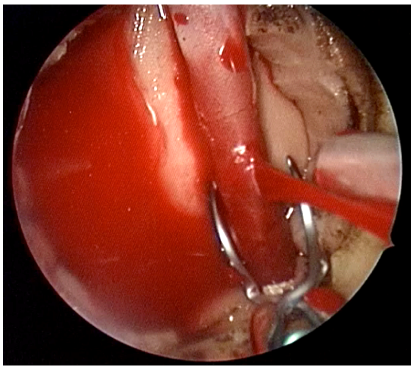
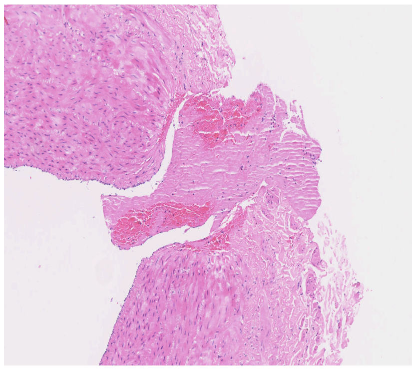
Management of Major Vessel Haemorrhage In Endonasal Surgery





By

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Abstract

Introduction

Endoscopic endonasal surgery (EES) is fast becoming the method of choice to address pathology of the paranasal sinuses and skull base. It carries with it advantages in regards to visualization, magnification, avoidance of scars, reduced length of stay and patient morbidity. With its greater utilization there needs to be an appreciation of its potential limitations as well. The most feared and potentially catastrophic complication for the endoscopic surgeon is that of inadvertent carotid artery injury (CAI). This represents a challenging surgical environment, a high pressure / high flow haemorrhagic scenario which can result in exsanguination of the patient. Current treatment recommendations, such as nasal packing, can result in increased patient morbidity. Despite acute management, patients may still be at risk in the long term due to the potential of vessel spasm, thrombosis, cerebral insult secondary to embolism, pseudoaneurysm or even carotico-cavernous fistula formation. The aims of the studies presented in this thesis are to develop and evaluate safe endoscopic haemostatic techniques on different injury types, explore their mechanisms of action, report on the value of training surgeons in these techniques, while assessing the success of their use in the clinical setting.

Methods

A sheep model of carotid artery injury was employed to simulate the high pressure / high flow arterial bleeding environment. This allowed for different endoscopic haemostats such as a crushed muscle patch, aneurysm clip and bipolar cautery, to be randomised and evaluated on different injury types. The muscle patch was

assessed further on a series of large animal carotid lacerations, which were harvested at different time points and histologically analysed. The direct vessel closure technique in the form the AnastoClip (LeMaitre, Burlington, MA) was evaluated in a separate prospective large animal study. A retrospective review of surgeons who had undergone vascular injury training in our workshops who subsequently managed a CAI was conducted to evaluate the outcomes after vascular injury training.

Results

A crushed muscle patch and aneurysm clip proved to be effective in gaining haemostasis in the endoscopic carotid haemorrhage setting as well as maintaining normal carotid characteristics in the long-term. The success of the crushed muscle patch appears to be due to its ability to provide a seal of the vessel injury site and promote platelet aggregation, which is compounded by an acute and chronic tissue healing response. The AnastoClip was successful in gaining control of high pressure / high flow bleeding and maintains carotid patency in the long-term with minimal endoluminal penetration. Vascular injury trained surgeons are able to appropriately manage this catastrophic situation, a review of their CAI cases revealed a mortality rate of 0% with no permanent morbidity for their patients.

Conclusions

Studies presented in this thesis present evidence for new endoscopic haemostatic techniques. These have proved to be effective in the immediate setting as well as safe in the long-term, reducing the probability of pseudoaneurysm formation and maintaining normal carotid patency and flow. The training of surgeons in these techniques has shown a direct benefit for patients, reducing the mortality and morbidity rate in the setting of CAI.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Vikram Padhye and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Presentations and Awards

Presentations

Australian Society of Otolaryngology Head & Neck Surgery Scientific Meeting
Perth, Australia 2013
Use of a muscle patch in carotid artery injury

American Academy of Rhinology Annual Scientific Meeting
Vancouver, Canada 2013
Early and late complications of endoscopic haemostatic techniques

TQEH Research Foundation / Basil Hetzel Institute Research Day
Adelaide, Australia 2013
Early and late complications of endoscopic haemostatic techniques

North American Masterclass in Endoscopic Sinus Surgery
Montreal, Canada 2013
Early and late complications of endoscopic haemostatic techniques
Merits of Vascular Injury Training

American Academy of Rhinology Annual Scientific Meeting
Orlando, USA 2014
Coping with Catastrophe: Value of vascular training
Endoscopic Direct Vessel Closure in Carotid Artery Injury

Australian Society of Otolaryngology Head & Neck Surgery State Meeting
Adelaide, Australia 2014
Early and late complications of endoscopic haemostatic techniques

Awards

Ron Gristwood Medal for Excellence in ENT Research
Australian Society of Otolaryngology Head & Neck Surgery State Award 2014

Best Junior PhD: Scientific Category
TQEH Research Foundation / Basil Hetzel Institute Research Day 2013

Chapter 1:   Aims

1.1 Aims of study

The aims of this study were:

- Evaluate the short term and long term complications of different endoscopic haemostatic techniques on different injury types in a large animal model of carotid artery injury
- Evaluate the short term and long term histopathological features of a crushed skeletal muscle patch used in haemostasis for carotid artery injury
- Evaluate the efficacy of a novel direct vessel closure technique in a large animal model of carotid artery injury
- Evaluate the outcomes of surgeon simulation training in vascular injuries

Chapter 2: Introduction

2.1 Indications for Endonasal Surgery: Chronic Rhinosinusitis

2.1.1 Definitions and Epidemiology

The paranasal sinuses are a group of paired pneumatised cavities of the human skull based upon the facial bones from which they arise. They are therefore named as maxillary, ethmoidal, sphenoidal and frontal sinuses, correlating with their respective facial bones, and communicating with the nasal cavity through a series of apertures or ostia.[1] Chronic rhinosinusitis (CRS) is a group of inflammatory disorders of the nose and paranasal sinuses in which symptoms persist in an individual for longer than 12 weeks duration. The recent widely accepted European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) suggests these symptoms always include either nasal blockage or nasal discharge (anterior or posterior), along with possible facial pain/pressure and reduction in smell.[2]

Chronic rhinosinusitis (CRS) is a common medical condition both in Australia and overseas.[2] A recent Australian National Health Survey[3] estimated that close to 1.9 million Australians suffered from CRS per annum. In Europe and the United States, recent data has shown up to 5-15% of the general population may be affected by CRS, with doctor diagnosed prevalence rates at 2-4%.[2] These patients may present to a wide range of clinicians ranging from primary care physicians and emergency clinicians to specialists such as allergists, pulmonologists and otolaryngologists.[2] They also suffer from significant socioeconomic stresses, with CRS sufferers likely to visit their primary care physicians twice as often as those without, as well as having five times more prescriptions filled.[4]

The management of CRS can therefore place a significant burden on health care systems. United States figures estimated that the 500,000 surgical procedures performed every year for CRS patients contribute to overall health care costs of around $5.8 billion per annum. In addition, restricted activities due to sinusitis can amount to almost 73 million days every year in the United States.[4]

2.1.2 Aetiology and Pathophysiology

Despite the large volume of research exploring the pathogenesis of CRS, the precise mechanisms of its development are yet to be elucidated. There have, however, been a variety of associations and hypotheses well described in the literature and thus widely accepted by clinicians.[2]

It is well known that impaired ciliary dysfunction has an association with CRS. Patients with primary ciliary dysfunction, Kartagener's syndrome (triad of situs inversus, bronchiectasis and CRS) and cystic fibrosis are unable to clear viscous mucus from their sinuses and as a result CRS is a common problem, often predisposing to a long history of respiratory infections.[5] Allergy is a well known cause of rhinitis, but its role in the pathophysiology of CRS remains controversial. It has been postulated that swelling of the nasal mucosa at the sinus ostia in allergic rhinitis may cause obstruction, mucous retention and subsequent infection.[6] Although epidemiological data does support an increased rate of allergic rhinitis in CRS patients, the exact causal relationship still remains unclear.[2] Asthma and aspirin sensitivity also have a strong association with CRS, in particular in those with nasal polyps (CRSwNP). Asthma has been reported in 26% of patients with

CRSwNP[7] and alternatively 7% of asthmatic patients have clinical evidence of nasal polyps.[8] In patients with aspirin sensitivity 36-96% have CRSwNP.[2] Immunocompromised states are also associated with CRS. Garcia-Rodrigues et al reported an incidence of 34% in HIV positive patients.[9]

One of the recent hypotheses as to the pathogenesis of CRS was the 'fungal hypothesis,' which described Alternaria fungi as the trigger to an excessive host response.[10] Most now, however, reject this proposal but agree that fungi may have a role as a disease modifier. 'The staphylococcal superantigen hypothesis' postulates that exotoxins affect multiple cell types, such as Th2 helper T cells, mast cells and eosinophils, resulting in the development of nasal polyps.[11,12] These superantigen effects however have only been found in half of CRSwNP patients and therefore their role as aetiological agents are disputed and they are seen more as disease modifiers.[13] 'The immune barrier hypothesis' suggests that CRS results from a defect in the mechanical or innate immune response of the sinonasal epithelium, which leads to increased microbial colonization, accentuated barrier damage and an upregulated adaptive immune response.[14,15] Biofilms, which form as a result of an impaired immune barrier, have also been suggested to cause CRS. These are clusters of microorganisms in which cells adhere to each other and are embedded within a self-produced matrix of extracellular polymeric substance, allowing cell colonies to persist and survive.[16] In addition to the identification of biofilms, intracellular *Staphylococcus aureus* has also been found in patients with CRSwNP, strengthening the theory that defects in local immune and/or barrier functions have a role.[17,18]

Regardless of the hypothesis proposed there appears to be a consensus that CRS develops from an impaired host-environment interaction in which a variety of exogenous agents are implicated along with changes in the sinonasal mucosa. Therefore CRS is currently described as being 'multifactorial' in nature with no one clearly identifiable pathway of development. Rather, it eventuates due to imbalances and interactions between host factors, commensal flora, pathogens and exogenous stressors.[2,19]

2.1.3 Medical Management

Like all chronic inflammatory disorders, the mainstay of CRS management is medically based. Current evidence based guidelines on the management of CRS advocate the use of multiple agents. There is high-level evidence (level 1a) to support the use of topical corticosteroids and nasal saline irrigation.[2,20] Other agents that have been utilized include oral steroids, oral antibiotics, mucolytics[2] and in some appropriate cases leukotriene modifiers may be of benefit.[2,21]

2.1.4 Surgical Management

Despite compliance with conservative, first line measures, a cohort of patients will invariably progress to needing second line treatments. In CRS patients who do not respond to maximal medical therapy, surgery is offered.[22] Endoscopic sinus surgery (ESS) has been shown to be safe and effective in the treatment of CRS. It is particularly useful in managing symptoms of nasal obstruction and discharge and studies have reported it leads to improvements in disease specific and generic quality of life measures.[2,23] Additionally, patients suffering with both asthma and

