0	0

de Divitiis et al., 2008 (561)	2004-2007	11	55.3 (35-80)	64	27	0	0
Dehdashti et al., 2008 (484)	2005-2007	12	49.4 (22-77)	33	33	0	0
El-Banhawy et al., 2008 (485)	1997-2006	10	NR	NR	0	0	0
El-Sayed et al., 2008 (486)	2006-2007	20	52 (18-56)	75	0	0	0
Gardner et al., 2008 (487)	1999-2006	16	55 (36-80)	38	69	0	0
Gardner et al., 2008 (555)	2002-2005	35	55 (39-79)	83	40	0	0
Kassam et al., 2008 (488)	2006-2007	48	47 (4-80)	58	17	0	0
Kassam et al., 2008 (531)	NR	10	44.4 (16-78)	30	50	0	0
Leng et al.., 2008 (577)	2005-2007	10	NR	NR	0	0	0
Nicolai et al., 2008 (490)	1996-2006	134	58.7 (4-85)	50	3	1	0
Stamm et al., 2008 (440)	2000-2007	7	23.4 (16.3)	14	29	0	0
Zhang et a., 2008 (570)	2002-2006	9	35 (14-63)	44	0	0	0
Arbolay et al., 2009 (543)	2006-2007	5	41.4 (25-60)	20	0	20	20
Cavallo et al., 2009 (495)	2004-2008	22	49.4 (18-80)	32	14	0	0
Cohen et al., 2009 (494)	2000-2006	18	53 (19-91)	50	17	0	0
Dehdashti et al., 2009 (496)	2005-2007	19	44 (20-78)	37	21	5	0
Eloy et al., 2009 (562)	1997-2006	18	61.2 (39-81)	44	6	0	0
Fatemi et al., 2009 (563)	2000-2008	14	45 (8-79)	57	36	0	0
Folbe et al., 2009 (564)	1994-2006	16	56.6 (15-79)	44	25	0	0
Harvey et al., 2009 (549)	2007-2008	22	45.5 (20.2)	59	5	0	0
Liu et al., 2009 (502)	2004-2008	10	38.4 (20-58)	50	10	0	0

Stippler et al., 2009 (556)	2003-2007	20	44.4 (4-76)	40	25	0	0
Vergez et al., 2009 (565)	1994-2008	17	68 (44-82)	12	0	6	0
Batra et al., 2010 (566)	2000-2008	31	57.5 (14-84)	42	6	3	0
Fraser et al., 2010 (508)	NR	17	52.4 (22-87)	35	6	6	0
Greenfield et al., 2010 (567)	2004-2009	43	55.4 (17-85)	63	7	0	0
Horiguchi et al., 2010 (512)	2005-2009	19	55.9 (20-79)	63	26	0	NR
Jane et al., 2010 (511)	2005-2009	12	50.8 (29-76)	58	0	8	NR
Madhok et al, 2010(514)	1998-2008	35	34 (12-67)	NR	0	0	0
Nyquist et al., 2010 (515)	2008-2008	5	56.4 (31-72)	60	0	0	0
Prevedello et al., 2010 (516)	NR	2	44.5 (42-47)	0	0	0	0
Villaret et al., 2010 (568)	1996-2008	62	61.7 (25-84)	29	13	0	0
Gallia et al., 2011 (569)	2005-2010	8	56.9 (44-72)	38	0	0	0
Kono et al., 2011 (572)	1998-2008	1000	49 (18.0)	50	14	2	0
Kurschel et al., 2011 (521)	2004-2009	58	39.9 (4-78)	50	10	7	0
Carta et al., 2011 (526)	2000-2009	16	59.0	NR	6	0	0

*EESB patients were defined by true intracranial surgery with dural resection. EESB, endoscopic endonasal skull base; NR: not reported. SD: standard deviation.

Table 15.3. Risk of Meningitis Following EESB Surgery

	Overall Meningitis risk	Meningitis with associated postoperative CSF leak	Meningitis with no associated postoperative CSF leak	*p* value
All studies (n=52)	1.8% (36/2005)	13.0% (35/269)	0.1% (1/1736)	<0.01
EESB to the anterior cranial base studies (n=32)	1.7% (11/664)	13.3% (10/75)	0.2% (1/589)	<0.00
EESB studies to the posterior cranial base (n=9)	1.0% (1/97)	6.3% (1/16)	0% (0/81)	<0.00

EESB, endoscopic endonasal skull base; CSF, cerebrospinal fluid.

