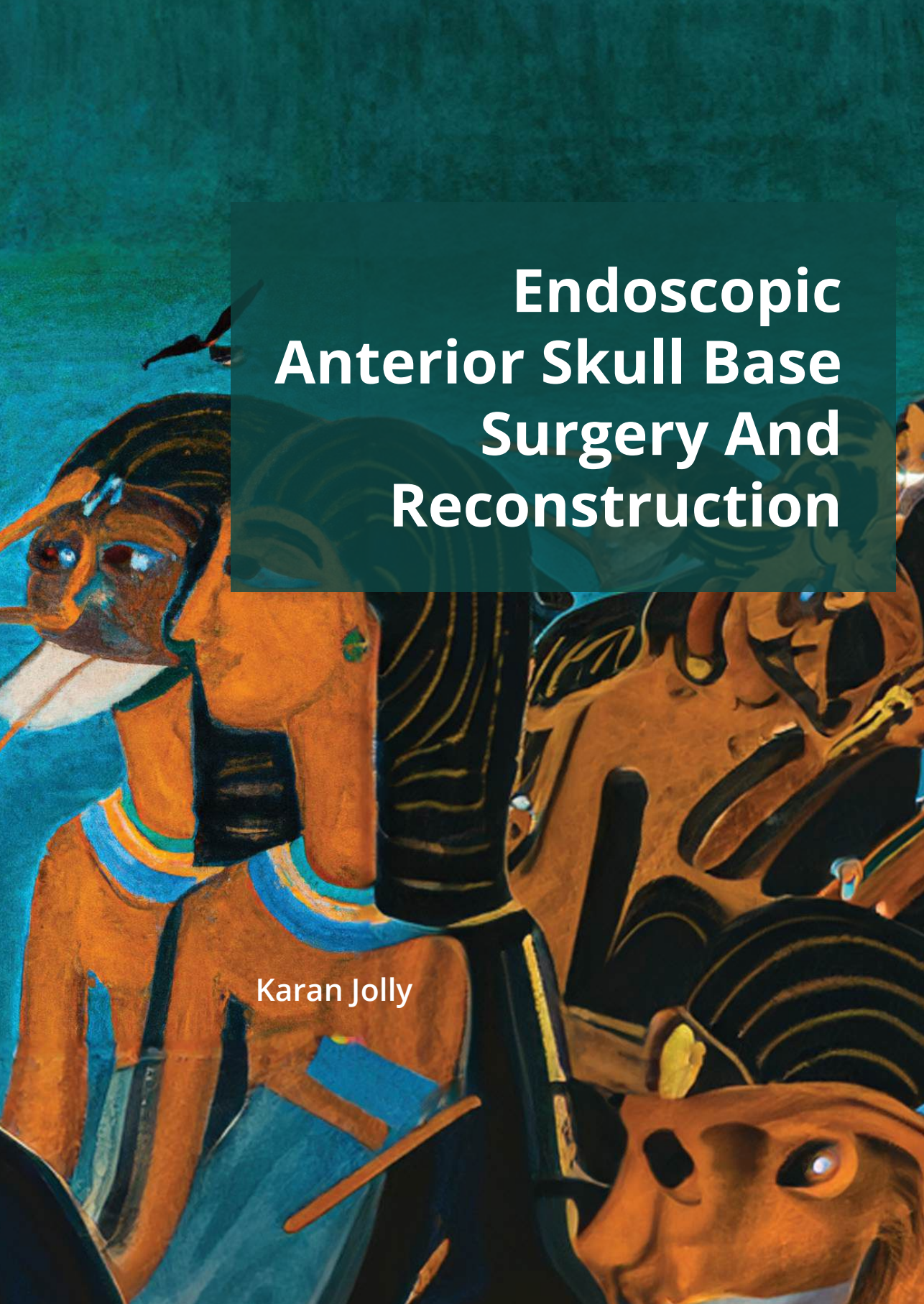

Endoscopic Anterior Skull Base Surgery And Reconstruction

Karan Jolly

ENDOSCOPIC ANTERIOR SKULL BASE SURGERY AND RECONSTRUCTION

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Karan Jolly
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by

Karan Jolly

born on 27 August 1988

Supervisor
Prof. M.K.S. Hol

Co-supervisors
Dr. S.K. Ahmed
Dr. A.G.W. Korsten-Meijer

Assessment Committee
Prof. Y. Temel
Prof. M.J.H. Witjes
Prof. J.M.C. van Dijk

Contents

General introduction and thesis outline

The evolution of endoscopic and minimally invasive surgery over the years has been nothing short of remarkable. Across all surgical specialities, including rhinology, advancements in technology have allowed clinicians to push the frontiers of endoscopic surgery to where it is now. Specific to nasal surgery, this has meant an evolution from basic nasal polyp surgery where it started, to complex cranial base pathologies with orbital and intracranial involvement.