CRS report that following ESS their asthma control is much improved, with a reduced requirement for oral steroid and inhaler therapy as well as less overall asthma attacks.[23] Furthermore, opening of the paranasal sinuses and ostia, together with correction of anatomical anomalies such as a deviated nasal septum and/or concha bullosa can improve topical drug delivery for long-term control of inflammation.[24]

2.1.5 Other Indications for Endoscopic Sinus Surgery

The expansion of techniques used in the endoscopic surgical management of CRS has led to the development of endoscopic surgery for a variety of other disorders. Transnasal approaches for indications such as allergic and vasomotor rhinitis, nasal polyps, turbinate surgery, mucoceles, retention cysts and refractory epistaxis have evolved and are now commonplace.[25,26] There has also been a shift toward utilizing the endoscopic approach for procedures such as orbital and optic nerve decompression, dacrocystorhinostomy, choanal atresia repair and cerebrospinal fluid (CSF) leak repair.[26-29]

Endoscopic surgery has also been introduced for the management of benign tumours of the nasal cavity. These include tumour types such as inverting papillomas; bony and fibro-osseous tumours such as osteomas and ossifying fibromas; and vascular tumours such as juvenile angiofibroma. Although evidence for rare tumour types is limited, the endoscopic approach for more common tumours such as inverting papillomas and juvenile angiofibromas has been validated.[30-34]

Ongoing growing experience with the endoscopic technique coupled with greater advances in visualization has also led to the endoscopic treatment of malignant sinonasal tumours. These tumours are somewhat rare, comprising about 1% of all malignancies and 3% of malignancies of the head and neck.[30] They occur twice as often in males than in females and are often diagnosed in the fifth to seventh decade of life.[30] The majority of these tumours are squamous cell carcinomas and adenocarcinomas, while other tumour types such as sarcoma, lymphoma, melanoma, olfactory neuroblastomas and minor salivary gland tumours also occur at this site.[30] There is a growing body of literature demonstrating that in appropriate cases, endoscopic resection of malignant sinonasal tumours has favourable results when compared to pre existing open techniques.[30,35-37]

2.2 Indications for Endonasal Surgery: Skull Base Tumours

While endoscopic sinus surgery has evolved to include the management of benign and malignant sinonasal tumours, over the last two decades further expansion of these techniques has given rise to endoscopic skull base surgery. The endonasal transphenoidal approach for tumours of the medial skull base confers a number of key advantages. It is the least traumatic route, avoids external scars, provides excellent visualization, has a lower morbidity and mortality rate when compared with transcranial techniques and reduces hospital stays for patients.[30] In anatomical terms the medial skull base encompasses the posterior wall of the frontal sinus, the cribiform plate and crista galli, the ethmoid portion of the frontal bone, the body of the sphenoid bone centrally and the clivus posteriorly and laterally. Tumours arising from this region include pituitary adenomas, craniopharyngiomas, meningiomas, clival chordomas, chondrosarcomas as well as some sinonasal tumour types, which can also occur in the skull base.

2.2.1 Pituitary Adenomas

Pituitary adenomas are the most common tumour of the skull base and account for up to 10% of all intracranial neoplasms.[38,39] Prevalence rates have been estimated between 14 – 22% in meta-analyses looking at epidemiologic, post-mortem and radiographic data, however only 1 in 600 will become clinically significant.[40] They can be subdivided into microadenomas (dimension <1cm) and macroadenomas (dimension >1cm) and may extend out of the sella into the suprasella region or remain within the sella itself. These tumours can arise from any cell type of the anterior pituitary and as a result can result in increased secretion of hormones or suppression due to pressure effect on adjacent cells.[41] As these tumours are biologically, endocrinologically and pathologically heterogeneous, the role of surgery differs for different subtypes. Surgery as a primary role has been established for non-functioning pituitary tumours, in those with Cushing's disease, for acromegalic patients in combination with medical treatment and in thyroid stimulating hormone (TSH) secreting tumours. Other indications for surgery include cases where the transcranial route elevates patient risk, advanced age, long-standing optic chiasm compression, acute endosellar hypertension, pituitary apoplexy, microadenomas and invasive or downward progressing adenomas.[30,42,43]

2.2.2 Craniopharyngioma

Craniopharyngiomas are benign epithelial tumours that arise from the embryological canal that connects the stomodeal ectoderm with Rathke's pouch, the so-called craniopharyngeal duct.[30] It is the most common mass arising from the sella region in the paediatric population. They represent around 6-13% of all childhood brain lesions and around 2-5% of all primary intracranial neoplasms.[44] Their presentation has a bimodal age distribution with the first peak at 5-14 years of age and a second peak at 50-74 years.[45] As craniopharyngiomas grow they can exert mass effect on important anatomical structures including the brain parenchyma, visual apparatus, ventricular apparatus and the hypothalamic-pituitary axis causing visual disturbances, neurologic dysfunction and growth failure in children.[46] As such surgical removal with possible adjuvant external beam radiation is the treatment of choice in these tumour cases. Recently the endoscopic expanded endonasal approach (EEA) has offered a safe and effective treatment modality by allowing direct access to the suprasellar region via a transplanum route.[47]

2.2.3 Meningioma

Meningiomas are benign tumours that originate from arachnoid cap cells of the meninges and can occur intracranially (90%), spinally (9%) and ectopically (1%). Anterior skull base meningiomas account for 40% of all intracranial meningiomas and originate predominantly in the tuberculum sellae, sphenoidal ridge and olfactory groove.[48,49] Presenting symptoms are varied and often depend on tumour location with seizures, neurological deficits, visual deterioration and headaches some of the most common clinical presentations.[50] Surgical resection is the primary treatment modality for symptomatic tumours and if resected, patients have a very good prognosis with a 5 year survival rate of over 90%.[51] Advances in endoscopic techniques and accessing tumours via the transnasal route have permitted surgeons to approach tumours from their base thereby protecting cranial nerves, vascular structures, all while avoiding brain retraction, which has resulted in reduced morbidity and mortality in meningioma surgery.[52-56]

2.2.4 Chordoma

Chordomas are rare, slow growing, locally destructive and aggressive tumours which arise from embryonic remnants of the primitive notochord. They have an incidence of less than 1% per 100,000 and account for less than 0.1% of all cranial based tumours and 1-4% of all primary bone tumours. These tumours can occur at any age, however have a peak incidence at 50-60 years and a male to female ratio of 2:1. Approximately 35% of cases involve the clivus in the skull base while 50% arise from the sacrococcygeal region and 15% from vertebral bodies. They are classified as a low-grade malignancy with a high propensity of local progression as well as possible metastatic dissemination.[57-60] The most common clinical findings upon presentation include diplopia and headache, but mass effect may result in hydrocephalus or brain stem compression, and thus presenting symptoms may be highly variable.[61,62] The best treatment option is currently radical surgery and adjuvant radiotherapy, with total removal rates placed at 43 – 79% of cases regardless of which surgical approach is used.[62]

The endoscopic endonasal technique has its advantage in that as the tumour is sited usually in the midline and growth tends to push vital nerves and blood vessels laterally. Open approaches often have to cross such structures to reach the tumour while the endoscopic approach starts in the midline and can follow the tumour to its limits without transgressing a major vascular or neural structure. This has resulted in reduced morbidity when compared to traditional open techniques and has in some instances actually resulted in a reduced CSF leak rate.[30]

2.2.5 Chondrosarcoma

Chondrosarcomas are malignancies of cartilage that are rare and slow growing. They mainly affect older adults and have a male predilection. These tumours can occur in the facial skeleton and sinonasal tract and account for 16% of sarcomas of the nasal cavity and sinuses. Skull base chondrosarcomas arise from remnants of cartilage after ossification and make up 0.15% of all intracranial and 6% of skull base tumours.[63] Surgical resection provides the best long-term results and endoscopic endonasal resection is appropriate for most tumours of the midline sinonasal tract. Skull base chondrosarcomas are more challenging to remove surgically and are often resected in a piecemeal fashion due to their location around critical neurovascular structures. The endonasal approach does however offer advantages in the avoidance of manipulation of cranial nerves, which is often required in external approaches.[30]

2.3 Evolution of Endoscopic Sinus and Skull Base Surgery

2.3.1 Historical Perspectives

Since ancient Egyptian times the nose has been a pathway utilized for medical procedures and as such there are early descriptions of brain removal via the nose and its replacement with saw dust.[64] The concept of the paranasal sinuses was first promoted by Italian anatomist and surgeon Berenger del Carpi.[65] However despite their recognition their exact function was poorly understood, with many thinking that they were a system of hollow spaces to which mucus produced by the brain would drain.[64] Surgical treatment of the sinuses began in the 17th century; surgery being the only option to provide relief to sufferers in an era before antibiotic therapy. A number of techniques to enlarge the maxillary ostium had been proposed around that time, however the limited instrumentation being used would have meant most were perforating the fontanelle region as opposed to truly enlarging the maxillary sinus ostium.[66]

It was subsequently appreciated that the middle meatal approach to the maxillary sinus was technically difficult and as a result the intranasal inferior antrostomy was pursued and published by Gooch, to be then later popularized by Lichtwitz, Krause and Mickulicz.[65] It wasn't until the late 1800s and early 1900s that the use of endoscopes emerged in sinonasal surgery. In 1879 Nitze developed a small cystoscope, which was subsequently used in 1901 by Hirschman to visualize the maxillary sinus through an oro-antral fistula.[67] In 1922 Spielberg[68] published a paper on the visualization of the maxillary sinus with an antroscope via inferior meatal access, which was followed by Maltz[69] in 1925 who coined the term ‘sinuscopy’ to usher in an era where endoscopes could be used in diagnosis. These early endoscopes were however rudimentary in their design and limited in their depth of vision and optical quality.[67]

Considerable improvements in technologic design occurred in the 1950s, especially in the area of fibreoptics, allowing Harold H. Hopkins of the Imperial College in London to develop the rod optic endoscope. This scope was eventually made available in the 1960s and had greatly improved light delivery and optical quality. Karl Storz built on this technology, developing a range of angled endoscopes with views from 0 to 120 degrees, instruments which are still used today.[67]

Meserklinger in 1978 was able to utilize these superior endoscopes, with their fibre optic cold light and endoscopic cameras, to further evaluate the paranasal sinuses and map the complex pathways in which they drain into the nasal cavity. This led to his landmark publication “Endoscopy of the Nose” and spawned the Meserklinger technique.[70] This approach shifted the surgical focus away from radical procedures and more towards treatment at the site of obstruction. Along with these developments grew an understanding that that mucociliary clearance of sinuses occurred via the natural ostium of the sinus, even if an alternative surgical opening was created.[71,72] Therefore surgical techniques further evolved towards removing diseased tissue, restoring natural drainage pathways and preserving normal mucosa. This gave birth to the modern term “Functional Endoscopic Sinus Surgery” (FESS) as named by Kennedy.[73-75]