CHAPTER 16

THESIS SUMMARY, CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

SUMMATION OF THESIS RESULTS

Chapter one presented the scientific foundation in the surgical evolution of intracranial aneurysms and explored the historical landmarks that gave rise to contemporary practice. Efforts have been made over time to minimise complications and the trauma inherently associated with surgery, through new instruments, improved techniques, and evolving surgical philosophy. Endovascular therapy represented a recent breakthrough in this evolutionary process. At this point, microsurgery has reached its highest level of sophistication. Innovations in the surgical treatment of intracranial aneurysms in the future will need to focus on utilising cranial and extracranial tissue morbidity in the approach, while maintaining the robustness in the repair.

Chapter two examined the paradigm changes in the management of intracranial aneurysms in Australia following the introduction of endovascular services. In keeping with the changes that are presently observed in other developed countries, the Australian cerebrovascular workforce has diminished. That this change was impacting on both the current and new generations of neurosurgeons in maintaining competency in aneurysm practice was thoroughly explored. The need to urgently develop guidelines and standards in order to maintain operative cerebrovascular proficiency was considered and discussed.

Chapter three investigated the frequency and location of aneurysm rupture in a population-based analysis, and presented the first nationwide incidence of SAH in Australia. The findings of this study demonstrated that Australia has a crude SAH incidence of approximately 10.3 per 100,000 person-years for the years 1998 to 2008. Contrary to contemporary observations in the literature, the incidence of SAH remained largely unchanged during this period. Implications of an increasing elderly population and a declining cerebrovascular workforce were considered. Given the changing complexity of aneurysm case mix and volume at present and in the future, this study underscored the importance of maintaining microsurgical proficiency for those who may wish to perform cerebrovascular neurosurgery.

Chapter four examined the incidence and early predictors of shunt-dependent hydrocephalus following aneurysm SAH. This investigation represented one of the largest population-based studies that examined the association between risk factors and shunt dependency. The results of the analysis illustrated that the development of shunt-dependent hydrocephalus following aneurysmal SAH were multifactorial, related to; poor admission neurological grade, acute hydrocephalus, the presence of intraventricular blood, ruptured vertebral artery aneurysms, surgical clipping, endovascular coiling, meningitis, and prolonged period of external

ventricular drainage. Indications for ventricular shunt placement, therefore, need to take into account various predisposing factors along the course of patients' SAH admission.

Chapter five addressed the controversial issue of return to driving following elective intracranial aneurysm treatment. With the increased popularity of endovascular services in Australia, there is a growing misconception that patients who are treated by coil embolisation are safer for return to driving immediately following treatment as compared those treated with open craniotomy. Based on the analysis of a large administrative database of unruptured intracranial aneurysm treatment in Australia for the years 1998 to 2008, this study showed that surgery was associated with a higher incidence of in-hospital seizures. The risk of seizure following an endovascular procedure, however, was also apparent and approximated 0.6% per year (95% CI 0.4-1.0). The need to urgently re-evaluate current driving recommendations from both the clinician and driving authorities' perspective was considered and discussed.

Chapter six, seven, and eight concentrated upon the risks of the surgical technique itself. These chapters include prospectively collected cohort series retrospectively analysed for unruptured ophthalmic segment artery aneurysms, unruptured anterior communicating artery aneurysms, and unruptured posterior communicating artery aneurysms, respectively. The data presented in these chapters represented the senior author's (MKM) surgical experience with unruptured intracranial aneurysms over a period of twenty years. The evidence presented support the continuing role of microsurgery in the treatment of unruptured intracranial aneurysms. Overall, the analyses illustrated favorable surgical outcomes when surgery was performed for younger patients (<50 years) with smaller size aneurysms (<15mm). Consistent with the literature, the significant advantage with open microsurgical treatment over an endovascular alternative was demonstrated by the robustness of aneurysm repair, with at least 95% of those aneurysms treated achieved complete aneurysm obliteration. With the long term follow-up data demonstrating higher rates of recurrence and retreatment for endovascular treated patients, surgical clipping continues to have a strong presence.

