HAEMOSTASIS AND WOUND HEALING FOLLOWING ENDOSCOPIC SINUS AND SKULL BASE SURGERY

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By

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ABSTRACT

Introduction

Endoscopic sinus surgery (ESS) is the gold standard treatment for medically refractory chronic rhinosinusitis (CRS), and endoscopic skull base surgery is rapidly becoming the treatment of choice for many skull base tumours. Intraoperative and postoperative bleeding can range from minor and troublesome, to catastrophic, increasing the risk of complications to the patient. Whilst there are a number of effective haemostats, they are associated with scar tissue formation, patient discomfort and risk disease transmission. Carotid artery haemorrhage during sinus and skull base surgery remains the most feared complication, with considerable challenges in controlling the surgical field and managing such an event. There is no prospective scientific investigation to guide the surgeon in how best to manage this scenario. The aim of this thesis is to explore different haemostatic techniques and agents that can be implemented during sinus and skull base surgery.

Methods

A novel haemostatic agent that has shown promise during *in vitro* investigation was identified and investigated in the sheep model of ESS. This randomized controlled trial (RCT) used the Boezaart surgical field grade scale to investigate the haemostatic efficacy. Macroscopic inspection of wound healing was performed for the first 2 post-operative weeks. Further evaluation of this agent was conducted in

patients undergoing ESS. Patient's symptoms were also investigated along with adhesion formation up to 3 months following surgery.

To investigate the catastrophic bleeding scenario, the sheep model of carotid artery injury was developed. Consecutive experience with this model allowed a retrospective review of surgical videos to be performed so that a number of important principles could be identified to control the surgical field. Following this the efficacy of various techniques at achieving haemostasis were compared in a prospective randomised fashion. Particular end points included time to haemostasis, total blood loss, and overall survival of the animal.

Results

Chitosan gel, in the sheep model of ESS, achieved rapid haemostasis at 2, 4 and 6 minutes after injury, with no adverse effects noted in the early post-operative period. These findings were replicated in patients following ESS, with the additional benefits of no adverse patient symptoms and prevention of adhesion formation.

The sheep model of carotid artery injury is a reproducible model of the high flow/high pressure vascular catastrophe that accurately recreates the anatomical constraints of the human nasal vestibule and is capable of training advanced endoscopic skull base surgeons in the techniques required to manage the surgical field. With specific instrumentation, the U-clip treatment and the muscle patch achieved complete haemostasis whilst maintaining vascular flow through the parent vessel.

Conclusions

Chitosan gel is the first effective haemostatic agent that improves macroscopic and microscopic features of wound healing, is well tolerated, and is rapidly dissolvable in the early post-operative period.

The sheep model of carotid artery injury is an important innovation that allows advanced skull base surgeons to be trained in the techniques required to control the surgical field during carotid injury. Additionally, in the sheep model, the U-clip treatment and muscle patch repair achieve rapid haemostasis and maintain vascular patency.

DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution, and that to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text

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- Valentine R, Athanasiadis T, Moratti S, Robinson S, Wormald PJ. The efficacy of a novel Chitosan gel on haemostasis after endoscopic sinus surgery in a sheep model of chronic rhinosinusitis. *Am J Rhinology* 2009; 23(1): 71-5

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- Valentine R, Boase S, Jervis-Bardy J, Dones Cabral JD, Robinson S, Wormald PJ. The efficacy of haemostatic techniques in the sheep model of carotid artery injury. *Int Forum Allergy Rhinol* 2011; 1:118-122

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PREFACE

A portion of the work described within this thesis has been submitted for publication, as listed below:

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CHAPTER 1 AIMS

The aims of the study were:

1. Review the literature on haemostasis and wound healing following endoscopic sinus surgery (ESS)
2. Develop and evaluate a novel haemostatic agent that reduces adhesions following ESS
3. Develop an animal model of carotid artery injury during endoscopic sinus and skull base surgery
4. Develop and evaluate the efficacy of a novel haemostatic agent and techniques during endoscopic carotid artery injury

CHAPTER 2 INTRODUCTION

Chronic Rhinosinusitis

Definition and Disease Burden

Chronic rhinosinusitis (CRS) is defined as a group of inflammatory disorders of the nose and paranasal sinuses present for more than 12 weeks without complete resolution of symptoms[1]. The nose and paranasal sinuses constitute a collection of air-filled spaces within the skull and communicate with the nasal cavity through small apertures. These cavities are lined by pseudostratified columnar ciliated epithelium, and named based upon the facial bone with which they arise ie. frontal, ethmoidal, sphenoid and maxillary sinuses[1]. CRS is a common disorder, affecting 1 in 7 adults in the United States, and results in 31 million individuals diagnosed with the condition each year[2]. The direct health-care costs are approximately $5.8 billion annually and includes over 500 000 surgical procedures performed on the paranasal sinuses each year[3,4]. Indirect costs due to sinusitis include 73 million days of restricted activity per year[5]. CRS also has significant socioeconomic implications with patients suffering from CRS visiting their primary car clinicians twice as often as those without CRS, and have 5 times more prescriptions filled[5]. CRS patients also self report a quality of life which is as debilitating as diabetes or heart failure[6].

Pathophysiology

A large amount of research has lead to many insights into the cause of sinonasal inflammation but the exact aetiology and mechanisms of CRS are still unknown. CRS is a multifactorial disorder, with a variety of environmental and host factors contributing to its development. Possible aetiological mechanisms postulated include staphylococcus superantigens[7], bacterial biofilms[8], fungus[9], aspirin intolerance and

cystic fibrosis[10]. These aetiologies result in mucosal inflammation and increased mucus production. The osteomeatal complex is the key region for frontal, anterior ethmoidal and maxillary sinus ventilation and obstruction of the orifice can induce a vicious cycle of stasis of secretions, proliferation of bacteria, enhanced mucosal inflammation, reduced sinus aeration and ciliary dysfunction, all of which contribute to the development of CRS[11]. Mucociliary transportation is required to allow for physiological sinus drainage and hence disorders in mucociliary clearance predispose for the development of CRS[12]. Abnormal cell-mediated immune responses, abnormal cytokine cascades[13], allergy and an immune compromised state (eg. Immunoglobulin deficiencies, HIV, immunosuppressive treatments) contributes to mucosal inflammation and swelling and may increase the risk of CRS[11]. Histologically these processes lead to desquamation of ciliated pseudostratified columnar epithelium, fibrosis, squamous metaplasia, hyperplasia of goblet cells and subepithelial thickening[14].

Management

Medical Management

The medical management of CRS involves a multifaceted approach and includes systemic and topical antibiotic therapies[15], nasal saline irrigation, topical and systemic corticosteroid therapy, and mucolytic treatments[16-18]. Other agents that have been advocated include topical antifungal therapies and leukotriene modifiers[19].

Surgical Management

Surgical management is indicated in those patients that fail maximal medical treatments[20]. The popularity of surgery as an effective treatment option has seen it become the second most common procedure performed by Australian otolaryngologists, with over 54 000 cases performed every year[21]. This figure is over ten times larger in the USA, with over 500 000 cases performed each year, and accounting for over 50% of procedures performed[4].

Historical Perspectives of Sinus Surgery

The nose has been utilized as a pathway for procedures since the ancient Egyptian era, with well described writings explaining the process of brain removal through the nose and its replacement with saw dust[22]. It wasn't until the 16th century that there was the first clear indication of the existence of paranasal sinuses, provided by an anatomist and surgeon at Bologna, Berenger del Carpi[23]. Despite the understanding of the existence of the paranasal sinuses they were poorly understood, and many thought this system of hollow spaces was through which the mucus produced by the brain would drain[22]. Surgical treatment began in the 17th century, in an era before antibiotic therapy, with surgical treatment offering the only reliable relief. A number of surgeons proposed maxillary ostial enlargement. The technique was published by a Bordelaise dentist, Jourdain[24], however instrumentation limitations means that, at best, his cannula was actually perforating the fontanelle region.

It was appreciated that the middle meatal approach was not always anatomically possible and often resulted in premature closure and hence the intranasal inferior antrostomy was first published by Gooch, and popularised by Lichtwitz, Krause[23] and

Mickulicz[25]. In an escalating attempt to manage those difficult to treat patient, the approach through the anterior wall was described as early as 1675 by Molinetti[26], but became popular when Caldwell, Spicer and Luc suggested the addition of removal of the irreversibly damaging the mucosa[23].

Surgery to the ethmoidal sinuses and lateral nasal wall was difficult until the advent of the operating microscope, however the techniques use of a nasal speculum still resulted in trauma to the lateral nasal wall and turbinate. Although ciliary action was first described in 1835, the concepts were largely forgotten, until the advent of the endoscope for intranasal examination. The theories and studies of the complex system of pathways by which the paranasal sinuses drain into the nasal cavity is based around the work of Messerklinger[27]. Most importantly was the concept that mucociliary clearance occurred via the sinuses natural ostium, even if an alternative surgical opening was created[28,29], with endoscopic techniques focusing on removing diseased tissue, restoring natural drainage pathways and preserving normal mucosa. These techniques led to the term 'Functional Endoscopic Sinus Surgery' (FESS), a term coined by Kennedy[30,31].

Indications for Endoscopic Sinus Surgery

Endoscopic sinus surgery is performed most commonly for medically refractory CRS[28,32]. However, with significant improvements in visualization, surgical technologies and instrumentation, this has expanded widely to include a range of pathologies. Endoscopic approaches for indications such as allergic and vasomotor rhinitis, posterior septal deviation, turbinate surgery, nasal polyposis, antrochoanal

polyps, mucocoeles, retention cysts, and refractory posterior epistaxis are now considered routine[32,33]. Expanding indications also include orbital and optic nerve decompression, dacrocystorhinostomy, choanal atresia repair and cerebrospinal fluid leak. [33-36].

Outcomes of Endoscopic Sinus Surgery

The success of endoscopic sinus surgery (ESS) has been well evaluated for the treatment of chronic rhinosinusitis both with and without nasal polyposis. Endoscopic sinus surgery has been demonstrated to have a statistically significant reduction in the use of medical resources such as use of antibiotics and health care visits, along with improved productivity and time away from work[37]. Patients suffering with concomitant asthma also report that their asthma control is improved following ESS, with patients reporting less need for oral steroid therapy and inhaler use, with less overall asthma attacks[38]. Patients also report a significant improvement in overall symptom relief and satisfaction based on quality of life questionaires[37], a finding in 98% of patients at a mean of 7.8 years following surgery[39-41]. Overall these studies demonstrate that ESS for medically refractory CRS is an effective treatment with significant improvement in symptom control, and patients view this therapy as beneficial and worthwhile.

Complications of Endoscopic Sinus Surgery

Major Complications

Complications of ESS are broadly divided up into major and minor groups. Major immediate complications include optic nerve damage and blindness, intra-orbital haemorrhage, injury to the ocular muscle and subsequent permanent diplopia, skull base penetration with dural injury, haemorrhage, CSF leak and possible meningitis. High flow/high pressure bleeding from injury to the internal carotid artery is also a catastrophic event that can result in death or permanent neurological injury. The risk of a major complication in early series of ESS was reported as high as 1-4%[42,43], however with increasing anatomical knowledge and improvements in training and technology this is now significantly less, less than 0.5% of all cases[44]. The risk of carotid artery injury during ESS was significantly higher before the innovation of the endoscope, but now is much lower at <0.001%[45].

Minor Complications

Minor complications of ESS include post operative epistaxis, adhesion formation and damage to the lamina papryacea[43]. The incidence of these complications is much more significant, with adhesion or synechia the most common with a reported incidence ranging from 15-30%[46-52]. Post-operative sequelae such as adhesions and stenosis hinder the success of this procedure, interfere with normal mucociliary transport and mucosal function, and lead to re-obstruction of functional sinus drainage pathways and the need for revision surgery[53,54]. Post-operative strategies for maintaining ostial patency and functional drainage are considered equally important as intra-operative measures[55]. Bleeding during ESS is inevitable, however,

as ESS is performed in narrow confines then even a little bleeding can adversely affect the intraoperative field. Regular contamination of the endoscope tip can be frustrating for the surgeon and lead to surgical manoeuvres being performed without clear visualization. Patients who continue to bleed following ESS are at risk of airway compromise from inhalation of blood clots or from aspiration of blood stained vomitus, and many surgeons resort to nasal packing materials to prevent ongoing bleeding[56].

Medial Skull Base Tumours

Medial skull base tumours are those lesions that involve and arise from the medial skull base. Anatomically the medial skull base involves the posterior wall of the frontal sinus, the cribriform plate and crista galli, the ethmoid portion of the frontal bone, the body of the sphenoid bone centrally, and the clivus posteriorly and inferiorly. Tumours involving this region include pituitary adenomas, craniopharyngiomas, meningiomas, clival chordomas, chondrosarcomas and sinonasal tumours. Pituitary adenomas are the most common skull base tumours, and are a diverse group of tumours arising from the pituitary gland. They can be divided into microadenomas (dimensions < 1cm) and macroadenomas (dimension > 1cm), of which may remain within the sella or extend into the suprasella compartment. These can also be further divided into functional and non-functional tumours depending on their hormonal activity. The incidence of these tumours has been estimated to be 16.7% on both radiographic and autopsy studies, however only 1 in 600 will become clinically significant[57].

The most common pituitary masses in children are craniopharyngiomas and they represent 6-13% of all childhood brain lesions[58], but these tumours are also found in all adult age groups[59]. They are histologically benign tumours that originate from the remnants of Rathke's pouch. They can be either intrasellar, found to originate or extend into the suprasellar area, or alternatively originate solely within the third ventricle[60].

Cranial base meningiomas are a group of tumours that can involve the crista galli, olfactory groove, planum sphenoidale, tuberculum sellae, anterior clinoid process, parasellar regions and petrous ridge. They arise from the arachnoid 'cap' cells of the arachnoid villi in the meninges, and are the most common primary intracranial tumours, reported in 2.3% of autopsy examinations[61].

Chordomas arise from the notochord remnants and are slow growing, locally aggressive tumours. These tumours arise in and around the upper and middle clivus and the spheno-occipital synchondrosis[62]. They are a rare tumour comprising about 0.15% of all primary intracranial neoplasms[63].

Chondrosarcomas of the skull base are rare and comprise approximately 0.1% of all intracranial tumours and 6% of all skull base lesions. These tumours commonly involve the temporo-occipital junction, parasella area, sphenoethmoid complex and the clivus[64].

Sinonasal tumors are rare and account for only 1% of all malignancies. These tumors can also involve the medial skull base and include Adenocarcinomas, squamous cell carcinomas, olfactory neuroblastomas, melanomas and sarcomas[65].

Surgical Management of Medial Skull Base Tumours

Historical Perspective of Endoscopic Skull Base Surgery

The era of endonasal skull base surgery begins with the forefather of neurosurgery, Harvey Cushing. Harvey Cushing was one of the first surgeons to utilized the transphenoidal corridor for pituitary disease, implementing the headlight for visualization, however then abandoned this approach in 1927 because of the difficulties with illumination[66]. Norman Dott, a trainee of Cushing, was not so easily deterred and invented the lighted speculum for transphenoidal visualization[66].

The invention of the first endoscopes 200 years ago was brought about due to the need for visualization of human and animal hollow organs[67]. Early designs in 1806 consisted of an eyepiece and a candle for illumination. Max Nitze made modifications to the light source with the use of water-cooled platinum wires, which were soon modified to the incandescent light bulb in 1879[68-70]. Endoscopic design however stalled until the mid-20th century when Harold Hopkins invented to rod lens system containing a series of glass rod lenses. This system improved visualization nine fold with greater light transmission, a wider view, better image quality, and a narrower diameter[71]. Gerald Guiot, an apprentice of Dott, attempted to improve the visualization and was the first neurosurgeon to use the endoscope for transphenoidal surgery[72]. Endoscopes where still inadequate at this time, and with the advent of the operating microscope, made way for Jules Hardy to establish the microsurgical transphenoidal approach to the skull base[73]. In 1965 Karl Storz realised that in addition to transmitting visual information, a system of glass fibres could be used to transmit light, leading to the licensing of the idea of fibreoptic external light transmission coupled with the rod lens optical system[70]. Apuzzo and coworkers then

reported the use of the endoscope as a technical adjunct in microscopic resection of pituitary tumours in the late 1970s[74,75]. The early 1990s then saw the collaboration between neurosurgeons and otorhinolaryngologists, leading to the first reports of a purely endoscopic approach to the sella[76].

More recent innovations include neuronavigation and microvascular Doppler ultrasonography, coupled with improved endonasal instrumentation. These innovations have allowed the endoscopic endonasal possibilities to expand and progress to lesions outside of the sella turcica[77-81]. These extended approaches to the skull base have increased in their popularity. Improvements in endoscopic training and understanding of the endoscopic endonasal skull base anatomy have allowed these extended approaches to progress quickly. With the sphenoid sinus as the fundamental anatomical landmark, extended approaches can be targeted to reach the supra and parasellar areas, planum sphenoidale, olfactory groove, and clivus. Inferolaterally the sphenoid floor can be removed to the clivus, and followed laterally to expose the petrous apex, foramen lacerum and the cavernous sinus[73]. Exposure of the infratemporal fossa through the pterygopalatine fossa allows exposure of the middle fossa skull base, from foramen ovale laterally to the carotid posteromedially[73].

Indications for Endoscopic Skull Base Surgery

The main limitations to choosing the endoscopic skull base approach depends on the anatomical location of the tumour, the location of important neurovascular structures, availability and expertise of dural reconstructive techniques, available technologies and the availability of a properly trained surgical team[82]. An important principle in determining the best approach for the removal of skull base pathologies

is choosing the surgical corridor that will allow complete removal of the disease. The anatomical limitations of anterior skull base tumours and their removal has been assessed by Dehdashti et al. The authors reviewed their experience in 22 patients, concluding that their limitations were large lesions (>4cms), significant lateral extension beyond the optic canals, encasement of neurovascular structures and brain invasion by malignant lesions[83]. Burkart et al assessed the extent of exposure of the clivus. Removal of the bony septum significantly improved exposure, with the only limitation being the lateral limits where exposure was limited by the medial pterygoid plates and the Eustachian tubes[84]. Other authors have overcome these limitations by utilizing the transpterygoid approach[85]. Complete exposure superiorly into the interpeduncular cistern can be achieved by performing the superior transposition of the pituitary gland[86]. The most inferior extent of exposure can be predicted by the nasopalatine line (the line connecting the inferior tip of the nasal bones to the posterior edge of the hard palate), with exposure to the odontoid process and body of C2[87]. Harvey et al demonstrated that an maxillary antrostomy allowed access to the area medial to the infraorbital nerve, but a medial maxillectomy with nasolacrimal duct resection allowed access lateral to the infraorbital nerve and the anterior wall of the maxilla[88].

The goals of tumour resection are identical to traditional craniofacial resection including complete removal of disease with minimal morbidity. Negative margins are pursued only not to compromise critical neurovascular structures (ICA, optic nerves etc)[82]. Resection margins during endoscopic skull base resections have been shown to be identical to the more traditional craniofacial approaches[89-91]. Innovation in dural reconstruction over the last 3 years has allowed vascularised mucosal pedicle flaps to reduce CSF leak rates to 5%[92]. Technological advances in endoscopic skull base

surgery includes image guidance, allowing the surgeon to properly identify important anatomical landmarks during endoscopic surgery[93]. Perhaps biggest limitation to endoscopic skull base surgery is the proper training of the surgical team, in endonasal techniques and avoiding complications[82].

Outcomes of Endoscopic Skull Base Surgery

Many authors have compared the traditional microscopic transphenoidal approach with the endoscopic transphenoidal approach. Outcome measures have been comparing overall operative time, symptom resolution, gross tumour resection, hospital length of stay, requirements for revision surgery and the complication profile. The endoscopic transphenoidal approach has been demonstrated to be on average 2 hours quicker in operative time[94], with significantly reduced hospital length of stay by at least 2 days[1,89,94-96] and no difference (and in some cases significant improvements) in gross tumour resection when compared to pre-operative imaging[94,97,98], or revision surgery rates[94]. A meta-analysis of pooled data on over 800 patients has demonstrated the safety and efficacy of the endoscopic approach, as well as showing higher rates of normalization of endocrine function and improved visual outcomes and gross total tumour removal[97]. Many other studies have also identified these important outcomes[96,98,99]. Others have also demonstrated the angled endoscopes superior role in identifying residual tumour within the sella following the microsurgical approach[100-102]. Overall, the complication rates have been comparable between the endoscopic and microscopic techniques[1,94,97,98].

Experience with endoscopic pituitary surgery has progressed and led to more extended approaches, with removal of the planum sphenoidale for access to suprasellar lesions, and those that extend into the cavernous sinus. Laufer et al, de

Divitiis et al and Frank et al showed that the endoscopic approach to these lesions afforded a high rate of complete resection with a low complication profile[103-105]. In a series of 20 patients with cavernous sinus extension 75% of prolactinomas and adrenocorticotropic secreting tumors demonstrated normalization of endocrine function when approach endoscopically[106,107]. Complete resection was achieved in 62-65% of cases of extended approaches[106].

Endoscopic approaches to other skull base lesion outside of the sphenoid sinus also has a number of advantages including less postoperative pain, reduced hospital length of stay and avoidance of brain retraction in the surgical approach[1,108]. With regards to the endoscopic approach to anterior cranial fossa meningiomas, Gardner et al series of 35 resections demonstrated gross total resection in 83% of olfactory groove meningiomas and 92% of tuberculum meningiomas. All patients experienced resolution or improvement of visual symptoms with no patient experiencing a decline in visual function, compared to approximately 20% in conventional open series[109-111]. Only 1 patient (3%) experienced a permanent pituitary deficit, diabetes insipidus[108], compared to open transcranial series ranging from 0 to 12.9%[109,112].

Finally, experience in resections of posterior fossa tumours has rapidly increased over the last decade. Stippler et al describes their experience in 20 consecutive patients undergoing an extended endoscopic approach. They achieved a gross total resection rate of 67% for newly diagnosed tumours, and a near total resection rate in a further 17% of patients[113]. These figures compare favourably with opens series, with gross total resection rates ranging from 44%-83%[114-116]. The incidence of new neurological injury was only 5%[113].

Complications of Endoscopic Skull Base Surgery

Endoscopic skull base surgery is performed for a variety of surgical pathologies associated with different tumour characteristics and associated with different anatomical areas. For example resection of an isolated pituitary fossa lesion will present different challenges when compared to a large clival chordoma resection. In an attempt to stratify complications following endoscopic skull base surgery Kassam et al retrospectively reviewed their complication profile with 800 consecutive endoscopic endonasal skull base resections[117]. A total of 48.4% of surgeries were isolated to the sella, and 52.5% considered extended approaches expanding outside of the sella. The most common complication of skull base surgery was CSF leak (15.9%), followed by 4.8% experiencing a procedure related complication such as seizure, infection (meningitis or abscess formation) or systemic complication (eg. pulmonary embolism). The postoperative intracranial infection rate was 1.9% (11 bacterial meningitis, 1 intradural abscess and 1 extradural abscess). Transient neurological deficits occurred in 2.5%, and permanent deficits in 1.8%. The mortality rate associated with endoscopic skull base surgery was 0.9% (6 patients from systemic complications, and 1 from meningitis) and there was an overall permanent morbidity/mortality rate of 2.6%. Major vascular injuries occurred in 0.9% of cases.

Not surprisingly extended skull base procedures are much more likely to suffer from complications. Kassam et al reported that 22% of patients that underwent intradural endoscopic dissection had a complication, and a combined mortality/morbidity rate of 6.1%. Infectious complications are 13 times more common in surgery involving extrasella intradural dissections and neural complications are more common in surgeries that transgress the dura[117]. The likely hood for a CSF leak, intracranial

infection, neurological sequalae or systemic complication was statistically significantly associated with extended approaches, $p<0.05$[117]. Comparing theses complication profiles to other consecutive series of extended endoscopic approaches to skull base surgery we can see similar findings with CSF leak rates ranging from 5.56%-30%[118-120], meningitis/abscess from 0.68%-10%[105,121] and neural injury from 10% to 33%[105,122] .

Large vascular injury during endoscopic skull base surgery is a major event, with internal carotid artery (ICA) injury considered the most feared and catastrophic complication. Injury to the cavernous ICA results in rupture and often overwhelming haemorrhage, with the frequent formation of a pseudoaneurysm[123,124]. Injury to the ICA during the endonasal transphenoidal approach to the sella ranges from 0.58%-1.1%[123-125]. More extended endonasal approaches (EEA) centre around the management of the internal carotid artery, and not surprisingly have a much higher incidence of ICA injury. Surgery performed around the carotid artery is 22 times more likely to suffer a vascular event[117]. Couldwell et al, Frank et al and Gardner et al reviewed their experience with consecutive EEA resections of craniopharyngiomas, clival chordomas and chondrosarcomas, demonstrating a 5-9% incidence of ICA rupture[120,126,127].

CHAPTER 3 HAEMOSTASIS IN ENDOSCOPIC SINUS AND SKULL BASE SURGERY

Coagulation Overview

Haemostasis is a complex process of forming clots within damaged blood vessels and preventing loss of blood whilst maintaining blood in a fluid state within the circulatory system. A collection of complex systems and mechanisms interact to maintain this delicate balance.

The immediate response to tissue damage and transection of blood vessels is to initiate vasoconstriction of the vessels and to form a temporary haemostatic plug of platelets. The activation and aggregation of platelets is triggered when platelets bind to the negatively charged surfaces of collagen[128]. Activated platelets liberate serotonin and other vasocontrictors that results in the constriction of an arteriole or small vessel, often so marked that the lumen is obliterated[128]. The loose aggregation of platelets in a temporary haemostatic plug is bound together and converted into a definitive clot by fibrin. A cascade of reactions occur in which inactive enzymes are converted to active enzymes, which in turn activates further enzymes resulting in the ultimate conversion of prothrombin to thrombin. This serine protease is responsible for the conversion of the soluble plasma protein fibrinogen into the insoluble protein fibrin, which is further cross linked by other fibrin molecules to form a stable clot[128]. This cascade of reactions can commence simplistically by 2 pathways; the intrinsic system where negatively charged collagen fibres fibres beneath the endothelium result in the activation of factor XII to factor XIIa, or by the extrinsic system where damaged tissue releases tissue factor (thromboplastin III) that then activates factor VII to fator VIIa.

The tendency for coagulation is balanced by the fibrinolytic system that modulates reactions to prevent clotting within the circulating system (figure 1). Antithrombin III is

a protease inhibitor that binds to the serine proteases of the coagulation cascade and blocks their activity. Endothelial cells also produce thrombomodulin which is expressed on their surface. Thrombomodulin binds to thrombin, a combination that results in a complex capable of activating protein C. Activated protein C, in combination with protein S, functions to reverse factor VIIIa and factor Va to their inactive froms[128]. Activated protein C also acts to increase the formation of plasmin, the enzyme responsible for the lyses of fibrin and fibrinogen. Plasmin is also activated by tissue Plasminogen Activator (tPA) and urokinase Plasminogen Activator (uPA), and modulated by the actions of Plasminogen Activator Inhibitor (PAI)[128].

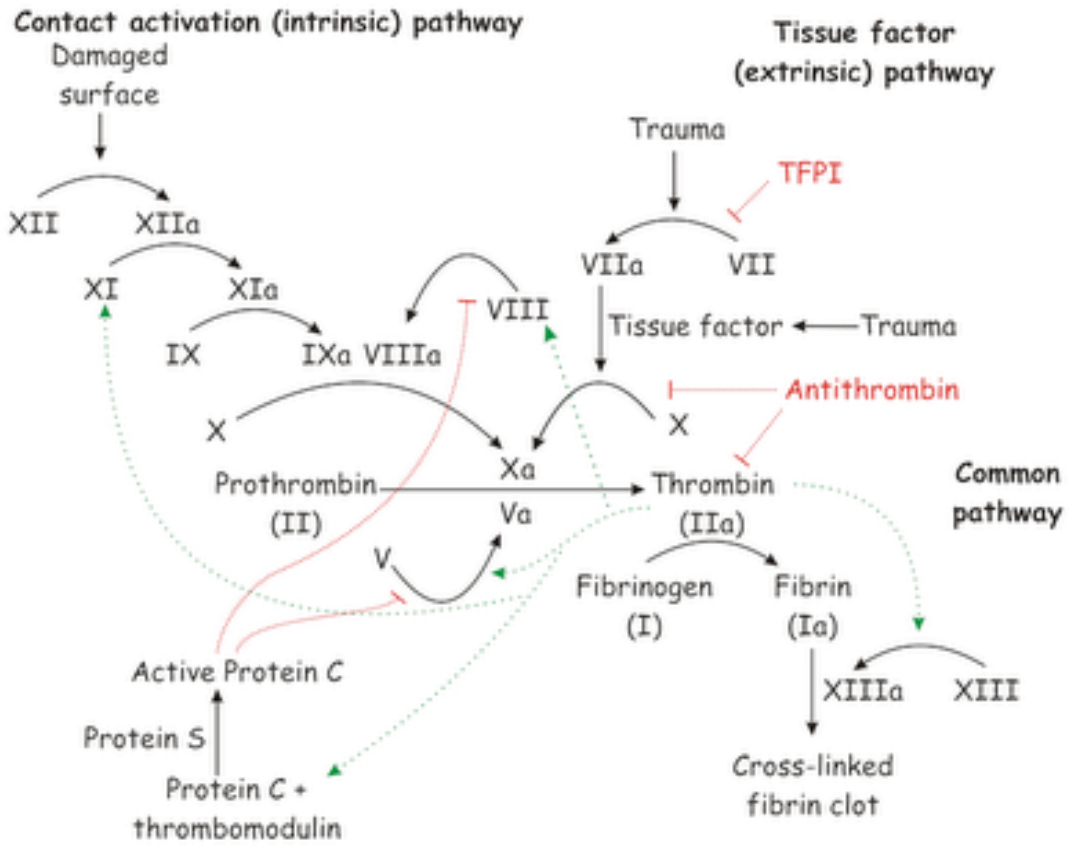

Figure 1 – The coagulation cascade[129]

There is also considerable evidence that inflammation and coagulation is a bidirectional process, with cross-talk that occurs at the level of platelet activation, fibrin formation and resolution, as well as the anticoagulation pathways[130,131]. Thrombin, in addition to activating fibrinogen, also has a number of additional actions including the activation of platelets, endothelial cells and leukocytes. Anticoagulant proteins such as activated protein C, along with thrombin, can activate specific cell receptors on endothelial cells and mononuclear cells which affects cytokine production[132]. Activated protein C and thrombin can also bind and activate fibroblasts[132]. The binding of tissue factor with factor VIIa up regulates the inflammatory responses in macrophages and affects neutrophil infiltration and cytokine expression such as tumour necrosis factor alpha[133]. Fibrinogen and fibrin directly stimulate the expression of proinflammatory cytokines on mononuclear cells and induce the production of chemokines by endothelial cells and fibroblasts[134].