The history of skull base surgery is closely aligned with that of pituitary surgery. In 1889 Sir Victor Horsley performed the first pituitary operation and although he did not publish his results at the time, compatriots Caton and Paul were the first in 1893 to publish theirs, which reported that their patient was cured of headaches for the three months he survived after the operation.[76] The father of modern pituitary surgery is however Schloffer, who in 1906 published a paper presenting the possibility of pituitary surgery via a transsphenoidal approach. He performed this operation in 1907 and despite no intraoperative complications, the patient unfortunately had residual tumour blocking the foramen of Monro and passed away from hydrocephalus two months after the surgery.[77]

One of the true pioneers of neurosurgery Harvey Cushing performed his first pituitary operation in 1909 using Schloffer's technique, but then rapidly adopted a transseptal transsphenoidal approach, which was first developed by Oskar Hirsch in 1910.[78,79] Utilizing this technique, Cushing undertook 231 procedures with a 5.6% mortality rate. However he incurred some difficulties with CSF leak, haemorrhage control, vision outcomes and tumour recurrence so abandoned this approach for the transcranial method. This was a setback for transnasal surgery as it meant for the next 35 years pituitary surgery was largely done transcranially.[80]

However during this period the transsnasal technique was kept alive by two principal surgeons. Firstly, Oskar Hirsch continued to utilize this method and eventually took it from Europe to the United States. The second was Norman Dott, a British surgeon, who learned the approach from Harvey Cushing. These two pioneers continued to advocate its use and teach it to others. One student of Dott's was French surgeon Gerard Guiot who brought the technique to Paris and went on to perform over a thousand hypophysectomies. The endonasal method was further revolutionized by the introduction of the operating microscope and microsurgical instrumentation in 1967. This was initiated by a student of Guiot, a surgeon by the name of Jules Hardy. With its increased illumination and magnification this advancement permitted a more thorough and safe dissection, which subsequently brought about a major paradigm shift in tumour surgery. Surgery could now be performed not only to debulk tumours but also to cure hormonal disease caused by microadenomas.[81,82]

Over time the initial procedure described by Hardy underwent numerous modifications, such as extended approaches to other skull base sites, but became the primary pituitary surgical procedure performed by neurosurgeons from the 1960s to the 1990s.[77] The next major addition to transsphenoidal surgery came with the introduction of the endoscope. After being popularized for use in surgery of the paranasal sinuses by Kennedy, Stammberger and others in the 1980s, it was first adopted by Guiot for use in transsphenoidal pituitary surgery although widespread use did not follow.[77] Jankowski later revisited it in 1992 but it was the 1997 landmark paper by Jho and Carrau, which was the birth of modern endoscopic pituitary surgery. Their series of 48 purely endoscopic endonasal transsphenoidal pituitary resections noted the safety, efficacy and decreased morbidity of this technique.[83] Cappabianca et al followed this by suggesting technical improvements and developing dedicated endoscopic equipment.[84] What had evolved at this point, was a technique that compared to the operating microscope offered shorter operating times, less blood loss, superior differentiation between normal tissue and tumour tissue, decreased need for nasal packing, reduced hospital stay and improved patient satisfaction. It was clear the endoscopic technique was a mutually beneficial platform for patient and surgeon, one, which has subsequently been built on and expanded to allow safe access and resection of a multitude of tumour types from different sites of the skull base.[77,85]

2.3.2 Aims and Outcomes of Endoscopic Sinus and Skull Base Surgery

The evolution of endoscopic surgery has allowed surgeons to provide overall better surgical outcomes for their patients. The role of surgery in the treatment of CRS is limited to patients with disease refractory to medical management. Principles of surgery include removing ostial obstruction and enhancing ventilation.[86] This usually results in an overall improvement in mucociliary function and more efficient mass transport of the mucus blanket.[87,88] There is also said to be a benefit in reducing the overall surface area of inflammatory mucosa.[89] ESS has been shown to be effective in these patients and in particular has led to improvements in quality of life and reduced use of other medications.[2,23] Furthermore, ESS improves the delivery of nasal solutions which is important in long-term control of this chronic condition.[24,90]

The extent of initial surgery is often tailored to the extent of disease and in the first instance conservative surgery is recommended. However, despite optimal surgery, up to 20% of patients may respond inadequately and therefore require a secondary surgical procedure.[2] Findings at the time of revision surgery in these patients include adhesions, scar formation, incompletely resected bone partitions and retained sinus air cells.[91] Predictors of revision surgery include those that have had previous revision surgery, extensive nasal polyps, bronchial asthma, aspirin sensitivity and cystic fibrosis. Inflammatory involvement of underlying bone is also thought to be a contributing factor.[2] Although complication rates are said to be higher with revision surgery, success rates are said to range from 50-70%.[2]

The overall aim of skull base tumour surgery is to attain complete tumour removal while minimising patient morbidity. Indications for the endoscopic approach in this setting are the same as for the conventional microsurgical technique.[30] However surgeons may base the decision to utilise the endoscopic transnasal method on a number of factors including anatomical location of the tumour, its relationship to important neurovascular structures, appropriate instrumentation and technology, as well as the availability of a trained and experienced surgical team.[92] Dehdashti et al reviewed their experience of twenty-two endoscopic skull base tumour resections and identified certain anatomical limitations to the procedure. These included large lesions greater than four centimetres, significant lateral extension beyond optic canals, encasement of neurovascular structures and brain invasion by malignant lesions.[93] Some of these limitations in time have been overcome by the introduction of new surgical approaches and modifications to previous ones. Nevertheless not every surgery can be successful in gaining complete tumour removal, whether it is endoscopically or via an alternative approach.[94] The main reason for leaving residual tumour is to avoid compromising critical neurovascular structures such as the internal carotid artery (ICA) and optic nerves.[92] Technological advances in endoscopic surgery, such as image guidance and Doppler ultrasonography, coupled with continuous refinement of instrumentation has improved resection capabilities by allowing surgeons to accurately identify critical landmarks.[95]

Studies comparing the traditional microscopic transsphenoidal approach with the endoscopic approach have been reported. The endoscopic approach has been found to be on average two hours quicker in operative time and contributes to a shorter length of stay in hospital.[96-99] In addition these studies have found no difference between the techniques with respect to gross tumour resection and revision surgery rates.[96-99] The safety and efficacy of the endoscopic approach has also been demonstrated in a meta-analysis on pooled data of over 800 patients conducted by Tabaee et al. This study demonstrated higher rates of normalisation of endocrine function, improved visual outcomes and better gross tumour removal with the endoscopic technique of pituitary removal.[100] Additionally, complication rates between the two approaches have been comparable.[97,100,101]

As experience with endoscopic pituitary surgery progressed, further extended endoscopic approaches (EEA) were developed in order to address disease of different portions of the skull base. EEAs to the anterior segment of the skull base offer access to the intraconal orbital space and optic canal. Access to the middle and posterior segments is usually achieved by a preceding transpterygoid approach. EEAs to the middle segment provide wide exposure of areas such as the petrous apex, middle cranial fossa (including cavernous sinus and Meckel's cave) and infratemporal and pterygopalatine fossae. EEAs to the posterior segment allow access to the hypoglossal canal, occipital condyle, and jugular foramen.[102]

These extended approaches have also been shown to have a high rate of complete resection with a low incidence of complications.[30,103] Most of the current literature on EEA describes tumour resection of the anterior and middle cranial fossa, but over the last decade experience in posterior cranial fossa tumour resection has also increased. A series of 20 patients published by Stippler et al reports a gross total resection rate of 67% for newly diagnosed tumours and a near total resection rate in 17% of patients, with only a 5% incidence of neurological injury.[104] This is comparable with series analysing open approaches, which quote gross resection rates ranging from 44-83%.[102,105] Overall the endoscopic route to the skull base has been gaining momentum across the world, with distinct advantages over traditional techniques. The four handed, two nostril, two surgeon technique employed has been shown to expedite surgery and increase its efficiency and safety. It allows one surgeon to focus on the operative field while the other can survey a more 'global' perspective. Recent technological advances in optics, video-monitors and computer-assisted navigation have significantly enhanced the accuracy of surgery as well.[106] Overall it offers patients a less traumatic surgical experience and shorter length of stay in hospital, while achieving parallel if not superior morbidity and mortality outcomes.[30]

2.3.3 Major and Minor Complications of Endoscopic Endonasal Surgery

As with any surgical technique or procedure one needs to not only be aware of their potential advantages, but more importantly appreciate their possible risks. Major complications of ESS include immediate ocular complications such as intra-orbital haemorrhage, injury to orbital muscles and resultant diplopia, dural injuries with penetration into the skull base, CSF leak, meningitis and haemorrhage.[26] Injury to the internal carotid artery (ICA) is also a possibility in ESS. This high pressure / high flow catastrophic complication can lead to permanent neurological injury or even death. In early reports the incidence rates were as high as 1-4%, however over time with the introduction of newer technologies and a better understanding of the anatomy the rate has dropped to 0.001%.[107-109] In essence, major complications in ESS are a rare occurrence with an overall incidence rate of less than 1%, regardless of surgical approach utilised.[110]

Minor complications in comparison are more common. These include post-operative epistaxis, adhesion formation and damage to the lamina papyracea.[108] Of these, adhesions or synechia are the most common occurrence with an incidence of 15-30%. They along with nasal stenosis can contribute to a difficult post-operative course for the patient, interfering with normal mucociliary transport and function, eventually leading to repeat obstruction of the sinuses and eventual requirement of revision surgery.[111-113] The nasal cavity itself has a large blood supply; therefore bleeding during sinus surgery is an inevitable occurrence. Even the smallest amount of haemorrhage during endoscopic surgery can provide a challenging operating field to the surgeon, resulting in frequent soiling of the endoscope and loss of vision. Patients who experience bleeding after surgery are at risk of morbidity. They may experience haemodynamic compromise and have their airway placed at risk of obstruction due to inhalation of blood clots or vomit stained blood. Therefore attention has now been focussed on minimising the amount of intraoperative blood loss and finding the optimal nasal packing materials to prevent prolonged post-operative bleeding.[114]

Skull base surgery in comparison with ESS is more likely to render complications. While most of the minor complications of ESS, such as synechiae (9%), hold true for endoscopic skull base surgery as well, there are a variety of other minor sinonasal issues that may eventuate. Trauma to the sinonasal tract during surgery can result in ciliary impairment, which commonly manifests as nasal crusting in around 90% of patients. Patients suffering from severe crusting require aggressive debridement and irrigations and with the appropriate attention 50% of these patients achieve a crust free nasal cavity at 3 months after surgery. Additional sinonasal complaints include alar sill burns (5%), maxillary nerve hypoaesthesia (2%), palatal hypoaesthesia (7%), incisor hypoaesthesia (11%), serous otitis media (2%), taste disturbance (7%) and malodour.[106]

The occurrence of major complications in endoscopic skull base surgery is naturally higher given the nature of the surgery required. Surgeons generally have two main goals to help prevent major complications; they are to achieve sound haemostasis and a water-tight skull base reconstruction.[102] Post-operative CSF leak is one of the most common complications with incidence rates that ranging from 5-30% depending on the type of tumour surgery. CSF leaks can lead to secondary complications of meningitis and/or intracranial infection. The introduction and refinement of pedicled vascularised nasoseptal flap has however reduced the incidence of post-operative CSF leaks.[102] More recently collagen based matrices have also been utilised to ensure tighter skull base repairs and reduce the incidence of CSF complications.[52] Intracranial infections as sequelae of dural breach are a rare occurrence with an incidence rate of about 1.9%. Treatment with broad spectrum antibiotics, a sound skull base repair and aggressive approaches to CSF leak repair ensure its low rate.[106] Haemostasis in skull base surgery is currently optimised in a variety of ways. These include the use of novel materials such as haemostatic pastes or polysaccharides and utilising electrocoagulation technology such as bipolar cautery. Preoperative embolization of select vascular tumours also enhances intraoperative and post-operative haemostasis.[106] The potential for a catastrophic haemorrhage such as an ICA injury in endoscopic skull base surgery or an EEA is increased. Its incidence can range from 1.1% in pituitary surgery to 5-9% in EEA.[115] This is one of the most feared scenarios for the endoscopic surgeon and the pursuit of its ideal management forms the basis of this thesis.