Understanding of the paranasal sinuses anatomy predates to the ancient Egyptian era (3700BC to 1500BC), where mummification rituals were performed routinely, extracting brain tissue through the nostrils. The progressive awareness of sinonasal anatomy of the centuries allowed for evolution of surgical techniques and approaches, with Louis Lamoier gaining access to the maxillary antrum through the oral cavity in 1768 (3,4). The concept of sinonasal inflammatory disease was already prevalent and drainage of paranasal sinuses for sinusitis, predominantly maxillary, started to happen in the 18th and 19th century both transorally and endonasally via the natural ostium and inferior meatus (5). It wasn't however till 1901 when the first attempt of nasal endoscopy was made by Hirschmann, using a modified cystoscope (6). Following from this, the first endoscopic assisted procedure was performed by Reichert through an existing oroantral fistula, and this was the beginning of what we now know to be endoscopic sinus surgery (7). In 1925, Maltz promoted the use of nasal endoscopes for diagnostic evaluation of the sinonasal cavitied and coined this 'sinoscopy' (8,9).

From here, there were several major advancements that were responsible for the evolution of sinus surgery as we know it today, allowing for a better understanding of sinus anatomy and subsequently better surgical approaches to sinonasal pathologies and beyond. This thesis will discuss the evolution of sinus surgery to endoscopic anterior skull base surgery as we know it today and the major developments that have allowed this to happen.

Endoscopic technological advancements

The first major breakthrough wasn't till the 1960's, when Professor Harold K Hopkins developed the rigid optic endoscope system, allowing for more detailed visualisation of the sinonasal anatomy (9,10). The new telescope design allowed for far superior light penetration and significantly improved optics (10). This allowed for Professor Walter Messerklinger and Professor Heinze Stammberger in the 1970s to better understand the sinonasal physiology and anatomy of the lateral nasal wall and eventually beyond into other paranasal sinuses. Their work continued to inspire many like Professor David Kennedy, and together

continued to publish many landmark papers on nasal endoscopy, helping define 'Functional Endoscopic Sinus Surgery' as we know it today (11,12,13,14). This was coupled with the second major breakthrough around the same era with the miniaturisation of cameras. At a similar time when telescopes were being made smaller, a similar advancement was occurring with cameras, allowing for cameras to be attached to the eyepiece of telescopes and better visualisation by not just the operator but all present in the room. This was fast adopted by many surgical specialities and it became the norm to operate off a screen as camera technology continued to exponentially improve (15). Not only was this ergonomically advantageous, but it also allowed for easier instrumentation of the sinonasal cavities and far better training and education opportunities at a stage where sinus surgery was in its infancy.

Radiology and adjuncts

The first Computed Tomography (CT) scanner was developed in the 1970s in London by Sir Godfrey Hounsfield and was very fast to be adopted worldwide (15,16). The advent of CT scanning was an additional huge breakthrough, revolutionising the clinician's ability to better understand the sinonasal anatomy and pathology. CT imaging became the road map to unlock the complex anatomy of the ethmoid sinus and its adjacent dependant sinuses. Over the years, the advancements towards high resolution CT imaging and rapid scanning times further facilitated assessment of sinus disease, whilst providing critical detail required for preoperative planning. Till date, CT scanning remains the predominant imaging modality in sinus/skull base surgery due to its better ability to define bone. Key anatomical details provided by CT imaging include but not limited to the depth and slope of the skull base, pneumatisation variance of the sinuses (particularly the frontal and sphenoid), dehiscence of anterior ethmoidal arteries and dehiscence of the orbit or skull base. Additionally, triplanar imaging allowed for a better understanding of complex pathways eg the frontal sinus drainage pathway, allowing us to better instrument and access these air spaces. The key to approaching the skull base and its associated pathologies is the ability to successfully navigate through the paranasal sinuses safely, and CT imaging allowed for a better understanding of how to achieve this (16).