Chapter nine examines the risk for the development of de novo intracranial aneurysms following surgical treatment when surveillance angiography (by CT scan or MRI) was routinely performed at interval of two to five years. With few studies in the literature reporting rigorous protocol of surveillance after treatment, this chapter is unique, presenting a detailed analysis of outcomes for the detection of de novo intracranial aneurysms. A history of smoking was found to increase the risk of de novo aneurysm detection rate. By using a Kaplan-Meier curve analysis, the five and ten-year detection rate was found to be 4.21% and

15%, respectively. This study presented a thorough literature review on the issue of de novo aneurysm detection and ruptures risk, and underscored the importance of routine surveillance angiography following aneurysm treatment.

Chapter ten investigated the role of Indocyanine Green (ICG) videoangiography in reducing the risk of postoperative ischaemic complications following aneurysm surgery. The data presented here represented a prospective investigation conducted over a two-year period between 2010 and 2012, in which patients were recruited into the ICGVA surgical cohort. Eligible patients treated with ICGVA assistance were matched with a historic control group who had similar; aneurysmal characteristics, general demographics and treatment. With all the limitations of a retrospective match-pair comparison, this study was the first to demonstrate the role of ICGVA in reducing the incidence of postoperative ischaemic complications following aneurysm surgery and supported its routine use.

Chapter eleven, twelve, and thirteen examined the surgical relevance of the endoscopic endonasal approach to the basilar artery, paraclinoid internal carotid artery segment and the anterior communicating artery complex. Such an approach would be an innovation for surgery as such approach, where appropriate, would be less invasive than current surgical approaches. In these preclinical experiments, the feasibility of an anterior endoscopic transnasal approach was established, and demonstrated superior visualisation of the vasculature as compared with that achieved by conventional microsurgery. Both clip application and surgical maneuverability of instruments was considered adequate for selected aneurysms in these approaches. A number of technical limitations were recognised from these studies including; the long and narrow operative corridor, limited freedom of surgical movement, lack of dedicated endonasal instrumentation and the need for advanced familiarity with endoscopic surgery. It also highlighted the need for adequate training in endoscopic arterial lesion management before the routine use of these types of surgery for intracranial aneurysms can be considered.

Chapter fourteen and fifteen presented two systematic analyses of the literature and investigated the incidence of postoperative seizures and meningitis following expanded endoscopic endonasal skull base surgery respectively. With the growing indications of these techniques for a variety of cranial base pathologies, determining the risk of postoperative seizures and meningitis is important. The results suggest that the overall risk of seizure was low (1%). However, the deficiency of reports on seizure outcomes among many EESB surgical series was recognised as a key limitation. The incidence of postoperative meningitis

following EESB surgery, as demonstrated in chapter eighteen, was 1.8%. This study illustrated the importance of maintaining watertight skull base closure (through the use of nasoseptal flap) to avoid the risk of meningitis. In the presence of a postoperative CSF leak, the risk of meningitis was 13%. The risk of developing meningitis without CSF leak, however, was uncommon (0.1%).

CLINICAL IMPLICATIONS

This thesis presented a series of scientific studies (through clinical investigations and preclinical experiments) that explored the history, evolution and contemporary surgical innovations in the management of intracranial aneurysms. Through these efforts, the importance of both embracing change and accepting continual innovation has been highlighted. The drift towards endovascular treatments has, in part, ignited a new evolution in the philosophy of intracranial aneurysm surgery. Clean, fast and effective neurosurgical operations can now be safely delivered. Improved imaging has enabled the application of smaller and more precise incisions with smaller bone flaps. Effective neuroanaesthesia provides slack brain, allowing for the gentle handling of brain and vessels with little or no retraction. Sharp dissection has replaced blunt dissection of the aneurysm. Total occlusion of the aneurysms can now be verified and objectively demonstrated by intraoperative ICGVA.

However, surgery is by nature invasive. The challenge for aneurysm surgery remains to be a problem of access and exposure at level of the skull base, necessitating extensive bony resection, brain retraction and cranial nerve manipulation. To circumvent for this limitation, we have developed an alternative access via the anterior transnasal endoscopic approach. Based on the results of our preclinical experiments, we determined that it was feasible to apply this technique to treat selected aneurysms along the skull base. Nonetheless, the endoscopic transnasal clip reconstruction of vascular pathologies presents a number of technical challenges. First, surgical manoeuvrability of instruments was severely restricted because of a loss of surgical “wrist action” with the endoscopic treatment. This prevented the ability to modulate clip angles, to manipulate aneurysm domes or to obtain watertight dural closure. Second, superior optics with 3-Dimensional microscopic vision was compromised for a 2-Dimensional endoscopic view. This resulted in an increased reliance on tactile feedback by the operator rather than visual cues. Third, a transnasal endoscopic approach to treat intracranial aneurysms demands the utmost endoscopic familiarity and advanced experience, which for the most part, is not inherent to many neurosurgeons. Finally, the validity of such a

technique has yet to be defined. The therapeutic value of this approach can be judged only when dedicated endonasal instruments have been developed, and a statistically meaningful number of clinical cases have been performed.