Chapter 3: Carotid Artery Injury in Endonasal Surgery

3.1 Evidence Based Review of the Literature

3.1.1 Incidence and Aetiology

Along with the increasing popularity of endoscopic endonasal surgery (EES) approaches, not only to the paranasal sinuses but also to address pathology of the skull base, a greater awareness of the potential for a catastrophic haemorrhage has emerged. There have been a number of series published on the outcomes of EES but few on the complications of EES, in particular there is limited literature on major events of haemorrhage such as carotid artery injury (CAI).[116] Despite the large volumes of sinus surgery performed today, CAI is relatively rare event in ESS, with some 28 cases reported in the literature.[115] In fact in May et al's review of 4691 sinus surgery patients, they found only one incidence of it.[109] The frequency of CAI in endonasal transsphenoidal pituitary surgery is somewhat higher. Published rates for traditional open approaches range from 3-8% and for standard microscopic transsphenoidal approaches from 0.2-1.4%.[116] In a survey conducted by Ciric et al, he interestingly reported that surgeons that had performed more than 500 transsphenoidal procedures were 50% more likely to have managed an ICA injury during their career.[117] Extended endonasal approaches (EEA) by nature often involve surgery in close proximity to the ICA and unsurprisingly have the highest incidence of associated CAI. Series published by Couldwell et al, Frank et al and Gardner et al reviewed their experience with EEA complications and demonstrated a CAI incidence of 5-9%.[116,118,119]

Although CAI can occur at any stage during surgery, most commonly it occurs during the process of gaining exposure of the artery or while resecting tumour adjacent to the artery. Gardner reviewed 2015 patients who underwent ESS for various skull base pathologies, of which there were 7 cases of ICA injury. These seven injuries occurred during either exposure or resection of tumour and were associated with use of cold instrumentation such as endoscopic punches/cutters or powered drill burrs.[116]

3.1.2 Identification of At Risk Patients

As is well known, prevention of any complication is always better than its treatment. Although there are no well documented risk factors for CAI occurrence, there have been some associations reported in the literature that can help a surgeon identify a patient who may be at higher risk. These include anatomical, tumour and patient factors.

3.1.2.1 Anatomical Factors

The appreciation of the anatomical proximity of the internal carotid artery in the lateral sphenoid wall is paramount for any endonasal surgeon, this being a particularly vulnerable area for potential injury. Fuji et al showed that the bony wall over the ICA in the anterior genu of the cavernous carotid is less than 0.5 millimetres (mm) thick and concluded it was insufficient to fully protect the artery.[120] Additionally, in up to 22% of cases the lateral sphenoid wall may be dehiscent; with only dura and sphenoid sinus mucosa protecting the ICA.[120,121] The anterior genu of the carotid may approach the midline in some patients making it more susceptible to injury. In an anatomical study by Renn and Rhoton, it was found that this region of the ICA bulges into the sphenoid sinus in 71% cases. Also, the artery may be located as close as 4mm to the midline in some.[122] Other authors have reported that the inter-carotid distance within the sphenoid can measure as little as 4mm.[123] Also, of note is that in 16% of patients, the bony sphenoid septum inserts onto the ICA canal wall, placing the artery at risk if the septum is fractured.[124]

The potential for anomalies of the cavernous ICA need also be taken into consideration. Cavernous ICA aneurysms account for 12.8% of all intracranial aneurysms and have an associated increased risk of intra-operative rupture. Additionally, an increased incidence of aneurysms in patients with pituitary adenomas has been documented.[125,126] There have been multiple reports of pre-operatively unrecognised aneurysms, which rupture during surgery. In a review by Valentine et al of 111 case reports of cavernous ICA rupture, 6 were reported to have had unrecognised ICA aneurysms.[115] In Koitschev et al's review, the three patients that had ruptured aneurysms incurred significant blood loss and died. He concluded that the presence of an unrecognised cavernous ICA aneurysm was associated with poorer prognosis.[127] This highlights the importance of meticulous pre-operative work up when working in the vicinity of the ICA.

3.1.2.2 Tumour Factors

The likelihood of an ICA injury may be linked to the tumour type being resected. Gardner et al's review of ICA injuries in patients that underwent endoscopic skull base tumour resections found that pituitary tumours had a low rate (0.3%) of inadvertent injury, a rate that was comparable with previous microsurgical series. In contrast, chondroid tumours (chordomas and chondrosarcomas) had a 10-fold higher risk of rupture. This was largely due to the fact that multiple portions of the ICA usually required exposure for resection of these tumours and their surgeries tend to carry with them more aggressive oncological goals. Also, these infiltrative tumours tend to obscure, displace and narrow the ICA, behaving quite differently to pituitary tumours.[116]

The tumour type may also give an insight to the expected distance between both ICAs in the sphenoid. If the inter-carotid distance (ICD) of cavernous segment at the anterior genu is reduced it may narrow the operative window to the sellar region and render the endoscopic approach to be risky. The closer the ICAs are to the midline, the more at risk they are of injury. Mascarella et al found that when compared with controls, those with sellar or parasellar pituitary macroadenomas had, in fact, an increased ICD at three different segments (clival, cavernous and paraclinoid). However, those with growth hormone secreting pituitary tumours had a reduced clival ICD, while those with anterior cranial fossa meningiomas had a reduced ICD in the paraclinoid region.[128]

Tumours that closely adhere to the ICA represent a particularly challenging scenario. Not only does vessel encasement by tumour predispose to potential rupture, but also to potential vasospasm if not carefully manipulated and dissected. Bejjani et al showed that 9 out 470 patients that underwent skull base tumour operations in his series had instances of vasospasm. This resulted in impaired cerebral flow and episodes of altered mental status and/or hemiparesis. Three of these patients suffered permanent neurological deficits.[129] Laws et al have also had experience with vasospasm in this setting. In this review of 24 cases of vascular complications following transsphenoidal surgery, three were reported to have had significant vasospasm, with one fatal case and two others non-fatal.[130] These examples stress the importance of good surgical technique when dissecting tumour free from the ICA, with an emphasis placed on limiting manipulation of the artery.

3.1.2.3 Patient Factors

In addition to anatomic and tumour characteristics, patient factors must be taken into consideration. Raymond et al reviewed a series of 17 ICA injuries, where it was found 5 patients had prior bromocriptine therapy, 5 were revision cases, 4 had previous radiation therapy and 6 had acromegaly.[131] Valentine et al found that these risk factors contributed to 27 ICA injuries, with some patients having multiple pre-operative risk factors. He found revision surgery contributed in 13 cases, radiotherapy 4, acromegaly 13 and bromocriptine therapy in 4 patients.[115] These factors may be associated with increased ICA fibrosis and tumour adherence. Furthermore, it should be appreciated that patients with acromegaly tend to have more tortuous and ectatic arteries, which are prone to injury.[132]

3.1.3 Intra-operative Management

A major vessel injury such as an injury to the carotid artery encapsulates one of the most challenging scenarios for the endoscopic surgeon. This high pressure / high flow scenario can result in rapid blood loss and place a patient's life at imminent risk. The surgical field is made even more difficult by frequent soiling of the tip of the endoscope and loss of vision, resulting in a loss of orientation for the surgeon. Thus far, techniques used to manage this catastrophic scenario have been instituted in the setting of limited published data. The introduction of the sheep model of carotid artery injury has been the most significant development in this area, allowing for various techniques to be employed, which are discussed later in this chapter.[133]

There have been a number of techniques trialled in the management of this catastrophic bleeding situation. Emergency surgical ligation in the neck has been a traditional approach. However, this manoeuvre may be ineffective in the patient with good collateral flow and carotid ligation also confers a risk of precipitating stroke or death. Additionally, ligation ultimately terminates access for radiological interventionists to pursue endovascular procedures.[127,134] Nasal packing is therefore the current treatment recommendation.[115]

A variety of adjunct procedures are also suggested in the literature to aid in haemostasis and nasal pack placement. Head elevation and controlled hypotension have been deemed unnecessary in this situation given the significant hypotensive effect of bleeding alone.[135] In fact it has been widely recommended that normotension be maintained through resuscitative measures in order to provide adequate cerebral perfusion.[136,137] If the use of suction and hypotension from blood loss cannot allow for nasal packing then ipsilateral common carotid compression can be performed to help facilitate it.[115] In this instance, Weidenbecher et al advocate bilateral carotid artery compression in the neck, with concurrent surgical widening of the sphenoid sinus ostium to help place nasal packing.[121]

There are several reports describing the use of different packing materials in cases of CAI. Valentine et al's review reported use of Teflon (Medox Medical, Oakland, NJ) and methylmethacrylate patch, fibrin glue, Gelfoam (Pfizer, New York City, NY), oxidised cellulose packing, thrombin-gelatin matrix, oxygel and muslin gauze. Despite reported use of a number of different materials , the most frequently used was gauze, due to its widespread availability and ease of use.[115] In essence, absorbable and biocompatible materials prove to be better options, as following placement, they do not require future removal, which may provoke further bleeding.

Nasal packing is, however, not without its own complications. In a series of 12 patients reported by Raymond et al, in which packing was used to manage CAI, 8 patients suffered from ICA occlusion and 4 patients from ICA stenosis secondary to packing placement.[131] 'Overpacking' can add significantly to morbidity and mortality. The very nature of skull base surgery requires wide exposure of the surgical field and therefore exposure of critical neurovascular structures and therefore 'overpacking' the surgical field is an important point to consider to avoid placing these structures at risk.[131] In addition, compressive nasal packing is considered a poor option if the dura has been opened in surgery as blood can track back into the subdural space. Attention therefore has been turned to alternate options, which include methods such as use of a crushed muscle patch, a focus of this thesis.[136]

Direct vessel closure methods have also been employed intra-operatively, with Laws et al reporting the successful suture repair of 2 ICA injuries, while in another case the use of a sundt-type clip was efficacious. The details and outcomes of these techniques remain largely unknown.[138] Authors, however, do agree that the inability to effectively repair large vessel injury is a limitation of the endoscopic technique, and more research needs to be undertaken to development methods to do so.[116,137] Work described in this thesis has contributed significantly to this aim.