Over the last two decades, Image Guidance Systems (IGS) gained popularity within sinus surgery due to the rigid bony anatomy of the sinuses. Initial attempts at image guidance systems emerged in the 1980's and were very bulky and difficult to setup, requiring head fixation (17). Subsequent early electromagnetic systems were heavily inaccurate due to significant field distortion, and as technology improved, so did the accuracy of these systems (18). Modern day systems we use today are less invasive and easier to setup, offering a range of traceable instruments. Whilst CT remains the preferred

modality for navigation devices, owed to its fixed bony anatomy, modern systems allow registration of Magnetic Resonance Imaging (MRI) imaging also with an option to merge both CT and MRI images for better soft tissue delineation (18-22). Current navigation systems use electromagnetic or optical signals to register CT/MRI imaging to the patient's head and localise instruments in a surgical field (23,24). Preference of which system to use often comes down to availability at the hospital centre and user preference. Although there is no evidence supporting reduced complication rates, image guidance systems have been shown to increase safety, especially with complex expanded cases, revision cases or approaches to skull base pathologies (24-26). Despite the benefits of IGS, access to these expensive systems may be difficult and as with all technology, they are not without user error and technical registration issues and do not replace sound anatomical awareness and detailed radiological assessment prior to any case. Future endeavours in IGS includes the use of augmented reality to help highlight key pre-operative findings in real time on the surgical screen whilst the surgeon operates. This may further improve safety of complex endoscopic procedures; however it seems the technology is currently still in its infancy (18,27,28).

Instrumentation

Instruments over the years have seen a significant evolution, which In turn has enabled to achieve more with respects to sinus surgery and skull base surgery. In addition to the Hopkins rod and improved optics, better hand tools and powered instruments have allowed us to be more complete with our endoscopic endonasal approaches, enabling for wider and more comprehensive expanded approaches.

Initially instruments were developed purely to grasp sinonasal tissue, which in turn lead to denuded bone and poorer healing due to osteitis and neo-osteogenesis (29). Over the years, finer through cutting hand tools were developed allowing for mucosal preservation, better tissue handling and improved post-operative outcomes (29).

Early sphenoid surgery was performed by in-fracturing bony walls with little emphasis of natural drainage pathways. This often lead to mucosal trauma but also had a significant risk of major vascular and skull base injury (30). The development of through cutting instruments and mushroom punches allowed more controlled widening of the natural sphenoid os. The same applies from frontal recess surgery, where angled through cutting instruments and forward and back cutting instruments allowed for comprehensive frontal sinusotomy whilst preserving native mucosa, resulting in less stenosis and scarring (29,30).

The microdebrider was originally developed for orthopaedic cases for cartilage shaving, and then quickly found itself being used for sinus surgery. Over the years the technology has progressed with respects to speed, angulation, blade cutting ability and suction, allowing for more controlled tissue debridement (30,31,32). Its use does not come without risks, however it serves to be arguably the single most versatile and useful instrument allowing for comprehensive sinus cavity openings. In addition, advancements in high powdered drills in the last 10-15 years have enabled for expanded endonasal approaches to the frontal sinus and also the skull base. There are a variety of sizes and angulations drills come in, with fine high-speed drills being used for controlled skull base osteotomy to access the anterior cranial fossa and skull base tumours. The evolution of high-powered instruments over the years has been hugely influential in the endoscopic skull base practice we see today (32).

Endoscopic Skull base surgery

With advancements in endoscopic instrumentation and improved anatomical awareness, indications for endoscopic endonasal approaches expanded to include skull base and orbital pathologies.

In 1907, Schloffer was the first to report successful removal of a pituitary tumour through the nose via a transsphenoidal approach (33). This involved an external nasolabial approach with significant cosmetic deformity and scarring post-operatively. Soon after in 1910 Oskar Hirsch described the endonasal transeptal transsphenoidal approach, which was adopted by many including Harvey Cushing who later modified the technique with a sublabial approach (34,35). All these operations were done with a head lamp thus poor visualisation resulted in high CSF leak and haemorrhage rates with a mortality of 5.6% and some surgeons reverted to transcranial approaches for such pituitary tumours. It wasn't until 1967 when Jules Hardy performed the first microscopic pituitary tumour excision using a transsphenoidal approach (36). Technological advancements, such as the microscope and microscopic instruments, enabled surgeons to innovate novel approaches to the skull base in this era, which was soon to be superseded by the creation of the Hopkins rod. The endoscope allowed us to introduce a point source of light with magnified images through smaller surgical corridors, up to the skull base allowing for better optics (37-39).