Controlling the Endoscopic Surgical Field – Low Flow/Low Pressure Mucosal Bleeding

Mucosal edge bleeding can be considerable troublesome during endoscopic sinonasal surgery. Mucosal edge bleeding from cut vessels maybe arterial, depending on the MAP, capillary depending on the capillary bed blood flow, or venous and dependant on venous return and venous tone[135]. Most simply bleeding can be defined from 2 important factors: the source (venous or arterial) and the rate (high-flow or low-flow). Venous bleeding can involve low flow bleeding, as occurs in diffuse mucosal oozing, or it can arise from high flow as occurs in focal bleeding from

the cavernous sinus[136]. Additionally, arterial bleeding may occur from small perforating vessels or from high flow vessels such as the carotid artery.

The nasal cavity is a narrow space where even just a small amount of bleeding can rapidly result in the inability to view the surgical field. The nature of endoscopic sinus surgery is operating within a diseased and inflamed nasal cavity where bleeding can be more rapid. When significant bleeding occurs then the recognition of anatomical landmarks becomes more difficult[137]. A poor surgical field results in the surgeon having increased difficulty in manipulating the endoscope and instruments into the site of dissection before the surgical field is covered in blood and the manoeuvre can no longer be performed[135]. Regular contamination of the endoscope tip can be frustrating for the surgeon and lead to surgical manoeuvres being performed without clear visualization[138]. This results in not only a frustrated surgeon, but significant delays in the surgery and may increased the risk of intraoperative complications. There are a number of techniques that have been employed in order to help improve the surgical field which can be broadly divided into pre-operative considerations, peri-operative consideration, anaesthetic considerations and intraoperative considerations.

Pre-operative Considerations

Preoperative inflammation of the sinuses increases local blood flow to the mucosa, and hence can increase bleeding during surgical procedures. Steriods have a favourable effect inhibiting inflammation but also increase the spastic reactivity of smooth muscle to endogenous adrenalin and noradrenaline[139]. There is one randomized controlled trial that investigates the use a 5-day 30mg/day course of pre-operative prednisolone to improve the intraoperative surgical field. Whilst

intraoperative blood loss wasn't significantly different, the visibility of the surgical field was significantly improved on the Boezaart scale in the pre-operative steroid treated group[139]. A similar study was performed by Wright et al demonstrating that pre-operative steroid administration was associated with significantly improved sinonasal inflammation, and that this was associated with ease of surgery. Haemostasis and the surgical field were not objectively measured in this study[140]. Antibiotics are also commonly used in the preoperative setting to decrease inflammation and infection, however there are no randomized controlled trials that have shown whether there is any effect on the surgical conditions or blood loss. Radiographic embolization of vascular tumours is considered important within 48 hours before surgery to reduce bleeding and improve the intraoperative surgical conditions[141,142].

Peri-operative Considerations

Firstly simple measures such as placing the patient in the reverse Trendelenburg position have been advocated and shown to reduce blood loss and improve the operating conditions during surgery. Ko et al conducted a randomized controlled trial; randomly enrolling 60 patients undergoing ESS to be placed in a 10 degree reverse Trendelenburg position or positioned supine. The reverse Trendelenburg position significantly reduced intraoperative blood loss and the Boezaart surgical field grade score, with a trend to reducing the surgical operating time[143].

Topical vasoconstriction can be utilized to reduce nasal mucosal blood flow. In 1941 Major Arthur James Moffett first published his work on the local anaesthesia of the nose in order to reduce blood loss[144]. There is some controversy regarding the various contributions of 'Moffett's' solution however in his original papers he describes the use of 2mls of 8% cocaine (160mg), 2 mls of 1% sodium bicarbonate,

and 1ml of 1:1000 adrenalin. Cocaine is a naturally occurring anaesthetic agent that is very popular in nasal surgery, often combined with adrenalin. Porter et al[145] demonstrated that the addition of adrenalin to cocaine shows a significant reduction in nasal blood flow, and also has a significant reduction in intraoperative blood loss[144].

Local infiltration of nasal mucosa with adrenalin has also been investigated. A total of 4.4mls of 1:80000 adrenalin produces a significantly better surgical field when compared to topical adrenalin, however causes a systemic rise in adrenalin concentrations by 43 times[146,147]. Local infiltration of the pterygopalatine fossa with 2mls of 2% lignocaine, combined with1:80000 adrenalin has been shown to improve the surgical field for the first 90 minutes following injection. As the greater palatine canal has been shown to be 25mm in length it is important to bend the needle 25mm from its end, at an angle of 45 degrees[137,148].

Anaesthetic Consideration

Intraoperative bleeding and maximising the surgical field during anaesthesia has been of significant interest since surgery and anaesthesia began. Once the practice of anaesthesia became established, although the surgeon still caused the bleeding, the anaesthetist took the blame. However this has some merit in that it was noted early on that conscious patients certainly bled less during surgery than those that were anaesthetised with volatile anaesthetics.

Controlled hypotension is defined as a reduction in systolic blood pressure to 80-90mmHg, a reduction of MAP to 50-65mmHg or a 30% reduction of baseline MAP[149]. The importance of controlled hypotension was first realized in 1946 where

the arteriotomy was utilized to reduce arterial blood pressure. Controlled hypotensive techniques have rapidly increased in popularity with the advent of new and improved pharmacotherapy. The advantages of hypotensive anaesthesia are well recognized including an improved surgical field, decreased operative time and a reduction in total blood loss and blood transfusions required[150,151]. These advantages have been shown in ESS, in 2 double blind RCT, with significant improvement in the Boezaart surgical grade score, blood loss and the operative time[151,152].

A reduction in mean arterial pressure (MAP) can be achieved via a reduction in cardiac output (CO), a reduction in systemic vascular resistance (SVR), or both.

$$MAP = SVR \times CO$$

Reducing the SVR by utilizing vasodilating agents has only been shown to be effective when profound levels of hypotension are reached (MAP<50mmHg). Moderate hypotensive levels do not improve the surgical field when compared to normotensive levels[135], and may actually worsen the surgical conditions[153]. A number of authors have demonstrated however that a reduction in CO by bradycardia improves the surgical conditions. Boezaart et al demonstrated that the use of the short-acting beta-blocker esmolol produces a better surgical field than the vasodilator sodium nitroprusside, even at equal MAPs[135]. Only a MAP<65mmHg was required to see this effect. Nair et al showed that preoperative blockage with 100mg of oral metoprolol improved the surgical conditions early during ESS[154]. A premedication with oral clonidine has also been shown to improve the surgical field and reduce intraoperative bleeding during ESS[155]. Magnesium infusions have also been shown to be effective in reducing CO and SVR, and significantly improve the

surgical field and reduce blood loss, however it increases the duration of anaesthesia and causes drowsiness post-operatively[151].

The goal of controlled hypotension is to maintain a pressure sufficiently low to allow a reduction in bleeding without suppressing the microcirculatory autoregulation of the vital organs. Improved understanding of organ autoregulation of blood supply such as the brain and kidneys means that these techniques can be employed with increasing confidence. Initial experience with controlled hypertension was reviewed by Lindop et al, where they noted no significant difference in higher cerebral functioning after surgery when compared to control, however in regards to overt cerebral damage they noted numerous case reports and case series describing cerebral thrombosis with subsequent morbidity and mortality[156]. However these were uncontrolled investigations of early experience, and there was no evidence that the mortality of controlled hypotension was any different to general anaesthesia alone[149]. Choi et al reviewed the literature between 1966-2008 regarding the safety of hypotensive anaesthesia, grading the level of evidence with more stringent criteria. Results demonstrated that there was no significant difference in cognitive performance between normotensive and hypotensive anaesthesia[157]. Additionally they concluded that no myocardial ischaemic events occurred, urine flow rates appeared to decrease but this was entirely reversed in the early post-operative period. With regard to hepatic effects there was a transient elevation of alpha-glutathione S-transferase however this returned to normal in the first few hours post-operatively. Most importantly the authors concluded that ASA 1 and 2 patients are fit and can tolerate controlled hypotension well without significant damage to organs[157]. In fact there is no current data that indicates that controlled hypotension within a MAP of between 50-65mmHg is a risk in young healthy patients[149].

There are 3 studies that have assessed the effect of anaesthetic technique on intraoperative blood loss during ESS, with 2 studies comparing propofol vs volatile agents. Average blood loss was significantly less with the use of propofol when compared to both isoflurane[158,159] and sevoflurane[159]. The last study failed to show any difference in blood loss between propofol and isoflurane[160]. When analysing the effects of different anaesthetic techniques for the surgical field then propofol/remifentanil based techniques have been shown to be superior to isoflurane/fentanyl, isoflurane/alfentanil, sevoflurane/sufentanil and sevoflurane/fentanyl[160-163].

Laryngeal mask airway (LMA) devices have replaced the endotracheal tubes (ETT) in anaesthesia for many surgical procedures. Atef et al performed an interesting study investigating the surgical field differences between the LMA or ETT. Anaesthesia was maintained by total intravenous anaesthesia (TIVA) using propofol and remifentanil. Results showed that in sustaining a target blood pressure the LMA group required significantly less remifentanil than the ETT group. Additionally the MAP and pulse rate during the first 15 mins of surgery was significantly higher in the ETT group of patients, with a corresponding improved surgical field in the LMA group of patients. However after the first 15 mins of surgery there was no significant difference. Induction of general anaesthesia is known to cause hemodynamic variables via sympathetic stimulation, probably as a result of direct laryngoscopy and ETT, however the LMA results in no direct laryngeal stimulation[164].

One of the main concerns regarding LMA usage is protection of the airway from blood and upper airway secretions. The LMA sits like an umbrella over the laryngeal inlet to protect the upper airway from contamination. Webster et al found similar

rates of airway contamination between LMA and ETT at the end of ESS (as assessed by bronchoscopy)[165]. Laryngeal cup contamination was found to occur in 2% of 200 patients undergoing ESS with no adverse outcomes[166]. Large case series without adverse events have been described with the use of the LMA in ESS[167]. The LMA also has a number of advantages in the emergence following ESS. Coughing and straining during emergence produces venous engorgement and increased bleeding from the surgical site. The LMA has been shown to offer a smoother emergence from general anaesthesia when compared to ETT[165,168,169]. Whilst the LMA usage is considered preferred, it doesn't protect the airway against regurgitation and high inspiratory pressures will results in gastric insufflation, hence the studies that compared LMA usage to ETT excluded patients with hiatus hernia, reflux disease and obesity[166,168,169].

Finally hypoventilation with hypercapnia is well known to produce vasodilation and tachycardia. Many have advocated to minimise bleeding and optimise the surgical field by maintaining normocapnia/hypocapnia[135,153,154]. Despite this Nekhendzy et al showed no difference in the surgical conditions or blood loss among ESS patients randomized to hypocapnia, normocapnia or hypercapnia anaesthesia when blood pressure and pulse were controlled[170].

Intraoperative Considerations

One of the most frequently utilized instruments for focal bleeding sites during surgery is the bipolar electrocautery. Standard bayonet designs are difficult to manoeuvre into position within the tight nasal confines and therefore the 'pistol grip' designs are preferred. Bipolar cautery allows accurate cauterization of a bleeding vessel with minimal thermal spread to surrounding areas.

Warmed water irrigation has also been shown to be almost as effective a surgical treatments for posterior epistaxis, however its efficacy during ESS, or the replacement of warmed water with warmed saline has not yet been evaluated[171]. Histological analysis in the rabbit model suggests that irrigation at the temperature of 40-44 degrees celsius is preferred[172]. Postulated mechanism of action includes activation of platelet aggregation, interstitial oedema and enhancement of the coagulation cascade[173].

Haemostatic Agents (table 1)

Nasal packing has been the traditional method of controlling ongoing bleeding following surgery to the paranasal sinuses and has been utilized in an attempt to prevent adhesion formation, middle turbinate lateralization and restenosis following surgery. Nasal packing was first described in the otorhinolaryngology literature in the 1951[174] and the use of absorbable biomaterials since 1969[175]. Removable nasal packing agents have been designed to tamponade mucosal bleeding and to act as a barrier to adhesion formation. Numerous packing agents are available and include vaseline soaked ribbon gauze, fingerstall packs, polyvinyl acetate sponge (Merocel), and various balloon tamponade devices. However these cause considerable discomfort for the patient involved, both in terms of pain and bleeding upon removal[176-180]. Unfortunately removable nasal packing has been rated by patients to be the most unpleasant aspect of the ESS surgical experience[176,177,181]. Other complications associated with removable nasal packing includes septal perforation, pack dislodgement, aspiration, toxic shock syndrome, foreign body granuloma, myospherulosis, obstructive sleep apnoea secondary to nasal obstruction and even death[182,183]. Animal studies investigated the mucosal trauma caused by removable

nasal packing has shown a 50-70% loss of the ciliated mucosal surface area[184]. Therefore a transient impairment of the patient's innate immune system, the mucociliary clearance, may be associated with the use of removable nasal packing[185]. These draw backs of removable nasal packing has lead to the ongoing development and application of absorbable biomaterials not requiring subsequent removal, that still achieves positive effects on hemostasis, promotes wound healing and provides middle turbinate support. Biomaterials have been extensively investigated and researched in the ENT literature well before the evolution of ESS, and this interest continues in the pursuit of surgical excellence.

Absorbable porcine gelatin/thrombin products: Absorbable porcine gelatin hemostatic matrix (Surgiflo) combined with thrombin is an absorbable porcine gelatin that has been investigated by Woodworth *et al* following sinus surgery in a prospective trial. Results showed that 96.7% of patients achieved hemostasis within 10 minutes, with the median time of 1 minute, however there was no control arm to this study[186]. The use of Surgiflo/thrombin combination did however result in a postoperative bleeding episode requiring nasal packing in 1/30 patients[186].

FloSeal is a topical hemostatic agent consisting of gelatin matrix (bovine derived) combined with human derived thrombin, and first became available to the market in 2000. Gall *et al* found that FloSeal was effective in achieving hemostasis in 17 of the 18 patients in which it was used, and additionally found that the average time to hemostasis was 2 minutes[187]. Additionally Jameson *et al* analysed the effects of FloSeal in a controlled, randomized, double-blinded study. This showed that there was a significantly faster time to hemostasis in the FloSeal group (16.4 minutes) when compared to the control (30.8 minutes). Baumann *et al* compared FloSeal vs

Merocel in a non-randomized trial, and found that intraoperative hemostasis was achieved within 3 minutes in both arms[188]. Finally Chandra et al analysed it effects on perioperative haemostasis, finding it was equivalent to thrombin soaked gelatin foam[185]. Significant variability is shown between these studies on the time to achieve hemostasis.

Fibrin glue (Quixil) is a combination of human thrombin and fibrinogen, in conjunction with amino acids and salts allowing this compound to form an easily applied gel. It imitates the final stages of coagulation aiding haemostasis and tissue sealing and has found favour in a number of surgical disciplines including cardiovascular surgery. It was first used in the rhinology literature in the early 1990s, largely for the management of cerebrospinal fluid rhinorrhoea, or endonasal/transsphenoidal pituitary surgery. Vaiman *et al* analysed the effects of Quixil , a fibrin glue, in patients following ESS. This double-blind randomised controlled trial involving 64 patients showed that all post-operative bleeding was controlled, however the time to achieving hemostasis was not analysed[189].

The adverse effects on wound healing, and concerns regarding antibody formation and disease transmission of fibrin/thrombin based products limits their usefulness for ESS.

Collagen products: microfibrillar collagen products such as Avitene and Gelfoam are frequently utilized as local topical hemostatic agents during endoscopic surgery and have the advantages of easy to use and at a low cost, even though most studies suggest that fibrin glue maybe more a more effective haemostat[190,191]. It has also been shown to be effective at holding dural grafts in place following skull base reconstructions[192].

Thrombin: Topical thrombin has been used as a effective haemostatic agent in many surgical fields, with its first use dating back to the 1950s[193]. However, there is concern regarding its potential for disease transmission and antibody formation, which has driven the development of a recombinant thrombin, with comparable efficacy to bovine thrombin[194]. At present recombinant thrombin is not approved for human use, and hasn't been trialled during ESS.

Hyaluronic Acid/Carboxymethylcellulose: Hyaluronic acid (Sepragel sinus) is a viscoelastic gel containing polymers of highly purified forms of hyaluronic acid and has been investigated for immediate hemostasis by Frenkiel *et al*. This study is a non-blinded RCT involved 20 self-controlled patients following ESS. Results showed that there was no significant difference between the total blood loss when comparing the Sepragel sinus side vs the no treatment side, however a subjective general improvement of hemostasis was noted with the intervention side[195]. MeroGel is also a hyaluronic acid containing product used widely following ESS, however there is no published data on its hemostatic capabilities.

Carboxymethylcellulose (CMC) nasal packing was developed in 2001, with its postulated ability to promote hemostasis by platelet aggregation. There are 2 reported studies regarding CMC's efficacy on hemostasis postoperatively. Karkos *et al* conducted a prospective, non-randomised, uncontrolled pilot study following ESS involving 15 patients after day surgery, where all patients were treated with CMC mesh nasal packing bilaterally. Nursing staff reported persistant oozing in 20% of patients, however no patient required intervention[196]. In a single blind RCT involving 41 self controlled patients (ie. no treatment) following ESS, Kastl *et al* showed that there was no significant effect of CMC mesh on postoperative bleeding[197].

Oxidised Regenerated Cellulose: Oxidised regenerated cellulose products such as surgicel have been used as haemostatic agents following nasal surgery since 1969[198]. It has been shown to have moderate haemostatic capabilities[199], however despite its popularity since this time there are still no studies that compare surgicel to no treatment. Shinkwin *et al* conducted a RCT comparing the incidence of postoperative hemostasis following ESS in 60 patients, comparing Surgicel Nu-knit to vaseline ribbon gauze and Merocel. All packing agents were equally effective with no incidence of postoperative epistaxis in any of the treatment arms[200].

Platelet Gel: Platelet gel is a fibrin tissue adhesive product manufactured from centrifugation of autologous whole blood giving a platelet rich plasma. It has the advantages of eliminating the risk of potential virus transmission and antibody formation to coagulation factors. Use in the rhinology community commenced in 2001, following a presentation to the American Rhinologic Society. Pomerantz *et al* conducted a retrospective study involving 16 patients receiving platelet gel following ESS. These patients were control matched to a previous group of patients who underwent Merocel packing following ESS. There was no reported postoperative epistaxis in either arm[178].

Antifibrinolytics: These agents have been in use since the 1960s and are now in widespread use within the medical field[201,202]. These agents function by blocking the lysine binding sites on plasminogen and preventing the activation of plasmin, functioning to preventing fibrinolysis and stabilizing the blood clot. The topical and systemic use of tranexamic acid in the management of epistaxis for hereditary haemorrhagic telangiectasia (HHT) has been favourable in case reports[203,204]. Topical antifibrinolytics such as epsilon-aminocaproic acid and tranexamic acid have

been investigated in a recent human study for their intraoperative hemostatic properties following ESS. This double-blinded randomised controlled trial (RCT) compared the effects of topical epsilon-aminocaproic acid, and tranexamic acid with normal saline following ESS. Results showed that topical epsilon-aminocaproic acid was ineffective at achieving hemostasis compared to saline, however tranexamic acid at low dose (100mg) improved hemostasis significantly ($p<0.05$). This observed effect was reduced at higher doses[205]. Of specific interest is this is only the second study in the literature to use an objective surgical grade score to monitor the hemostatic efficacy.

Polyethylene Glycol: There are a number of polyethylene glycol products on the market for intranasal use, including CoSeal and Nasopore. CoSeal has not been evaluated following ESS, but has been shown in 2 vascular anastomosis studies to be equally as haemostatic as a gelatin/thrombin combination product[206,207]. To date there is no published literature investigating the hemostatic or wound healing properties of polyethylene glycol (NasoPore) following ESS.

Chitosan: Chitosan is prepared from chitin, a polymer that is found in a large number of natural sources including crustaceans, fungi, insects, annelids, molluscs and coelenterata[208]. It has a low toxicity and is inert in the gastrointestinal tract of mammals. Currently chitosan is used as a preservative to foods, an antimicrobial coating on fruits and vegetables for human consumption, a coating for seeds prior to planting, a hydrating cosmetic product as well as an additive to shampoos and toothpaste[209]. Chitosan has long been known to be an effective hemostatic agent, Klokkevold et al reported that chitosan solution added to bilateral tongue incisions in a rabbit model resulted in a 43% improvement in bleeding time as compared to

controls[210]. Aguilera et al found, in a high flow arterial wound model in swine, that a chitosan acetate dressing was 100% effective for maintaining hemostasis for a period of at least 30mins, compared to a 21% effectiveness in the gauze arm[211]. The mechanism by which chitosan gel initiates hemostasis is unknown. Preparations of chitosan have been shown to initiate hemostasis independent of platelets or coagulation factors[212]. Scanning electron microscopy has shown that chitosan increases the affinity of red blood cells[213].

Chitosan has been used within the nasal cavity as a carrying agent to deliver medications such as prednisolone, vaccines, growth hormones, anti-inflammatory agents, antibiotics and insulin[214-219]. However, it has never been used following nasal surgery. Recently our department has developed a novel gel, formed by the cross-linking chitosan and dextran derivatives (CD gel). Athanasiadis et al, to determine the effect on sheep nasal mucosal wound healing, has recently investigated this gel and adhesion formation, compared to polyethylene glycol and recombinant tissue factor (rTF). The results showed that CD significantly improved the microscopic features of wound healing, and reduced the adhesion formation[220]. However the effects of this gel on haemostasis remains unknown, and has been the subject of analysis in this thesis (chapter 6 and 7).

Cyanoacrylate: Tissue adhesives have been popular within medicine for their success in closing lacerations and surgical incisions. They are also reports of their success in achieving haemostasis on the skin[221,222]. There is also a porcine epistaxis model where cyanoacrylate glue has been shown to be beneficial in controlling nasal bleeding in heparinised animals[223]. Due to its known ability to cause chronic inflammation and fibrosis it is unlikely to be utilized following ESS[224].

Microporous Polysaccharide Hemispheres: Microporous polysaccharide hemispheres (MPH) is a novel absorbable agent that is produced from purified potato starch, and acts to quickly extract fluids from blood thereby concentrating serum proteins and platelets at the site of injury, and was approved for use in 2006. One recent study investigates the effects of MPH on hemostasis. Sindwani et al showed in a non-randomised, uncontrolled prospective trial that MPH resulted in rapid hemostasis in 65 patients following ESS, with hemostasis achieved between 30-45 seconds following application[225].

CHAPTER 4 WOUND HEALING IN ENDOSCOPIC SINUS SURGERY

Wound Healing

Wound healing is a complex but essential process, and is defined as an attempt by the organism to repair traumatised tissues in an effort to maintain homestasis[226]. The main reason for repair is to protect the organ from repeated injury, prevent the loss of vital substances and to replace or repair damaged anatomical structures[226].

The nasal mucosa is a physical barrier to foreign materials, and also aids in conditioning the inhaled air ready for the lower airways. The nasal epithelium lies on the basement membrane, which is situated on the lamina propria. The lamina propria consists of 2 layers of seromucous glands: a superficial layer that is situated just beneath the nasal epithelium, and a deep layer beneath the vascular layer. Beneath the basement membrane lies the lymphoid layer, consisting of plasma cells and lymphocytes. The vasculature of the nose contains specialized capacitance vessels, allowing the nasal mucosa to regulate airflow, condition the inspired air and allow an organized first line of immune defense[227]. The nasal epithelium consists of pseudostratified columnar epithelium and is composed largely of ciliated cells, non-ciliated cells, goblet cells and basal cells. These 4 main cell types allow for mucus production and transport, resolution of surface materials, and the formation of new epithelial cells[227].

Elegantly summarized by Watelet et al, the outcome of wound healing lies on a continuum between complete replacement of injured tissue with newly regenerated cells or with scar tissue formation[227]. Growth factors and cytokines are the mediators responsible for the coordination of processes involved including inflammation, cell proliferation, matrix deposition and remodelling. Growth factors activate their target cells by binding to their corresponding high-affinity surface membrane receptors.

Specific knowledge of sinonasal wound healing is limited, with most histopathological studies based on cutaneous and gingival tissues[228,229], however there are 4 overlapping stages of wound healing that are common to all tissues. These stages are the coagulation phase, the inflammatory phase, and proliferative phase and finally the maturation/remodelling phase[226,227].

Coagulation Phase

The haemostasis phase precedes the inflammatory stage. Surgical trauma to the nasal epithelium results in the obligatory rupture of vessels and their exposure of subendothelial collagen to platelets. The result is activation and aggregation of platelets to form a haemostatic plug, with the release of vasoactive substances such as histamine, bradykinin and serotonin[230]. These vasoactive substances allow vasoconstriction to occur over the next 5-10 minutes, which assists in allowing the haemostatic plug to develop, and prevent blood loss. Activation of the intrinsic part of the coagulation cascade and the contact between platelets and collagen (in the presence of thrombin and fibronectin) results in the release of cytokines and growth factors from platelet alpha-granules, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), platelet-activating factor (PAF), fibronectin, and serotonin[230]. Fibrin within the clot also stimulates the release of PDGF, epidermal growth factor (EGF), Insulin like growth factor-1 (IGF-1), TGF-β, and fibroblast growth factor (FGF) from the platelet derived alpha-granules[227]. The locally formed fibrinous clot at the end of the coagulation cascade serves as an important scaffolding for migrating cells that are the hallmark of the inflammatory phase: such as neutrophils, monocytes, fibroblasts, and endothelial cells[231]. In fact

inadequate clot formation is associated with impaired wound healing due to either decreased adhesion of cells into the area or decreased chemotaxis[232,233].

Inflammatory Phase

This phase is characterised by an increase in vascular permeability due to inflammation and release of prostaglandins. This is coupled with a concentration gradient of chemotactic substances such as complement factors, interleukin-1, tumor necrosis factor-alpha, TGF-β, platelet factors and bacterial products[230]. These locally released cytokines and growth factors result in the stimulation of predominantly polymorphonuclear neutrophils during the first 24-48 hours. Along with neutrophil derived integrins, neutrophils assist their penetration into the extracellular matrix (ECM) by the release of collagenases and elastase. After the first 72 hours neutrophils begin to be replaced by monocytes over the next 3-5 days, then becoming activated macrophages[226]. Their role in debridement, matrix synthesis and angiogenesis is essential in the continuation of wound healing[234]. Macrophages control over the continuation of the wound healing process is effected by secreting cytokines such as TGF-β, basic FGF, EGF, TGF-α and PDGF[227]. If a prolonged inflammatory phase occurs, as may during a postoperative microbial infection, this may result in an excited phase of fibroplasia[230].

Proliferation Phase

The proliferation phase lasts between 3-21 days and is characterised by the proliferation of fibroblasts, endothelial cells and epithelial cells. It is the macrophages located in the nasal lamina propria that provide the continuing source of cytokines necessary to stimulate the proliferation of these cells[227]. Cytokines from platelets and

macrophages are responsible for the migration and attraction of fibroblast to the wound area. This phase is characterised by the corresponding increased blood flow to the healing tissue and angiogenesis, and is recognised by the development of granulation tissue (consisting of fibroblast, macrophages and neovasculature). Once the nasal fibroblasts have migrated to the area they then switch their major function to protein synthesis, reaching their maximum in the first 2 weeks, with wound collagen levels at their highest within 3 weeks following the injury[226].

Epithelial regeneration and migration begins from the adjacent uninjured areas, and begins within a few hours, at an estimated velocity of 4 μm/hour within the nasal cavity[235,236]. The epithelial cells at the wound edge slowly develop cytoplasmic extensions into the wound area. Four different processes occur simultaneously to allow for re-epithelialisation: epithelial cell migration, multiplication, reorientation and differentiation, all occurring from the respiratory basal cells (the main source of epithelial cells)[237]. Whilst epithelial regeneration occurs rapidly, ciliogenesis and differentiation can take several months[238-240].

Maturation/Remodelling Phase

Nasal extracellular matrix remodelling, cell apoptosis, cell apoptosis and wound remodelling may continue for up to 6 months after surgery[227], however a full thickness mucosal injury may take much longer, and not be completely mature for more than 18 months[241]. Most cells produce proteinases that are able to degrade the ECM, including serine proteinases, cysteine proteinases and matrix metalloproteinases[242]. Ongoing inflammation can up regulate and prolong the process of remodelling. As remodelling occurs, the levels of different collagen types are replaced. Initially the ECM is composed mainly of hyaluronic acid, fibronectin and

collagen types I/III/V, however as remodelling occurs collagen type III is replaced to collagen type I[243]. Other changes that occur also include the formation of larger bundles of fibres, reduced levels of hyaluronic acid and water, altered cross-linking[230] and the production of elastin fibres and proteoglycans within the matrix[227]. In the end the maturation/remodelling phase is the dynamic balance between collagen synthesis and lysis, with an increase in the wound tensile strength and resilience over time[227].

Sinonasal Wound Healing

Animal Models

Interest into the effect of surgery on the sinonasal epithelium began early in the 20th century, with pioneers including Knowlton[244] and Hilding[245]. Using the canine and rabbit model different histological patterns were noted following sinus surgery. The regenerated epithelium was found to be either: normal ciliated respiratory mucosa, acute and chronic inflammatory changes, fibrosis, ulcerations or granulation tissue[50]. Subepithelial glands don't always regenerate and dense connective tissue may replace the lamina propria. New bone formation may also occur, particularly when denuded of periosteum, and may affect the mucosal function. In fact bone remodelling, fibroblast proliferation and the formation of polyps are characteristic of regenerating mucosa[246,247]. As mentioned previously, the depth of mucosal injury has an impact on the wound healing characteristics. If the basement membrane remains intact after a local injury, then the respiratory epithelium may recover as quickly as 3 days, but if the basement membrane is damaged then the regeneration

process lasts weeks and maybe somewhat disordered[248]. However, even though the respiratory epithelium may regenerate, functional regeneration of cilia maybe absent[50].

Human Models

The advent of the endoscope allowed the close observation of mucosal healing after sinus surgery by videoendoscopy[249,250]. Four overlapping phases of wound healing were defined, with these phases differing significantly. The first 7-12 days postoperatively are characterized by blood crusts covering the whole wound. The second phase differs from the first by the formation of granulation tissue that persists from 2-4 weeks postoperatively. This second phase finishes with the advent of the oedematous phase, the third phase. The fourth and final phase is the macroscopic normalization phase, occurring between the 12^{th} and 18^{th} postoperative weeks[249].

Pathophysiology of Adhesion Formation

An adhesion can be defined as a band of scar tissue that joins together 2 or more surfaces that are normally separated from each other. Sinonasal adhesions form where 2 adjacent surfaces are traumatized forming a fibrinous bridge between these 2 surfaces. This bridging fibrinous clot may allow migration of fibroblasts to occur, leading to the formation of an adhesion. Studies also suggest that patients with CRS express greater levels of TGF-β, shown to lead to greater levels of fibrosis, and may predispose CRS patients to adhesion and ostial stenosis postoperatively[251].