3.1.4 Endovascular Techniques

In some patients haemostasis may not be achievable intra-operatively and in these instances urgent endovascular intervention is pursued.[127,139,140] These radiological interventions are aimed at either occluding the vessel entirely or sealing the injury site while maintaining vascular flow.[115] In these cases bleeding is stemmed as much as possible in order to transfer the patient to an angiography suite for treatment. Occlusion of the artery is generally performed using a balloon or coil and done at the wall defect to prevent blood extravasation from anterograde and retrograde filling of the vessel.[127] This method can however be associated with a risk of distal migration of the balloon or coil due to the high pressure / high flow environment in which it has been placed.[141] As a result the ophthalmic artery is placed at risk due to its location distal to the cavernous portion of the ICA.[131] If the best course of management entails occlusion of the artery then assessment of the patient's collateral circulation should be undertaken prior to intervention. This can be performed in a variety of ways. In addition to traditional angiography, tests such as balloon test occlusion (BTO) in combination with electroencephalography, transcranial Doppler, xenon-CT and single-photon emission computed tomography have been proven efficacious.[121] Of note however, is that Mathis et al found that of 192 patients that underwent BTO and were deemed to have passed it, 4.7% developed permanent stroke.[142]

The alternative to occlusive intervention is the placement of an endovascular stent graft in order to maintain vascular flow while sealing the injury site. This would be most appropriate in those patients with poor collateral flow. It has however been noted that placement of a stent-graft is technically difficult due to the need for placement in the tortuous cavernous carotid siphon. In addition, stent-grafts have associated complications; these include the potential for distal migration, ICA spasm and a 4.4% risk of stroke within the 30 days of placement. It also requires the patient to be on concurrent anticoagulation therapy, which is not without its own risks.[115,140,143]

3.1.5 Post-operative Considerations and Outcomes

Post operative care of the patient who has suffered a CAI is largely based on the prevention of complications. After an injury to the carotid artery a communicating channel can be created between the sidewall of the ICA and the sphenoid and/or cavernous sinus. This may present as an acute haemorrhage, pseudoaneurysm or carotico-cavernous fistula (CCF). CCF most often results in proptosis, opthalmoplegia and the presence of an orbital bruit in the patient.[115,127,136,144] Therefore once haemostasis has been achieved intra-operatively the patient should be transferred for urgent angiography. Angiogram should include the external carotid artery if no abnormality is found within the ICA. In addition the co-surgeons should be on hand to loosen any nasal packing if the injury site cannot be elucidated due to 'over-packing.'[136] If the initial post-operative angiogram is normal, then it is advisable for the patient to be monitored in an intensive care unit until packing is removed and a follow up angiogram is performed, usually at 1 week post surgery. If this is again normal, then subsequent angiograms should be repeated at 6 weeks, 3 months and 1 year.[26,115]

The most common complication following CAI is pseudoaneurysm. By definition a pseudoaneurysm is a tear through all layers of an artery with persistent flow outside the vessel into the surrounding soft tissue space.[145] It can present in some instances up to 10 years later, however its peak incidence is usually within 3 months of injury. Some authors have reported that if not repaired by a direct method, all CAIs will ultimately result in a pseudoaneurysm.[131,138,146] Valentine et al reviewed cases of ICA injuries, which had reported pseudoaneurysm follow up and found an incidence of 60%. The majority of these were discovered on routine follow up angiography, while a proportion (27%) ruptured and required immediate management.[115] A ruptured pseudoaneurysm presents an imminently life threating situation and requires emergency treatment, necessitating airway control, rapid resuscitation and local packing, followed by prompt endovascular intervention. Identification of a pseudoaneurysm in a controlled situation, such as a post-operative angiogram, requires planned follow up treatment. This would entail three main treatment options; endovascular stent-graft placement, isolated endovascular balloon or coil occlusion of the pseudoaneurysm (usually with preceding BTO as in the case of CAI) or surgery. Surgery may include bypass surgery or aneurysmal clipping. It is however well known that extracranial/intracranial bypass surgery is associated with a high complication rate and so is preferentially avoided.[147]

An intra-operative CAI is a significant event, one that is associated with a significant rate of morbidity and mortality. There is a paucity of literature reporting on the outcomes of inadvertent major arterial injury. Valentine et al's review of 111 cases of ICA rupture identified 89 cases that had established end points. A mortality rate of 15% and a permanent morbidity rate of 26% were reported. In fact only 59% of patients that had a CAI suffered no permanent sequelae, a significant if not damning statistic.[115]

3.2 Animal Models and Surgical Simulation in CAI

3.2.1 Simulation in surgery

Evidenced based medicine in surgery remains a challenge. It is often not ethical or possible to perform clinical randomised controlled trials to investigate new surgical procedures or instruments. This is even more pertinent with regards to research in to catastrophic bleeding events such as CAI; where literature is largely limited to retrospective series, case reports and anecdotal type evidence. Surgical simulation has become a useful tool to promote and harvest the training and skills of practitioners, especially in instances where the traditional 'apprentice' type model is difficult. The origins of simulators are found in flight simulation, utilised to improve pilot safety and reduce resource cost.[148] In-flight emergencies are analogous to those of the operating room, with respect to their unpredictability and risk to life.

In addition to skill acquisition, surgical simulation is also useful in research and development, allowing investigators to trial techniques in as close to a real world scenario as possible. There are a range of different simulators each with their own advantages and disadvantages. Bench models are cheap and portable, but are the least realistic and inanimate. Though they provide anatomical detail that cannot be replicated, cadavers are a limited resource, and are less useful in the vascular setting due to absence of blood flow. Virtual reality simulators are reusable and depending on their manufacture, are anatomically accurate and can provide haptic feedback, but their realism can vary greatly. Animal models have been utilised in medicine since 384 BC. They have a high level of fidelity, realism and their live physiology can be extremely beneficial to reproduce real-life occurrences, such as bleeding and tissue behaviour. Their limitations include the potential ethical issues surrounding their use, high costs and specialist facilities that are required for their involvement.[148-151]

Animal models of haemorrhage have been developed in the past and range from low volume / low pressure models to high pressure / high volume models. Low pressure / low volume models usually encompass a visceral injury, such as Schwaitzberg et al's use of a swine splenic laceration to compare different commercial topical haemostats. High volume / low pressure models also involve injuries to visceral organs, usually the liver, however the injury sizes tend to be greater. The swine model of severe large venous injury is an example of this, and has been utilised in numerous studies to compare the efficacy of haemostats.[152-154] High pressure / high volume scenario is unique and can only be accomplished by a large arterial injury. This has been most commonly accomplished in swine models utilising different segments of the aorta or major peripheral arteries such as the femoral artery. Key factors in the model's success include appropriate haemodynamic monitoring and aggressive resuscitation with an aim to restore the animal's mean arterial blood pressure to the pre-injury reading.[155-159] The endoscopic carotid artery injury scenario is a high pressure / high flow situation in which haemostats need to be evaluated in a narrow surgical field akin to the nasal cavity. To date there has only been one such model that has been developed.[133]

3.2.2 Sheep Model of CAI

The development of a sheep model of carotid injury by Valentine and Wormald has ushered in a new era in endoscopic vascular injury research. In this model, sheep are induced with an anaesthetic and then positioned on their backs on an operating table. A midline neck incision is made and the carotid artery on the right side identified and skeletonised. The jugular vein and carotid artery on the contralateral side are also identified and cannulated for the purpose of rapid resuscitation and invasive arterial monitoring. A modified SIMONT (Sinus Model Otorhino Neuro Trainer, ProDelphus, Brazil) model is then placed over the right sided artery. This synthetic model mimics the nasal cavity, consisting of anatomically accurate structures in the nose and allowing the artery to be placed within the model in a manner that replicates its position in a human. A scalpel blade can then be used to create an injury, with the subsequent bleeding contained within the 'nasal cavity.' Simultaneous fluid resuscitation is then initiated with the aim of maintaining blood pressure to as close to the pre-injury reading as possible.[133]

This novel model has many advantages. Firstly, it is an accurate recreation of the high pressure / high flow scenario found in a CAI, one which provides the natural physiological processes for haemostasis. Secondly, by recreating the narrow confines of the nasal cavity it allows for the accurate evaluation of haemostats in the endoscopic setting. Additionally, investigators are able to use standard endoscopic equipment and instrumentation when employing the model and as a result encounter common equipment issues when managing a haemorrhagic situation, such as soiling of the endoscope tip. This culminates in the creation of an environment of high anxiety, an outcome invaluable in training surgeons to manage catastrophic situations.

3.2.3 Lessons Learnt: Controlling the Surgical Field

The sheep model of CAI was utilised by Valentine et al to develop a set of techniques to aid in the control of a major haemorrhage during endoscopic surgery.[160] These include:

- Two surgeon approach to allow one surgeon to control the bloodstream, by directing it away from the endoscope, while the other obtains vision of the injury site in order to attempt haemostasis
- Two large bore (10 French) suctions and, if available, a lens cleaning system for the endoscope

- Second surgeon places suction down side of nose with predominant bleeding to direct flow away from the contralateral side, clearing the path for the endoscope
- Primary surgeon places endoscope down contralateral side and uses the posterior septal edge as shield from blood flow
- Primary surgeon clears blood ahead of endoscope using second suction. Pedicled septal flap should also be manipulated and cleared into the nasopharynx
- Second surgeon is then free to 'hover' suction directly over site of injury to help gain vision for the primary surgeon

Through out this process, clear communication is advocated between all members of the surgical team. This is the first paper to describe steps to aid in haemorrhage control in this setting.[160] By upholding this advice surgeons have a clear step-wise approach to dealing with this situation, enabling them to manage their anxiety and affording them the best chance of achieving control.

3.2.4 Lessons Learnt: Endoscopic Haemostatic Techniques

There is a paucity of literature describing effective endoscopic haemostatic techniques in the high flow arterial setting. A review of existing literature has identified nasal packing as the technique most frequently advised.[115] Kassam et al's review of 400 endoneurosurgical cases identified that packing related morbidity is important to take into consideration and advocated instead for use of bipolar cautery to seal the injury site if possible.[137] He also identified that a great limitation of the endoscopic approach was the 'inability to repair large arteries primarily', a point that Gardner et al also made in their review of 7 ICA injuries, identifying this issue as 'the most obvious area where significant improvement is needed.'[116,137]

Prior to the publication of works in this thesis there was only one prospective trial that compared different haemostats in the endoscopic haemorrhagic environment. Valentine et al's 2011 publication of the efficacy of five different endoscopic haemostatic techniques identified that a crushed skeletal muscle patch and U-clip anastomotic device (Medtronic, Jacksonville, Fl) were able to reliably achieve primary haemostasis, improve survival and reduce blood loss in a sheep model of major haemorrhage.[161] The success of the U-clip showed that direct vessel closure was indeed possible in this setting. This work has formed the platform for the studies presented in this thesis, which endeavour to uncover further reliable and safe endoscopic haemostatic techniques for different injury types, to better understand their mechanisms of action and assess the value of training other surgeons in these techniques.