The first attempts of endoscopic malignant sinonasal tumour resections and orbital decompressions took place in the 1980's with one of the largest limiting factors to endoscopic skull base approaches being the ability to repair post-surgical defects. The ability to take on more complex skull base pathologies was hugely dependent on the success of endoscopic CSF leak repairs (46,47). The first endoscopic pituitary cases were performed in the 1990's which was

then popularised by Jho and Carrau from the University of Pittsburgh in 1996, enabling for better tumour resection outcomes with significantly reduced morbidity (18,40,41). From there on, more expanded endonasal corridors were developed to tackle more complex pathologies via transcribiform, transplanum and transclival approaches, with improved reconstruction options allowing for this to happen. Some of these approaches were first outlined and published by Kassam and Snyderman at the University of Pittsburgh, who demonstrated expanded bilateral endonasal approaches to tackle complex lesions from the Crista galli to C-2 vertebrae, whilst adopting a team approach (42-44). By doing so, they furthered our understanding of the endoscopic anatomical corridors one can take to the skull base and developed instruments that enabled us to tackle complex pathologies through these approaches (45).

Anterior of the skull base

The midline skull base anatomically extends from the posterior table of the frontal sinus, posteriorly and inferiorly towards foramen magnum. Endoscopic approaches to these areas through the paranasal sinuses confer the advantage of direct trajectory of access, no need for no brain retraction and no traversing of major neurovascular structures (48). Broadly speaking the midline skull base can be divided into 3 segments: Anterior from frontal sinus to posterior ethmoid artery, middle the sphenoid sinus cavity and posterior from dorsum sellae to the cranio-vertebral junction.

The anterior skull base corresponds to the roof of the cavities with the septum in the middle. This rectangular space is bounded laterally by the lamina papyracea, posteriorly by planum sphenoidale and anteriorly by the frontal air spaces (49). The roof is formed laterally by the fovea ethmoidale with the olfactory clefts and cribriform plates from either side joining in the midline with the nasal septum. The arterial supply of this anatomic space is from the anterior and posterior ethmoid artery, both branches of the ophthalmic artery (48). Lateral cranial osteotomies gives access to anterior cranial fossa lesions through this corridor.

The middle skull base corresponds to the posterior and lateral walls of the sphenoid sinus. Superiorly the planum extends posteriorly to form the sellae tuberculum beneath which in the midline is the sella, housing the pituitary gland (50). Lateral to the sella are bony protuberances of the Internal Carotid Artery with the optic nerve superior to this. Between the two structures is the lateral Optico-Carotid Recess (OCR) which correlates to the anterior clinoid process. The corridor between the ICAs gives access to sella and suprasellar pathologies extending into the prechiasmatic or post chiasmatic spaces.

Lastly, the posterior midline skull base corresponds to the face of the clivus, extending from the dorsum sellae down towards the cranio-cervical junction. The clivus can further be divided into upper, middle and lower thirds, bounded laterally in the upper third by the paraclival segment of the ICA (51). Removal of the soft tissue of the nasopharynx and the floor of the sphenoid gives access to the lower portion of the clivus, extending down towards the atlanto-axial junction. This corridor gives great access to midline ventral lesions in close relation the brainstem and petrous apex, such as clival chordomas and chondrosarcomas (52).

Scope and outline of this thesis

The specialty of Endoscopic Anterior Skull Base surgery has rapidly evolved over the last 15 years because of several technical advancements highlighted above. This has been partly down to advanced surgical understanding and instrumentation but largely due to advancements in reconstruction methods with the main outcome measure of post-operative CSF leak rates.

In **Chapter 2** we will look at the trend of endoscopic sinus procedures of the last decade and how there has been a growth in minimally invasive procedures.