Whilst the pathogenesis of adhesion formation has been poorly studied within sinonasal surgery, it has had extensive investigation within the abdominal cavity, where adhesion occur in up to 97% of patients undergoing abdominal surgery[252]. Adhesion formation within the abdomen depends to a large degree on the dynamic relationship between the fibrinolytic process and epithelial recovery vs failure of fibrinolysis and over exuberant proliferation, differentiation and migration of fibroblasts[253]. Fibroblasts migrate into the fibrinous clot, secrete ECM proteins and initiate the adhesion formation process[254].

An extensive study has demonstrated that peritoneal fibroblasts that cause adhesions display a different phenotype to those peritoneal fibroblasts which do not form adhesions[255], and that these fibroblasts have a higher proliferative rate and a higher resistance to apoptotic signals[256]. There is a delicate balance between too much apoptosis preventing normal wound healing vs too little with overzealous scar tissue formation. Phenotypic changes include a reduction in tissue plasminogen activator resulting in a reduced fibrinolytic pathway effect. Other changes also include a greater ability to produce TGF-β and ECM molecules[256].

TGF-β is a critical factor involved in the regulation of the inflammatory response and ECM production[257]. Antibodies to TGF-β, when given during cutaneous wound healing, reduce collagen deposition and result in normal tissue architecture[258].

Adhesion Formation Following Endoscopic Sinus Surgery

Adhesion formation is the most common complication of nasal and sinus surgery, and its rates are reported to be between 15-30%[46-52] in both RCTs and retrospective

reviews. Adhesions have long been know to result in the interference of normal mucociliary transport, resulting in retained secretions, with the first published descriptions of adhesion interference dating back to 1933[245]. Adhesions and scaring may also narrow or obstruct the sinus ostia, resulting in a predisposition to recurrent disease and recurrent symptoms[28,227].

Revision surgery primarily relates to the management of adhesions and ostial outflow obstruction, with some authors stating that adhesions are the causative factor in up to 60% or revision surgeries[259,260], in fact it has been shown that up to 25% of patients with adhesion formation will require revision surgery in the future[260]. The incidence of ostial stenosis following ESS has been reported in the literature to be in the order of 25%[261]. Even higher rates of up to 59.5% have been shown in studies evaluating the frontal sinus in isolation[262-265]. The propensity of the frontal sinus towards stenosis can be attributed to surgery performed within narrow confines with consequent mucosal loss, sensitive adjacent surrounds including the skull base and orbit with bony septations left after surgery, as well as its structural variability[55,266-268]. In addition, the maximal dimension of a frontal sinusotomy at best is always smaller than the sphenoethmoidal and maxillary sinuses. Revision surgery often involves more extensive surgery, and in regards to recalcitrant frontal sinus disease may often involve a modified endoscopic Lothrop procedure[269].

Adhesion Prevention Following Endoscopic Sinus Surgery

Many surgeons consider that the postoperative treatment regime is equally as important as the surgery itself. All sinus surgeons have the common objective of

achieving excellent hemostasis and postoperative healing that avoids adhesion formation and lateralization of the middle turbinate, however, there is little agreement on how this is best achieved. The use of various interventions from post-operative medications, stents, removable nasal packing, and absorbable nasal packing through to no packing at all is widely debated.

Stents

A number of authors have recommended stents and silicon tubes in order to maintain ostial size and patency following ESS. Some of the prospected advantages include preventing middle turbinate lateralization, acting as a spacer and decrease the clott/mucus filling the middle meatus/ostium, providing a matrix for epithelial migration and acting as an occlusive dressing[270,271]. Removable middle meatal stents comprising of a glove finger and a polyvinyl acetate sponge are frequently used. Specifically, frontal sinus stenting is also performed due to the narrow nature of the frontal sinus ostium and its tendency to stenosis over time. Outcomes are particularly difficult to evaluate and to compare because of the inherent difficulty of providing adequate control. Stents have been advocated to remain in situ for up to 6 month following surgery[270,272]. One of the main indications for stent placement is extensive mucosal disruption, and under these circumstances the wound healing process is significantly prolonged (6-12 months), and as such would require the stent to remain in place for an extended period of time[273]. Some authors have found great success in preventing ostial stenosis[270], whilst others have found no significant benefit[274]. On reviewing the literature recommendations regarding stent placement lack definitive direction. Their use is currently lacking adequate data, and considering the increased patient discomfort and possibility of adverse events such as a foreign

body reaction then it would seem that they are not recommended for routine use, but reserved for specific patient groups.

Post-operative Debridement

Debridement of the nasal cavity following surgery is considered critical to the outcome following ESS, however there is a lack of sufficient data. Pioneers of endoscopic sinus surgery techniques, such as Stammberger and Kennedy, have differed significantly on their cleaning regimen, but all believe that the removal of crusts, blood clots and mucous are important to improve outcomes[28,275]. However there is a lack of consensus regarding post-operative care, indicating a lack of knowledge about how to treat patients optimally after surgery. This is important to consider, especially when taking into account the costs incurred with equipment, time and expenses for the patient and healthcare system. Stammberger recommends cleaning the nasal cavity 2-4 days following surgery, and then every 3-5 days for the following 10 days[28]. Kennedy's debridement regimen involves debridement on days 1, 3 or 4 postoperatively, and then weekly until re-epithelialisation has occurred. Kuhn and Citardi recommends the first debridement 1-2 days post-operatively, then every 3-4 days for 2 wks, followed by weekly until the 6th week post-operatively[275,276].

Many surgeons attribute their excellent results to their intensive debridement and postoperative management, describing the advantages of debridement as a reduction of trapped mucus to reinfect sinuses, removal of nutrients for bacterial growth and removal of bony fragments that maybe potential sites of infection[277]. Bugten et al performed a blinded RCT, randomising patients into either a debridement group vs a non-debrided group. Patients that received debridement (at

day 6 and day 12 post-operatively) had a significant reduction in adhesion formation. However the debrided group of patients had significantly more pain, requiring a longer duration of analgesics use. Interestingly they also found that those patients with worse post-operative crusting had significantly worse adhesions, indicating that crusts and fibrinous exudate act as a bridge over which adhesions can form[278].

Other centres and surgeons recommend minimal intervention in the postoperative period and describe equivalent results. In a review of 120 patients that underwent minimal debridement at 2 weeks postoperatively the study reported similar adhesion outcomes to other centres[279]. Nilssen et al randomized 16 patient nasal cavities to receive either debridement or no debridement, with no difference in adhesion incidence noted[280]. In the paediatric population it is frequently not possible to perform post-operative debridement, and success rates are similar between the intensively debrided adult patients when compared to their paediatric counterparts[277,281,282].

It is also important to consider any adverse effects to the wound healing processes that may occur due to debridement. In an important histological study, Kuhnel et al found that debridement in the first week results in epithelial avulsion in 23% of cases, however debridement at the second week didn't have this effect. Therefore the authors recommended debridement be withheld until the second week[283]. It appears therefore that there is some evidence for gentle debridement on 2 occasions in the postoperative period, however this should not be commenced until within the second postoperative week.

Saline Irrigation

A recent Cochrane review has examined closely the evidence for saline irrigation in patients with CRS, demonstrating that it appears to be useful in the treatment of CRS symptoms and hypertonic saline increases the mucociliary clearance, however its effects in the postoperative period are less clear[16]. Many leading rhinologists advocate for its routine inclusion into the postoperative regimen, however evidence for its use is scarce. Proposed advantages for saline irrigation include improved mucociliary clearance, reduced crusting, pus and debris, reducing oedema and removing the fibrinous exudate bridging the middle meatus[276,284].

Antibiotics

Many rhinologists also advocate for the use of post-operative antibiotics, however again there are few studies that examine their role[275]. Some authors suggest prescribing antibiotics only if an infection is noticed at the time of surgery, targeted to the intraoperative culture result[276,285]. Annys et al prospectively randomised patients to receive a course of oral cefuroxime following ESS, finding no benefit on patient symptoms, endoscopic appearance or the incidence of infections in the early postoperative period[286]. Jiang et al also investigated the effects of a course of postoperative Augmentin Duo following ESS in 84 patients. These patients were randomised to receive postoperative antibiotics. There were no differences between groups in postoperative symptoms or the endoscopic scores, and postoperative antibiotics did not relieve rhinosinusitis symptoms or reduce bacterial growth rates[287].

Corticosteriods

Steroid therapy is advocated to reduce excessive inflammation and poor wound healing, as well as reduce bleeding when given preoperatively[275]. Systemic and topical corticosteroid therapy, both pre and postoperatively have been supported. This is particularly true if there is severe nasal polyposis, with systemic steroid advocated in a tapered dose fashion and topical steroids commenced in the first week postoperatively[275,276,285]. Rowe-Jones et al conducted an extensive study spaning 5 years, examining the postoperative effects of long term intranasal fluticasone propionate spray, commenced at 6 weeks postoperatively, in a prospective randomized placebo controlled trial. Endoscopic scores of oedema and polyps were significantly better in the treatment group a 5 years, and a significantly higher number of control placebo patients required the prescription of rescue prednisolone[288]. Interestingly the CT and polyp scores were the most significant predictors of patients likely to benefit from postoperative systemic steroids[289]. Djikstra et al also performed a similar placebo controlled RCT, however with only a 12 month follow-up period, showing no difference in the recurrence or persistence of disease between the study groups. Both these studies commenced steroid use only after 6 weeks following surgery, and as such the effects of steroid therapy during the early inflammatory phase of healing remains unknown.

Removable Nasal Packs

Nasal packing has been the traditional method of controlling ongoing bleeding and preventing adhesion formation, middle turbinate lateralization and re-stenosis following surgery. Unfortunately removable nasal packing has been rated by patients to be the most unpleasant aspect of the ESS surgical experience[176,177]. Some

surgeons have advocated the practice of not packing the middle meatus[30], while others continue to explore the option in order to prevent middle turbinate lateralization and scaring[290]. Controversy still exists around the decision to pack or not to pack.

Nasal packing had been in use in the otorhinolaryngolic literature for over 60 yearsi[174]. Removable nasal packing has been designed to tamponade mucosal bleeding and to act as a barrier to adhesion formation. Numerous removable packing agents are available and include vaseline soaked ribbon gauze, fingerstall packs, polyvinyl acetate sponge, and various balloon tamponade devices. However, these cause considerable discomfort for the patient involved, both in terms of pain and bleeding upon removal[176-180]. Other complications associated with removable nasal packing includes septal perforation, pack dislodgement, aspiration, toxic shock syndrome, foreign body granuloma, myospherulosis, obstructive sleep apnoea secondary to nasal obstruction and even death[182,183]. Pack removal has also been shown to be detrimental to wound healing. Removal can cause the surface tissue to be peeled away, leading to trauma, bleeding, inflammation resulting in a fibrinous exudate and potential scar formation[226]. Animal studies have investigated the mucosal trauma caused by removable nasal packing. Shaw *et al* aimed at examining the effects of ribbon gauze packing and cottonoids on the nasal mucosa in a single blinded RCT. Nasal packing was left in situ for 10 minutes followed by removal of packing and the associated mucosa. Blinded histological analysis was then performed. Results showed that both packing agents resulted in > 50% loss of ciliated mucosal surface area ($p<0.005$)[184]. Therefore a transient impairment of the patient's innate immune system, the mucociliary clearance, may be associated with the use of removable nasal packing[185].

These draw backs of removable nasal packing has led to the ongoing development and application of absorbable biomaterials not requiring subsequent removal, that still achieves positive effects on hemostasis, promotes wound healing and provides middle turbinate support. Absorbable biomaterials function by either providing clotting factors or a substrate to stimulate clotting. One of the drawbacks of some biomaterials is the promotion of hemostasis by stimulating the intrinsic coagulation cascade, which also stimulate inflammation[130,131]. Inflammatory responses are linked to hemostatic activation by a network of humoral and cellular components, including protease factors involved in the clotting and fibrinolytic cascades. There is the potential of potent coagulation cascade activation leading to adverse wound healing. Biomaterials have been extensively investigated and researched in the ENT literature well before the evolution of ESS, with the first use of absorbable biomaterials published in 1969[175]**.** This interest continues today with both human and animal trials contributing significantly to our understanding of these products and their role in ESS.

Biomaterials and Adhesion Prevention

Human Studies

Miller *et al* conducted a double-blinded RCT involving 37 patients following bilateral ESS. Randomisation occurred between the Merocel removable pack(5-7 days) vs hyaluronic acid (MeroGel). MeroGel is a hyaluronic acid which is the major constituent of the extracellular matrix, and therefore acts as a scaffold for wound healing[291]. Additionally it has been shown to be the cause of absence of scarring in

fetal wounds[292]. Patients underwent follow-up up to 8 weeks postoperatively. Results showed both packing agents were associated with an 8% adhesion rate[293]. This contrasts to the Vaiman *et al* and Pomerantz *et al* which showed no evidence of adhesion formation with Merocel packing[178,189]. Discrepancies between these studies maybe related to the timing of pack removal. The effects of Merocel vs no nasal packing was investigated by Bugten *et al* in an attempt to determine whether removable nasal packing had any role following ESS. This single-blinded RCT involved 61 patients randomised into a Merocel arm vs no nasal packing arm. Video recordings taken 10-14 weeks following surgery showed 7/62 adhesions in the Merocel arm, vs 29/54 adhesions in the no packing arm, a finding that was highly significant ($p=0.001$)[294].

A single-blinded RCT was also performed by Franklin and Wright into the effects of MeroGel compared to a non-absorbable nasal packing (2-3 days). This study involved 35 patients following ESS with the follow-up time points of 2 weeks, and 1, 3 and 6 months. Results showed a trend towards improved endoscopic scores postoperatively however this failed to reach significance at all time points[295], and no overall adhesion incidence was given making comparison to previous studies difficult. Wormald *et al* aimed to investigate whether MeroGel had any effect on wound healing following ESS by performing a single-blinded RCT involving 42 patients. Nasal cavities were randomised to receive either MeroGel or no packing at all. Results showed that there was no significant difference between the sides at 2 weeks, 4 weeks and 8 weeks in the endoscopic features of adhesions, edema or infection. At 8 weeks the incidence of adhesions for MeroGel vs no packing was 16.7% and 19% respectively[296].

Quixil is a Fibrin glue, containing human thrombin and fibrinogen, in conjunction with amino acids and salts allowing this compound to form an easily applied gel. Vaiman *et al* compared Quixil vs Merocel in 158 patients in a non-randomised prospective trial, with follow up up to 1 month postoperatively. Results showing no adhesions in any of the 77 patients treated with Quixil, compared to 1 adhesion in the 81 patients treated with Merocel packing. The authors continued their interest in the efficacy of Quixil by conducting a double-blinded RCT involving 64 patients, again comparing Quixil vs Merocel (2 days). These results showed no incidence of adhesion formation in either group at 3 months of followup[189]. The adhesion incidence in these studies significantly less then the reported rates following ESS, which maybe due to differences in adhesion grading.

Chandra *et al* investigated the wound healing effects of FloSeal in a double- blinded RCT in 20 patients following bilateral ESS, by comparing FloSeal vs thrombin-soaked Gelfoam. Patients were followed up at 1 and 6 weeks postoperatively. Results showed that the mean adhesion score was increased in the FloSeal side, a highly significant finding ($p = 0.006$). There were a total of 11 FloSeal sides that developing adhesions, vs only 2 on the Gelfoam side. Additionally similar findings were noted in respect to granulation tissue formation ($p=0.007$). Follow up of these patients occurred for an average of 21 months following surgery and showed that there was an incidence of 56% of FloSeal sides having an adhesion, compared to 11% on the thrombin soaked Gelfoam side ($p=0.013$). Twenty eight percent of FloSeal sides required lysis vs none on the thrombin soaked Gelfoam side ($p=0.046$)[297]. Histological examination of an adhesion on the FloSeal side showed incorporation of the foreign material[297]. Shrime *et al* conducted a retrospective chart review involving 172 patients, aimed at determining the incidence, outcomes, and

risk factors for adhesion formation following ESS with middle turbinate medialization with and without FloSeal. Patients who were noted to have bled at the end of the procedure received FloSeal in the middle meatus. A statistically significant higher incidence of adhesion formation was noted in patients that underwent medialization with FloSeal (18.9%) vs those that just underwent medialization alone (6.7%; p=0.009)[260]. Interestingly statistical multivariate analysis between adhesion formation and surgical and demographic variables showed a statistically significant correlation to only the use of FloSeal (p=0.0063; odds ratio, 5.3330; 95% CI, 1.61-17.71)[260]. Explanation for this effect maybe the bidirectional relationship between coagulation and inflammation[131]. These results contrast to the findings of Jameson *et al* who compared FloSeal vs no treatment in a double-blinded RCT in patients following ESS. Results showed no significant difference between sides in 45 patients enrolled, and followed for up to 3 months.

These results are similar to a retrospective analysis by Pomerantz *et al*, who compared platelet gel and Merocel, showing no incidence of adhesion formation in either arm, or evidence of exuberant granulation tissue [178]. Postoperative adhesion formation was not observed in a non-randomised, uncontrolled prospective pilot study with the use of CMC mesh[196]. Kastl *et al* conducted a non-blinded RCT comparing the effects of CMC mesh, CMC gel and no nasal packing in 26 patients following ESS. All patients acted as their own control. Results showed no significant clinical effect on wound healing (unpublished to date). Sindwani continued his observation of 65 patients who underwent treatment with MPH following ESS, and found that there was a 12.3% incidence of adhesion formation, however there was no control group for comparison[225].

There is only one published article investigating the effects on wound healing of a surgiflo/thrombin combination. In this uncontrolled prospective trial involving 30 patients following ESS there was no incidence of reported adhesion formation. However, as indicated by the authors further RCT's are indicated[186].

Denatured porcine collagen (Gelfilm) has also been developed in an attempt at reducing adhesion formation. It is an absorbable biomaterial manufactured from denatured porcine collagen. Catalano and Roffman conducted a non-randomized non-blinded study comparing 115 patients following MIST (minimally invasive sinus techniques), comparing the effects of Gelfilm stent placed on the left and MeroGel placed on the right. Follow-up occurred up to 3 months post-operatively and results showed a significant increase in adhesions on the Gelfilm side compared to the MeroGel side ($p<0.05$)[298]. Additionally Tom *et al* conducted a RCT comparing Gelfilm stenting vs no treatment in 51 paediatric patients undergoing ESS, acting as their own control. Follow-up endoscopy was performed at 2-3 weeks postoperatively under general anaesthesia. Results showed no significant difference in adhesion formation, however showed a significant increase in granulation tissue formation on the Gel film side ($p<0.05$)[299].

Mitomycin C is a topically applied agent that has been shown to reduce scar formation[300]. Additionally it has been shown to inhibit nasal fibroblast proliferation and increase apoptosis[301]. It is isolated from the *Streptomyces caespitosus* strain of actinomyces, and used to cross-link DNA and inhibit cellular mitosis. Chung *et al* analysed Mitomycin C applied to cottonoids (0.4mg/ml) and placed in the middle meatus of patients undergoing ESS in a double blind RCT. The opposite side was treated with a saline soaked cottonoid. Results showed that overall 16/55 patients

developed adhesion within 2 months of follow up. 6 patients had bilateral adhesions and 10 had unilateral adhesions. There was a trend toward less adhesions associated with Mitomycin C however this didn't reach significance[48]. Additionally similar findings were found by Anand *et al*[302] and Chan *et al*[265]. Both these studies involved double-blinded RCT involving 29 self-controlled patients and 38 self-controlled patients respectively. Control sides were treated with saline cottonoids in both studies. Both studies found no significant difference in the incidence of adhesion between the active and control sides, with a follow-up period of at least 3 months.

Animal Studies

Animal trials also have contributed significantly to our understanding of wound healing of the paranasal sinuses and there is a large number of trials that reflect this. The predominant models used in this regard are the sheep, rabbit and mice models. Sheep are an ideal model as they are a large animal model where routine sinus surgical techniques can be used, and histologically their mucosa is identical to that of humans[303]. Models of bacterial rhinosinusitis have also been developed by the blockage of the maxillary sinus ostia using Merocel, along with *Bacteroides fragilis* inoculation resulting in a histologically confirmed persistent, localized bacterial rhinosinusitis[304]. Finally rabbits have well-pneumatized sinus cavities, and both their sinonasal anatomy and immunologic reactions are very similar to those of humans, making them a useful animal model for the study of biomaterials[305].

Sheep models – McIntosh et al conducted a double-blinded RCT, comparing the effects of Merocel (5 days) vs no packing in the sheep model. Serial biopsies were taken at 4, 8, 12 and 16 weeks following treatment. Results showed no significant

difference in the rate of reepithelialisation, total surface of ciliation, and overall maturity of cilia between the packed vs non-packed sides at any time point[306]. A further study was performed aimed at determining the effects of MeroGel vs no treatment in a sheep model of chronic sinusitis. This study created standardized mucosal injuries following by histological analysis of healing mucosa at 1, 2, 3 and 4 months postoperatively. Results showed no significant difference in adhesion formation or on histological features of reepithelialisation, cilial height, and reciliation between the 2 arms[240].

There is one study investigating the efficacy of chitosan gel on mucosal wound healing following ESS in the sheep model of CRS. Athanasiadis *et al* conducted a double blind RCT involving 20 sheep infested with nasal bot fly (causing an eosinophilic sinusitis). Standardized mucosal injuries were created, followed by the application of either chitosan gel, poly-ethylene glycol (SprayGel), recombinant tissue factor (rTF) or no treatment. Histological analysis was then performed of mucosal biopsies. Results showed that chitosan gel significantly decreased adhesion formation compared to rTF, with a noticeable trend when compared to SprayGel and control (14% vs 0%, 40% vs 0% respectively). Chitosan gel significantly improved re-epithelialisation, re-ciliation and cilial grade($p<0.05$)[220]. In conjunction to this it has been shown to have an inhibitory effect on fibroblast proliferation[307,308].

The sheep model has also been used to examine the effects of drug delivery associated with nasal packing. Robinson *et al* studied the effects of prednislone-impregnated MeroGel vs MeroGel alone and found no difference. Finally growth factors have also been shown to be important in epithelialisation and collagen deposition, including insulin-like growth factor[227]. Insulin-like growth factor (IGF)

impregnated MeroGel was analysed in the same sheep model following ESS and found to have a positive effect on mucosal regrowth and maturity in healthy sheep, however when introduced in a model of chronic sinusitis this effect was negated[309].

Mice models - There is only one study using a murine model to examine the effects of biomaterials. Jacob *et al* conducted a RCT involving 20 mice aimed at evaluating the histological effects of MeroGel. Findings were of induced bone formation within the sinonasal cavity, concluding that MeroGel may have osteogenic potential[310].

Rabbit models - Maccabee *et al* studied the effects of MeroGel in 6 self controlled rabbits by denuding the maxillary sinuses and performing histological analysis of the regenerating mucosa. At 2 weeks postoperatively the MeroGel sinuses showed extensive fibrosis when compared to control sinuses, with minimal reabsorption of the biomaterial along with incorporation of the biomaterial within the regenerating mucosa[311]. Proctor *et al* confirmed these findings, analysing the effects of MeroGel in a rabbit model. Results showed that MeroGel caused significant stenosis of the ostia over a 2-3 week followup[312].

Maccabee *et al* studied the effects of FloSeal in 6 self controlled rabbits by denuding the maxillary sinuses and performing histological analysis of the regenerating mucosa. At 2 weeks postoperatively FloSeal sinuses showed extensive fibrosis when compared to control sinuses, with minimal reabsorption of the biomaterial along with incorporation of the biomaterial within the regenerating mucosa[311]. Antisdel *et al* conducted a single blind RCT investigating the effects of MPH vs FloSeal in 14 self controlled rabbits. Ten rabbits underwent bilateral maxillary sinus stripping, with 5 received unilateral FloSeal placement, and 5 received unilateral MPH placement (opposite side acting as control). An additional 2 animals underwent

unilateral FloSeal placement in an unstripped maxillary sinus, and 2 animals underwent unilateral MPH placement (opposite side acting as control). Results showed that MPH treated sinuses showed no significant changes compared to respective controls, however FloSeal sides showed extensive loss of cilia, inflammation and fibrosis, both in the denuded and mucosa intact sinuses[313], a finding consistent with Maccabee *et al*[311].

Mitomycin C has also been investigated in the rabbit model, with one pilot study showing that increasing concentrations of Mitomycin C can delay healing of an intranasal antrostomy (0.4mg/ml, 1.0mg/ml)[314]. These results were confirmed by Rahal *et al*, again in the rabbit model[315]. It is important to note however that these trials were conducted in healthy rabbits without chronic rhinosinusitis, perhaps explaining the discrepancies between findings of human studies. There are two published studies investigating the effect of retinoic acid treated mucosa in rabbits. Maccabee *et al* conducted a RCT involving rabbits treated with retinoic acid, finding improved mucosal regeneration with less ciliary loss and fibrosis[316]. These findings were also supported by Hwang *et al*, again involving the healthy rabbit model[317].

Conclusions on Biomaterials and Adhesion Prevention (Table 1)

There are 2 double-blinded RCT comparing MeroGel vs removable nasal packing, both showing no significant effects at all time points in patients undergoing ESS for chronic rhinosinusitis (CRS). Additionally there is 1 single-blinded RCT showing no effect of MeroGel when compared to the no packing control. Three double blind RCT's in the sheep model of CRS confirms that MeroGel alone and with

prednisolone or IGF has no effect of adhesion formation or cilial recovery. Two prospective, controlled rabbit trials suggested that MeroGel increases fibrosis and is incorporated within regenerating mucosa, and another showed that MeroGel displayed osteogenic potential. There is 1 single-blinded RCT showing a highly significant reduction in adhesion formation when Merocel is used.

To conclude on the effects of FloSeal on regenerating mucosa there is 1 double blind RCT that shows increased adhesion formation and granulations, with this finding confirmed by 1 large retrospective case series. Again the rabbit model has shown that FloSeal increases fibrosis and is incorporated within the healing mucosa, a finding supported by a second independent study.

CMC mesh and gel appears to have no appreciable effect on postoperative wound healing when compared to no treatment. MPH appears to have an adhesion incidence comparative to that reported by most endoscopic sinus surgeons. Additionally MPH has no appreciable detrimental effect on mucosal healing in the rabbit model. Finally chitosan gel, in the sheep model of chronic rhinosinusitis, significantly improves microscopic features of wound healing and reduces adhesion formation following ESS.

Mitomycin C has shown promising results on healing ostia in 2 RCT's in the healthy rabbit model, however these effects were not translated to the post-ESS CRS patient. Three double-blinded RCT's demonstrated no additional benefit with Mitomycin C application in patients following ESS, a conclusion also supported by Tabaee *et al*[318].

Gelfilm stents have shown in 1 RCT to have no effect on adhesion formation following ESS, but increase granulations in the middle meatus. However one prospective trial suggests that Gelfilm stenting results in significantly more adhesions. One double-blinded RCT shows that fibrin glue has no effect on adhesion formation, and 1 prospective trial suggests the same. Finally there is only 1 uncontrolled prospective trial investigating the effects of surgiflo/thrombin combination, with no adhesions observed by the authors. Whilst the positive effects of vitamin A have been shown in healthy rabbit sinuses further human trials are needed in the CRS patient.

Sepragel sinus appears to have no objective effect on immediate hemostasis, and wound healing effects unknown. Whilst oxidised regenerated cellulose (surgicel) are widely known to have hemostatic properties[175], and advocated as an absorbable nasal dressing following ESS[200], there is no published literature investigating its wound healing properties following ESS.

In summary the literature suggests that the use of dissolvable agents to improve wound healing is largely unfounded and the anticipated beneficial effect of nasal packing is wishful thinking rather than a clinical reality. In some cases the use of dissolvable agents actually has an adverse effect on the wound healing processes. There is no commercially available product that improves wound healing when compared to no treatment at all. Recent animal studies indicate that Chitosan may be of benefit but further research is required before recommendations can be made.

Table 1 **Human studies on Biomaterials**					
Biomaterial	**Study**	**Study design**	**Intra-op Hemostasis**	**Post-op Hemostasis**	**Adhesions /wound healing**
Surgiflo/Thrombin combination[186]	30 pts	Prospective (uncontrolled)	29/30 in 10 minutes	29/30 (1 req packing)	No adhesions
Epsilon-aminocaproic acid[205]	10 pts	DB RCT	Ineffective vs saline	10/10 pts	
Tranexamic acid[205]	10 pts	DB RCT	Better vs saline ($p<0.05$)	10/10 pts	
Sepragel sinus[195]	20 pts	RCT	Same as no treatment		
Quixil (fibrin glue)[179,189,319]	158 pts[179] & 64 pts[189]	DB RCT[179], prospective (controlled)[189]	Same as Merocel[179]		Same as Merocel[189]
Merocel[178,294]	16 pts[178] & 61 pts[294]	Cohort[178], SB RCT[294]		16/16 pts[178]	No adhesions, ↓sed adhesions vs no packing ($p=0.001$)[294]
Surgicel Nu-knit[200]	60 pts	RCT		60/60 pts, same as gauze and Merocel	
MeroGel[293,295,296]	37 pts[293], 42 pts[296] & 35 pts[295]	DB RCT,[293] SB RCT[296], RCT[295]			ame as Merocel /37 adhesions)[293], me as no ck[296], Same as movable pack[295]
Gelfilm[298,299]	115 pts[298] & 51 pts[299]	Prospective (controlled)[298], RCT[299]			↑sed adhesions vs MeroGel ($p<0.05$)[298], ↑sed granulations vs no pack ($p<0.05$)[299]
Mitomycin C[48,265,302]	55 pts[48], 29 pts[302] & 38 pts[265]	3 DB RCT's			All show same as no pack
FloSeal[185,187,188,260,320]	18 pts[187], 45 pts[320], 50 pts[188], 20 pts[185] & 172 pts[260]	Prospective (uncontrolled)[187], DB RCT[320], DB RCT[188], DB RCT[185], retrospective[260]	Rapid hemostasis 17/18 pts[187], $p=0.028$[320]	17/18 pts (1 req packing)[187], FloSeal same as Merocel[188]	↑sed adhesions and granulations ($p=0.006$)[185], ↑sed adhesions ($p=0.009$)[260], No effect (same as removable pack)[320]
MPH[225,321]	65 pts[225], 40 pts[321]	Prospective (uncontrolled)[225], SB RCT[321]	Rapid hemostasis (30-45 sec)[225]	65/65 pts[225], less bleeding on POD#1 vs. untreated side[321]	8/65 adhesions[225]
Platelet gel[178]	16 pts	Prospective		16/16 pts (same as Merocel)	No adhesions (same as Merocel)
CMC Mesh[196,197,322], CMC gel[197,322]	15 pts[196] & 41 pts[197]	Prospective (uncontrolled)[196], SB RCT[197]	20% persistant bleeding[196]	15/15 pts[196], 41/41 pts (same as no pack)[197]	No adhesions[196], No effect (same as no pack)[322]

CHAPTER 5 ENDONASAL ENDOSCOPIC CAROTID ARTERY INJURY

Carotid Artery Injury

Over the last two decades there has been a paradigm shift from traditional external approaches to the skull base, paranasal sinuses and intracranial cavities to the completely endonasal surgical approach. Endonasal microscopic techniques to the sella turcica rapidly became the preferred approach following the introduction of the operating microscope in 1951. The introduction of the surgical endoscope has seen a rejuvenated interest into the paranasal sinus and endonasal skull base anatomy and the endoscopic approach to pituitary and other skull base tumours is rapidly being adopted as the standard of care by otolaryngologists and neurosurgeons worldwide[323]. The popularity of endonasal techniques is largely due to the well recognized advantages including the avoidance of external skin incisions, minimal sacrifice of intervening structures, improved visualization, reduced postoperative pain and shorter hospital admissions[324].