Chapter 4: Early and Late Complications of Endoscopic Haemostatic Techniques Following Different Carotid Artery Injury Characteristics

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Chapter 5: Sequential Histological Evaluation of Muscle Patches Used for Haemostasis in a Sheep Model of Carotid Artery Injury

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Sequential Histologic Evaluation of Muscle Patches Used for Haemostasis in a Sheep Model of Carotid Injury

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Abstract

Introduction

As endoscopic surgery becomes the method of choice for resection of pathology of the skull base an appreciation for potential complications in this area. Injury to the internal carotid artery is a known occurrence and current treatment recommendations can result in patient morbidity. Recently a crushed skeletal muscle patch has been shown to be effective in gaining haemostasis in this setting, however its method of action remains largely unknown. This study aims to evaluate the histological features over time of muscle patches used to obtain haemostasis over following carotid artery injury in a sheep model.

Methods

5 sheep underwent neck dissection and carotid artery isolation. A 4mm linear injury was made in the anterior wall of the artery and a free autologous skeletal muscle graft used to gain haemostasis. Carotid artery specimens were resected at 5 different time points: 1 hour, 2 days, 1 week, 2 weeks and 3 months and histologically analysed.

Results

Muscle patch gained haemostasis in all instances. Histology at Day 1 showed fibrin plug at the injury site. From Day 2 to Week 1 evolving muscle necrosis took place, with associated granulation tissue development. At Week 2 large sections of muscle have necrosed with some areas of retained peripheral viability and by 3 months muscle has dissappeared leaving a carotid artery with largely normal structure.

Conclusion

The muscle patch has been shown to be an effective haemostat in the major arterial bleeding setting. It success is due to its ability to provide a seal of the vessel injury site and promote platelet aggregation, which is compounded by an acute and chronic tissue healing response with eventual disappearance of the muscle patch.

Introduction

The last two decades has seen a paradigm shift in the resection of tumours of the skull base. Increasingly the midline transnasal route has been utilised over the craniotomy approach and carries with it a variety of advantages.[1] These include advances in visualisation, magnification, avoidance of scars, a shorter hospital length of stay for patients and reduced post-operative morbidity.[2] The progression of the endonasal technique has also seen a rise in inadvertent injury to the internal carotid artery.[3] This catastrophic situation presents as a major haemorrhage scenario and can place a patient's life at imminent risk. The most advocated technique to stop bleeding in this situation is nasal packing.[4] But this has the potential to cause significant morbidity, with over-packing placing significant neurovascular structures at risk.[5] It may also predispose to long-term complications such as pseudoaneurysm formation.[4]

As a result, a number of alternate haemostats have been trialled in this setting, facilitated by the development of a sheep model of carotid injury.[6] These studies have uncovered the success of an autologous crushed muscle patch on a high pressure / high flow arterial bleed both in the short and long-term.[7,8] Earliest reports on the use of muscle in haemostasis were by Cushing[9] and Horsely[10], who identified that when compared to gauze or cotton, muscle was able to secure prompt haemostasis when held in direct contact with a bleeding point.

Although the effectiveness of muscle in bleeding control has long been known[11], there exists a paucity in the literature as to the mechanism of action. Theories include the associated pressure effect, action as a welding conduction agent and possible release of muscle thromboplastin or tissue factor.[12] Rajiv et al recently reported that higher concentrations of muscle extract were associated with increased platelet aggregation when used in the haemorrhagic setting.[12] The aim of this study is to evaluate the histological features associated with muscle patches that have been used for a major arterial haemorrhage.

Methods

Approval for this prospective large animal study was gained from the animal ethics committees of The University of Adelaide and South Australian Health & Medical Research Institute (SAHMRI).

5 sheep were utilised in this study. Induction of anaesthesia was performed via injection of sodium thiapenthone (19 mg/kg) into the Left jugular vein. Endotracheal intubation then followed with anaesthesia maintained with inhalation of 1.5 – 2.0% halothane to a depth that allowed for spontaneous ventilation. The sheep were then positioned on their backs and a midline neck incision made, followed by neck dissection to isolate the Right carotid artery. Once identified a 4mm linear incision was created in the anterior wall of the artery and free bleeding allowed for a period of five seconds. An autologous free skeletal muscle graft was harvested from the sheep sternocleidomastoid and lightly crushed. This graft was then placed over the site of injury and held in situ until haemostasis was achieved. Injury site was marked with a non-absorbable suture. The carotid artery and adherent muscle 'patch' was then harvested in each sheep at five different time points. Time points were 1 hour, 2 day, 1 week, 2 weeks and 3 months. After harvest tissue was histologically analysed.

Results

Slides presented are a representation of vessel injury sites treated with muscle patch. These were marked with a non-absorbable suture at the time of surgery and are not the only slides evaluated from each vessel injury site. Vessel injury sites from the time point of 2 days onwards were found to have healed to a point where it was difficult to accurately identify the exact point of injury. So slides with the best representation of muscle patch – carotid interface have been displayed.

1 hour

At 1 hour the artery displays breach of its wall delineating the injury site. This is filled in with fibrin and haemorrhage and displays the occasional neutrophil. *(Figure 1 & 2)* The muscle patch in this instance has artefactually detached from the artery wall after harvest.

Figure 1: Muscle patch (black arrow) and carotid at 1 hour (H&E stain 40x) showing fibrin plug filling defect (blue arrow)

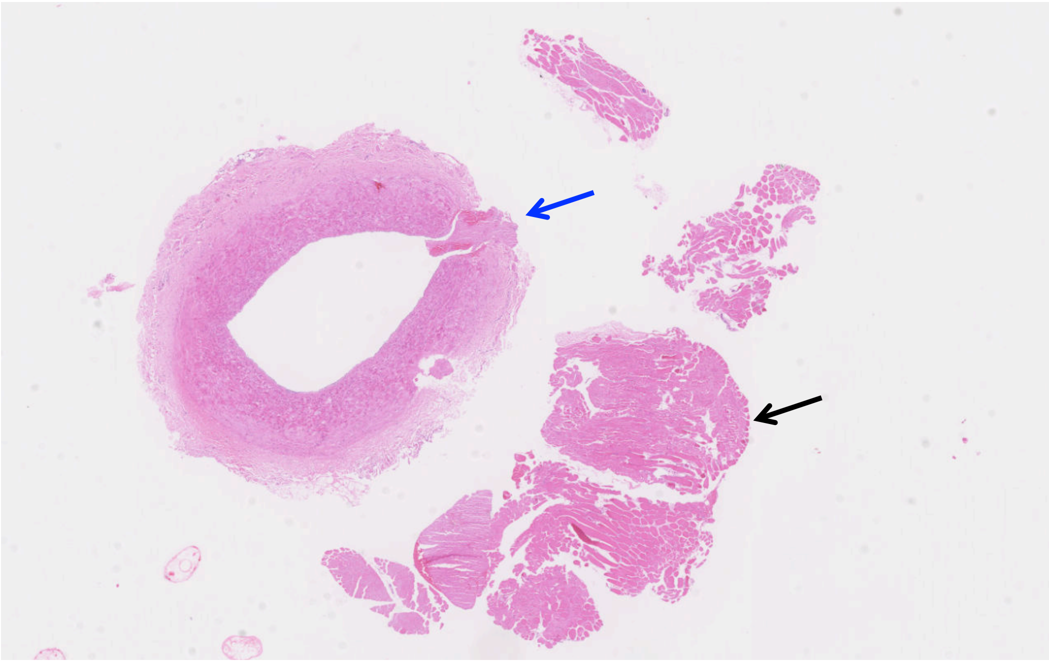
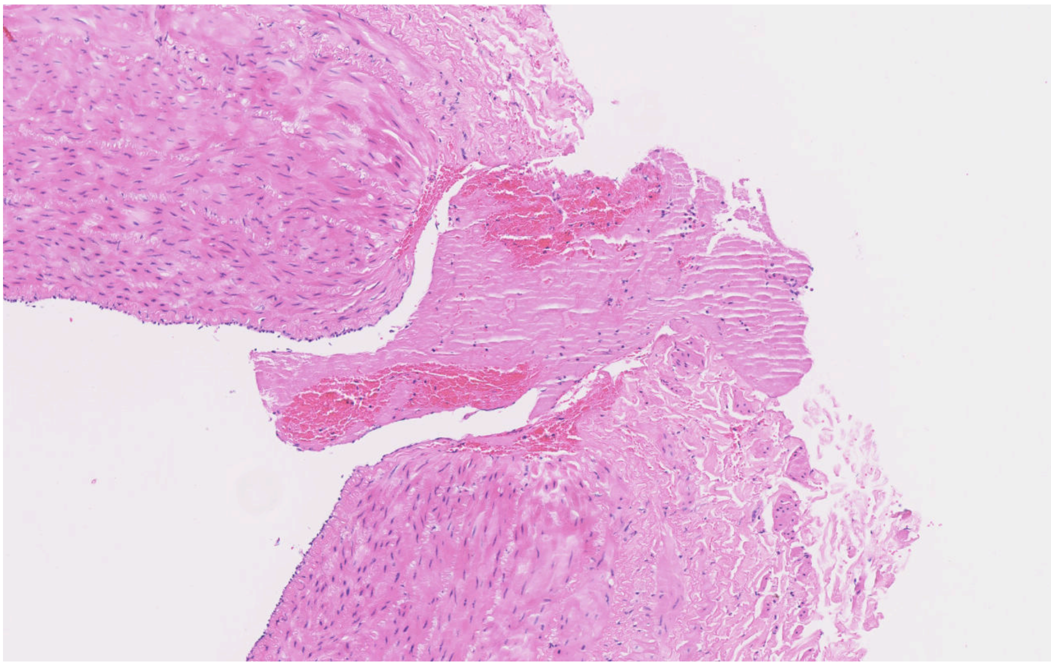


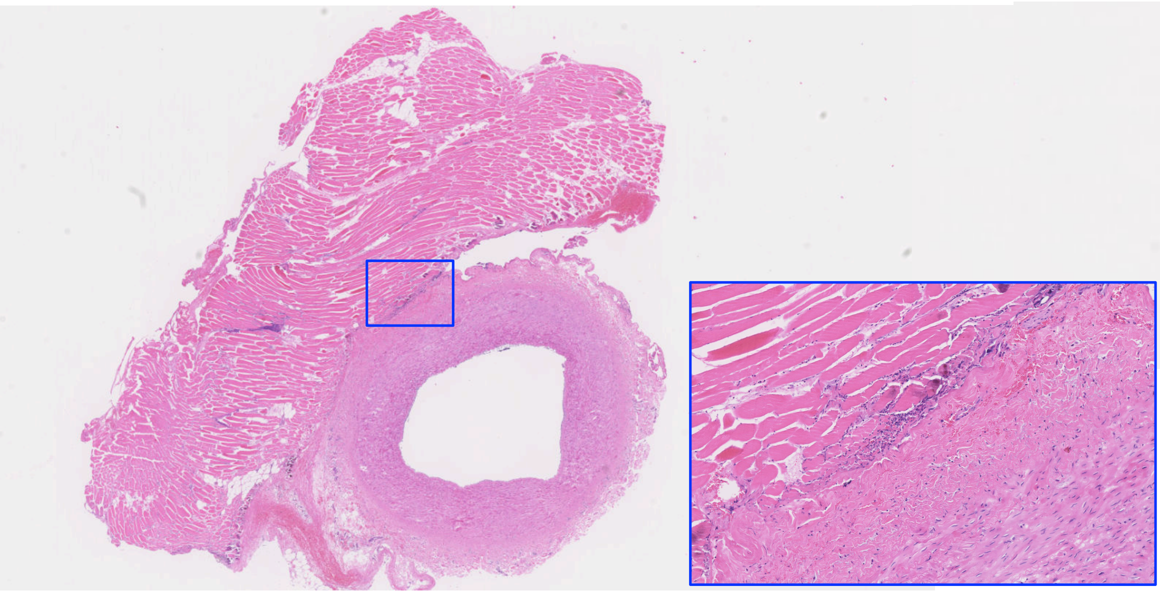
Figure 2: Fibrin plug filling injury defect at 1 hour (H&E stain 200x)



2 Day

2 days after muscle graft application fibrin and haemorrhage is noted. The muscle shows nuclear pyknosis and evolving necrosis. There is also evidence of microcalcifications, neutrophillic inflammatory infiltrate within the muscle *(Figure 3),* along with early development of granulation tissue plus a chronic inflammatory cell reaction of histiocytes and lymphocytes.