Chapter 3 and 4 will explore how our improved anatomical understanding of the skull base alongside more detailed imaging and Image Guidance Systems have enabled us to navigate around the complex anatomy of the skull base whilst reducing morbidity and improving overall patient outcomes.

The final 7 chapters (**chapters 5.1-5.7**) will explore different aspects of skull base reconstruction which have really allowed for the growth of Anterior Skull Base Surgery as we know it today. Without sound reconstruction and repair of skull base large defects, the morbidity associated with CSF leaks from large endoscopic approaches would not justify the use of endoscopic approaches, and a greater understanding of this topic has really allowed us to be bolder with our resections.

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2

The evolution of sinus surgery in England in the last decade – an observational study

Keshav Kumar Gupta
Karan Jolly
Navdeep Bhamra
Max Sallis Osborne
Shahzada Khuram Ahmed

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Abstract

Introduction

Sinus surgery has seen significant changes over the years with advancements in instruments, endoscopes and imaging. This study aimed to use HES data to review the total number of sinus related procedures performed in both adults and children across England and identify whether there were any trends across the study period. We predicted an increase in endoscopic sinus procedures with a decline in open approaches to the paranasal sinuses.

Methods

Data from Hospital Episode Statistics (HES) was extracted for the years 2010-2019. The operative (OPCS-4) codes relevant to all sinus procedures between E12.1 to E17.9 were analysed. After examination of overall sinus related procedures, further subgroup analysis was performed with regards to open or endoscopic techniques.

Results

The total number of sinus procedures performed between 2010-2019 was 89,495. There was an increase in endoscopic surgeries by 21.1% and a decrease of open surgeries 35.3% during this time. There was an overall increase in maxillary, frontal and sphenoid sinus procedures, with a decrease in ethmoid sinus and lateral rhinotomy operations. There was an increase in the proportion of endoscopic cases overall by 5.7% and for all sinuses individually.

Conclusion

Overall, we see an increase in sinus surgery over the last 9 years from 2010 to 2019. These findings are in keeping with our initial hypotheses. Although our data set is limited by coding, and lack of patient factors, it represents most, if not all, of the data in England over a large study period. It is therefore useful to add to previous studies when demonstrating the increasing popularity of endoscopic sinus surgery over open procedures.

Introduction

Endoscopic sinus surgery has evolved massively from the first attempt made at nasal endoscopy in 1901[1]. Creation of the Hopkins rod in the 1960s allowed for more detailed examination of the paranasal sinuses which allowed improved understanding of the anatomy and drainage pathways[2]. Since then, there have been marked improvements in surgical instruments and imaging. Development of intranasal, fine, through-cutting instruments allowed bone and mucosa to be operated on with less mucosal stripping and subsequent reduction in post-operative scarring, chronic inflammation and neo-osteogenesis[3]. There has been a similar improvement in microdebrider and telescopic technology including high-definition screens and 4K cameras.

The adaptation of CT guided navigation to rhinology has also improved pre-operative planning and allowed a greater understanding of sinonasal anatomy. This has enabled rhinologists and even anterior skull base surgeons to tackle more complex sinus pathology. Modern imaging systems are minimally intrusive and allow for rapid feedback from trackable instruments[4]. Furthermore, since the introduction of image guidance in the 1990s, it has become more accessible to a wider range of hospitals with many surveyed surgeons reporting access to the technology[5].

The Hospital Episode Statistics (HES) database is maintained by the Department of Health and contains details of all procedures performed at NHS hospitals across England[6]. While private hospitals are not included, private patients treated in NHS hospitals are. Each surgical procedure and its related statistics can be isolated for analysis by selecting its unique four-character OPCS-4 code.

This study aimed to use HES data to review the total number of sinus related procedures performed in both adults and children across England and identify whether there were any trends across the study period. As a result of the numerous developments related to sinus surgery, we predicted an increase in endoscopic sinus procedures with a decline in open approaches to the paranasal sinuses.

Method

"Main procedures and intervention" data from HES was extracted for relevant sinus surgery between 2010-2019 using MS Excel version 16.31. The operative (OPCS-4) codes relevant to all sinus procedures between E12.1 to E17.9 were analysed. After examination of overall sinus related procedures, further subgroup analysis was performed with regards to open or endoscopic

techniques. Procedures coded as "other specified operation of" or "unspecified operation of" were excluded due to uncertainty of the approach used and the inability to further scrutinise this within the HES database.