FUTURE DIRECTIONS

The future of surgery should aim to combine the robustness of surgical repair, the safety of surgery and endovascular treatments (whichever is better in the specific aneurysm circumstance) with the minimum invasive approaches (such as endoscopic) that are a characteristic of other surgical innovative pathways. One such innovation may be with robotics. The features inherent to surgical robotic technology may be potentially advantageous to the treatment of intracranial aneurysms via a combined transcranial/transnasal access by providing the freedom of instrument movement, depth perception and intuitive surgery. Robot-assisted surgery is an emerging technology that could be seen as a further development of this evolution, given adequate training and experience of the surgical team performing the interventions. Robot-assisted instruments will allow for more flexibility, stability and enhanced vision, enabling more precise interventions and arterial reconstructions. Cranial and extracranial tissue morbidity can be minimised in the approach, while the robustness can be maintained in the aneurysm repair.

At present, the use of robotic for head and neck pathologies is still in the developmental stage. The size of current robotic surgical equipment hinders its use in the narrow confines of the head and neck, and in particular, the endonasal corridor. The lack of dedicated instrumentations (such as the drill or bone rongeur) has limited its application in the paranasal sinuses and at the cranial base. The preclinical works presented in this thesis have defined the endonasal dimensions and its limitations for the potential application of robotic surgery. Future research will need to focus on developing specific instrumentation and unraveling alternative accesses through the skull base using robotic assisted techniques. With the integration of image-guidance, the development of haptic feedback, and the implementation of dedicated instrumentation (all of which are anticipated), the utility of the surgical robot in the clip reconstruction of intracranial aneurysms is a thing of the near future.

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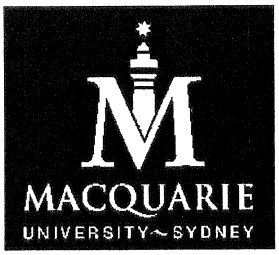
APPENDIX

FILE COPY



29th October' 2008

Dr. Andrew S Davidson
Australian School of Advanced Medicine
Level 1
Dow Corning Building
3 Innovation Road
Macquarie University
NSW 2109

Reference: HE26SEP2008-R06107

Dear Dr. Davidson

Final Approval

Title of project: "The use of prospectively collected cerebrovascular database for the purposes of surgical audit"

The above application was reviewed by the Ethics Review Committee (Human Research). Approval of the above application is granted, effective 29th October' 2008 and you may now proceed with your research.

Please note the following standard requirements of approval:

1. Approval will be for a period of twelve (12) months. At the end of this period, if the project has been completed, abandoned, discontinued or not commenced for any reason, you are required to submit a Final Report on the project. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. The Final Report is available at: http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms
2. However, at the end of the 12 month period if the project is still current you should instead submit an application for renewal of the approval if the project has run for less than five (5) years. This form is available at http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms if the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report (see Point 1 above) and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).
3. Please remember the Committee must be notified of any alteration to the project.
4. You must notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that might affect continued ethical acceptability of the project.
5. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University http://www.research.mq.edu.au/researchers/ethics/human_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project **it is your responsibility** to provide Macquarie University's Research Grants Officer with a copy of this letter as soon as possible. The Research Grants Officer will not inform external funding agencies that you have final approval for your project and funds will not be released until the Research Grants Officer has received a copy of this final approval letter.

Yours sincerely

P.P. **Dr Margaret Stuart**
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

ETHICS LETTER 2

Dear Prof Morgan

Re: **"The effects of hemodynamic insults on vascular wall biology in intracranial aneurysms" (Ethics Ref: 5201000813)**

Thank you for your recent correspondence. Your response has addressed the issues raised by the Human Research Ethics Committee and you may now commence your research.

The following personnel are authorised to conduct this research:

Prof Michael Morgan- Chief Investigator/Supervisor
Dr Leon Lai, Prof Yi Qian & Prof Alberto Avolio- Co-Investigators

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports. Your first progress report is due on 17th September 2011.