Figure 3: Inflammatory cells within muscle at 2 Days (blue box 200x)



1 week

At 1 week further granulation tissue has developed and organising fibrin is noted. Scattered neutrophils remain. Focal fat necrosis is detected *(Figure 4)*. There is an increase in overall vasculature, along with greater numbers of lymphocytes, histiocytes and fibroblasts *(Figure 4b)*.

Figure 4: Carotid and muscle at 1 week exhibiting focal fat necrosis (black arrow) and lymphocytes, histiocytes and fibroblasts (black box)

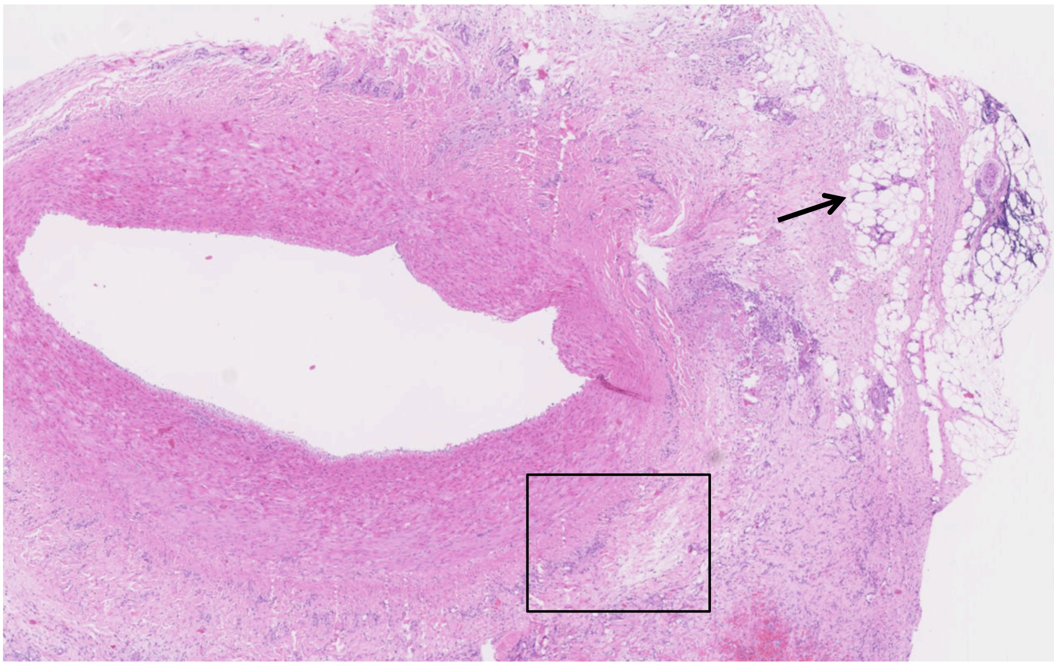
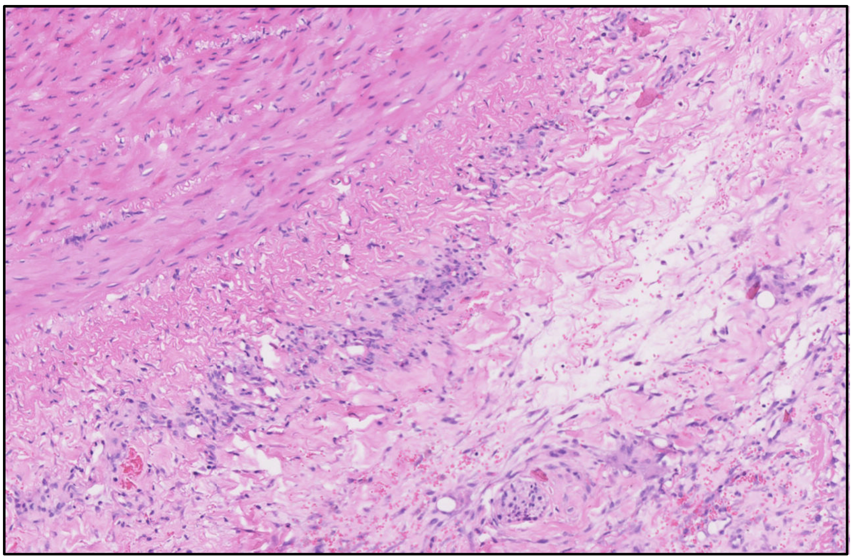


Figure 4b: Black box from Figure 4 - lymphocytes, histiocytes and fibroblasts within muscle



2 weeks

At 2 weeks there is greater incorporation of the muscle into the organising inflammatory reaction. The residual necrotic muscle is embedded in scar tissue. Inner aspect of muscle appears more affected with sections of outer muscle still viable *(Figure 5b)*. Angioplasia is prominent.

Figure 5: Muscle patch incorporated into inflammatory reaction at 2 weeks

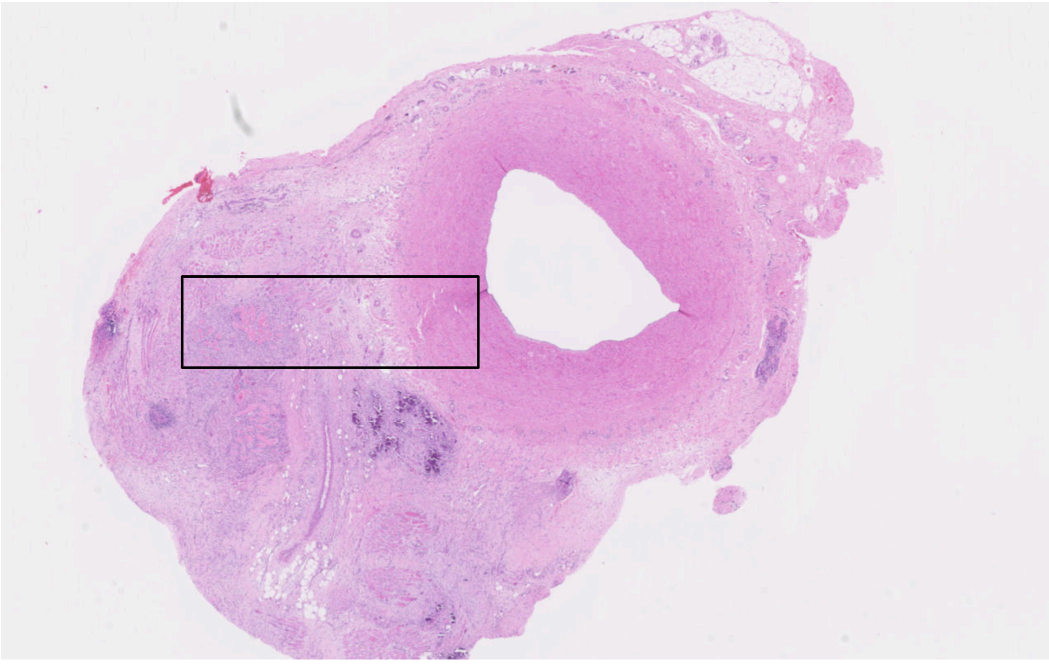
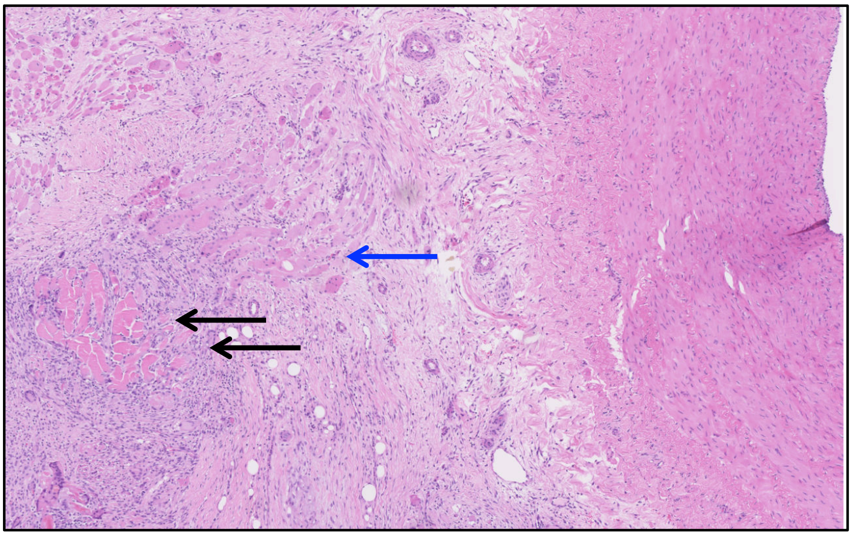


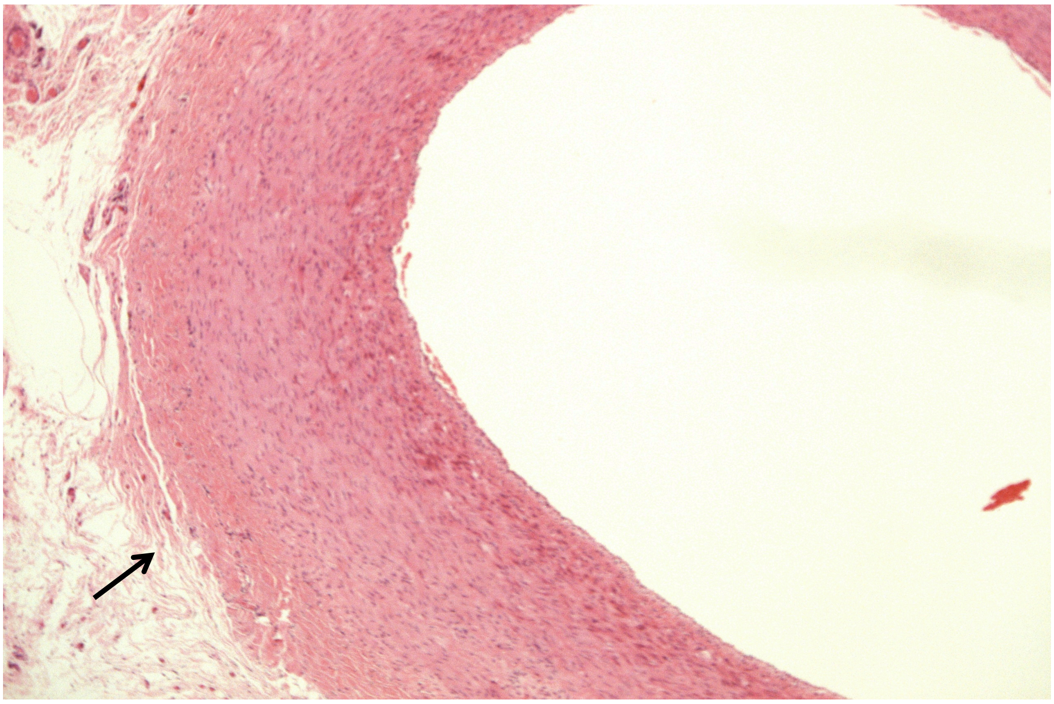
Figure 5b: Black box from Figure 5 – areas of viable (black arrow) and necrotic (blue arrow) muscle



<u>3 months</u>

No evidence of residual muscle patch is present in sections at 3 months and there is over all normal structure of vessel wall. The original injury site was not clearly identified. Minor other features of note include small pockets of lymphocytic inflammation and some slight adventitial fibrosis. .