Rupture of the internal carotid artery (ICA) is the most feared and devastating complication of endoscopic sinus and skull base surgery that may result in death of the patient[124]. Injury to the cavernous ICA most commonly results in rupture and overwhelming haemorrhage, with the frequent formation of a pseudoaneurysm[123,124]. Injury may also cause spasm, thrombosis, embolism, or the formation of a carotico-cavernous fistula (CCF)[123] with significant associated morbidity.

Injury to the cavernous ICA is a rare event during endoscopic sinus surgery (ESS). May et al reviewed their experience with ICA injury during ESS and only found 1 case from 4691 patients[45]. Despite the frequency of ESS within the community, a review of the English literature demonstrates a total of only 28 case reports of ICA injury since the advent of the endoscopic approach to the paranasal sinuses

(appendix 1). The frequency of cavernous ICA injury is much more significant during endonasal, transphenoidal skull base surgery. Ciric et al and Raymond et al showed a 1.1% incidence of ICA injury following the microscopic transphenoidal pituitary approach[124,125]. Interestingly, surgeons that have performed more than 500 transphenoidal approaches had a 50% risk of having to managed a ICA injury at some stage during their career[125]. More extended endonasal approaches (EEA) centre around the management of the internal carotid artery, and not surprisingly have a much higher incidence of ICA injury. Couldwell et al, Frank et al and Gardner et al reviewed their experience with consecutive EEA resections of craniopharyngiomas, clival chordomas and chondrosarcomas, demonstrating a 5-9% incidence of ICA rupture[120,126,325]. All of this demonstrates that with the increasing subspecialisation of endoscopic transphenoidal surgery, it increasing the likelihood a specialist endoscopic skull base surgeon will have to manage a carotid artery injury at some stage.

Although experience and knowledge of the relevant anatomy can prevent many potential complications associated with transphenoidal surgery, ICA injury cannot be completely eliminated considering the frequency of these procedures and the increasing complexity of the skull base pathologies encountered.

Patients At Risk

Prevention of the catastrophic bleeding scenario is better than treatment. It is important to recognize the patient that maybe at risk of an ICA injury. The anatomical relationship between the ICA and the sphenoid sinus makes it particularly vulnerable. Fujii et al demonstrated that the bony wall overlying the ICA is not sufficient to protect the artery, at less than 0.5mm thick[326]. Additionally, in 4-22% of

cases the lateral sphenoid wall is dehiscent over the carotid with only dura and the sphenoid sinus mucosa separating the ICA from the sphenoid[326,327]. Renn and Rhoton also found that the ICA bulges into the sphenoid sinus in 71% of cases, and that the artery maybe located as close as 4mm from the midline[328]. Some authors have found that the distance between the internal carotid arteries within the sphenoid maybe as little as 4mm[329], and that the bony sphenoid septum inserts on to the ICA canal wall 16.3%[330] of occasions.

Cavernous ICA anomalies are also not infrequent, with cavernous ICA aneurysm making up 12.8% of all intracranial aneurysms. Some authors have shown an increased incidence of aneurysms in patients with pituitary adenomas[331,332], leading some to suggest mechanisms such as mechanical influence, infiltration by the tumor, growth hormone and an IGF-1 effect on the arterial wall[332,333]. There have been numerous reports of unrecognized pre-operative cavernous ICA aneurysms resulting in ICA rupture. When reviewing all 111 case reports of endonasal cavernous ICA ruptures (appendix 1), there are a total of 6 patients that had a pre-operative unrecognized ICA aneurysm. In the 3 patients reported by Koitschev et al, all 3 patients died as a result of uncontrolled haemorrhage, perhaps as a result of a larger defect of the vessel wall with a consecutively higher blood loss[334].

Numerous authors have linked the association of a number of important patient risk factors associated with a cavernous ICA injury. Raymond et al reviewed their series of 17 ICA injuries showing that 5/17 patients had prior bromocriptine therapy, 5/17 were revision cases, 4/17 had previous radiation therapy and 6/17 pts had acromegaly[124]. Additionally patients with acromegaly tend to have more tortuous and ectatic carotid arteries[123,335]. Whilst most case reports and series do not discuss the

specific case risk factors, a review of the literature demonstrates that it is known that these risk factors contributed in 27 ICA injury cases (table 2), some cases with multiple risk factors (revision surgery = 13, radiotherapy = 4, acromegaly = 13, bromocriptine therapy = 4). These features may cause more fibrosis and adherence to the carotid artery, or may simply reflect a more aggressive attempt at complete resection of invasive lesions.

Tumours closely adherent to the ICA require close and careful dissection. Bejjani et al demonstrated that vasospasm occurred in 9 of 470 patients undergoing skull base tumour dissection. In this series vasospasm manifested as altered mental status and/or hemiparesis with risk factors including preoperative embolization, tumour size, vessel encasement/narrowing and total operative time. Three of these patients suffered permanent neurological deficits[336]. Laws et al also cautions regarding dissection of tumour away for the cavernous ICA, or displacement of the carotid within the cavernous sinus during attempted hemostasis. They describe 1 fatal, and 2 non-fatal cases as a result of carotid spasm and thrombosis following endonasal transphenoidal surgery[123].

It is imperative that the ‘at risk’ patient is identified by a thorough pre-operative assessment so that a cavernous ICA injury can be minimized (table 2). A thorough and careful preoperative assessment of the sella region should be obtained, with the use of a CT scan to help delineate vessel anatomy and its relationship to the sphenoid sinus. MRI scans can demonstrate preoperative ICA aneurysms, with any suspicion confirmed with MRA or digital subtraction angiography[333,337].

Risk Factors for ICA Rupture
Anatomical relationships - carotid dehiscence - sphenoid septal attachment to ICA - midline ICA
Revision surgery
Prior radiotherapy
Prior bromocriptine treatment
Acromegaly

Table 2 – Risk factors for ICA rupture

Controlling the Surgical Field

Intra-operative ICA rupture creates an immediately challenging surgical field, with a high pressure/high flow bleeding scenario, which may rapidly result in exsanguination of the patient. Massive bleeding leads to a loss of orientation and an obscured surgical field often resulted in the surgeon blindly attempting nasal packing in order to control the haemorrhage. Additional suction is important to regain orientation of the surgical field. The advantages of the '2 surgeon' skull base team allows for dynamic handling of the endoscope, rather than the single surgeon scenario. Currently there is no prospective experience or scientific enquiry into the techniques required to control such a large volume bleed, leaving the surprised surgical team to manage the event without prior training or experience. As part of this thesis we have developed a reproducible animal model for the carotid artery catastrophe that recreates the intranasal confines of the human nasal cavity, paranasal sinuses and nasal vestibule (chapter 8). Experience with this model has

allowed a number of important surgical steps to be identified that will aid the surgical team in controlling the haemorrhage and maintain vision of the injury site (chapter 9).

Intra-operative Haemostatic Techniques

Every surgical team should have a plan in place should this unexpected complication occur; formulating and executing a plan of action during a crisis is difficult. Emergency proximal surgical ligation has traditionally been used to treat an ICA injury, however this treatment is often associated with a high incidence of major complications such as death and stroke[124,338], and is often an ineffective and harmful treatment. In good collateralization or contralateral compensation the bleeding is likely to still be rapid. Ligation of the internal and external carotid arteries would not only waste time but also block the interventional radiologists access to the site of injury.

In the event of unexpected massive bleeding during endonasal surgery then immediate packing is required. A number of techniques have been described and advocated in order the aid this. Some authors advocated for head elevation, and controlled hypotension to reduce the hemorrhage[339]. These measures are likely unnecessary considering the immediate and significant hypotension that will result from massive bleeding whilst the anaesthetic team is trying to implement active resuscitation[340]. If large bore suction devices and the immediate state of hypotension are not enough to keep pace with the bleeding and allow nasal packing then ipsilateral common carotid artery compression is frequently advocated to slow the bleeding rate and can aid the accurate placement of nasal packing[124,327,339,341]. Regarding blood pressure control, Kassam et al, Solares et al and Pepper et al all recommend maintaining normotension through resuscitative measures and fluid

replacement in order to maintain contralateral cerebral perfusion[136,173,342]. However, normotension is unlikely to be achieved until the haemorrhage has been controlled. Once vascular control is assured then attention should focus on maintaining adequate cerebral perfusion.

There is a number of different packing agents that have been used during an ICA rupture. A review of the literature demonstrates that gauze packing is overwhelmingly the most frequently used material, likely due to its availability and easy of use. However a number of different agents have been used including Teflon and methyl methacrylate patch[341], Syvek marine polymer[325], muscle patch[124,327,343], fibrin glue[343,344], gel foam and oxidized cellulose packing[343,345,346], thrombin-gelatin matrix[347], Oxygel and glue[348] and muslin gauze[349,350]. Packing materials ideally should be placed with just enough force to control the haemorrhage but not to occlude vascular flow[123]. Absorbable and biocompatible haemostatic agents are advantageous, as they don't require subsequent removal, which can result in re-bleeding if no additional endovascular procedures are undertaken.

Raymond et al describe their success with oxidized regenerated cellulose, muscle plugs and tissue adhesives. Profuse intra-operative bleeding occurred in 14 patients and was controlled in all cases, however later reoccurred in 3 patients requiring either a return to theatre or endovascular balloon occlusion[124]. Packing was the only method of treatment in 9 patients, with no endovascular treatment, however 1 patient died on day 7 from concurrent basilar artery compression, and another from recurrent tumour at 2 months of follow-up. The other seven patients had no further bleeding events (follow-up 6mths – 10yrs)[124].

Over-packing of the injury site can also be a problem. Endonasal packing often can

result in occlusion or stenosis of the cavernous ICA and other major vascular structures[351]. Raymond et al reviewed their angiographic data in 12 patients showing that 8/12 had ICA occlusion, and 4/12 patients had carotid stenosis. They concluded that over-packing could contribute to the morbidity and mortality of the patient[124]. Laws et al also concedes that whilst patency of the ICA is preferred, there our some occasions that the only option is to occlude the ICA with packing and raise the blood pressure in the hope that the collateral circulation will prevent stroke formation[123].

Direct vascular closure has also been used intra-operatively. Laws et al described the successful use of direct suture repair in 2 cases, and the use of a sundt-type clip graft, however the details and outcomes of these techniques are not described[123].

Currently, haemostatic recommendations following an endoscopic carotid artery injury are based on case reports only, without prospective scientific investigation into which is the best haemostat during this scenario. Work described in this thesis (chapter 10) focuses on the hemostatic efficacy of various absorbable and biocompatible materials in the endoscopic carotid artery injury scenario. This work investigates the efficacy of a thrombin-gelatin matrix, oxidized regenerated cellulose and the crushed muscle patch treatment.

Unfortunately it is not always possible to achieve intra-operative hemostasis, and transfer to the angiography suite is needed so that endovascular intervention can be performed whilst the airway is secured[337,345]. Even though intra-operative hemostasis and vascular control is achieved in most cases, all patients need to have an immediate angiogram so that ICA injury complications can be sought. Angiography should also include the external carotid artery if no abnormality is found within the ICA territory. The otolaryngologist should be available and present to consider

loosening the packing if localization of the ICA injury is not possible due to over tight nasal packing[136]. The optimal management is a balloon test occlusion (BTO), however this requires a cooperative and awake patient to allow for a full neurological examination. Awaking the patient and removal of a secure airway is unwise in the face of ongoing ICA bleeding, and hemodynamic instability[344,352,353]. Other measures that have been used to determine the presence of adequate collateral flow include analysis of the preoperative MR angiography[344], transcranial doppler analysis[354], SPECT imaging[355] and Xenon CT[339]. Even with a well performed and normal BTO there is still a 5-10% risk of delayed infarction after therapeutic carotid artery occlusion[356].

Endovascular techniques

Endovascular techniques that are available to the interventional radiologist include both balloon and coil embolization, however there are increasing reports of the successful use of endovascular stent-graft placement. Numerous authors recommend the use of endovascular balloon or coil embolization in those patients that have adequate collateral blood flow[352,355,357,358]. Otherwise either an endovascular or surgical bypass procedure is required. Stent-graft placement is advised in those that don't tolerate ICA occlusion[352,354,355,358]. Some have suggested that all patients have a trial of stent placement, but if this is unsuccessful, then those patients should undergo embolization if tolerated, otherwise a extracranial/intracranial bypass procedure is required[173].

Endovascular techniques aimed at closing a vascular wall defect can either occlude the parent vessel or maintain vascular flow. When performing endovascular techniques it is important to remember that carotid artery injury most frequently

occurs only a few millimeters below the origin of the ophthalmic artery[124]. Both the deployment of an endovascular balloon and coil can be associated with subsequent distal migration and slippage[358]. The main difficulty is deployment in a high-flow vessel where distal migration may occur, resulting in blindness or death[339]. The distal balloon should be detached from the introducer only after the more proximal balloon is inflated (minimizing migration)[358]. Regarding the deployment of an endovascular coil, Park et al describe a technique of digital compression of the cervical ICA and creating an angiographically confirmed low-flow system. This enabled more accurate distal and proximal trapping of the injury site[344].

Balloon occlusion techniques should be performed at the level of the vascular injury, thus preventing ongoing bleeding from both antegrade and retrograde vessel filling. It is also important that a more proximal balloon is placed as balloon deflation can occur[359]. If a balloon cannot be placed at the site of injury then a balloon proximal to the injury, and a balloon distal to the injury should be sited. Endovascular coil occlusion uses stainless steel or platinum based material that is helically shaped with multiple attached Dacron wool strands that increase its thrombogenicity. As the straightened coil is released into the parent vessel it resumes its spiral shape and wedges against the vessel wall to form a thrombus. This thrombus formation may take a little time and theoretically there is an increased risk of thromboembolic events, however this has not been shown in the literature. Finally, Higashida et al recommends close post-intervention monitoring to keep the blood pressure between 110-160 Hg systolic and 60-110 mmHg diastolic for a 2-3 days post occlusion[360].

Over the last 10yrs transluminal endovascular stent-grafts have increased in popularity, and grafts within the aorta, peripheral vessels and coronary arteries have

been reported as safe and effective[361]. The main technical difficulty associated with stent-graft placement within the cavernous ICA is the limited longitudinal flexibility of the graft. Newer sent grafts have improved significantly and there are 12 successful case reports (appendix 1), however 3 of these had poor longitudinal flexibility and poor intravascular seating requiring additional procedures. These 3 cases required further coiling and a novel 'stent-in-stent' technique[339,358,362]. ICA spasm has also been reported as a result of difficult positioning of the stent-graft[337]. The most frequently used stent is the coronary stent-graft, consisting of both sides (luminal and abluminal sides) covered with polytetrafluoroethylene. Stent-graft placement also risks distant migration. In the future improved longitudinal flexibility may see endovascular stent-graft placement become the preferred option of management in all patients regardless of BTO results.

Complications following endovascular occlusion or repair include thromboembolic events or stent-graft thrombosis. A survey performed by Wholey et al showed a 4.4% risk of stroke within the first 30 days following carotid stent placement[363]. However the risk of stroke from the placement on endovascular stent is likely to be significantly less than performing endovascular occlusion in a patient that can't tolerate BTO. Antiplatelet therapy and heparin treatment can provide effective prophylaxis and reversal in cases of TIA or stroke[357]. Regarding the anticoagulation and antiplatelet regimen used, most authors advocate for some preventative treatment. Heparin therapy is recommended prior to endovascular intervention and prior to the BTO[354,358,364]. De Souza uses oral ticlopidine for 4 weeks following stent placement[355], Park et al and Leung et al recommended aspirin and clopidogrel therapy for up to 3 months[358,364].

Delayed Cavernous ICA Injury

It is important to remember that not all ICA injuries manifest during the intra-operative period. The occurrence of vasospasm in the ICA following transphenoidal surgery has been described as early as a few hours following surgery and up to 1 month following[123], and can be recognized as altered consciousness or stroke formation. Laws et al also notes 2 cases of carotid artery thrombosis following transphenoidal surgery[123]. Delayed formation of a pseudoaneurysm following uneventful transphenoidal surgery is also well known, with 9 known case reports (appendix 1), developing anywhere from 1 week post-operatively to over 20 years later[353]. Perhaps the most surprising, to both the patient and the surgical team, is the delayed presentation of a ruptured pseudoaneurysm in the post-operative period following an uneventful transphenoidal surgical procedure. Raymond et al reported 3 patients that underwent uneventful surgery, with one ruptured pseudoaneurysm presenting on day 9, another on day 12 and the last some 10 years after the surgical procedure. This scenario is likely to present out of the hospital setting, and patients will present in severe haemodynamic compromise, with a particularly poor prognosis (figure 5). Review of the literature shows there are 6 case reports of a delayed ruptured pseudoaneurysm following uneventful surgery. Two patients survived without long-term sequelae, 1 patient died, and 3 patients suffered permanent neurological deficits (appendix 1).

Complications of Cavernous ICA Rupture

Following an ICA rupture it is important that all patients receive a post-operative

angiogram. If this is normal then all patients should receive a repeat angiogram after the packing has been removed. Iatrogenic ICA injury can create a communicating channel between the sphenoid and/or the cavernous sinus and the sidewall of ICA. This situation may present as an acute haemorrhage, pseudoaneurysm or a CCF. A CCF can most easily be recognized clinically by the presence of proptosis with opthalmoplegia and an orbital bruit.

The most frequent complication following cavernous ICA rupture is the formation of a pseudoaneurysm. A pseudoaneurysm is a tear through all the layers of the artery with persistent flow outside the vessel into a space contained by surrounding tissue[365]. Pseudoaneurysm formation is a common occurrence following intra-operative rupture and trauma to the cavernous ICA, and hence active follow-up and regular angiographic screen is recommended in all patients, both postoperatively and following discharge. Pseudoaneurysm as a complication of ICA rupture may present 10yrs later[124]. Some authors state that all direct injuries to the ICA repaired by indirect measures will result in a pseudoaneurysm[123,351], however Laws et al also concedes that placing muscle as a hemostat offers an opportunity for effective healing without the formation of a pseudoaneurysm[123]. There are a total of 72 reports of intraoperative ICA rupture events (undergoing local packing treatment) where the pseudoaneurysm status is published. A review of these cases demonstrates that 43 subsequently developed a pseudoaneurysm, a 60% incidence (appendix 1). A total of 12/43 ruptured post-operatively and required subsequent treatment. The other 25/43 were identified at routine angiography and underwent prophylactic treatment. Six cases were managed conservatively. It is interesting to note that only 3/17 patients in Raymond et al series developed a pseudoaneurysm. This maybe to due to the high rate of permanent vascular occlusion during intra-operative packing

control[124].

Pseudoaneurysms frequently rupture and treatment begins with airway control, rapid resuscitation and local packing measures. Similar hemostatic measures can be performed as described above. Whilst most advocate for prompt neuroradiological intervention, some authors transfered the patient directly to theatre for haemorrhage control first[124]. Once again a BTO is preferred, but in the intubated patient this makes neurological assessment difficult. Ideally, in the patient that is not actively bleeding and where local packing measures are adequate, then the patient should undergo a formal BTO. When a pseudoaneurysm is found at a routine follow-up angiogram it is more easily managed. In this situation a 30-minute BTO is performed, where tolerance is assessed by a complete neurological examination, with collateral circulation assessed by angiography[124]. This can be performed in conjunction with other neurophysiologic techniques. Once again there are a number of techniques described to manage a pseudoaneurysm including endovascular balloon or coil isolation and stent-graft placement. Endovascular isolation techniques are preferred in those patients that can tolerate the BTO. Once again a period of close observation to ensuring normotension/mild hypertension is warranted. In the patient that cannot tolerate BTO there are 3 main treatment options; stent-graft placement, isolated endovascular occlusion of the pseudoaneurysm lumen and surgery (either bypass surgery, or aneurismal clipping). It is well accepted that extracranial/intracranial bypass surgery is associated with a high complication rate and that stent-graft placement represents a safer treatment option[366].

There is much controversy regarding endovascular coil or balloon occlusion of the pseudoaneurysm lumen whilst preserving the parent artery in an attempting to

maintain parent vessel patency. Most authors state that a pseudoaneurysm is fragile and has no wall to contain the embolus[123,355,367], and that there is a considerable risk of fatal rebleeding due to compression on the fragile wall[348,368]. Fox et al demonstrated in a series of 68 patients that isolated pseudoaneurysm lumen occlusion was associated with an increased complication profile[369]. Higashida et al have demonstrated an increased morbidity and mortality when treated in this fashion[370]. This treatment is probably reserved for those patients that cannot tolerate complete occlusion of the cavernous ICA, and in which stent-graft placement is not possible. Despite this, pseudoaneurysm lumen occlusion with preservation of patency of the cavernous ICA has been achieved following transphenoidal injury. A review of the literature demonstrates that there a 7 cases of ICA injury that resulted in the formation of a pseudoaneurysm that was subsequently treated by isolated coiling or balloon therapy of the lumen, with preservation of ICA vascular flow[349,357,371,372] (appendix 1). However, 1 case resulted in subsequent migration of the balloon embolus through the wall of the pseudoaneurysm[357] and another resulted in asymptomatic migration of the coil within the pseudoaneurysm necessitating stent-graft placement[362]. CCF is probably the only injury in which treatment with detachable balloons or coils is appropriate, whilst attempting to preserve the patency of the parent vessel. This situation is more likely to be successful as this injury is somewhat less urgent than other arterial injuries[337].

Outcomes of Cavernous ICA Rupture

Rupture of the cavernous ICA represents a significant insult to the hemodynamic stability of the patient and is not surprising associated with a significant morbidity and

subsequent mortality. It is difficult to draw any significant conclusions from a comprehensive literature review as these are case reports only. Many cases of intraoperative ICA rupture may not be published, especially considering death and neurological injury are a common endpoint. Reviewing the 111 cases of ICA rupture, there are a total of 89 cases where the endpoint was published. Whilst likely underestimated, there was a mortality rate of 15% (13/89) and a permanent morbidity rate of 26% (23/89). A total of 59% of patients (53/89) that suffered from a ruptured ICA escaped the event without any permanent sequalae (appendix 1). This is similar to the series published by Raymond et al that described a 17% mortality and 29% related morbidity[124].

Animal Models of Haemorrhage

Animal models of haemostasis are important to allow for analysis of efficacy of therapeutic treatments during challenging bleeding scenarios. Animal models of haemorrhage have been extensively investigated and utilized, and can be divided up into low pressure/low volume models, low pressure/high volume models and high pressure/high volume models.

Low Volume/Low Pressure Haemorrhage Models

There are a large number of low volume/low pressure animal models. These models all replicate traumatic injury visceral structures. Schwaitzberg etal[390] investigated haemostatic efficacy using a splenic haemorrhage model. This involved a midline laparotomy followed by 2 x 2cm area of capsular stripping to the depth of 3mm. Free bleeding for 10 seconds was allowed prior to the application of the test haemostat.

No simultaneous resuscitation or monitoring of mean arterial pressure was performed. Modification to this model was created by the use of a capsular incision of depth 3mm and length 8mm[391]. This model represents a low volume/low pressure model largely of capillary type bleeding from a visceral organ.

High Volume/Low Pressure Haemorrhage Models

A popular swine model of severe large venous haemorrhage and hepatic injury has been used extensively in the literature[392-394]. Arterial and jugular venous catheters are placed surgically for monitoring and resuscitation purposes. Initially a stable period of the mean arterial pressure (15 minutes) was required for continuation with the injury model. Liver injuries were created using a specially designed clamp with two 4.5cm sharpened tines configured in the form of an X. This clamp was positioned at the intersection of the left and right medial lobes with the instruments base plate positioned beneath the quadrate lobe. The tines of the instrument were then clamped through the parenchyma so that the tines seated in the corresponding grooves in the base plate. The instrument was then opened and repositioned to the left of the first injury, so that there was an overlap to the first injury by 50%. The liver was then penetrated a second time. The authors documented the liver injury by excision and inspection of the liver at the conclusion of the experiment. They noted complete penetration of the liver and one or more of the left medial lobar veins, right medial lobar vein and portal hepatic vein. Resuscitation was initiated 30 seconds post-injury with warmed ringers lactate solution. Resuscitation commenced at 260ml/min if the mean arterial pressure dropped below baseline[392-394]. This model represents a high volume/low pressure model as no arterial injury was noted[392].

High Volume/High Pressure Haemorrhage Models

Sondeen etal[394] and Kheirabadi etal[395] used an aortic model of haemorrhage in swine to investigate the efficacy of topically applied haemostats. In this model a laparotomy and splenectomy was performed with replacement of splenic weight again with ringers lactate. A 10cm section of intrarenal aorta was then exposed and cross-clamped. A aortotomy was then created with a 4.4mm diameter aortic punch with clamps then subsequently removed and free bleeding permitted for 5 seconds before the application of the test haemostat. Simultaneous fluid resuscitation was not administered in this model, and only after complete haemostasis was achieved. Initially this model represents a high volume/high pressure injury. However, without active and aggressive resuscitation the dynamics change as the mean arterial pressure drops, and it may become a low pressure/high flow injury model.

Alam etal[396] also utilized a swine model, involving a complex groin injury with complete transection of the proximal thigh soft tissues and complete division of the femoral artery and vein just below the inguinal ligament. No resuscitation of fluids was given until 30 minutes after injury. Then limited resuscitation measures were employed (1000mls of 0.9% saline over 30 minutes independent of MAP). This injury caused a rapid drop in arterial blood pressure (up to 30mmHg) and a 75% drop in cardiac output. With the onset of hypotension, arterial spasm and the formation of clot at the injury site, the flow of arterial haemorrhage rapidly decreased in the first 3 minutes following injury. Renewal of haemorrhage typically occurred when the blood pressure improved after resuscitation[397]. Modifications by Alam etal[397] allowed only 3 minutes of free bleeding prior to intervention as opposed to the prior 5 minutes. Additionally intravenous resuscitation was commenced 15 minutes after injury. This

resulted in a return to higher mean arterial pressures earlier in the post-injury period. Modifications hence resulted in a low to moderate volume/low to moderate pressure model[199].

Acheson et al investigated the efficacy of 3 topically applied haemostatic dressings in a swine model of extremity arterial haemorrhage[398], with repeat of this model by Ward et al[399]. This model involved the arterial monitoring of blood pressure and a jugular venous catheter for intravenous fluid administration. Animal inclusion criteria into the study included that the animals were required to maintain a minimum of mean arterial pressure of 50mmHg after induction of anaesthesia. Initially a midline laparotomy and splenectomy was performed to exclude the discrepant hematologic changes resulting from autotransfusion by varying sizes of the contractile porcine spleen. Ringers solution was given at 3 times the splenic weight to replace approximate volume of blood. The groin was then incised for exposure of the femoral artery. The artery was clamped proximally and distally and a arteriotomy was made in the anterior surface with a 6mm hole punch creating a highly reproducible injury. Authors took particular note to leave the posterior wall intact and therefore minimize the effects of artery retraction and vasospasm, which could result in spontaneous haemostasis. After 45 seconds of bleeding the test haemostat was applied followed by immediate resuscitation with pre-warmed ringers lactate at 100mls/min whenever the mean arterial pressure dropped below 65mmHg[398]. This model most accurately describes a model of high volume/high pressure due to an arterial model of injury with simultaneous rapid intravenous resuscitation in attempts to maintain the pre-injury mean arterial pressure. Whilst the animals never reach their pre-injury MAP levels they did approach normalization more than any other animal model.

The endoscopic carotid artery injury scenario is a high flow/high pressure surgical situation, within narrow nasal confines and poor instrument access. It is clear that for a high flow/high pressure vascular injury model to maintain these characteristics it is important that the arterial injury is performed in a longituidinal direction, involves only the anterior wall of the vessel, and does not result in complete transection of the vessel. Continuous blood pressure monitoring is required so that active and aggressive resuscitation can ensure, attempting to meet the pre-injury MAP level. Current animal models of haemorrhage attempt to replicate the trauma situation, with wide access, and do not replicated the difficulties of major haemorrhage during minimal access endoscopic surgery. Investigation into haemostatic techniques during a high flow/high pressure surgical scenario requires an animal model that accurately re-creates the narrow confines of the nasal cavity (chapter 8).

Advanced Haemostatic Products

Most current literature pertaining to advanced haemostatic agents arises from the trauma setting. Currently over 90% of combat deaths occur on the battlefields prior to the injured reaching definitive casualty care[395]. Uncontrolled haemorrhage is the leading cause of death amongst this group of patients[400]. Exsanguination most frequently occurs from torso injuries, which are exceedingly difficult to manage with standard techniques such as pressure dressings, tourniquets, and clamping[401,402]. There is a great need for an advanced haemostatic agent effective against high flow, high pressure bleeding.