If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

http://www.mq.edu.au/policy/

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this email as soon as possible. Internal and External funding agencies will not be informed that you have final approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this email.

If you need to provide a hard copy letter of Final Approval to an external organisation as evidence that you have Final Approval, please do not hesitate to contact the Ethics Secretariat at the address below.

Please retain a copy of this email as this is your official notification of final ethics approval.

Yours sincerely
Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

ETHICS LETTER 3

Dear Prof Morgan,

Title of project: 'Computational haemodynamic evaluation of patients with intracranial aneurysms and cerebrovascular bypass surgery ' (Ref No. 5201000234)

Thank you for your Progress Report. Approval of the Progress Report has been granted, effective 1 June 2011.

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports. Your next progress report is due on 1 June 2012.

If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report on the project.

Progress Reports and Final Reports are available at the following website:
http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. Please notify the Committee of any amendment to the project.

5. Please notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that might affect continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University.

This information is available at:
http://www.research.mq.edu.au/about/research_@_macquarie/policies,_procedure

Yours sincerely,

Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

NSW GOVERNMENT Health

Trim: H11/5683-2

Dr Nigel Biggs
ENT Department Chairman
Suite 1002A, Level 10
St Vincent's Clinic
438 Victoria Street
DARLINGHURST NSW 2010

Dear Dr Biggs

I refer to the application for renewal of the anatomy licence under the *Anatomy Act 1977* (the Act) for the purposes of anatomical dissection and surgical procedures. The anatomy laboratory is located at Level 4, deLacy Building, St Vincent's Hospital, Victoria Street, Darlinghurst.

As an approved delegate of the Director-General under section 6 of the Act, I am pleased to advise that I have approved the Anatomy licence for a period of two (2) years from the date of issue.

An inspection of the facility was undertaken by Dr Mark Ferson, Director Public Health Unit, South Eastern Sydney & Illawarra Health on 21 January 2011, who confirmed that the facility complies with the Act.

Please note that the anatomy licence is issued subject to conditions. As the Licensee, it is your responsibility to ensure compliance with the provisions of the Act as well as with the conditions of the licence. Failure to comply may result in a breach of the Act.

Should you require any further information please contact Deborah Best, A/Manager Compliance and System Performance on 9424 5952.

Yours sincerely

Dr Kerry Chant
Deputy Director-General, Population Health
and Chief Health Officer
4/2/11

Cc Dr Mark Ferson
Director Public Health Unit

NSW Department of Health
ABN 92 697 899 630
73 Miller St North Sydney NSW 2060
Locked Mail Bag 961 North Sydney NSW 2059
Tel (02) 9391 9000 Fax (02) 9391 9101
Website www.health.nsw.gov.au

NSW GOVERNMENT | Health

ANATOMY ACT 1977

LICENCE TO CONDUCT THE STUDY AND PRACTICE OF ANATOMY

Pursuant to section 6 of the Anatomy Act 1977, I Dr Kerry Chant, Deputy Director-General Population Health and Chief Health Officer of the NSW Department of Health, do hereby:

ISSUE a licence under that section:

TO Dr Nigel Biggs, ENT Department Chairman

To facilitate the study and practice of anatomy within the terms of that Act by using anatomical specimens for the purposes of anatomical dissection and surgical procedures.

AT The Microsurgical Skills Laboratory, Level 4, deLacy Building, St Vincent's Hospital, Victoria Street, Darlinghurst 2010.

AND for a period of two (2) years from date of issue.

This licence is issued subject to the following conditions:

- The provisions of the *Anatomy Act 1977*, the *Human Tissue Act 1983*, and the *Public Health Act 1991* are to be complied with at all times.
- The anatomical specimens to be used are consented to or obtained from a similarly licensed anatomy facility, transported, stored and documented in an appropriate manner commensurate with the requirements of the *Anatomy Act 1977* and any other conditions as directed by the Anatomy Inspector.
- That a system of registration for all donated bodies and for the cross reference of all parts or dissected specimens from those bodies be implemented and maintained at all times.
- The material when not in use must be kept under security adequate to prevent access to those remains by persons not having a legitimate involvement in the study and practice of anatomy.
- That the Licensee comply with any other conditions as directed by the anatomy inspector.

Dr Kerry Chant
Deputy Director-General, Population Health and Chief Health Officer

Date of Issue: 4/2/11