Figure 6: Slight advential fibrosis (arrow) over otherwise normal artery structure



Discussion

This is the first paper to evaluate the histological features associated with a free muscle graft used for haemostasis over time. In the acute setting the muscle patch's effect stems from its ability to physically seal the injury site and allow for platelet aggregation with subsequent thrombin binding and conversion of soluble fibrinogen to fibrin. This is evidenced by the fibrin plug filling the breach of the vessel wall.

At two days we start to see early features of muscle necrosis, with nuclei pyknosis and microcalcifications. There is progression of the inflammatory response as well, with initially neutrophillic infiltration. Granulation tissue also starts to develop at this time point. This healing fibroinflammatory and vascular process advances over the next week. Neutrophils start to diminish while a chronic inflammatory cell response overrides with increased numbers of lympochytes and histiocytes present as well. At 2 weeks the muscle patch is very much incorporated into the granulation tissue. Inner aspects of the muscle seem to have established necrosis and are embedded within scar tissue. Interestingly outer aspects of the muscle appear to have remained viable at this time point.

3 months represents the time when the majority of pseudoaneurysms have occurred after an injury to the carotid and as such was selected as the end point of this study.[4] Use of the muscle patch has been associated with a low risk of pseudoaneurysm formation and a strong ability to preserve the natural characteristics of the artery, as found in a large animal study by Padhye et al.[7] In this study, we find at 3 months that there is no residual evidence of the muscle patch. It seems over time it has necrosed and its constituents phagocytosed and cleared by the cells from the ensuing inflammatory cascade. What remains is relatively normal vessel structure with minor lymphocytic infiltration and fibrosis of the adventia. There is a slight increase in the endothelial cells lining the carotid.

Although the benefits of muscle inducing haemostasis are known, there is very little in the published literature as to its mechanisms of action. It is apparent from this study that the initial tamponade effect of the muscle is beneficial, with all five sheep having bleeding controlled with muscle application. This was also identified by Remzi et al who utilised the pressure effect of skeletal muscle harvested from rectus abdominus to gain haemostasis in 2 cases of presacral haemorrhage.[13] Rajiv et al found that muscle extract in fact induces a greater amount of platelet aggregation when compared to controls.[12] It has been proposed that it may be the actin and myosin components of skeletal muscle, which are central in inducing platelet aggregation via adenosine bi-phosphate (ADP). ADP on filamentous actin (F-actin) provides multiple interaction sites for platelets.[14,15] The initial tamponade and scaffolding effect of muscle actin and myosin, with subsequent promotion of the coagulation cascade, are likely contributors to its initial success in haemostasis.

Another hypothesis as to its effect was proposed by James et al.[14] He postulated that muscle thromboplastin or tissue factor could activate the extrinsic coagulation cascade and promote clot formation.[14] This has been somewhat discounted by Drake et al, who used immunohistochemical techniques to localize tissue factor distribution in the body. He reported that amongst all muscular tissue, tissue factor was nearly undetectable in skeletal muscle, with cardiac muscle having the strongest expression and smooth muscle exhibiting variable expression.[16] The other commentary on the use of muscle in haemostasis alludes to its use as a conducting agent. Xu and Lin report use of rectus abdominus muscle graft on prescral bleeding. Once held in place with forceps over the bleeding site, electrocautery was applied to the forceps conducting it to the muscle, "welding" it in place. This was successful in 11 patients, with the high water content of the muscle being boiled and contributing to indirect coagulation.[17] Other authors have also reported success with this technique.[18,19]

The use of the direct method of application and haemostasis of the muscle patch has been validated in a sheep model in a series by Valentine et al[8] and followed up in a study by Padhye et al.[7] In Padhye et al's study sheep were followed up for up to 3 months after the application of a muscle patch. In each case it was able to gain haemostasis successfully. There was however a low risk of destabilisation of the muscle patch in the long-term and while the mechanism of this is unknown, it may be attributed to suboptimal inflammatory and healing response of the muscle-vessel complex.

The muscle patch does however carry many advantages. Not only is it an effective haemostat, but also it is autologous, biocompatible tissue that is freely available, unlikely to become infected, adherent and does not require precise placement. In a series of carotid artery injuries during endonasal surgery reported by Padhye et al[20], it was reported to have gained haemostasis in every case as well an incurring less morbidity when compared to traditional techniques. Proof of the great value in its clinical utilisation.

This study has allowed us to better evaluate the mehanisms at play of the action of the muscle patch when used for the haemostasis of major vessel haemorrhage.

Conclusion

The use of a free autologous skeletal muscle graft for haemostasis has been described in the literature, however the mechanisms of action remain largely unknown. This histological study of the muscle patch over time confirms its ability to gain prompt haemostasis by providing a seal of the vessel injury site and promoting platelet aggregation, compounded by an acute and chronic tissue healing response with eventual disappearance of the muscle patch.

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Chapter 6: Endoscopic Direct Vessel Closure in Carotid Artery Injury

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Summary and Conclusion

An inadvertent injury to the carotid artery or other major vessel during endoscopic surgery has long been viewed as a catastrophic surgical event. This high pressure / high flow haemorrhagic scenario poses many challenges to the surgeon, placing imminent risk to the patient's life.[131] The work described in this thesis has contributed to the relative paucity in the literature as to the safe management of this situation.

The role of endoscopic surgery in the management of chronic rhinosinusitis (CRS) is an important one. There will invariably be patients who fail first line medical therapy and require progression of their management.[2,22] In this instance surgery is offered and has been shown to be effective in managing CRS symptoms and leads to improvements in disease specific and generic quality of life measures.[23] However, CAI while rare has been reported during ESS. The endoscopic approach to skull base tumours is relatively new and carries many advantages. It is a technique, which has superior visualization, magnification, avoids scars, and reduces length of stay and patient morbidity.[162] There however are some limitations to this technique, with the most widely reported being that of post-operative CSF leak.[116] The potential for CAI is also known albeit less widely explored in the literature with evidence largely relegated to anecdotes and case reports.[115] Current treatment recommendations for CAI are based on a deficiency of scientific work and overzealous packing has shown to result in patient morbidity and potentially contribute to patient mortality.[131] Prospective work in the area of CAI is minimal, which is where the work described in this thesis makes its contribution to the existing knowledge base.

With the use of a sheep model of CAI, different endoscopic haemostatic techniques were trialled on different injury types. This study showed that irrespective of the injury type, in the immediate setting, a muscle patch or aneurysm clip were the most reliable in gaining haemostasis. In the long-term the muscle patch had a low associated risk of pseudoaneurysm formation and the success of the aneurysm clip was based on the accuracy of its placement. The findings of this study have shown the viability of these novel endoscopic haemostatic techniques in the CAI setting. They have the potential to add to a surgeon's armoury when managing a catastrophic bleed and carry with them the potential to maintain the normal characteristics of the carotid, thereby reducing the potential for patient morbidity.

The ability of muscle to gain haemostasis has been known for sometime, however the exact mechanism of action remains somewhat unclear.[163] Theories include its pressure effect, action as a welding conducting agent and possible release of muscle thromboplastin or tissue factor. More recently it has been found that muscle extract is associated with a greater degree of platelet aggregation when compared with controls.[164] In this thesis the histological study assessing the muscle patch's interaction with a carotid artery over time has shown that both acute and chronic inflammatory processes contribute to the over all tissue healing process, allowing for preservation of normal carotid structure. This has provided further insight into the efficacy of muscle as a haemostat and why its autologous and biocompatible nature is beneficial.

A major limitation of the endoscopic technique identified by authors has been the inability to directly repair large vessel injuries.[116,137] The success of the aneurysm clip has shown that direct vessel closure techniques have merit in this situation. The other direct vessel closure technique trialled was the AnastoClip and this was able to achieve haemostasis in all cases. Its novel 'pincer' clip design accommodates for pulsatile flow, maintains endothelial integrity as well as preserves vessel patency. Traditional suture closure of an artery is almost impossible in the endoscopic setting. The AnastoClip offers a viable solution to the endoscopic repair of a large vessel injury, potentially ushering in a new era of endoscopic haemostatic technique.

The Vascular Injury Workshop has trained over 118 participants in endoscopic haemostatic techniques. A review of cases managed by vascular trained surgeons revealed 9 instances of CAI. Each was managed successfully with use of a muscle patch. Although instances of impaired carotid flow, carotid dissection and pseudoaneurysm were encountered in this series, surgeons were able to identify these issues early and action the necessary management in each instance, such as embolization, stent placement or close observation. In this series none of these CAI resulted in patient morbidity. Existing literature reports 89 cases of ICA rupture, with mortality rate of 15%, incidence of permanent neurological sequelae of 40% and incidence of other non-neurological permanent morbidity of 26%.[115] In this series of 9 patients, there were no deaths, no instances of permanent neurological sequelae and no other permanent morbidity encountered. This represents a remarkable statistic, one that shows the value in vascular training in improving patient outcomes.

The body of work contained within this thesis has contributed markedly to the existing knowledge base surrounding the management of CAI. New techniques have been discovered and validated using a physiological simulation of a catastrophic event. Surgeons have been trained in the techniques reported and subsequently patient's lives have been influenced as a direct result.

Future directions of this work include the further development of different haemostatic techniques. This work shows there is no one solution to best deal with instances of CAI, as it can manifest with injury sizes, shapes, and locations and under variety of circumstances and constraints. The more options available to the surgeon, the safer surgery can become. Direct vessel closure has shown to be a distinct possibility and further repair techniques should be pursued. The muscle patch has shown how effective biocompatible materials can be in this situation and further development and research is encouraged in regards to haemostats that can be safely used both extra and intra cranially. Patient outcomes can be further enhanced with a better understanding of the complications after CAI. A model of pseudoaneurysm formation would encourage the development and evaluation of techniques that may be able to prevent its occurrence and provide confidence to the surgeon who may experience this potentially catastrophic situation.

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