Dry Fibrin Sealant Dressing

The dry fibrin sealant dressing was developed by the American Red Cross and U.S. Army scientists. This product consists of clotting proteins purified from pooled human plasma from donated blood. Mechanism of action is direct application of highly concentrated coagulation factors to the site of injury causing polymerization and crosslinking of fibrin[199]. It is a 10 X 10 cm dressing consisting of two outer layers of human fibrinogen (13.5 mg/cm^2) and a middle layer of human thrombin (40 units activity/cm^2) and $CaCl_2$ (75 µg/cm^2). These are freeze-dried onto an absorbable Dexon mesh backing. The haemostatic efficacy of this dressing has been evaluated in a number of experimental models involving traumatic injuries in large animals[392,393,403-405]. Kheirabadi et al compared the dry fibrin sealant dressing against a chitosan dressing and the standard gauze army field dressing in a swine aortic injury model. Results of this randomised controlled trial showed that the fibrin sealant dressing provided initial haemostasis in all pigs (n=6) and maintained haemostasis in 5 pigs (failure of one dressing at 2.2hrs). However haemostasis was not achieved in any of the gauze dressings. Five of the 7 chitosan dressing pigs achieved initial haemostasis however prolonged haemostasis wasn't achieved and all animals exsanguinated[395]. Pusateri et al compared the effect of nine haemostatic dressings on blood loss using a model of severe venous haemorrhage and hepatic injury in swine. Dressings studied included a dry fibrin sealant dressing, oxidized cellulose dressing, a propyl gallate dressing, a epsilon aminocaproic acid and thrombin dressing, microfibrillar collagen dressing, a fibrillar oxidated regenerated cellulose dressing, a fully acetylated poly-N-acetyl glucosamine dressing and finally a dressing containing human fibrinogen, thrombin and a equine collagen backing. Results showed that dry fibrin sealant dressing was the only effective dressing at

reducing post-treatment blood loss and increased the percentage of animals that achieved haemostasis when compared to gauze controls. No other dressing was effective. Additionally this study also showed that the dry fibrin sealant dressing had the highest adherence strength score ($p<0.01$)[392]. Finally Acheson et al investigated the effect of the dry fibrin sealant dressing against zeolite granule dressing and a chitosan dressing in a femoral arterial injury model in swine. This model used a standard gauze dressing as control. Results showed that the zeolite granules showed no haemostatic effect and the chitosan dressing only had a temporary effect on bleeding in 1/15 swine. The dry fibrin sealant dressing achieve stable haemostasis in 10 of 15 swine, preventing their deaths[398].

Zoelite granule dressing

This product is designed to rapidly absorb water, thereby concentrating red blood cells, clotting factors and platelets at the site of bleeding in an exothermic reaction[199]. Zeolite granules were compared against a standard gauze dressing in a randomised controlled trial involving a swine femoral artery and vein injury model. Results showed that application of 1% Zeolite granules result in a cessation of bleeding in all 7 animals, the lowest volume of blood loss and complete survival of this group. However, the authors noted that the dressing caused an exothermic reaction[397]. Zeolite granule dressing use in swine showed an average increase in temperature, when applied to a wound, of up to 100 degrees celcius, which resulted in histological changes within the artery wall, vein, nerves and muscle[397,398,406]. Histological changes at the wound margins included granulomas and abscesses formation in all three animals investigated long-term. Additionally one animal required euthanasia due to extensive morbidity and muscle necrosis at the site of injury[406]. Pusateri et al

also showed a significant reduction in the post-treatment blood loss and survival in a liver injury model when compared to gauze control, however required the use of two surgical gloves and surgical tape to protect them from the thermal effects of the dressing and additionally noted extensive thermal injury to contact tissues[407].

Poly-N-acetyl-glucosamine

This is an algae-derived dressing that is distinct from chitosan in that it is fully acetylated. It is a polysaccharide produced by a fermentation process and isolated from microalgal cultures grown on culture medium. Mechanism of its haemostatic ability remains unclear but it has been suggested to result in red blood cell aggregation, platelet activation, activation of the clotting cascade and local vasoconstriction[408-410]. Use of this dressing was first shown to be superior to fibrin glue, absorbable collagen and oxidised regenerated cellulose in a splenic injury model in both non-coagulopathic and coagulopathic swine[391]. Hypothermia seems to have no effect on the efficacy of Poly-N-acetyl-glucosamine[390]. The Poly-N-acetyl-glucosamine patch has also been investigated in a model of severe large venous haemorrhage and hepatic injury in swine. This more challenging injury showed that Poly-N-acetyl-glucosamine patch was ineffective in increasing survival or decreasing blood loss[392,396]. The Poly-N-acetyl-glucosamine patch was then further modified to increase the active ingredient from 5mg/cm^2 to 16mg/cm^2. This modified patch was investigated in a liver crushing/avulsion injury in swine and proved to reduce mortality, total blood loss and total intravenous fluid requirements when compared to control (gauze packing alone). However, this study administered the patch whilst performing the 'Pringle manoeuvre' changing the characteristics of this model from a

low pressure, high flow animal model to one of less flow and hence less challenging[411].

In summary it appears that the Poly-N-acetyl-glucosamine patch is useful as a haemostatic agent in the low flow, low pressure animal model however further research is required to delineate its role in the management of a high pressure, high flow vascular injury.

Chitosan Dressing

This chitosan dressing is a freeze-dried dressing made from high-molecular-weight chitosan, with the addition of a foam adhesive-coated backing. Mechanism of action is thought to be primarily from its tissue adherence and therefore its ability to seal a wound[393,397]. Pusateri et al investigated this dressing against a well known swine model of severe large venous haemorrhage and hepatic injury. This study compared gauze dressing to chitosan dressing and showed that chitosan dressing reduced blood loss (264ml vs 2879ml), attained haemostasis more frequently in the chitosan group after 3 minutes and additionally resulted in less intravenous fluid use and increased survival (7/8 vs 2/7)[393]. These results were similar for the dry fibrin sealant dressing (investigated using the same animal model), the only dressing out of nine others to show a significant increase in survival or a reduction of intravenous fluid usage[392]. Interestingly both the dry fibrin sealant dressing and the chitosan dressing showed significantly higher tissue adherence scores[392,393]. The chitosan dressing was subsequently investigated in a complex groin injury model in swine involving complete transaction of the femoral artery and vein. Results showed no significant difference in mortality or blood loss, however the authors did note that 5 of the 7 dressings adhered excellently resulting in ‘superb’ haemorrhage control and no

animals died. The other 2 dressings failed to develop adherence and both these animals died. It appears that adherence to the site of injury is most important for achieving haemostasis[397].

Investigation of this patch in a high flow, high pressure animal model has also been performed. The aortic haemorrhage model in swine showed that the chitosan dressing was significantly more effective in achieving initial haemostasis when compared to gauze controls (5/7 vs 0/6). However more prolonged observation revealed that all animals had resumed bleeding by at least 102 minutes after application[395]. Acheson et al showed that chitosan dressing failed to show haemostasis in all but 1 animal in a femoral artery injury model in swine[398]. Englehart et al recently investigated this chitosan dressing against a modified chitosan dressing by the addition of silica and polyethylene. A randomised controlled trial involving a groin injury model in swine (transaction of the femoral artery and vein) showed that the modified chitosan dressing showed a significant reduction in median blood loss, and animals had a greater hematocrit at the conclusion of the observation period. The authors found that there was only 1 failure (1/10) with the modified chitosan dressing compared to 8 (8/10) with the traditional chitosan dressing[412].

Smectite Mineral and Absorbent Polymer

The combination of smectite mineral (a class of hydrated alumina silicates) and a salt of a cross-linked polyacrylic acid has recently been developed and investigated. The haemostatic mechanism of this product is thought to be a combination of its ability to absorb blood as well as its tissue adherence, along with its significant negative charge and thus likely ability to activate the intrinsic clotting system[399].

To date there is only one published article investigating the effects of smectite mineral with an absorbent polymer. Ward et al compared the effects of a smectite mineral dressing in a swine model of lethal extremity arterial haemorrhage, comparing the effects of a gauze dressing, a zeolite granule dressing with and without a permeable pouch and a chitosan dressing in 25 swine (5 per group). This RCT found that only the smectite mineral dressing achieved complete haemostasis without the need to apply a second dressing. There was a 100% survival rate associated with this dressing, which was highly significant compared with all other groups. Only 1 animal in the chitosan dressing group survived to 180 minutes with all other animals in all other treatment groups exsanguinating prematurely. Additionally, there was a significant reduction in the total blood loss with the smectite dressing compared to all other dressings. No significant difference in wound/dressing temperatures were noted in the use of the smectite mineral dressing although the authors did note a slight warming effect of up to 42 degrees celcius[399]. This study shows that smectite mineral dressing has a promising role in high pressure, high volume arterial injury however further research is needed.

Summary of Advanced Haemostatic Products

Current research and development of advanced haemostatic products involves the use of trauma models of proximal extremity and abdominal injuries. These products are manufactured as a patch based treatment that can be applied with direct pressure on to the injury site. In summary, the dry fibrin sealant dressing has been extensively investigated in the low-pressure, high flow bleeding model and has been shown to be universally effective in reducing blood loss and achieving haemostasis.

Additionally there is some data to suggest that this product maybe effective in the high-pressure, high flow bleeding model. Whilst it appears that this dressing is very effective, it is unfortunately very expensive, not approved for human use and currently does not come in a form easily applied during endoscopic sinus and skull base surgery[199].

Zoelite granule dressings are very effective at achieving rapid haemostasis in high flow/high pressure vascular injuries however they result in significant thermal injury to surrounding tissues that make this dressing undesirable for use.

A RCT shows that a smectite mineral based dressing is useful in an extremity arterial haemorrhage model of a high pressure/high volume arterial injury. Poly-N-acetyl-glucosamine based patch is useful in the low flow/low pressure injury scenario but is ineffective in a more challenging vascular/visceral injury.

Chitosan dressing is very effective in a low pressure, high flow animal model of vascular and visceral injury. Additionally, in the model of low to moderate pressure and flow vascular injury, the chitosan dressing seemed very effective in the instances of wound adherence. However due to the variability of this dressing overall significance was not reached. Recently in a detailed review of advanced haemostatic agents recommended that the chitosan dressing should be the first advanced haemostatic agent used in situations in which severe external bleeding that cannot be controlled by standard methods, largely because of its safety and it previous success in controlling bleeding in models up to those that include high pressure/high-flow bleeding[199].

CHAPTER 6: THE EFFICACY OF A NOVEL CHITOSAN GEL ON HAEMOSTASIS AFTER ENDOSCOPIC SINUS SURGERY IN A SHEEP MODEL OF CHRONIC RHINOSINUSITIS

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American Journal of Rhinology & Allergy, v. 23(1), pp. 71-75

CHAPTER 7: THE EFFICACY OF A NOVEL CHITOSAN GEL ON HAEMOSTASIS AND WOUND HEALING AFTER ENDOSCOPIC SINUS SURGERY

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The efficacy of a novel chitosan gel on hemostasis and wound healing following endoscopic sinus surgery

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CHAPTER 8: A VASCULAR CATASTROPHE DURING ENDONASAL SURGERY: AN ENDOSCOPIC SHEEP MODEL

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ORIGINAL ARTICLE

A Vascular Catastrophe during Endonasal Surgery: An Endoscopic Sheep Model

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ABSTRACT

Internal carotid artery (ICA) injury is a dramatic complication of endonasal skull base approaches with massive bleeding. This study aims to design an animal model of ICA injury during endonasal skull base surgery. Eight sheep underwent ICA isolation followed by arterial pressure monitoring and placement of a rapid infuser. The Sinus Model Otorhino Neuro Trainer (Pro Delphus, Pernambuco, Brazil) nasal model was then modified. A novel posterior sphenoid wall was created, allowing the artery to be placed within and fixed to the model in a watertight fashion. A diamond-tipped bur allowed surgical exposure of the carotid artery. A standardized injury was created endoscopically. The "two-surgeon technique" allowed local packing measures to be performed. Outcome measures were mean arterial pressure (MAP) following injury, resuscitation fluid volume, survival time, and total blood loss. Mean preinjury weight was 51.8 ± 4.59 kg. All baseline hematologic parameters fell within normal limits. The mean preinjury and postinjury MAP was 65.7 ± 9.3 mm Hg versus 39.1 ± 6.9 mm Hg, respectively. The mean survival time was 50.25 ± 17.89 minutes, with mean resuscitation fluid volume of 10.89 ± 2.40 L and mean blood loss of 4943 ± 1089 mL. This model replicates the endoscopic surgical field of an ICA injury, with the potential to train endoscopic skull base teams in the skills require to manage an ICA injury.

KEYWORDS: Endonasal surgery, carotid, packing, hemostasis

Skull base surgery has undergone a dramatic change in the last decade with the advent of improved technological developments and surgical instrumentation and an improved understanding of the endonasal skull base anatomy. This had led to the introduction of the expanded fully endoscopic endonasal skull base approaches.[1] Endonasal surgical techniques have several advantages to their more tradition open approaches including the avoidance of external skin incisions, minimal sacrifice of intervening structures, improved visualization, reduced postoperative pain, and shorter hospital admission times.[2] These advantageous have led to endonasal approaches rapidly becoming the standard of care for pituitary and other skull base tumors by both otolaryngologists and neurosurgeons worldwide.[3]

Endonasal skull base surgery was first introduced in 1961, and since then surgeons have considered internal carotid artery (ICA) injury the most dramatic complication of skull base surgery. ICA injury creates an immediately challenging surgical field, which may result in death of the patient. Although ICA injury during endoscopic sinus surgery is a relatively rare event, its frequency in endonasal skull base surgery is more significant. Ciric et al sent a questionnaire to 3172 neurosurgeons regarding the complications of transsphenoidal pituitary surgery. Results demonstrated that 52% of

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surgeons who had performed more than 500 endonasal pituitary approaches had experienced an ICA injury.[4] More advanced surgical approaches have a higher incidence of ICA rupture. Four separate consecutive series of extended endonasal resections show an incidence of ICA injury of between 4% and 9%.[5–8] These data demonstrate that increasing expertise and experience in endonasal skull base surgery and the increasingly challenging surgical pathologies encountered mean that it is likely that all specialist endonasal skull base surgeons will need to manage an ICA injury at some stage.

A review of the literature demonstrates that there is a lack of information with regards to the appropriate techniques and protocols in managing an ICA injury during endonasal surgery. Some authors advise that a hypotensive state should be avoided to maintain collateral cerebral perfusion[9,10]; however, others advise that a controlled hypotensive technique should be implemented,[11] with the addition of carotid compression on those that fail.[10,11] Weidenbecher et al advise immediate bilateral common carotid compression to maintain a surgical view.[12] There are also conflicting reports regarding the best intervention for achieving hemostasis control. Although nasal packing is the most frequent technique employed, there are also case reports describing the use of bipolar diathermy, the muscle patch, and the use of a thrombin/gelatin matrix.[9,12,13] An angiographic review of ICA injuries treated with nasal packing showed that 8 of the 12 patients had complete occlusion of the carotid, with a further patient suffering from occlusion of the middle cerebral and basilar artery. Another 4 of the 12 patients suffered from carotid stenosis. The authors concluded that "overpacking" contributes to the morbidity and mortality of the patient.[14] Once the hemorrhage is controlled, many patients are transferred for immediate endovascular stenting or embolization; however, it is unclear which patients are suitable for this. Delayed complications include secondary hemorrhage, pseudoaneurysm formation, and carotid-cavernous fistula; however, the incidence of these complications remains unknown. Laws suggests that virtually all ICA injuries repaired by indirect measure will develop a pseudoaneurysm requiring endovascular embolization.[15]

To allow for further prospective scientific investigation of the management options and complications of an ICA injury, an animal model is needed. This model needs to be a large-animal model that recreates the hemodynamic similarities with the patient, creating a high-flow and high-pressure style injury. It needs to maintain the challenging anatomic constraints of the human nasal vestibule and nasal cavity. Additionally, the model needs to replicate the variable boney exposure that may be encountered during an unexpected vascular injury. Currently, there is no such model that can reproducibly recreate this challenging surgical scenario. The aim of this study is to design an animal model of ICA injury during endonasal skull base surgery.

METHODS

All sheep were weighed and underwent coagulation profiling and a full blood examination prior to general anesthesia. Animals were fed a standard diet and observed for 3 days prior to surgery to ensure a good state of health. All sheep were fasted 12 to 18 hour before surgery with free access to water. Induction of general anesthesia was performed via injection with sodium thiopentone (19 mg/kg body weight) into the left jugular vein. Endotracheal intubation then followed with anesthesia maintained by inhalation of 1.5 to 2.0% isoflurane, to a depth that allowed spontaneous ventilation. The sheep were positioned on their backs, and a midline neck incision was performed from the thyroid cartilage to the base of the neck, extending down to the superficial layer of the deep cervical fascia. The fascia was incised, and dissection continued to the anterior tracheal wall. The visceral fascia was then dissected from the lateral tracheal walls to reveal the right carotid sheath. The sheath was then incised and the carotid artery dissected free for a length of 15 cm from the angle of the mandible to the base of the neck. The left carotid artery was also identified as described above. Both carotid arteries were cannulated at the level of the mandible to allow for continuous invasive arterial pressure monitoring bilaterally. The left internal jugular vein was identified by dissection posterior to the left sternocleidomastoid muscle and then cannulated with a rapid infusion catheter exchange set (Arrow International Inc., Reading, PA) to allow for rapid fluid resuscitation (Fig. 1).

The Sinus Model Otorhino Neuro Trainer (SIMONT, Pro Delphus, Pernambuco, Brazil) was chosen to simulate the endoscopic environment so that the carotid injuries could be managed with the anatomic limitations and confines seen in the human nasal

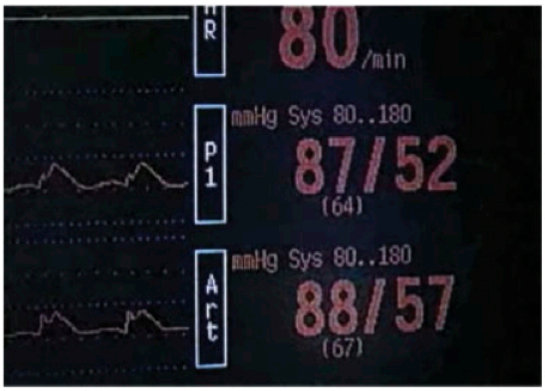

Figure 1 Continuous bilateral invasive carotid arterial pressure monitoring ensuring no compression of vessel on entry/exit through model.

plate to reveal carotid artery.

mm carotid injury.

boney exposure that may be experienced during an unanticipated vascular event. An 11-blade scalpel was used to create an approximately 4-mm longitudinal incision through the anterior wall of the carotid artery. Immediately rapid bleeding occurred, obstructing the surgical view. To confirm a challenging and high-pressure injury, local packing was performed of the injury site only, ensuring that vascular flow was still maintained. This was confirmed by observing a pulse pressure on the invasive pressure monitor placed distal to the carotid injury site.

Simultaneous fluid resuscitation with warmed normal saline (Baxter, New South Wales, Australia) was commenced at 200 mL/min. Resuscitation was stopped once hemostasis was achieved and the MAP achieved its preinjury level. Aggressive simultaneous fluid resuscitation ensured a high-flow, high-pressure vascular injury model. A thermal blanket was used to ensure a constant temperature and prevent the adverse affects of hypothermia on the coagulation cascade. Specific outcome measures for this study were the preinjury and postinjury MAP despite rapid fluid resuscitation, the resuscitation fluid volume used, and survival time and total blood loss.

RESULTS

A total of eight sheep were used for validation of this animal model. The mean weight was 51.8 ± 4.59 kg. Baseline coagulation and hematologic parameters were similar for all animals with no significant difference between each animal. All parameters fell within standard means as set by the Institute of Medical and Veterinary Pathology, Adelaide, Australia. The mean preinjury MAP, pulse, and temperature were 65.7 ± 9.3 mm Hg, 100 ± 14.84 beats per minute, and $40.9 \pm 0.64^{\circ}$C, respectively. The mean postinjury MAP (10 minutes postinjury) was 39.1 ± 6.9 mm Hg despite maximal resuscitation efforts at 200 mL/min. The mean resuscitation fluid used at time of exsanguination was 10.89 ± 2.40 L, with a mean total blood loss of $4943 \pm$ mL. With the performance of local packing measures only, which did not obstruct vascular flow, hemostasis was not achieved and resulted in all animals exsanguinating with a mean survival time for each animal of 50.25 ± 17.89 minutes with local cottonoid packing only.

DISCUSSION

Modern skull base surgery has undergone a paradigm shift in recent years from traditional external approaches to the expanded fully endoscopic endonasal skull base approach. Limited access surgery has several advantages; however, the surgeon needs to be aware of the potential for catastrophic vascular complications to occur. This article describes a reproducible animal model of a lethal endonasal carotid artery injury. Importantly, this model recreates the endonasal confines and limitations of the human nasal cavity and nasal vestibule, with hemodynamic similarities to the human patient. The pulsatile nature of this injury recreates the difficult surgical view encountered by the surgeon.

With appropriate safe surgical principles, most endoscopic sinus surgeons are unlikely to manage an ICA injury. However, ICA injury is a more likely event to the endoscopic skull base surgeon. All literature to date relies on retrospective studies and case reports to dictate the management options in such a catastrophic event. The surprised surgeon maybe ill equipped to deal with such a challenging surgical scenario. Surgeons rely on indiscriminate nasal packing in an attempt to achieve immediate hemorrhage control, often resulting in complete occlusion of the vessel, which contributes to the mortality and morbidity of the patient.[14]

The high-flow, high-pressure bleeding characteristics of an ICA injury creates an immediately challenging surgical scenario with massive blood loss that may prove fatal for the patient. The narrow nasal corridor means that even a little blood rapidly obstructs the surgeon's view, and the pulsatile nature of bleeding results in the endoscope tip rapidly becoming soiled with blood. These characteristics cause the surgical team to rapidly becoming disorientated and lose control of the surgical field. Frequently, a significant amount of experience, coordination, and teamwork is needed by both surgeons for the "two-surgeon team" to navigate through the bleeding and maintain a surgical view.[9] It is these challenging surgical characteristics that may result in exsanguination of the patient, and indiscriminate nasal packing is often all surgeons are equipped to do in an attempt to achieve hemostasis.

Animal models have played an important role in surgical education and training and have been used in the medical field since 384 B.C.[16] Remaining challenges in endoscopic skull base techniques include the ability to train a new generation of endonasal endoscopic skull base surgeons in a stepwise fashion including training in the potential for vascular injuries to occur.[17] This reproducible model allows the surgical steps that a skull base team should undertake to be defined in this catastrophic scenario. Importantly, it provides the opportunity to train endonasal endoscopic surgical teams in the skills required to manage the surgical field in such a catastrophic arterial injury, in a stepwise fashion.

Kassam et al concluded that the most significant limitation of endoneurosurgical hemostasis is the inability to repair large arteries primarily.[9] This model creates the opportunity for further research and development to be performed and allows the design and investigation of different treatment techniques that may be employed. It is important to recognize that not every vascular injury

will have the same anatomic constraints, and this reproducible model allows scientific investigation into developing the surgical techniques required to manage both a minimally accessible injury and also a maximally exposed injury site. With animal recovery following carotid injury control, it allows investigation into both the short-term and long-term complications of these techniques.

CONCLUSION

The increasing frequency of extended endoscopic endonasal skull base approaches means that specialist endonasal skull base surgeons need to be familiar with the techniques required to manage an inadvertent carotid injury. This model is the first to replicate the challenging endoscopic surgical management of a high-flow/high-pressure vascular injury, with the potential to train future endoscopic skull base surgeons in the skills required to manage such an event. Additionally, it allows for the development of novel hemostatic techniques and surgical instrumentation.

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REFERENCES

1. Kassam AB, Gardner P, Snyderman C, Mintz A, Carrau R. Expanded endonasal approach: fully endoscopic, completely transnasal approach to the middle third of the clivus, petrous bone, middle cranial fossa, and infratemporal fossa. Neurosurg Focus 2005;19:E6
2. Casler JD, Doolittle AM, Mair EA. Endoscopic surgery of the anterior skull base. Laryngoscope 2005;115:16–24
3. Carrau RL, Kassam AB, Snyderman CH. Pituitary surgery. Otolaryngol Clin North Am 2001;34:1143–1155; ix
4. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 1997;40: 225–236; discussion 236–237
5. Gardner PA, Kassam AB, Snyderman CH, et al. Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas: a case series. J Neurosurg 2008; 109:6–16
6. Stippler M, Gardner PA, Snyderman CH, Carrau RL, Prevedello DM, Kassam AB. Endoscopic endonasal approach for clival chordomas. Neurosurgery 2009;64:268–277; discussion 277–278
7. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. Neurosurgery 2006;59(Suppl 1):ONS50–ONS57; discussion ONS50–ONS57
8. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T. Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. Neurosurgery 2004;55: 539–547; discussion 547–550
9. Kassam A, Snyderman CH, Carrau RL, Gardner P, Mintz A. Endoneurosurgical hemostasis techniques: lessons learned from 400 cases. Neurosurg Focus 2005;19:E7
10. Pepper JP, Wadhwa AK, Tsai F, Shibuya T, Wong BJ. Cavernous carotid injury during functional endoscopic sinus surgery: case presentations and guidelines for optimal management. Am J Rhinol 2007;21:105–109
11. Park AH, Stankiewicz JA, Chow J, Azar-Kia B. A protocol for management of a catastrophic complication of functional endoscopic sinus surgery: internal carotid artery injury. Am J Rhinol 1998;12:153–158
12. Weidenbecher M, Huk WJ, Iro H. Internal carotid artery injury during functional endoscopic sinus surgery and its management. Eur Arch Otorhinolaryngol 2005;262: 640–645
13. Cappabianca P, Esposito F, Esposito I, Cavallo LM, Leone CA. Use of a thrombin-gelatin haemostatic matrix in endoscopic endonasal extended approaches: technical note. Acta Neurochir (Wien) 2009;151:69–77; discussion 77
14. Raymond J, Hardy J, Czepko R, Roy D. Arterial injuries in transsphenoidal surgery for pituitary adenoma; the role of angiography and endovascular treatment. AJNR Am J Neuroradiol 1997;18:655–665
15. Laws ER Jr. Vascular complications of transsphenoidal surgery. Pituitary 1999;2:163–170
16. Cohen BJ, Loew FM, eds. Laboratory Animal Medicine: Historical Perspectives in Laboratory Animal Medicine Orlando, FLAcademic Press, Inc.1984
17. Mehta RP, Cueva RA, Brown JD, et al. What's new in skull base medicine and surgery? Skull Base Committee Report. Otolaryngol Head Neck Surg 2006;135:620–630

CHAPTER 9: CONTROLLING THE SURGICAL FIELD DURING A LARGE ENDOSCOPIC VASCULAR INJURY

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Laryngoscope, v. 121(3), pp. 562-566

CHAPTER 10: THE EFFICACY OF HAEMOSTATIC TECHNIQUES IN THE SHEEP MODEL OF CAROTID ARTERY INJURY

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SUMMARY AND CONCLUSION

Review of ESS and ongoing concerns

Chronic rhinosinusitis is a term that encompasses a common group of disorders that has significant debilitating effects on society[3,413]. Patients that are refractory to maximal medical treatment undergo endoscopic sinus surgery, with this surgery being one of the most commonly performed procedures worldwide by otolaryngologists[4,20]. The 2 main problems following ESS are

- Ongoing bleeding following ESS that requires nasal packing, causing considerable discomfort for the patient and additional mucosal trauma
- Adhesion formation with subsequent narrowing and obstruction of the sinus drainage pathways, with the subsequent need for revision surgery

Currently there is a wide array of products and biomaterials that have been market for haemostasis and their positive effects on wound healing. However, these products are either ineffective in achieving haemostasis, or represent a compromise, excelling in haemostasis but adversely affecting the wound healing process[185,296,297]. The mechanism for this effect maybe the bidirectional co-stimulatory relationship between the haemostatic and inflammatory pathways, resulting in potent haemostasis but also leading to granulation tissue, fibrosis and adhesion formation[131,133].

One of the most common indications for biomaterials following ESS is to improve wound healing and prevent adhesion formation. However, currently there is no

product on the market that has been shown to improve wound healing when compared to no treatment at all[414]. The ideal post-ESS dressing is one that is haemostatic without stimulating the inflammatory cascade, improves wound healing and decreases adhesion formation, has no potential for disease transmission, is comfortable for the patient, and is inexpensive and simple to apply.

Chitosan Gel

Chitosan is a natural polymer that is derived from chitin, found in the exoskeleton of crustaceans. Experience with its use is wide, with applications in agriculture, waste treatment, cosmetics, foods and biomedical applications[415]. It has also been well know to be a potent haemostatic agent and to have positive effects on wound healing[210, 211, 212, 220].

The wound healing processes are complex with variations between patients and disease states. Some materials have been shown to be beneficial in normal healthy wound healing however detrimental under different disease states[309]. As such, fibroblasts chosen from patients suffering from CRS have been utilized to investigate the relationship between the Chitosan and Dextran components of the gel with diseased nasal fibroblasts. This study showed the a 5% Chitosan and 5% dextran gel resulted in fibroblast inhibition which translated to a slowing of their activity by some 3-5 days[416]. These effects have been noted in the literature before, and may well be due to the negative charge allowing it to strongly attach to the surface and prevent attachment of cell adhesion molecules[307]. Investigation of the *in vivo* effects of Chitosan gel showed that it prevents adhesion formation between the middle

turbinate and the lateral nasal wall. It is likely that the temporary inhibition effect of Chitosan on nasal fibroblasts has a temporary effect of preventing fibroblast migration across the blood clot. This effect lasts long enough to allow subsequent epithelialisation of the mucosa and for fibrinolysis to proceed without organisation and subsequent formation of an adhesion. Chitosan gels ability to prevent adhesion formation makes it the first such dissolvable product to prevent adhesion formation when compared to no treatment. This finding may potentially prevent revision surgery for patients in the future.

Microscopically packing materials disrupt the mucosal lining and delicate cilia, and therefore interrupt the mucociliary clearance of the nasal cavity[184,185]. An advantage of the dissolvable agents is that they don't require subsequent removal and additional mucosal trauma that contributes to the fibrinous exudate within the middle meatus and subsequent adhesion formation[226]. Improved microscopic features of wound healing with Chitosan gel have been demonstrated, with rapid rates of re-epithelialization and re-ciliation when compared to control. Additionally, cilial maturation has been shown to be more rapid compared to control 3-4 months following surgery[220].

Whilst there are some removable nasal dressings that have been shown to have positive effects on adhesion prevention they are associated with significant side effects that patients rate as detrimental, and would prevent them from recommending surgery again[176,177]. Patients report no increase in post-operative pain, nasal obstruction or nasal secretions with the topical use of Chitosan gel following ESS. These findings are important, especially when a dressing following routine ESS is to be recommended routinely.

Haemostasis still remains a common reason for endoscopic surgeons to utilize nasal dressings following surgery. Most currently available haemostatic agents act by potently activating the intrinsic and extrinsic coagulation cascade by incorporating human thrombin derived from human blood products, or animal based thrombin's and collagens. These products risk disease transmission such as CJD, HIV and Hepatitis and limit their recommendations for routine use during and following surgery[189,417,418]. Chitosan is a natural product that has undergone considerable chemical modifications during the de-acetylating processes. These manufacturing processes result in allergic reactions being unlikely, although still a possibility. To date there are no published reports of allergic reactions to Chitosan.

Chitosan gel was shown to be rapidly haemostatic in both the animal model of ESS, and in patients with CRS. Rapid haemostasis was achieved throughout all time points, including 2, 4, 6, 8 and 10 mins following application, when compared to control. The mechanisms by which Chitosan gel causes haemostasis are unknown but research is currently underway to investigate this mechanisms. Preparations of Chitosan have been shown to initiate haemostasis independent of platelets and coagulation factors[419]. Scanning electron microscopic images have shown that Chitosan can increase the affinity of red blood cells and platelets, and contribute to the haemostatic plug[420, 421-424]. Bidirectional pathways between inflammation and the intrinsic coagulation cascade maybe responsible for the observation that potent haemostatic products adversely effect wound healing. This may explain the adverse wound healing features noted with human thrombin derivatives[185,297].

In this thesis, both animal and human trials have demonstrated that Chitosan gel is a favourable post-operative dressing following ESS. It is well tolerated by patients with

no attributable side effects, is not associated with disease transmission, is cheap and easily applied topically and a dissolvable dressing agent. Most importantly however, it is not only an effective haemostatic agent but is the first product to improve the microscopic and macroscopic features of wound healing following ESS, making Chitosan gel an ideal routine dressing following ESS.

Endoscopic Animal Model of Carotid Artery Injury

In 1961 endonasal skull base surgery was first introduced, and since this time the most feared complication by all surgeons is the dramatic ICA injury. ICA injury immediately creates the scenario of massive haemorrhage with a challenging surgical field to control, often resulting in indiscriminate nasal packing of the area, contributing to the mortality and morbidity of the patient[124]. Important to consider is that 52% of specialist skull base surgeons will experience an ICA injury at some stage[125]. Increasingly complex pathologies encountered endoscopically, and more extended endonasal approaches being performed has seen a great increase in the potential for endoscopic ICA injuries to occur, up to a 4-9% incidence[113,120,126,127].

Animal models have played an important role in surgical education and training, and have had a valued role in the medical field since as far back as 384BC[425]. It is therefore not surprising that leaders in endonasal endoscopic skull base surgery have defined that one of the most important limitations to endonasal skull base surgery in the future is training in the management of vascular injuries[426]. This reproducible animal model of endonasal endoscopic carotid artery injury accurately recreates the nasal confines and limitations of the human nasal cavity and nasal

vestibule. This allows surgeons to use routine instrumentation that they are familiar with, and helping to create a 'life like' scenario. Rapid resuscitation during a large arterial injury helps to maintain the most challenging vascular injury scenario, a high flow/high pressure injury[398].

There is a lack of information with regards to how the surgical field of vascular catastrophe should best be managed, some advising that relative hypotension should be created[344], whilst other suggest a hypertensive state should be maintained[173,342]. Other authors have suggested bilateral carotid artery compression is required for field control[327]. These experiences however rely only on case reports and isolated experiences of large vascular injuries.

Our experience with 42 endoscopic endonasal carotid artery injuries in the animal model has allowed a scientific analysis of effective strategies to controlling the surgical field. The '2 surgeon technique' was particularly important in navigating the endoscope away from the vascular stream, with experience required in both surgeons working as a team. Considered placement of the endoscopic down the nasal cavity that was protected from the vascular stream by the posterior septal edge was important in preventing frequent soiling of the endoscope tip. Placing the large bore suction down the opposite nostril was particularly useful. If the suction was placed beneath the endoscope (as is routine during sinus surgery) it frequently resulted in the jet of blood tracking up the suction and soiling the endoscope tip. The suction could also be used to hover above the vascular stream, and guide the stream away from the endoscopes tip.

The animal model has also lead to the development of new technologies and instruments that can be utilised during vascular events[427]. This is an important

contribution so that technological innovation of new technologies and instruments can continue. The surprised surgeon maybe ill equipped to deal with such a challenging surgical scenario and perhaps the most important outcome of this model is the ability to train advanced endoscopic skull base surgeons in the techniques required to manage the surgical field and repair a vascular injury. The endoscopic management of large vascular injuries training course is now run annually in Australia, Asia and Europe, and has been met with great international success.

Haemostatic Techniques in the Sheep Model of Carotid Artery Injury

Every surgical team should have a plan in place should this unexpected complication occur; formulating and executing a plan of action during a crisis is difficult. Nasal packing is the most frequent technique employed, however this often causes complete carotid occlusion and carotid artery stenosis, which contributes to the mortality and morbidity of the patient[124]. The animal model of ICA injury has allowed prospective scientific investigation into which is the most effective technique of management. The muscle patch hemostasis and the U-Clip anastomotic device were significantly more effective at achieving primary hemostasis rapidly, reducing total blood loss, survival time and time MAP >55 mmHg than Floseal, oxidised regenerated cellulose and Chitosan gel. All muscle patch and U-Clip device treated sheep achieved primary hemostasis and reached the endpoint of observation, whilst maintaining vascular patency. Floseal and oxidised regenerated cellulose failed to achieve hemostasis in any animal with all animals exsanguinating prematurely.

When considering that pseudoaneurysm formation occurs up to 60% of ICA injuries it is important that this complication is prevented. The U-clip repairs offers a direct vascular close technique with reduced incidence of pseudoaneurysm formation[123], however does require a greater level of surgical exposure and skill to perform. The muscle patch treatment is perhaps the most useful technique in that it is readily and easily accessible, doesn't require a great level of skill to apply, and maintains vascular patency through the parent vessel. As it is an indirect method of closure it does have a great chance of pseudoaneurysm formation, but however Laws et al also concedes that placing muscle as a hemostat offers an opportunity for effective healing without the formation of a pseudoaneurysm[123].

Endoscopic sinus and skull base surgeons need to be familiar with the methods in which the surgical field can be controlled and haemostasis achieved during all types of surgical scenarios. Low flow/low pressure capillary style bleeding has many available haemostats available, however consideration to the wound healing process needs to be born in mind. Chitosan gel has is not only an effective haemostat, but has also been shown to improve wound healing and prevent adhesion formation. High flow/high pressure vascular catastrophes are more challenging, and training in how to manage the surgical field is beneficial. The muscle patch and U-clip treatments offer the ability to achieve haemostasis, whilst maintaining vascular patency.

APPENDIX 1

English Literature Case Reports of ICA Rupture Following Endonasal Surgery								
Article	ESS	S.B.	Pres.	Management	Out.	Patency	Comp.	Risk F.
Chen [357]		*	I + D	packing/balloon	-	×	PA	-
		*	I + D	packing/balloon	✓	×	PA	-
		*	I + D	packing/conservative	-	✓	PA	-
		*	I + D	packing/coil	✓	✓	PA	R
Frank[120]		*	I	packing/unknown	×	-	PA	R
Fukushima[341]		*	I	bipolar + surgicel packing	✓	-	×	-
		*	I	bipolar + surgicel packing	✓	-	×	-
		*	I	teflon + m. methacrylate	✓	✓	×	-
		*	I	teflon + m. methacrylate	✓	✓	×	-
		*	I	teflon + m. methacrylate	✓	✓	×	-
		*	I	teflon + m. methacrylate/surgery	-	-	PA/CCF	-
Gardner[325]		*	I	syvek patch	×	-	-	-
Koitschev[334]	*		I	packing/balloon	✓	×	×	-
	*		I	packing/balloon	✓	×	×	-
Laws[123]		*	I	exanguination	✞	-	-	-
		*	I	direct suture repair	-	-	-	-
		*	I	direct suture repair	-	-	-	-
		*	I	sundt-type clip graft	-	-	-	-
		*	I	balloon	-	-	-	-
		*	I	balloon	-	-	-	-
Lippert[339]		*	D	rubber foam/stent	✓	✓	PA	-
	*		I	stent/stent	✓	✓	PA	-
Park[344]	*		I	carotid tie off/packing/coil	✓	×	-	-
Pepper[342]		*	I	packing/balloon	✓	×	PA	-
	*		I	packing/balloon	×	×	×	-
Raymond[124]		*	D	surgicel +/- muscle +/- glue/balloon	✓	×	PA	-
		*	I	surgicel +/- muscle +/- glue	×	s	×	-
		*	I	surgicel +/- muscle +/- glue	✓	×	×	B
		*	I + D	surgicel +/- muscle +/- glue/balloon	×	×	×	-
		*	I	surgicel +/- muscle +/- glue	×	×	×	A
		*	I	surgicel +/- muscle +/- glue/balloon/bypass	×	×	×	-
		*	I	surgicel +/- muscle +/- glue	✓	×	×	R
		*	I	surgicel +/- muscle +/- glue	✓	×	×	A
		*	I + D	surgicel +/- muscle +/- glue/balloon	×	×	×	R
		*	D	exanguination	✞	-	PA	-
		*	I	surgicel +/- muscle +/- glue	✞	×	×	B
		*	D	surgicel +/- muscle +/- glue	✓	×	×	A
		*	I	surgicel +/- muscle +/- glue	✓	×	PA	A, R, RT,B
		*	I	surgicel +/- muscle +/- glue	✓	-	-	B
		*	I	surgicel +/- muscle +/- glue/balloon	×	×	×	-
		*	I + D	surgicel +/- muscle +/- glue/exanguination	✞	-	PA	R
		*	I	surgicel +/- muscle +/- glue/balloon	×	×	×	-
Stippler[113]		*	I	unknown	×	-	-	R, RT
Weidenbecher[327]	*		I	packing	✞	-	-	-
	*		I	muscle	✓	-	×	-
	*		I	muscle/surgical clipping	✓	-	PA	-
	*		I	muscle/balloon occlusion	✓	-	PA	-
Ahuja[343]		*	I	packing	✓	✓	CCF	-
		*	I + D	muscle + fibrin glue/balloon	✓	×	PA/CCF	-
		*	I	gelfoam + surgicel pack/balloon	✓	×	PA	A
Cappabianca[373]		*	I	packing/coil	-	×	PA	R, A
Fatemi[374]		*	I	packing/balloon	✓	×	PA	A
		*	I	packing	✓	×	×	R
		*	I	packing	✓	×	×	-
		*	I	packing	✓	✓	×	-
Zhao[375]		*	I	packing	×	-	-	-
		*	I	packing/stent	×	-	×	-
Lister[376]	*		I + D	packing/surgical	×	×	PA/CCF	-
Kaptain[80]		*	I	unknown	×	-	-	R, RT
Couldwell[126]		*	I	unknown	×	-	-	-
		*	I	unknown	-	-	-	-
		*	I	unknown	-	-	-	-
		*	I	unknown	-	-	-	-
Maniglia[377]	*		I	unknown	✞	-	PA	-
Bavinzski[353]		*	D	balloon	✓	×	PA	-
Cappabianca[347]		*	I	floseal/coil	-	-	CCF	-
Weber[378]	*		I	Packing	-	-	-	-
	*		I	unknown	✞	-	-	-
	*		I	unknown	✞	-	-	-
Park[358]		*	I	fleece coated fibrin glue/stent/coil	✓	✓	-	-
Reddy[379]		*	I + D	packing/surgical	✓	×	PA	A
Berker[333]		*	I	packing/stent	✓	-	PA	R
Biswas[345]		*	D	surgicel/coil	×	-	PA	-
Kocer[337]		*	I	packing/stent	-	-	CCF	-
Kadyrov[362]		*	I	packing/coil/stent	✓	×	PA	-
Zada[349]		*	I	muslin gauze + glue + fat/coil	✓	✓	PA	A
Kim[340]		*	I	cottonoid pressure/coil	✓	×	PA	R
Isenberg[380]	*		I	packing/balloon	✓	×	PA	-
Hudgins[381]	*		I	packing/balloon	✓	×	PA	-
Wigand[382]	*		I	unknown	✞	-	-	-
De Souza[355]		*	I	unknown/stent	-	✓	PA	A
Leung[364]	*		I	packing/stent	-	✓	×	-
Keerl[383]	*		I	unknown	✞	-	-	-
	*		I	unknown	✞	-	-	-
	*		I	unknown	✞	-	-	-
	*		I	unknown	✓	-	-	-

	*		I	unknown	✓	-	-	-
	*		I	unknown	×	-	-	-
	*		I	unknown	×	-	-	-
	*		I	unknown	×	-	-	-
	*		I	unknown	×	-	-	-
Charalampaki[384]		*	I	packing/stent	✓	-	-	-
Ghatge[352]		*	I	packing/Amplazt embolization	✓	×	×	-
		*	I	packing/stent	✞	×	-	R, RT
Crowley[385]		*	D	packing/coil	×	×	PA	-
Cathelinaud[147,354]	*		I + D	packing/coil/stent	✓	✓	PA	-
Ciceri[386]		*	D	no management	-	✓	PA	-
		*	I	bipolar	-	-	PA	-
		*	D	stent/coil	-	✓	PA	-
		*	I	coil/balloon	-	×	PA	-
Vanninen[348]		*	I + D	Oxygel + glue/stent	✓	✓	PA	-
Dolenc[346]		*	I	surgicel packing/surgery	✓	✓	PA/CCF	-
Pigott[372]		*	I + D	packing/balloon	×	✓	PA/CCF	-
Dusick[350]		*	I	Muslin gauze + fibrin glue/coils	✓	-	PA	A
		*	I	Muslin gauze + fibrin glue/coils	✓	×	PA	-
Lempert[371]		*	I	packing + foley balloon/coil	✓	✓	PA	-
		*	I	unknown/coil	✓	✓	PA	-
		*	D	unknown/coil	✓	✓	PA	-
Paullus[387]		*	I	surgicel packing/surgery	✓	×	PA/CCF	-
Cabezudo[388]		*	I + D	surgicel + gauze packing/surgery	✓	×	PA/CCF	A
Wilson[389]		*	I + D	packing/surgery	-	×	PA	A

Appendix 1 – Case reports and case series of ICA rupture events following endonasal surgery

✓ = no sequalae, × = permanent neurological morbidity or occlusion of ICA, - = unknown, ✞ = death, PA = pseudoaneurysm, CCF = cartico-cavernous fisula, I = intraopeative, D = delayed, A = acromegaly, B = bromocriptine, R = revision surgery, RT = radiotherapy, Out. = outcome, Pres. = presentation, S.B. = skull base surgery, Comp. = complication

REFERENCES

1. Higgins TS, Courtemanche C, Karakla Det al. Analysis of transnasal endoscopic versus transseptal microscopic approach for excision of pituitary tumors. *Am J Rhinol* 2008;22:649-652.

2. Lethbridge-Cejku M, Rose D, Vickerie J. Summary health statistics for U.S. adults: National Health Interview Survey, 2004. National Center for Health Statistics. *Vital Health Stat* 2006;10:19-22.

3. Anand VK. Epidemiology and economic impact of rhinosinusitis. *The Annals of otology, rhinology & laryngology* 2004;193:3-5.

4. Owings MF, Kozak LJ. Ambulatory and inpatient procedures in the United States, 1996. *Vital Health Stat 13* 1998:1-119.

5. Rosenfeld RM, Andes D, Bhattacharyya Net al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 2007;137:S1-31.

6. Kinney WC, Benninger MS. Assessment of quality of life among patients with sinonasal disease as determined by an Internet survey based on the Rhinosinusitis Disability Index. *Ear Nose Throat J* 2007;86:482, 484-486.

7. Seiberling KA, Conley DB, Tripathi Aet al. Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxins in nasal polyps. *The Laryngoscope* 2005;115:1580-1585.

8. Foreman A, Jervis-Bardy J, Wormald PJ. Do biofilms contribute to the initiation and recalcitrance of chronic rhinosinusitis? *Laryngoscope*;121:1085-1091.

9. Sasama J, Sherris DA, Shin SH, Kephart GM, Kern EB, Ponikau JU. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:2-8.

10. Vining EM. Evolution of medical management of chronic rhinosinusitis. *The Annals of otology, rhinology & laryngology* 2006;196:54-60.

11. Van Cauwenberge P, Van Hoecke H, Bachert C. Pathogenesis of chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2006;6:487-494.

12. Wagenmann M, Naclerio RM. Anatomic and physiologic considerations in sinusitis. *J Allergy Clin Immunol* 1992;90:419-423.

13. Perez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. *J Allergy Clin Immunol* 2005;115:1189-1196.

14. Gerstner AO, Gutsche M, Bucheler Met al. Eosinophilia in nasal polyposis: its objective quantification and clinical relevance. *Clin Exp Allergy* 2004;34:65-70.

15. Lim M, Citardi MJ, Leong JL. Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. *Am J Rhinol* 2008;22:381-389.

16. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane database of systematic reviews (Online)* 2007:CD006394.

17. Scarupa MD, Kaliner MA. Adjuvant therapies in the treatment of acute and chronic rhinosinusitis. *Clin Allergy Immunol* 2007;20:251-262.

18. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. *Annals of internal medicine*;154:293-302.

19. Wood AJ, Douglas RG. Pathogenesis and treatment of chronic rhinosinusitis. *Postgrad Med J*;86:359-364.

20. Aukema AA, Fokkens WJ. Chronic rhinosinusitis: management for optimal outcomes. *Treat Respir Med* 2004;3:97-105.

21. Australia M. Medicare Benefits Schedule Statistics: Australian Government 2007.

22. Stevenson RG. *A History of Oto-Laryngology*. Edinburgh: E&S Livingstone, Ltd, 1949.

23. Lund V. The evolution of surgery on the maxillary sinus for chronic rhinosinusitis. *The Laryngoscope* 2002;112:415-419.

24. Lund VJ. Inferior meatal antrostomy. Fundamental considerations of design and function. *J Laryngol Otol Suppl* 1988;15:1-18.

25. Mickulicz J. Zur operativen Behandlung das Empyens der Highmorshohle. *Lagenbeck Arch Klin Chir* 1887;34:626-634.

26. Molinetti A. Dissertationes anatomico-pathologicae quibus humani corporis partes accuratissime describunture morbique singulas divexantes explicantur. *Lagenbeck Arch Klin Chir* 1887;34:626-634.

27. Kennedy DW. Sinus surgery: a century of controversy. *The Laryngoscope* 1997;107:1-5.

28. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part II. Surgical technique. *Otolaryngol Head Neck Surg* 1986;94:147-156.

29. Stammberger H. [Personal endoscopic operative technic for the lateral nasal wall--an endoscopic surgery concept in the treatment of inflammatory diseases of the paranasal sinuses]. *Laryngol Rhinol Otol (Stuttg)* 1985;64:559-566.

30. Kennedy DW. Functional endoscopic sinus surgery. Technique. *Arch Otolaryngol* 1985;111:643-649.

31. Vining EM, Kennedy DW. The transmigration of endoscopic sinus surgery from Europe to the United States. *Ear Nose Throat J* 1994;73:456-458, 460.

32. Mackay IS. Endoscopic Sinus Surgery. *Annals of the Academy of Medicine, Singapore* 1991;20:690-695.

33. Womald PJ. *Endoscopic Sinus Surgery - Anatomy, Three-Dimensional Reconstruction, and Surgical Technique*. New York: Thieme, 2005.

34. Karim R, Ghabrial R, Lynch T, Tang B. A comparison of external and endoscopic endonasal dacryocystorhinostomy for acquired nasolacrimal duct obstruction. *Clin Ophthalmol* 2011;5:979-989.

35. Wang EW, Vandergrift WA, 3rd, Schlosser RJ. Spontaneous CSF Leaks. *Otolaryngol Clin North Am* 2011;44:845-856, vii.

36. Ramsden JD, Campisi P, Forte V. Choanal atresia and choanal stenosis. *Otolaryngol Clin North Am* 2009;42:339-352, x.

37. Baumann I, Blumenstock G, Klingmann C, Praetorius M, Plinkert PK. [Chronic rhinosinusitis. Subjective assessment of benefit 1 year after functional endonasal sinus surgery]. *HNO* 2007;55:858-861.

38. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza DC. Long-term impact of functional endoscopic sinus surgery on asthma. *Otolaryngol Head Neck Surg* 1999;121:66-68.

39. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza D. Long-term results of functional endoscopic sinus surgery. *The Laryngoscope* 1998;108:151-157.

40. Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. *Am J Rhinol* 2004;18:131-136.

41. Gliklich RE, Metson R. Effect of sinus surgery on quality of life. *Otolaryngol Head Neck Surg* 1997;117:12-17.

42. Maniglia AJ. Fatal and other major complications of endoscopic sinus surgery. *Laryngoscope* 1991;101:349-354.

43. Castillo L, Verschuur HP, Poissonnet G, Vaille G, Santini J. Complications of endoscopically guided sinus surgery. *Rhinology* 1996;34:215-218.

44. Schnipper D, Spiegel JH. Management of intracranial complications of sinus surgery. *Otolaryngol Clin North Am* 2004;37:453-472, ix.

45. May M, Levine HL, Mester SJ, Schaitkin B. Complications of endoscopic sinus surgery: analysis of 2108 patients--incidence and prevention. *Laryngoscope* 1994;104:1080-1083.

46. Brennan LG. Minimizing postoperative care and adhesions following endoscopic sinus surgery. *Ear Nose Throat J* 1996;75:45-48.

47. Stankiewicz JA. Complications of endoscopic intranasal ethmoidectomy. *Laryngoscope* 1987;97:1270-1273.

48. Chung JH, Cosenza MJ, Rahbar R, Metson RB. Mitomycin C for the prevention of adhesion formation after endoscopic sinus surgery: a randomized, controlled study. *Otolaryngol Head Neck Surg* 2002;126:468-474.

49. Nayak DR, Balakrishnan R, Hazarika P. Prevention and management of synechia in pediatric endoscopic sinus surgery using dental wax plates. *Int J Pediatr Otorhinolaryngol* 1998;46:171-178.

50. Benninger MS, Sebek BA, Levine HL. Mucosal regeneration of the maxillary sinus after surgery. *Otolaryngol Head Neck Surg* 1989;101:33-37.

51. Davis WE, Templer JW, Lamear WR, Davis WE, Jr., Craig SB. Middle meatus anstrostomy: patency rates and risk factors. *Otolaryngol Head Neck Surg* 1991;104:467-472.

52. Schaefer SD, Manning S, Close LG. Endoscopic paranasal sinus surgery: indications and considerations. *Laryngoscope* 1989;99:1-5.

53. Rajapaksa SP, Ananda A, Cain TM, Oates L, Wormald PJ. Frontal ostium neo-osteogenesis and restenosis after modified endoscopic Lothrop procedure in an animal model. *Clinical otolaryngology and allied sciences* 2004;29:386-388.

54. Wormald PJ. Salvage frontal sinus surgery: the endoscopic modified Lothrop procedure. *Laryngoscope* 2003;113:276-283.

55. Hunter B, Silva S, Youngs R, Saeed A, Varadarajan V. Long-term stenting for chronic frontal sinus disease: case series and literature review. *J Laryngol Otol* 2010;124:1216-1222.

56. Eliashar R, Gross M, Wohlgelernter J, Sichel JY. Packing in endoscopic sinus surgery: is it really required? *Otolaryngol Head Neck Surg* 2006;134:276-279.

57. Ezzat S, Asa SL, Couldwell WTet al. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004;101:613-619.

58. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 1998;89:547-551.

59. Yang I, Sughrue ME, Rutkowski MJet al. Craniopharyngioma: a comparison of tumor control with various treatment strategies. *Neurosurg Focus* 2010;28:E5.

60. Maira G, Anile C, Colosimo C, Cabezas D. Craniopharyngiomas of the third ventricle: trans-lamina terminalis approach. *Neurosurgery* 2000;47:857-863; discussion 863-855.

61. Nakasu S, Hirano A, Shimura T, Llena JF. Incidental meningiomas in autopsy study. *Surgical neurology* 1987;27:319-322.

62. Forsyth PA, Cascino TL, Shaw EGet al. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. *J Neurosurg* 1993;78:741-747.

63. Sen CN, Sekhar LN, Schramm VL, Janecka IP. Chordoma and chondrosarcoma of the cranial base: an 8-year experience. *Neurosurgery* 1989;25:931-940; discussion 940-931.

64. Koch BB, Karnell LH, Hoffman HTet al. National cancer database report on chondrosarcoma of the head and neck. *Head Neck* 2000;22:408-425.

65. Nicolai P, Castelnuovo P, Bolzoni Villaret A. Endoscopic resection of sinonasal malignancies. *Curr Oncol Rep* 2011;13:138-144.

66. Liu JK, Das K, Weiss MH, Laws ER, Jr., Couldwell WT. The history and evolution of transsphenoidal surgery. *J Neurosurg* 2001;95:1083-1096.

67. Reuter HJ. Philipp Bozzini and Endoscopy in the 19th Century. Stuttgart: Max Nitze Museum, 1988.

68. Jackson C. *Bronchoscopy and Esophagoscopy: A Manual of Peroral Endoscopy and Larnyngeal Surgery*. Philadelphia: WB Saunders, 1922.

69. Mouton WG, Bessell JR, Maddern GJ. Looking back to the advent of modern endoscopy: 150th birthday of Maximilian Nitze. *World journal of surgery* 1998;22:1256-1258.

70. Linder TE, Simmen D, Stool SE. Revolutionary inventions in the 20th century. The history of endoscopy. *Archives of otolaryngology--head & neck surgery* 1997;123:1161-1163.

71. Cockett WS, Cockett AT. The Hopkins rod-lens system and the Storz cold light illumination system. *Urology* 1998;51:1-2.

72. Griffith HB. Endoneurosurgery: endoscopic intracranial surgery. *Proc R Soc Lond B Biol Sci* 1977;195:261-268.

73. Prevedello DM, Doglietto F, Jane JA, Jr., Jagannathan J, Han J, Laws ER, Jr. History of endoscopic skull base surgery: its evolution and current reality. *J Neurosurg* 2007;107:206-213.

74. Apuzzo ML, Heifetz MD, Weiss MH, Kurze T. Neurosurgical endoscopy using the side-viewing telescope. *J Neurosurg* 1977;46:398-400.

75. Bushe KA, Halves E. [Modified technique in transsphenoidal operations of pituitary adenomas. Technical note (author's transl)]. *Acta Neurochir (Wien)* 1978;41:163-175.

76. Sethi DS, Pillay PK. Endoscopic management of lesions of the sella turcica. *J Laryngol Otol* 1995;109:956-962.

77. Jho HD, Ha HG. Endoscopic endonasal skull base surgery: Part 3--The clivus and posterior fossa. *Minim Invasive Neurosurg* 2004;47:16-23.

78. Jho HD, Ha HG. Endoscopic endonasal skull base surgery: Part 2--The cavernous sinus. *Minim Invasive Neurosurg* 2004;47:9-15.

79. Jho HD, Ha HG. Endoscopic endonasal skull base surgery: Part 1--The midline anterior fossa skull base. *Minim Invasive Neurosurg* 2004;47:1-8.

80. Kaptain GJ, Vincent DA, Sheehan JP, Laws ER, Jr. Transsphenoidal approaches for the extracapsular resection of midline suprasellar and anterior cranial base lesions. *Neurosurgery* 2001;49:94-100; discussion 100-101.

81. Locatelli D, Castelnuovo P, Santi L, Cerniglia M, Maghnie M, Infuso L. Endoscopic approaches to the cranial base: perspectives and realities. *Childs Nerv Syst* 2000;16:686-691.

82. Solares CA, Ong YK, Snyderman CH. Transnasal endoscopic skull base surgery: what are the limits? *Curr Opin Otolaryngol Head Neck Surg*;18:1-7.

83. Dehdashti AR, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for anterior cranial base and suprasellar lesions: indications and limitations. *Neurosurgery* 2009;64:677-687; discussion 687-679.

84. Burkart CM, Theodosopoulos PV, Keller JT, Zimmer LA. Endoscopic transnasal approach to the clivus: a radiographic anatomical study. *Laryngoscope* 2009;119:1672-1678.

85. Fortes FS, Sennes LU, Carrau RLet al. Endoscopic anatomy of the pterygopalatine fossa and the transpterygoid approach: development of a surgical instruction model. *Laryngoscope* 2008;118:44-49.

86. Kassam AB, Prevedello DM, Thomas Aet al. Endoscopic endonasal pituitary transposition for a transdorsum sellae approach to the interpeduncular cistern. *Neurosurgery* 2008;62:57-72; discussion 72-54.

87. de Almeida JR, Zanation AM, Snyderman CHet al. Defining the nasopalatine line: the limit for endonasal surgery of the spine. *Laryngoscope* 2009;119:239-244.

88. Harvey RJ, Sheehan PO, Debnath NI, Schlosser RJ. Transseptal approach for extended endoscopic resections of the maxilla and infratemporal fossa. *Am J Rhinol Allergy* 2009;23:426-432.

89. Eloy JA, Vivero RJ, Hoang Ket al. Comparison of transnasal endoscopic and open craniofacial resection for malignant tumors of the anterior skull base. *Laryngoscope* 2009;119:834-840.

90. Cohen MA, Liang J, Cohen IJ, Grady MS, O'Malley BW, Jr., Newman JG. Endoscopic resection of advanced anterior skull base lesions: oncologically safe? *ORL J Otorhinolaryngol Relat Spec* 2009;71:123-128.

91. Kim BJ, Kim DW, Kim SWet al. Endoscopic versus traditional craniofacial resection for patients with sinonasal tumors involving the anterior skull base. *Clin Exp Otorhinolaryngol* 2008;1:148-153.

92. Kassam AB, Thomas A, Carrau RLet al. Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. *Neurosurgery* 2008;63:ONS44-52; discussion ONS52-43.

93. Wise SK, Harvey RJ, Goddard JC, Sheahan PO, Schlosser RJ. Combined image guidance and intraoperative computed tomography in facilitating endoscopic orientation within and around the paranasal sinuses. *Am J Rhinol* 2008;22:635-641.

94. O'Malley BW, Jr., Grady MS, Gabel BCet al. Comparison of endoscopic and microscopic removal of pituitary adenomas: single-surgeon experience and the learning curve. *Neurosurg Focus* 2008;25:E10.

95. Neal JG, Patel SJ, Kulbersh JS, Osguthorpe JD, Schlosser RJ. Comparison of techniques for transsphenoidal pituitary surgery. *Am J Rhinol* 2007;21:203-206.

96. Zhang Y, Wang Z, Liu Yet al. Endoscopic transsphenoidal treatment of pituitary adenomas. *Neurological research* 2008;30:581-586.

97. Tabaee A, Anand VK, Barron Yet al. Endoscopic pituitary surgery: a systematic review and meta-analysis. *J Neurosurg* 2009;111:545-554.

98. Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. *Neurosurgery* 2008;62:1006-1015; discussion 1015-1007.

99. D'Haens J, Rompaey KV, Stadnik T. Fully endoscopic transphenoidal surgery for functioning pituitary adenomas: a restrospective comparison with traditional transsphenoidal microsurgery in the same institution. *Surgical neurology* 2009;72:336-340.

100. Jarrahy R, Berci G, Shahinian HK. Assessment of the efficacy of endoscopy in pituitary adenoma resection. *Archives of otolaryngology--head & neck surgery* 2000;126:1487-1490.

101. Kim EY, Park HS, Kim JJet al. Endoscopic transsphenoidal approach through a widened nasal cavity for pituitary lesions. *J Clin Neurosci* 2001;8:437-441.

102. Baussart B, Aghakhani N, Portier F, Chanson P, Tadie M, Parker F. [Endoscope-assisted microsurgery for invasive endo- and suprasellar pituitary macroadenomas: a consecutive retrospective study with 13 patients]. *Neurochirurgie* 2005;51:455-463.

103. Laufer I, Anand VK, Schwartz TH. Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. *J Neurosurg* 2007;106:400-406.

104. de Divitiis E, Cavallo LM, Cappabianca P, Esposito F. Extended endoscopic endonasal transsphenoidal approach for the removal of suprasellar tumors: Part 2. *Neurosurgery* 2007;60:46-58; discussion 58-49.

105. Frank G, Pasquini E, Doglietto Fet al. The endoscopic extended transsphenoidal approach for craniopharyngiomas. *Neurosurgery* 2006;59:ONS75-83; discussion ONS75-83.

106. Ceylan S, Koc K, Anik I. Endoscopic endonasal transsphenoidal approach for pituitary adenomas invading the cavernous sinus. *J Neurosurg* 2009;112:99-107.

107. Zhao B, Wei YK, Li GLet al. Extended transsphenoidal approach for pituitary adenomas invading the anterior cranial base, cavernous sinus, and clivus: a single-center experience with 126 consecutive cases. *J Neurosurg* 2009;112:108-117.

108. Gardner PA, Kassam AB, Thomas Aet al. Endoscopic endonasal resection of anterior cranial base meningiomas. *Neurosurgery* 2008;63:36-52; discussion 52-34.

109. Fahlbusch R, Schott W. Pterional surgery of meningiomas of the tuberculum sellae and planum sphenoidale: surgical results with special consideration of ophthalmological and endocrinological outcomes. *J Neurosurg* 2002;96:235-243.

110. Goel A, Muzumdar D, Desai KI. Tuberculum sellae meningioma: a report on management on the basis of a surgical experience with 70 patients. *Neurosurgery* 2002;51:1358-1363; discussion 1363-1354.

111. Park CK, Jung HW, Yang SY, Seol HJ, Paek SH, Kim DG. Surgically treated tuberculum sellae and diaphragm sellae meningiomas: the importance of short-term visual outcome. *Neurosurgery* 2006;59:238-243; discussion 238-243.

112. Bassiouni H, Asgari S, Stolke D. Tuberculum sellae meningiomas: functional outcome in a consecutive series treated microsurgically. *Surgical neurology* 2006;66:37-44; discussion 44-35.

113. Stippler M, Gardner PA, Snyderman CH, Carrau RL, Prevedello DM, Kassam AB. Endoscopic endonasal approach for clival chordomas. *Neurosurgery* 2009;64:268-277; discussion 277-268.

114. Iaconetta G, Fusco M, Cavallo LM, Cappabianca P, Samii M, Tschabitscher M. The abducens nerve: microanatomic and endoscopic study. *Neurosurgery* 2007;61:7-14; discussion 14.

115. Menezes AH, Gantz BJ, Traynelis VC, McCulloch TM. Cranial base chordomas. *Clin Neurosurg* 1997;44:491-509.

116. Menezes AH, Traynelis VC, Heth J. Tumors of the craniovertebral junction, in Winn H.R. *Youmans Neurological Surgery*. New York: Saunders, 2004:4799-4816.

117. Kassam AB, Prevedello DM, Carrau RLet al. Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients. *J Neurosurg* 2011;114:1544-1568.

118. Rutka JT. Endonasal resection of craniopharyngiomas. *J Neurosurg* 2008;109:1; reply 3-5.

119. de Divitiis E, Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A. Extended endoscopic transsphenoidal approach for extrasellar craniopharyngiomas. *Neurosurgery* 2007;61:219-227; discussion 228.

120. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. *Neurosurgery* 2006;59:ONS50-57; discussion ONS50-57.

121. Cappabianca P, Cavallo LM, Colao A, de Divitiis E. Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. *J Neurosurg* 2002;97:293-298.

122. de Divitiis E, Esposito F, Cappabianca P, Cavallo LM, de Divitiis O. Tuberculum sellae meningiomas: high route or low route? A series of 51 consecutive cases. *Neurosurgery* 2008;62:556-563; discussion 556-563.

123. Laws ER, Jr. Vascular complications of transsphenoidal surgery. *Pituitary* 1999;2:163-170.

124. Raymond J, Hardy J, Czepko R, Roy D. Arterial injuries in transsphenoidal surgery for pituitary adenoma; the role of angiography and endovascular treatment. *AJNR Am J Neuroradiol* 1997;18:655-665.

125. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery* 1997;40:225-236; discussion 236-227.

126. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T. Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. *Neurosurgery* 2004;55:539-547; discussion 547-550.

127. Gardner PA, Kassam AB, Snyderman CHet al. Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas: a case series. *J Neurosurg* 2008;109:6-16.

128. Ganong WF. Review of Medical Physiology. San Francisco: McGraw-Hill, 2005:515-546.

129. Steinsky J. Coagulation full: Wikipedia (online), 2007.

130. Levi M, van der Poll T. Two-way interactions between inflammation and coagulation. *Trends in cardiovascular medicine* 2005;15:254-259.

131. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. *Circulation* 2004;109:2698-2704.

132. Coughlin SR. Thrombin signalling and protease-activated receptors. *Nature* 2000;407:258-264.

133. Cunningham MA, Romas P, Hutchinson P, Holdsworth SR, Tipping PG. Tissue factor and factor VIIa receptor/ligand interactions induce proinflammatory effects in macrophages. *Blood* 1999;94:3413-3420.

134. Szaba FM, Smiley ST. Roles for thrombin and fibrin(ogen) in cytokine/chemokine production and macrophage adhesion in vivo. *Blood* 2002;99:1053-1059.

135. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium nitroprusside- and esmolol-induced controlled hypotension for functional endoscopic sinus surgery. *Can J Anaesth* 1995;42:373-376.

136. Solares CA, Ong YK, Carrau RLet al. Prevention and management of vascular injuries in endoscopic surgery of the sinonasal tract and skull base. *Otolaryngol Clin North Am*;43:817-825.

137. Wormald PJ, Athanasiadis T, Rees G, Robinson S. An evaluation of effect of pterygopalatine fossa injection with local anesthetic and adrenalin in the control of nasal bleeding during endoscopic sinus surgery. *Am J Rhinol* 2005;19:288-292.

138. Wormald PJ. *Endoscopic Sinus Surgery - Anatomy, Three-Dimensional Reconstruction, and Surgical Technique*. New York: Thieme, 2005.

139. Sieskiewicz A, Olszewska E, Rogowski M, Grycz E. Preoperative Corticosteriod Oral Therapy and Intraoperative Bleeding During Functional Endoscopic Sinus Surgery in Patients With Severe Nasal Polyposis: A Preliminary Investigation. *Annals of Otology, Rhinology and Laryngology* 2006;115:490-494.

140. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel Perioperative Sinus Endoscopy (POSE) scoring system. *Laryngoscope* 2007;117:1-28.

141. Wormald PJ, Van Hasselt A. Endoscopic removal of juvenile angiofibromas. *Otolaryngol Head Neck Surg* 2003;129:684-691.

142. Douglas R, Wormald PJ. Endoscopic surgery for juvenile nasopharyngeal angiofibroma: where are the limits? *Curr Opin Otolaryngol Head Neck Surg* 2006;14:1-5.

143. Ko MT, Chuang KC, Su CY. Multiple analyses of factors related to intraoperative blood loss and the role of reverse Trendelenburg position in endoscopic sinus surgery. *Laryngoscope* 2008;118:1687-1691.

144. Benjamin E, Wong DK, Choa D. 'Moffett's' solution: a review of the evidence and scientific basis for the topical preparation of the nose. *Clinical otolaryngology and allied sciences* 2004;29:582-587.

145. Porter MJ, Marais J, Tolley N. Comparison of cocaine alone or with adrenaline on nasal mucosal blood flow. *J Laryngol Otol* 1991;105:918-920.

146. John G, Low JM, Tan PE, van Hasselt CA. Plasma catecholamine levels during functional endoscopic sinus surgery. *Clinical otolaryngology and allied sciences* 1995;20:213-215.

147. van Hasselt CA, Low JM, Waldron J, Gibb AG, Oh TE. Plasma catecholamine levels following topical application versus infiltration of adrenaline for nasal surgery. *Anaesth Intensive Care* 1992;20:332-336.

148. Douglas R, Wormald PJ. Pterygopalatine fossa infiltration through the greater palatine foramen: where to bend the needle. *Laryngoscope* 2006;116:1255-1257.

149. Degoute CS. Controlled hypotension: a guide to drug choice. *Drugs* 2007;67:1053-1076.

150. Lessard MR, Trepanier CA, Baribault JPet al. Isoflurane-induced hypotension in orthognathic surgery. *Anesthesia and analgesia* 1989;69:379-383.

151. Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. *Br J Anaesth* 2006;96:727-731.

152. Saricaoglu F, Celiker V, Basgul E, Yapakci O, Aypar U. The efffect of hypotensive anaesthesia on cognitive functions and recovery at endoscopic sinus surgery. *European Journal of Anaesthesiology* 2005;22:154-163.

153. Jacobi KE, Bohm BE, Rickauer AJ, Jacobi C, Hemmerling TM. Moderate controlled hypotension with sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. *Journal of clinical anesthesia* 2000;12:202-207.

154. Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of beta-blocker premedication on the surgical field during endoscopic sinus surgery. *Laryngoscope* 2004;114:1042-1046.

155. Jabalameli M, Hashemi M, Soltani H, Hashemi J. Oral clonidine premedication decreases intraoperative bleeding in patients undergoing endoscopic sinus surgery. *J Res Med Sci* 2005;1:25-30.

156. Lindop MJ. Complications and morbidity of controlled hypotension. *Br J Anaesth* 1975;47:799-803.

157. Choi WS, Samman N. Risks and benefits of deliberate hypotension in anaesthesia: a systematic review. *International journal of oral and maxillofacial surgery* 2008;37:687-703.

158. Blackwell KE, Ross DA, Kapur P, Calcaterra TC. Propofol for maintenance of general anesthesia: a technique to limit blood loss during endoscopic sinus surgery. *Am J Otolaryngol* 1993;14:262-266.

159. Manola M, De Luca E, Moscillo L, Mastella A. Using remifentanil and sufentanil in functional endoscopic sinus surgery to improve surgical conditions. *Otorhinolaryngol* 2005;67:83-86.

160. Pavlin JD, Colley PS, Weymuller EA, van Norman G, Gunn HC, Koerschgen ME. Propofol versus isoflurance for endoscopic sinus surgery. *Am J Otolaryngol* 1999;20:96-101.

161. Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. *Laryngoscope* 2003;113:1369-1373.

162. Wormald PJ, van Renen G, Perks J, Jones JA, Langton-Hewer CD. The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery. *Am J Rhinol* 2005;19:514-520.

163. Tirelli G, Bigarini S, Russolo M, Lucangelo U, Gullo A. Total intravenous anaesthesia in endoscopic sinus-nasal surgery. *Acta Otorhinolaryngol Ital* 2004;24:137-144.

164. Atef A, Fawaz A. Comparison of laryngeal mask with endotracheal tube for anesthesia in endoscopic sinus surgery. *Am J Rhinol* 2008;22:653-657.

165. Webster AC, Morley-Forster PK, Janzen Vet al. Anesthesia for intranasal surgery: a comparison between tracheal intubation and the flexible reinforced laryngeal mask airway. *Anesthesia and analgesia* 1999;88:421-425.

166. Ahmed MZ, Vohra A. The reinforced laryngeal mask airway (RLMA) protects the airway in patients undergoing nasal surgery--an observational study of 200 patients. *Can J Anaesth* 2002;49:863-866.

167. Danielson R, Gravningsbraten R, Olofsson J. Anaesthesia in endoscopic sinus surgery. *Eur Arch Otorhinolaryngol* 2003;260:481-486.

168. Kaplan A, Crosby GJ, Bhattacharyya N. Airway protection and the laryngeal mask airway in sinus and nasal surgery. *Laryngoscope* 2004;114:652-655.

169. Williams PJ, Thompsett C, Bailey PM. Comparison of the reinforced laryngeal mask airway and tracheal intubation for nasal surgery. *Anaesthesia* 1995;50:987-989.

170. Nekhendzy V, Lemmens HJ, Vaughan WCet al. The effect of deliberate hypercapnia and hypocapnia on intraoperative blood loss and quality of surgical field during functional endoscopic sinus surgery. *Anesthesia and analgesia* 2007;105:1404-1409.

171. Stangerup SE, Dommerby H, Lau T. Hot-water irrigation as a treatment of posterior epistaxis. *Rhinology* 1996;34:18-20.

172. Stangerup SE, Thomsen HK. Histological changes in the nasal mucosa after hot-water irrigation. An animal experimental study. *Rhinology* 1996;34:14-17.

173. Kassam A, Snyderman CH, Carrau RL, Gardner P, Mintz A. Endoneurosurgical hemostasis techniques: lessons learned from 400 cases. *Neurosurg Focus* 2005;19:E7.

174. Stevens RW. Nasal packing; the rubber pneumatic pack. *A.M.A* 1951;54:191-194.

175. Huggins S. Control of hemorrhage in otorhinolaryngologic surgery with oxidized regenerated cellulose. *Eye, ear, nose & throat monthly* 1969;48:420-423.

176. von Schoenberg M, Robinson P, Ryan R. Nasal packing after routine nasal surgery--is it justified? *J Laryngol Otol* 1993;107:902-905.

177. Samad I, Stevens HE, Maloney A. The efficacy of nasal septal surgery. *J Otolaryngol* 1992;21:88-91.

178. Pomerantz J, Dutton JM. Platelet gel for endoscopic sinus surgery. *The Annals of otology, rhinology, and laryngology* 2005;114:699-704.

179. Vaiman M, Eviatar E, Segal S. Effectiveness of second-generation fibrin glue in endonasal operations. *Otolaryngol Head Neck Surg* 2002;126:388-391.

180. Vaiman M, Eviatar E, Segal S. The use of fibrin glue as hemostatic in endonasal operations: a prospective, randomized study. *Rhinology* 2002;40:185-188.

181. von Schoenberg M, Robinson P, Ryan R. The morbidity from nasal splints in 105 patients. *Clinical otolaryngology and allied sciences* 1992;17:528-530.

182. Weber R, Keerl R, Hochapfel F, Draf W, Toffel PH. Packing in endonasal surgery. *American journal of otolaryngology* 2001;22:306-320.

183. Weber R, Hochapfel F, Draf W. Packing and stents in endonasal surgery. *Rhinology* 2000;38:49-62.

184. Shaw CL, Dymock RB, Cowin A, Wormald PJ. Effect of packing on nasal mucosa of sheep. *J Laryngol Otol* 2000;114:506-509.

185. Chandra RK, Conley DB, Kern RC. The effect of FloSeal on mucosal healing after endoscopic sinus surgery: a comparison with thrombin-soaked gelatin foam. *American journal of rhinology* 2003;17:51-55.

186. Woodworth BA, Chandra RK, LeBenger JD, Ilie B, Schlosser RJ. A gelatin-thrombin matrix for hemostasis after endoscopic sinus surgery. *American journal of otolaryngology* 2009;30:49-53.

187. Gall RM, Witterick IJ, Shargill NS, Hawke M. Control of bleeding in endoscopic sinus surgery: use of a novel gelatin-based hemostatic agent. *The Journal of otolaryngology* 2002;31:271-274.

188. Baumann A, Caversaccio M. Hemostasis in endoscopic sinus surgery using a specific gelatin-thrombin based agent (FloSeal). *Rhinology* 2003;41:244-249.

189. Vaiman M, Eviatar E, Shlamkovich N, Segal S. Use of fibrin glue as a hemostatic in endoscopic sinus surgery. *The Annals of otology, rhinology, and laryngology* 2005;114:237-241.

190. Kheirabadi BS, Field-Ridley A, Pearson R, MacPhee M, Drohan W, Tuthill D. Comparative study of the efficacy of the common topical hemostatic agents with fibrin sealant in a rabbit aortic anastomosis model. *The Journal of surgical research* 2002;106:99-107.

191. Harris WH, Crothers OD, Moyen BJ, Bourne RB. Topical hemostatic agents for bone bleeding in humans. A quantitative comparison of gelatin paste, gelatin sponge plus bovine thrombin, and microfibrillar collagen. *J Bone Joint Surg Am* 1978;60:454-456.

192. Citardi MJ, Cox AJ, 3rd, Bucholz RD. Acellular dermal allograft for sellar reconstruction after transsphenoidal hypophysectomy. *Am J Rhinol* 2000;14:69-73.

193. Amante S, Mancini M. [Various topical applications of thrombin and its supports]. *Riforma Med* 1955;69:263-267.

194. Chapman WC, Singla N, Genyk Yet al. A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. *J Am Coll Surg* 2007;205:256-265.

195. Frenkiel S, Desrosiers MY, Nachtigal D. Use of hylan B gel as a wound dressing after endoscopic sinus surgery. *The Journal of otolaryngology* 2002;31 Suppl 1:S41-44.

196. Karkos PD, Thinakararajan T, Goodyear P, Srinivasan VR. Day-case endoscopic sinus surgery using dissolvable haemostatic nasal packs: a pilot study. *Eur Arch Otorhinolaryngol* 2007;264:1171-1174.

197. Kastl KG, Betz CS, Siedek V, Leunig A. Control of bleeding following functional endoscopic sinus surgery using carboxy-methylated cellulose packing. *Eur Arch Otorhinolaryngol* 2008.

198. Hadi HA, Maw A, Hay DJ. A simple technique to control iatrogenic solid organ injury haemorrhage. *Surgeon* 2004;2:339-340, 361.

199. Pusateri AE, Holcomb JB, Kheirabadi BS, Alam HB, Wade CE, Ryan KL. Making sense of the preclinical literature on advanced hemostatic products. *The Journal of trauma* 2006;60:674-682.

200. Shinkwin CA, Beasley N, Simo R, Rushton L, Jones NS. Evaluation of Surgicel Nu-knit, Merocel and Vasolene gauze nasal packs: a randomized trial. *Rhinology* 1996;34:41-43.

201. Okamoto S, Sato S, Takada Y, Okamoto U. An Active Stereo-Isomer (Trans-Form) of Amcha and Its Antifibrinolytic (Antiplasminic) Action in Vitro and in Vivo. *Keio J Med* 1964;13:177-185.

202. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003;63:1417-1433.

203. Klepfish A, Berrebi A, Schattner A. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Archives of internal medicine* 2001;161:767.

204. Sabba C, Gallitelli M, Palasciano G. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001;345:926.

205. Athanasiadis T, Beule AG, Wormald PJ. Effects of topical antifibrinolytics in endoscopic sinus surgery: a pilot randomized controlled trial. *American journal of rhinology* 2007;21:737-742.

206. Glickman M, Gheissari A, Money S, Martin J, Ballard JL. A polymeric sealant inhibits anastomotic suture hole bleeding more rapidly than gelfoam/thrombin: results of a randomized controlled trial. *Arch Surg* 2002;137:326-331; discussion 332.

207. Hagberg RC, Safi HJ, Sabik J, Conte J, Block JE. Improved intraoperative management of anastomotic bleeding during aortic reconstruction: results of a randomized controlled trial. *The American surgeon* 2004;70:307-311.

208. Muzzarelli RAA. Encyclopedia of Polymer Science and Engineering, 1990.

209. Kurita K. Chitin and chitosan: functional biopolymers from marine crustaceans. *Mar Biotechnol (NY)* 2006;8:203-226.

210. Klokkevold PR, Lew DS, Ellis DG, Bertolami CN. The effect of chitosan on lingual hemostasis in rabbits. *J Oral Maxillofac Surg* 1991;49:858-863.

211. Aguilera L, Bildrell R, Fulkerson P, Hazzard TM, Gustafson SB. Chitosan Dressing Provides Hemostasis In Swine Femoral Arterial Injury Model. *Preshospital Emergency Care* 2007;11:172-178.

212. Yang J, Tian F, Wang Z, Wang Q, Zeng Y, Chen S. Effect of Chitosan Molecular Weight and Deacetylation Degree on Hemostasis. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 2007:131-137.

213. Klokkevold PR, Fukayama H, Sund EC, Bertolami CN. The effects of chitosan (poly-N-acetyl glucosamine) on lingual hemostasis in heparinised rabbits. *J Oral Maxillofac Surg* 1999;57:49-52.

214. Read RC, Naylor SC, Potter CWet al. Effective nasal influenza vaccine delivery using chitosan. *Vaccine* 2005;23:4367-4374.

215. Davis SS, Illum L. Absorption enhancers for nasal drug delivery. *Clinical pharmacokinetics* 2003;42:1107-1128.

216. van der Lubben IM, Verhoef JC, Borchard G, Junginger HE. Chitosan and its derivatives in mucosal drug and vaccine delivery. *Eur J Pharm Sci* 2001;14:201-207.

217. Illum L. Nasal drug delivery--possibilities, problems and solutions. *J Control Release* 2003;87:187-198.

218. Illum L, Watts P, Fisher ANet al. Intranasal delivery of morphine. *The Journal of pharmacology and experimental therapeutics* 2002;301:391-400.

219. Soane RJ, Hinchcliffe M, Davis SS, Illum L. Clearance characteristics of chitosan based formulations in the sheep nasal cavity. *International journal of pharmaceutics* 2001;217:183-191.

220. Athanasiadis T, Beule AG, Robinson BH, Robinson SR, Shi Z, Wormald PJ. Effects of a novel chitosan gel on mucosal wound healing following endoscopic sinus surgery in a sheep model of chronic rhinosinusitis. *The Laryngoscope* 2008;118:1088-1094.

221. Bessermann M. Cyanoacrylate spray in the treatment of prolonged oral bleeding. *International journal of oral surgery* 1977;6:233-240.

222. Collins JA, Pani KC, Seidenstein MM, Brandes G, Leonard F. Cyanoacrylate adhesives as topical hemostatic aids. I. Experimental evaluation on liver wounds in dogs. *Surgery* 1969;65:256-259.

223. Singer AJ, McClain SA, Katz A. A porcine epistaxis model: hemostatic effects of octylcyanoacrylate. *Otolaryngol Head Neck Surg* 2004;130:553-557.

224. Herrera O, Kawamura S, Yasui N, Yoshida Y. Histological changes in the rat common carotid artery induced by aneurysmal wrapping and coating materials. *Neurol Med Chir (Tokyo)* 1999;39:134-139; discussion 139-140.

225. Sindwani R. Use of novel hemostatic powder MPH for endoscopic sinus surgery: Initial impressions. *Otolaryngol Head Neck Surg* 2009;140:262-263.

226. Weber R, Keerl R, Huppmann A, Draf W, Saha A. Wound Healing after Endonasal-Sinus Surgery in Time-Lapse Video: A New Way of Continous in Vivo Observation and Documentation in Rhinology. In: Stamm A, ed. *Micro-endoscopic surgery of the paranasal sinuses and the skull base*. Berlin: Springer, 2000.

227. Watelet JB, Bachert C, Gevaert P, Van Cauwenberge P. Wound healing of the nasal and paranasal mucosa: a review. *Am J Rhinol* 2002;16:77-84.

228. Hakkinen L, Uitto VJ, Larjava H. Cell biology of gingival wound healing. *Periodontol 2000* 2000;24:127-152.

229. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res* 2010;89:219-229.

230. Witte MB, Barbul A. General principles of wound healing. *The Surgical clinics of North America* 1997;77:509-528.

231. Kurkinen M, Vaheri A, Roberts PJ, Stenman S. Sequential appearance of fibronectin and collagen in experimental granulation tissue. *Lab Invest* 1980;43:47-51.

232. Fukai F, Suzuki H, Suzuki K, Tsugita A, Katayama T. Rat plasma fibronectin contains two distinct chemotactic domains for fibroblastic cells. *The Journal of biological chemistry* 1991;266:8807-8813.

233. Grinnell F, Feld M, Minter D. Fibroblast adhesion to fibrinogen and fibrin substrata: requirement for cold-insoluble globulin (plasma fibronectin). *Cell* 1980;19:517-525.

234. Gibran NS, Isik FF, Heimbach DM, Gordon D. Basic fibroblast growth factor in the early human burn wound. *The Journal of surgical research* 1994;56:226-234.

235. Wilhem DL. Regeneration of tracheal epithelium. *J Pathol Bacteriol* 1956;65:543-550.

236. Hosemann W, Wigand ME, Gode U, Langer F, Dunker I. Normal wound healing of the paranasal sinuses: clinical and experimental investigations. *Eur Arch Otorhinolaryngol* 1991;248:390-394.

237. Inayama Y, Hook GE, Brody ARet al. The differentiation potential of tracheal basal cells. *Lab Invest* 1988;58:706-717.

238. Carson JL, Collier AM, Knowles MR, Boucher RC, Rose JG. Morphometric aspects of ciliary distribution and ciliogenesis in human nasal epithelium. *Proc Natl Acad Sci U S A* 1981;78:6996-6999.

239. Shaw CK, Cowin A, Wormald PJ. A study of the normal temporal healing pattern and the mucociliary transport after endoscopic partial and full-thickness removal of nasal mucosa in sheep. *Immunology and cell biology* 2001;79:145-148.

240. Rajapaksa SP, Cowin A, Adams D, Wormald PJ. The effect of a hyaluronic acid-based nasal pack on mucosal healing in a sheep model of sinusitis. *American journal of rhinology* 2005;19:572-576.

241. Moriyama H. Endoscopic sinus surgery: Mucosal Preservation. In: Stamm A, Draf W, eds. *Micro-Endoscopic surgery of the paranasal sinuses and the skull base*. Berlin: Springer, 2000.

242. Mignatti P, Rifkin DB. Biology and biochemistry of proteinases in tumor invasion. *Physiol Rev* 1993;73:161-195.

243. Clark RA, Ashcroft GS, Spencer MJ, Larjava H, Ferguson MW. Re-epithelialization of normal human excisional wounds is associated with a switch from alpha v beta 5 to alpha v beta 6 integrins. *Br J Dermatol* 1996;135:46-51.

244. Knowlton CD, MacGregor GW. How and when the mucous membrane of the maxillary sinus regenerates. *Arch Otolaryngol* 1928;8:647-656.

245. Hilding A. Experimental surgery of the nose and sinuses. *Arch. Otolaryngol* 1933;17:321-327.

246. Forsgren K, Stierna P, Kumlien J, Carlsoo B. Regeneration of maxillary sinus mucosa following surgical removal. Experimental study in rabbits. *Ann Otol Rhinol Laryngol* 1993;102:459-466.

247. Hilding AC, Banovetz J. Occluding Scars in the Sinuses: Relation to Bone Growth. *Laryngoscope* 1963;73:1201-1208.

248. Hilding DA, Hilding AC. Ultrastructure of tracheal cilia and cells during regeneration. *Ann Otol Rhinol Laryngol* 1966;75:281-294.

249. Weber R, Keerl R, Jaspersen D, Huppmann A, Schick B, Draf W. Computer-assisted documentation and analysis of wound healing of the nasal and oesophageal mucosa. *J Laryngol Otol* 1996;110:1017-1021.

250. Weber R, Keerl R. Healing in the nasal mucosa. *Journal of wound care* 1998;7:101-102.

251. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodeling: differences between chronic rhinosinusitis and nasal polyposis. *Am J Rhinol* 2004;18:267-272.

252. van Goor H. Consequences and complications of peritoneal adhesions. *Colorectal Dis* 2007;9 Suppl 2:25-34.

253. Diamond MP, Decherney AH. Pathogenesis of adhesion formation/reformation: application to reproductive pelvic surgery. *Microsurgery* 1987;8:103-107.

254. Falanga V. Wound healing and chronic wounds. *J Cutan Med Surg* 1998;3 Suppl 1:S1-1-5.

255. Rout UK, Saed GM, Diamond MP. Expression pattern and regulation of genes differ between fibroblasts of adhesion and normal human peritoneum. *Reprod Biol Endocrinol* 2005;3:1.

256. Saed GM, Abu-Soud HM, Diamond MP. Role of nitric oxide in apoptosis of human peritoneal and adhesion fibroblasts after hypoxia. *Fertil Steril* 2004;82 Suppl 3:1198-1205.

257. Saed GM, Zhang W, Diamond MP. Molecular characterization of fibroblasts isolated from human peritoneum and adhesions. *Fertil Steril* 2001;75:763-768.

258. Lucas PA, Warejcka DJ, Young HE, Lee BY. Formation of abdominal adhesions is inhibited by antibodies to transforming growth factor-beta1. *The Journal of surgical research* 1996;65:135-138.

259. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. *Laryngoscope* 1990;100:79-84.

260. Shrime MG, Tabaee A, Hsu AK, Rickert S, Close LG. Synechia formation after endoscopic sinus surgery and middle turbinate medialization with and without FloSeal. *American journal of rhinology* 2007;21:174-179.

261. Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. *Laryngoscope* 1999;109:27-29.

262. Jacobs JB. 100 years of frontal sinus surgery. *Laryngoscope* 1997;107:1-36.

263. Wigand ME, Hosemann W. Endoscopic surgery for frontal sinusitis and its complications. *Am J Rhinol* 1991;5:85-89.

264. Hosemann W, Kuhnel T, Held P, Wagner W, Felderhoff A. Endonasal frontal sinusotomy in surgical management of chronic sinusitis: a critical evaluation. *Am J Rhinol* 1997;11:1-9.

265. Chan KO, Gervais M, Tsaparas Y, Genoway KA, Manarey C, Javer AR. Effectiveness of intraoperative mitomycin C in maintaining the patency of a frontal sinusotomy: a preliminary report of a double-blind randomized placebo-controlled trial. *American journal of rhinology* 2006;20:295-299.

266. Friedman M, Landsberg R, Schults RA, Tanyeri H, Caldarelli DD. Frontal sinus surgery: endoscopic technique and preliminary results. *Am J Rhinol* 2000;14:393-403.

267. Casiano RR, Livingston JA. Endoscopic Lothrop procedure: the University of Miami experience. *Am J Rhinol* 1998;12:335-339.

268. Gross CW, Zachmann GC, Becker DGet al. Follow-up of University of Virginia experience with the modified Lothrop procedure. *Am J Rhinol* 1997;11:49-54.

269. Scott NA, Wormald P, Close D, Gallagher R, Anthony A, Maddern GJ. Endoscopic modified Lothrop procedure for the treatment of chronic frontal sinusitis: a systematic review. *Otolaryngol Head Neck Surg* 2003;129:427-438.

270. Weber R, Mai R, Hosemann W, Draf W, Toffel P. The success of 6-month stenting in endonasal frontal sinus surgery. *Ear Nose Throat J* 2000;79:930-932, 934, 937-938 passim.

271. Alvarez OM, Mertz PM, Eaglstein WH. The effect of occlusive dressings on collagen synthesis and re-epithelialization in superficial wounds. *The Journal of surgical research* 1983;35:142-148.

272. Orlandi RR, Knight J. Prolonged stenting of the frontal sinus. *Laryngoscope* 2009;119:190-192.

273. Moriyama H, Yanagi K, Ohtori N. Healing process of sinus mucosa after endoscopic sinus surgery. *Am J Rhinol* 1996;10.

274. Kikawada T, Fujigaki M, Kikura M, Matsumoto M, Kikawada K. Extended endoscopic frontal sinus surgery to interrupted nasofrontal communication caused by scarring of the anterior ethmoid: long-term results. *Arch Otolaryngol Head Neck Surg* 1999;125:92-96.

275. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* 1992;102:1-18.

276. Kuhn FA, Citardi MJ. Advances in postoperative care following functional endoscopic sinus surgery. *Otolaryngol Clin North Am* 1997;30:479-490.

277. Thaler ER. Postoperative care after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 2002;128:1204-1206.

278. Bugten V, Nordgard S, Steinsvag S. The effects of debridement after endoscopic sinus surgery. *Laryngoscope* 2006;116:2037-2043.

279. Ryan RM, Whittet HB, Norval C, Marks NJ. Minimal follow-up after functional endoscopic sinus surgery. Does it affect outcome? *Rhinology* 1996;34:44-45.

280. Nilssen EL, Wardrop P, El-Hakim H, White PS, Gardiner Q, Ogston S. A randomized control trial of post-operative care following endoscopic sinus surgery: debridement versus no debridement. *J Laryngol Otol* 2002;116:108-111.

281. Hebert RL, 2nd, Bent JP, 3rd. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. *Laryngoscope* 1998;108:796-799.

282. Jiang RS, Hsu CY. Functional endoscopic sinus surgery in children and adults. *Ann Otol Rhinol Laryngol* 2000;109:1113-1116.

283. Kuhnel T, Hosemann W, Wagner W, Fayad K. [How traumatising is mechanical mucous membrane care after interventions on paranasal sinuses? A histological immunohistochemical study]. *Laryngorhinootologie* 1996;75:575-579.

284. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope* 1997;107:500-503.

285. Orlandi RR, Hwang PH. Perioperative care for advanced rhinology procedures. *Otolaryngol Clin North Am* 2006;39:463-473, viii.

286. Annys E, Jorissen M. Short term effects of antibiotics (Zinnat) after endoscopic sinus surgery. *Acta Otorhinolaryngol Belg* 2000;54:23-28.

287. Jiang RS, Liang KL, Yang KYet al. Postoperative antibiotic care after functional endoscopic sinus surgery. *Am J Rhinol* 2008;22:608-612.

288. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology* 2005;43:2-10.

289. Sil A, Mackay I, Rowe-Jones J. Assessment of predictive prognostic factors for functional endoscopic sinus surgery in a 5-year prospective outcome study. *Am J Rhinol* 2007;21:289-296.

290. Kennedy DW. Middle turbinate resection: evaluating the issues--should we resect normal middle turbinates? *Archives of otolaryngology--head & neck surgery* 1998;124:107.

291. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. *Wound Repair Regen* 1999;7:79-89.

292. Samuels P, Tan AK. Fetal scarless wound healing. *The Journal of otolaryngology* 1999;28:296-302.

293. Miller RS, Steward DL, Tami TAet al. The clinical effects of hyaluronic acid ester nasal dressing (Merogel) on intranasal wound healing after functional endoscopic sinus surgery. *Otolaryngol Head Neck Surg* 2003;128:862-869.

294. Bugten V, Nordgard S, Skogvoll E, Steinsvag S. Effects of nonabsorbable packing in middle meatus after sinus surgery. *The Laryngoscope* 2006;116:83-88.

295. Franklin JH, Wright ED. Randomized, controlled, study of absorbable nasal packing on outcomes of surgical treatment of rhinosinusitis with polyposis. *American journal of rhinology* 2007;21:214-217.

296. Wormald PJ, Boustred RN, Le T, Hawke L, Sacks R. A prospective single-blind randomized controlled study of use of hyaluronic acid nasal packs in patients after endoscopic sinus surgery. *American journal of rhinology* 2006;20:7-10.

297. Chandra RK, Conley DB, Haines GK, 3rd, Kern RC. Long-term effects of FloSeal packing after endoscopic sinus surgery. *American journal of rhinology* 2005;19:240-243.

298. Catalano PJ, Roffman EJ. Evaluation of middle meatal stenting after minimally invasive sinus techniques (MIST). *Otolaryngol Head Neck Surg* 2003;128:875-881.

299. Tom LW, Palasti S, Potsic WP, Handler SD, Wetmore RF. The effects of gelatin film stents in the middle meatus. *American journal of rhinology* 1997;11:229-232.

300. Kao SC, Liao CL, Tseng JH, Chen MS, Hou PK. Dacryocystorhinostomy with intraoperative mitomycin C. *Ophthalmology* 1997;104:86-91.

301. Hu D, Sires BS, Tong DC, Royack GA, Oda D. Effect of brief exposure to mitomycin C on cultured human nasal mucosa fibroblasts. *Ophthalmic plastic and reconstructive surgery* 2000;16:119-125.

302. Anand VK, Tabaee A, Kacker A, Newman JG, Huang C. The role of mitomycin C in preventing synechia and stenosis after endoscopic sinus surgery. *American journal of rhinology* 2004;18:311-314.

303. Illum L. Nasal delivery. The use of animal models to predict performance in man. *Journal of drug targeting* 1996;3:427-442.

304. Jacob A, Faddis BT, Chole RA. Chronic bacterial rhinosinusitis: description of a mouse model. *Archives of otolaryngology--head & neck surgery* 2001;127:657-664.

305. Liang KL, Jiang RS, Wang Jet al. Developing a rabbit model of rhinogenic chronic rhinosinusitis. *The Laryngoscope* 2008;118:1076-1081.

306. McIntosh D, Cowin A, Adams D, Wormald PJ. The effect of an expandable polyvinyl acetate (Merocel) pack on the healing of the nasal mucosa of sheep. *American journal of rhinology* 2005;19:577-581.

307. Zhou J, Liwski RS, Elson C, Lee TD. Reduction in postsurgical adhesion formation after cardiac surgery in a rabbit model using N,O-carboxymethyl chitosan to block cell adherence. *The Journal of thoracic and cardiovascular surgery* 2008;135:777-783.

308. Xia CS, Hong GX, Dou RR, Yang XY. Effects of chitosan on cell proliferation and collagen production of tendon sheath fibroblasts, epitenon tenocytes, and endotenon tenocytes.

Chinese journal of traumatology = Zhonghua chuang shang za zhi / Chinese Medical Association 2005;8:369-374.

309. Rajapaksa S, McIntosh D, Cowin A, Adams D, Wormald PJ. The effect of insulin-like growth factor 1 incorporated into a hyaluronic acid-based nasal pack on nasal mucosal healing in a healthy sheep model and a sheep model of chronic sinusitis. *Am J Rhinol* 2005;19:251-256.

310. Jacob A, Faddis BT, Chole RA. MeroGel hyaluronic acid sinonasal implants: osteogenic implications. *The Laryngoscope* 2002;112:37-42.

311. Maccabee MS, Trune DR, Hwang PH. Effects of topically applied biomaterials on paranasal sinus mucosal healing. *American journal of rhinology* 2003;17:203-207.

312. Proctor M, Proctor K, Shu XZ, McGill LD, Prestwich GD, Orlandi RR. Composition of hyaluronan affects wound healing in the rabbit maxillary sinus. *American journal of rhinology* 2006;20:206-211.

313. Antisdel JL, Janney CG, Long JP, Sindwani R. Hemostatic agent microporous polysaccharide hemospheres (MPH) does not affect healing or intact sinus mucosa. *The Laryngoscope* 2008;118:1265-1269.

314. Ingrams DR, Volk MS, Biesman BS, Pankratov MM, Shapshay SM. Sinus surgery: does mitomycin C reduce stenosis? *The Laryngoscope* 1998;108:883-886.

315. Rahal A, Peloquin L, Ahmarani C. Mitomycin C in sinus surgery: preliminary results in a rabbit model. *The Journal of otolaryngology* 2001;30:1-5.

316. Maccabee MS, Trune DR, Hwang PH. Paranasal sinus mucosal regeneration: the effect of topical retinoic acid. *American journal of rhinology* 2003;17:133-137.

317. Hwang PH, Chan JM. Retinoic acid improves ciliogenesis after surgery of the maxillary sinus in rabbits. *The Laryngoscope* 2006;116:1080-1085.

318. Tabaee A, Brown SM, Anand VK. Mitomycin C and endoscopic sinus surgery: where are we? *Current opinion in otolaryngology & head and neck surgery* 2007;15:40-43.

319. Vaiman M, Sarfaty S, Shlamkovich N, Segal S, Eviatar E. Fibrin sealant: alternative to nasal packing in endonasal operations. A prospective randomized study. *Isr Med Assoc J* 2005;7:571-574.

320. Jameson M, Gross CW, Kountakis SE. FloSeal use in endoscopic sinus surgery: effect on postoperative bleeding and synechiae formation. *American journal of otolaryngology* 2006;27:86-90.

321. Sindwani R. In press. *In press* 2009.

322. Kastl KG, Betz CS, Siedek V, Leunig A. Effect of carboxymethylcellulose nasal packing on wound healing after functional endoscopic sinus surgery. *American journal of rhinology & allergy* 2009;23:80-84.

323. Carrau RL, Snyderman CH, Kassam AB, Jungreis CA. Endoscopic and endoscopic-assisted surgery for juvenile angiofibroma. *Laryngoscope* 2001;111:483-487.

324. Casler JD, Doolittle AM, Mair EA. Endoscopic surgery of the anterior skull base. *Laryngoscope* 2005;115:16-24.

325. Snyderman CH, Carrau RL, Kassam ABet al. Endoscopic skull base surgery: principles of endonasal oncological surgery. *J Surg Oncol* 2008;97:658-664.

326. Fujii K, Chambers SM, Rhoton AL, Jr. Neurovascular relationships of the sphenoid sinus. A microsurgical study. *J Neurosurg* 1979;50:31-39.

327. Weidenbecher M, Huk WJ, Iro H. Internal carotid artery injury during functional endoscopic sinus surgery and its management. *Eur Arch Otorhinolaryngol* 2005;262:640-645.

328. Renn WH, Rhoton AL, Jr. Microsurgical anatomy of the sellar region. *J Neurosurg* 1975;43:288-298.

329. Lee KJ. The sublabial transseptal transsphenoidal approach to the hypophysis. *Laryngoscope* 1978;88:Suppl 10: 11-65.

330. Koitschev A, Baumann I, Remy CT, Dammann F. [Rational CT diagnosis before operations on the paranasal sinuses]. *HNO* 2002;50:217-222.

331. Wakai S, Fukushima T, Furihata T, Sano K. Association of cerebral aneurysm with pituitary adenoma. *Surg Neurol* 1979;12:503-507.

332. Imamura J, Okuzono T, Okuzono Y. Fatal epistaxis caused by rupture of an intratumoral aneurysm enclosed by a large prolactinoma--case report. *Neurol Med Chir (Tokyo)* 1998;38:654-656.

333. Berker M, Aghayev K, Saatci I, Palaoglu S, Onerci M. Overview of vascular complications of pituitary surgery with special emphasis on unexpected abnormality. *Pituitary*;13:160-167.

334. Koitschev A, Simon C, Lowenheim H, Naegele T, Ernemann U. Management and outcome after internal carotid artery laceration during surgery of the paranasal sinuses. *Acta Otolaryngol* 2006;126:730-738.

335. Hatam A, Greitz T. Ectasia of cerebral arteries in acromegaly. *Acta Radiol Diagn (Stockh)* 1972;12:410-418.

336. Bejjani GK, Sekhar LN, Yost AM, Bank WO, Wright DC. Vasospasm after cranial base tumor resection: pathogenesis, diagnosis, and therapy. *Surg Neurol* 1999;52:577-583; discussion 583-574.

337. Kocer N, Kizilkilic O, Albayram S, Adaletli I, Kantarci F, Islak C. Treatment of iatrogenic internal carotid artery laceration and carotid cavernous fistula with endovascular stent-graft placement. *AJNR Am J Neuroradiol* 2002;23:442-446.

338. Chaloupka JC, Putman CM, Citardi MJ, Ross DA, Sasaki CT. Endovascular therapy for the carotid blowout syndrome in head and neck surgical patients: diagnostic and managerial considerations. *AJNR Am J Neuroradiol* 1996;17:843-852.

339. Lippert BM, Ringel K, Stoeter P, Hey O, Mann WJ. Stentgraft-implantation for treatment of internal carotid artery injury during endonasal sinus surgery. *Am J Rhinol* 2007;21:520-524.

340. Kim SH, Shin YS, Yoon PH, Kim DI. Emergency endovascular treatment of internal carotid artery injury during a transsphenoidal approach for a pituitary tumor --case report. *Yonsei Med J* 2002;43:119-122.

341. Fukushima T, Maroon JC. Repair of carotid artery perforations during transsphenoidal surgery. *Surg Neurol* 1998;50:174-177.

342. Pepper JP, Wadhwa AK, Tsai F, Shibuya T, Wong BJ. Cavernous carotid injury during functional endoscopic sinus surgery: case presentations and guidelines for optimal management. *Am J Rhinol* 2007;21:105-109.

343. Ahuja A, Guterman LR, Hopkins LN. Carotid cavernous fistula and false aneurysm of the cavernous carotid artery: complications of transsphenoidal surgery. *Neurosurgery* 1992;31:774-778; discussion 778-779.

344. Park AH, Stankiewicz JA, Chow J, Azar-Kia B. A protocol for management of a catastrophic complication of functional endoscopic sinus surgery: internal carotid artery injury. *Am J Rhinol* 1998;12:153-158.

345. Biswas D, Daudia A, Jones NS, McConachie NS. Profuse epistaxis following sphenoid surgery: a ruptured carotid artery pseudoaneurysm and its management. *J Laryngol Otol* 2009;123:692-694.

346. Dolenc VV, Lipovsek M, Slokan S. Traumatic aneurysm and carotid-cavernous fistula following transsphenoidal approach to a pituitary adenoma: treatment by transcranial operation. *Br J Neurosurg* 1999;13:185-188.

347. Cappabianca P, Esposito F, Esposito I, Cavallo LM, Leone CA. Use of a thrombin-gelatin haemostatic matrix in endoscopic endonasal extended approaches: technical note. *Acta Neurochir (Wien)* 2009;151:69-77; discussion 77.

348. Vanninen RL, Manninen HI, Rinne J. Intrasellar latrogenic carotid pseudoaneurysm: endovascular treatment with a polytetrafluoroethylene-covered stent. *Cardiovasc Intervent Radiol* 2003;26:298-301.

349. Zada G, Kelly DF, Cohan P, Wang C, Swerdloff R. Endonasal transsphenoidal approach for pituitary adenomas and other sellar lesions: an assessment of efficacy, safety, and patient impressions. *J Neurosurg* 2003;98:350-358.

350. Dusick JR, Esposito F, Malkasian D, Kelly DF. Avoidance of carotid artery injuries in transsphenoidal surgery with the Doppler probe and micro-hook blades. *Neurosurgery* 2007;60:322-328; discussion 328-329.

351. Oskouian RJ, Kelly DF, Laws ER, Jr. Vascular injury and transsphenoidal surgery. *Front Horm Res* 2006;34:256-278.

352. Ghatge SB, Modi DB. Treatment of ruptured ICA during transsphenoidal surgery. Two different endovascular strategies in two cases. *Interv Neuroradiol*;16:31-37.

353. Bavinzski G, Killer M, Knosp E, Ferraz-Leite H, Gruber A, Richling B. False aneurysms of the intracavernous carotid artery--report of 7 cases. *Acta Neurochir (Wien)* 1997;139:37-43.

354. Cathelinaud O, Bizeau A, Rimbot A, Arteaga C, Verdalle P. Endoscopic endonasal surgery complication: new methods of intracavernous internal carotid artery injury treatment. *Rev Laryngol Otol Rhinol (Bord)* 2008;129:305-308.

355. de Souza JM, Domingues FS, Espinosa G, Gadelha M. Cavernous carotid artery pseudo-aneurysm treated by stenting in acromegalic patient. *Arq Neuropsiquiatr* 2003;61:459-462.

356. Segal DH, Sen C, Bederson JBet al. Predictive value of balloon test occlusion of the internal carotid artery. *Skull Base Surg* 1995;5:97-107.

357. Chen D, Concus AP, Halbach VV, Cheung SW. Epistaxis originating from traumatic pseudoaneurysm of the internal carotid artery: diagnosis and endovascular therapy. *Laryngoscope* 1998;108:326-331.

358. Park YS, Jung JY, Ahn JY, Kim DJ, Kim SH. Emergency endovascular stent graft and coil placement for internal carotid artery injury during transsphenoidal surgery. *Surg Neurol* 2009;72:741-746.

359. Higashida RT, Halbach VV, Tsai FYet al. Interventional neurovascular treatment of traumatic carotid and vertebral artery lesions: results in 234 cases. *AJR Am J Roentgenol* 1989;153:577-582.

360. Higashida RT, Halbach VV, Dowd Cet al. Endovascular detachable balloon embolization therapy of cavernous carotid artery aneurysms: results in 87 cases. *J Neurosurg* 1990;72:857-863.

361. Parodi JC. Endovascular repair of abdominal aortic aneurysms and other arterial lesions. *J Vasc Surg* 1995;21:549-555; discussion 556-547.

362. Kadyrov NA, Friedman JA, Nichols DA, Cohen-Gadol AA, Link MJ, Piepgras DG. Endovascular treatment of an internal carotid artery pseudoaneurysm following transsphenoidal surgery. Case report. *J Neurosurg* 2002;96:624-627.

363. Wholey MH, Jarmolowski CR, Eles G, Levy D, Buecthel J. Endovascular stents for carotid artery occlusive disease. *J Endovasc Surg* 1997;4:326-338.

364. Leung GK, Auyeung KM, Lui WM, Fan YW. Emergency placement of a self-expandable covered stent for carotid artery injury during trans-sphenoidal surgery. *Br J Neurosurg* 2006;20:55-57.

365. Kalapatapu VR, Shelton KR, Ali AT, Moursi MM, Eidt JF. Pseudoaneurysm: a review. *Curr Treat Options Cardiovasc Med* 2008;10:173-183.

366. Fox AJ, Vinuela F, Pelz DM. Results of the international extracranial/intracranial arterial bypass: implications for radiologists. *AJNR Am J Neuroradiol* 1986;7:736-737.

367. Kinugasa K, Mandai S, Tsuchida S, Kamata I, Ohmoto T. Direct thrombosis of a pseudoaneurysm after obliteration of a carotid-cavernous fistula with cellulose acetate polymer: technical case report. *Neurosurgery* 1994;35:755-759; discussion 759-760.

368. Crow WN, Scott BA, Guinto FC, Jr.et al. Massive epistaxis due to pseudoaneurysm. Treated with detachable balloons. *Arch Otolaryngol Head Neck Surg* 1992;118:321-324.

369. Fox AJ, Vinuela F, Pelz DMet al. Use of detachable balloons for proximal artery occlusion in the treatment of unclippable cerebral aneurysms. *J Neurosurg* 1987;66:40-46.

370. Higashida RT, Halbach VV, Dowd CF, Barnwell SL, Hieshima GB. Intracranial aneurysms: interventional neurovascular treatment with detachable balloons--results in 215 cases. *Radiology* 1991;178:663-670.

371. Lempert TE, Halbach VV, Higashida RTet al. Endovascular treatment of pseudoaneurysms with electrolytically detachable coils. *AJNR Am J Neuroradiol* 1998;19:907-911.

372. Pigott TJ, Holland IM, Punt JA. Carotico-cavernous fistula after trans-sphenoidal hypophysectomy. *Br J Neurosurg* 1989;3:613-616.

373. Cappabianca P, Briganti F, Cavallo LM, de Divitiis E. Pseudoaneurysm of the intracavernous carotid artery following endoscopic endonasal transsphenoidal surgery, treated by endovascular approach. *Acta Neurochir (Wien)* 2001;143:95-96.

374. Fatemi N, Dusick JR, de Paiva Neto MA, Kelly DF. The endonasal microscopic approach for pituitary adenomas and other parasellar tumors: a 10-year experience. *Neurosurgery* 2008;63:244-256; discussion 256.

375. Zhou WG, Yang ZQ. Complications of transsphenoidal surgery for sellar region: intracranial vessel injury. *Chin Med J (Engl)* 2009;122:1154-1156.

376. Lister JR, Sypert GW. Traumatic false aneurysm and carotid-cavernous fistula: a complication of sphenoidotomy. *Neurosurgery* 1979;5:473-475.

377. Maniglia AJ. Fatal and major complications secondary to nasal and sinus surgery. *Laryngoscope* 1989;99:276-283.

378. Weber R, Draf W, Keerl R, Schick B, Saha A. Endonasal microendoscopic pansinusoperation in chronic sinusitis. II. Results and complications. *Am J Otolaryngol* 1997;18:247-253.

379. Reddy K, Lesiuk H, West M, Fewer D. False aneurysm of the cavernous carotid artery: a complication of transsphenoidal surgery. *Surg Neurol* 1990;33:142-145.

380. Isenberg SF, Scott JA. Management of massive hemorrhage during endoscopic sinus surgery. *Otolaryngol Head Neck Surg* 1994;111:134-136.

381. Hudgins PA, Browning DG, Gallups Jet al. Endoscopic paranasal sinus surgery: radiographic evaluation of severe complications. *AJNR Am J Neuroradiol* 1992;13:1161-1167.

382. Wigand ME, Hosemann W. Paranasal sinus surgery. *Journal of Otolaryngology* 1991;20:386-390.

383. Keerl R, Weber R, Drees G, Draf W. [Individual learning curves with reference to endonasal micro-endoscopic pan-sinus operation]. *Laryngorhinootologie* 1996;75:338-343.

384. Charalampaki P, Ayyad A, Kockro RA, Perneczky A. Surgical complications after endoscopic transsphenoidal pituitary surgery. *J Clin Neurosci* 2009;16:786-789.

385. Crowley RW, Dumont AS, Jane JA, Jr. Bilateral intracavernous carotid artery pseudoaneurysms as a result of sellar reconstruction during the transsphenoidal resection of a pituitary macroadenoma: case report. *Minim Invasive Neurosurg* 2009;52:44-48.

386. Ciceri EF, Regna-Gladin C, Erbetta Aet al. Iatrogenic intracranial pseudoaneurysms: neuroradiological and therapeutical considerations, including endovascular options. *Neurol Sci* 2006;27:317-322.

387. Paullus WS, Norwood CW, Morgan HW. False aneurysm of the cavernous carotid artery and progressive external ophthalmoplegia after transsphenoidal hypophysectomy. Case report. *J Neurosurg* 1979;51:707-709.

388. Cabezudo JM, Carrillo R, Vaquero J, Areitio E, Martinez R. Intracavernous aneurysm of the carotid artery following transsphenoidal surgery. Case report. *J Neurosurg* 1981;54:118-121.

389. Wilson CB, Dempsey LC. Transsphenoidal microsurgical removal of 250 pituitary adenomas. *J Neurosurg* 1978;48:13-22.

390. Schwaitzberg SD, Chan MW, Cole DJet al. Comparison of poly-N-acetyl glucosamine with commercially available topical hemostats for achieving hemostasis in coagulopathic models of splenic hemorrhage. *The Journal of trauma* 2004;57:S29-32.

391. Chan MW, Schwaitzberg SD, Demcheva M, Vournakis J, Finkielsztein S, Connolly RJ. Comparison of poly-N-acetyl glucosamine (P-GlcNAc) with absorbable collagen (Actifoam), and fibrin sealant (Bolheal) for achieving hemostasis in a swine model of splenic hemorrhage. *The Journal of trauma* 2000;48:454-457; discussion 457-458.

392. Pusateri AE, Modrow HE, Harris RAet al. Advanced hemostatic dressing development program: animal model selection criteria and results of a study of nine hemostatic dressings in a model of severe large venous hemorrhage and hepatic injury in Swine. *The Journal of trauma* 2003;55:518-526.

393. Pusateri AE, McCarthy SJ, Gregory KWet al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. *The Journal of trauma* 2003;54:177-182.

394. Sondeen JL, Pusateri AE, Coppes VG, Gaddy CE, Holcomb JB. Comparison of 10 different hemostatic dressings in an aortic injury. *The Journal of trauma* 2003;54:280-285.

395. Kheirabadi BS, Acheson EM, Deguzman Ret al. Hemostatic efficacy of two advanced dressings in an aortic hemorrhage model in Swine. *The Journal of trauma* 2005;59:25-34; discussion 34-25.

396. Alam HB, Uy GB, Miller Det al. Comparative analysis of hemostatic agents in a swine model of lethal groin injury. *The Journal of trauma* 2003;54:1077-1082.

397. Alam HB, Chen Z, Jaskille Aet al. Application of a zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in Swine. *The Journal of trauma* 2004;56:974-983.

398. Acheson EM, Kheirabadi BS, Deguzman R, Dick EJ, Jr., Holcomb JB. Comparison of hemorrhage control agents applied to lethal extremity arterial hemorrhages in swine. *The Journal of trauma* 2005;59:865-874; discussion 874-865.

399. Ward KR, Tiba MH, Holbert WHet al. Comparison of a new hemostatic agent to current combat hemostatic agents in a Swine model of lethal extremity arterial hemorrhage. *The Journal of trauma* 2007;63:276-283; discussion 283-274.

400. Bellany RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med* 1984;149:55-62.

401. Holcomb JB. Clinical outcomes from the war: introduction. *J Trauma* 2008;64:S1.

402. Mabry RL, Holcomb JB, Baker AMet al. United States Army Rangers in Somalia: an analysis of combat casualties on an urban battlefield. *J Trauma* 2000;49:515-528; discussion 528-519.

403. Holcomb J, MacPhee M, Hetz S, Harris R, Pusateri A, Hess J. Efficacy of a dry fibrin sealant dressing for hemorrhage control after ballistic injury. *Arch Surg* 1998;133:32-35.

404. Holcomb JB, Pusateri AE, Harris RAet al. Effect of dry fibrin sealant dressings versus gauze packing on blood loss in grade V liver injuries in resuscitated swine. *J Trauma* 1999;46:49-57.

405. Holcomb JB, Pusateri AE, Harris RAet al. Dry fibrin sealant dressings reduce blood loss, resuscitation volume, and improve survival in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 1999;47:233-240; discussion 240-232.

406. Wright JK, Kalns J, Wolf EAet al. Thermal injury resulting from application of a granular mineral hemostatic agent. *The Journal of trauma* 2004;57:224-230.

407. Pusateri AE, Delgado AV, Dick EJ, Jr., Martinez RS, Holcomb JB, Ryan KL. Application of a granular mineral-based hemostatic agent (QuikClot) to reduce blood loss after grade V liver injury in swine. *The Journal of trauma* 2004;57:555-562; discussion 562.

408. Thatte HS, Zagarins SE, Amiji M, Khuri SF. Poly-N-acetyl glucosamine-mediated red blood cell interactions. *The Journal of trauma* 2004;57:S7-12.

409. Thatte HS, Zagarins S, Khuri SF, Fischer TH. Mechanisms of poly-N-acetyl glucosamine polymer-mediated hemostasis: platelet interactions. *The Journal of trauma* 2004;57:S13-21.

410. Favuzza J, Hechtman HB. Hemostasis in the absence of clotting factors. *The Journal of trauma* 2004;57:S42-44.

411. Jewelewicz DD, Cohn SM, Crookes BA, Proctor KG. Modified rapid deployment hemostat bandage reduces blood loss and mortality in coagulopathic pigs with severe liver injury. *The Journal of trauma* 2003;55:275-280; discussion 280-271.

412. Englehart MS, Cho SD, Tieu BHet al. A novel highly porous silica and chitosan-based hemostatic dressing is superior to HemCon and gauze sponges. *The Journal of trauma* 2008;65:884-890; discussion 890-882.

413. Kinney WC, Benninger MS. Assessment of quality of life among patients with sinonasal disease as determined by an Internet survey base on the Rhinosinusitis Disability Index. *Ear Nose Throat J* 2007;86:484-486.

414. Valentine R, Wormald PJ, Sindwani R. Advances in absorbable biomaterials and nasal packing. *Otolaryngol Clin North Am* 2009;42:813-828, ix.

415. Kurita K. Chitin and chitosan: functional biopolymers from marine crustaceans. *Marine biotechnology (New York, N.Y* 2006;8:203-226.

416. Athanasiadis T. The Effect of Topical Antifibrinolytics and a Novel Chitosan Gel on Haemostasis and Wound Healing in Endoscopic Sinus Surgery *Department of Surgery*. Adelaide: University of Adelaide, 2009:186.

417. Dorion RP, Hamati HF, Landis B, Frey C, Heydt D, Carey D. Risk and clinical significance of developing antibodies induced by topical thrombin preparations. *Archives of pathology & laboratory medicine* 1998;122:887-894.

418. Flaherty MJ, Henderson R, Wener MH. Iatrogenic immunization with bovine thrombin: a mechanism for prolonged thrombin times after surgery. *Ann Intern Med* 1989;111:631-634.

419. Yang J, Tian F, Wang Z, Wang Q, Zeng YJ, Chen SQ. Effect of chitosan molecular weight and deacetylation degree on hemostasis. *J Biomed Mater Res B Appl Biomater* 2008;84:131-137.

420. Klokkevold PR, Fukayama H, Sung EC, Bertolami CN. The effect of chitosan (poly-N-acetyl glucosamine) on lingual hemostasis in heparinized rabbits. *J Oral Maxillofac Surg* 1999;57:49-52.

421. Klokkevold PR, Lew DS, Ellis DG, Bertolami CN. Effect of chitosan on lingual hemostasis in rabbits. *J Oral Maxillofac Surg* 1991;49:858-863.

422. Chou TC, Fu E, Wu CJ, Yeh JH. Chitosan enhances platelet adhesion and aggregation. *Biochem Biophys Res Commun* 2003;302:480-483.

423. Brandenberg G, Leibrock LG, Shuman R, Malette WG, Quigley H. Chitosan: a new topical hemostatic agent for diffuse capillary bleeding in brain tissue. *Neurosurgery* 1984;15:9-13.

424. Smith CJ, Vournakis JN, Demcheva M, Fischer TH. Differential effect of materials for surface hemostasis on red blood cell morphology. *Microscopy research and technique* 2008;71:721-729.

425. Cohen BJ, Loew FM. Laboratory Animal Medicine: Historical Perspectives in Laboratory Animal Medicine. In: Fox JG, Cohen BJ, Loew FM, eds. Orlando, Florida: Academic Press, Inc., 1984.

426. Mehta RP, Cueva RA, Brown JDet al. What's new in skull base medicine and surgery? Skull Base Committee Report. *Otolaryngol Head Neck Surg* 2006;135:620-630.

427. Valentine R, Wormald PJ. Controlling the surgical field during a large endoscopic vascular injury. *Laryngoscope* 2011;121:562-566.