Statistical analysis was conducted and graphs were produced using MS Excel version 16.31.

Results

The total number of sinus procedures performed in the England between 2010-2019 was 89 495. There was an increase over the decade of 6.94% from 9205 cases in 2010-11 to 9844 in 2018-19. The maximum number of cases during the study period were performed in 2016-17 with 10,714 cases (an increase of 16.4% from 2010-11). Following exclusion of procedures with unclear coding (OPCS-4 codes E13.8 'other specified other operations on maxillary antrum', E14.6 'trephine of frontal sinus', E17.8 'other specified operations on unspecified nasal sinus' and E17.9 'unspecified operations on unspecified nasal sinus'), 4543 cases were excluded, leaving 84 952 procedures included in the analysis. This included 71 518 (84.2%) endoscopic and 8054 (9.5%) open procedures as well as 5380 (6.3%) procedures involving nasal sinus biopsy/excision.

The number of endoscopic cases increased from 6772 in 2010 to 8201 in 2019. For open cases, there was a decrease from 1026 in 2010 to 664 in 2019. This represented a percentage change of +21.1% and -35.3% respectively. The proportion of endoscopic cases making up the total number of cases increased from 86.8% in 2010 to its highest proportion of 92.5% in 2019 (an absolute increase of 5.7%). These findings are summarised in figure 1.

The breakdown of total procedures performed with respect to each specific sinus is summarised in Table 1. There was an overall increase in maxillary, frontal and sphenoid sinus procedures as well as nasal sinus biopsy/excision procedures over the last 9 years, with a decrease in ethmoid sinus operations and lateral rhinotomy to access the sinuses. Despite this, there was an increase in the proportion of endoscopic procedures for each maxillary, ethmoid and frontal sinus procedures.

Analysis of the sinus specific procedures in more detail reveals a general increase in endoscopic maxillary sinus, frontal sinus and sphenoid sinus procedures. The number of maxillary sinus cases increased by 1393 cases (3569 in 2010 to 4962 in 2019). This represented a percentage change of +39.0% and an overall increase in the proportion of endoscopic procedures of 6.6%.

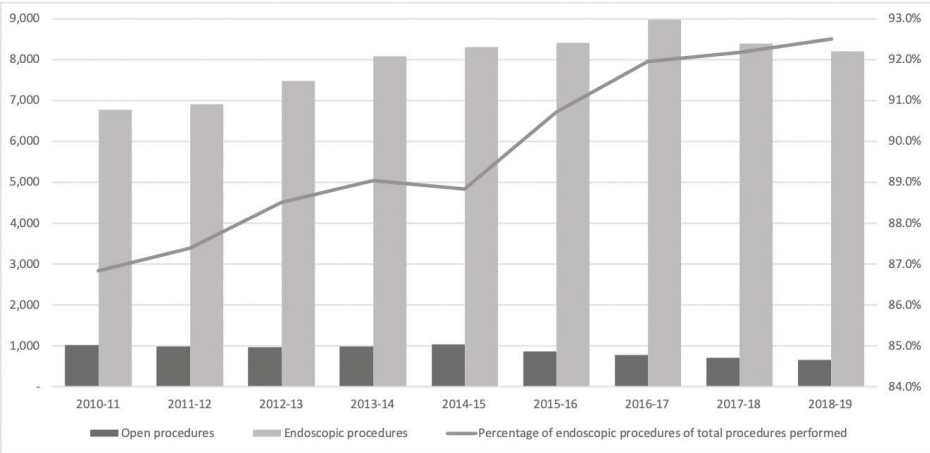

Figure 1. Open and endoscopic procedures and the change in percentage of endoscopic cases performed between 2010-2019

	Maxillary sinus	Ethmoid sinus	Frontal sinus	Sphenoid sinus	Lateral rhinotomy into nasal sinus	Nasal sinus biopsy/ excision
2010-11	3569	3181	786	220	42	598
2011-12	3693	3061	903	228	16	659
2012-13	3916	3191	1111	212	26	565
2013-14	4193	3245	1358	266	19	545
2014-15	4350	3366	1287	327	14	538
2015-16	4497	3186	1201	364	16	570
2016-17	4872	3191	1295	384	18	589
2017-18	4765	2878	1035	412	13	635
2018-19	4962	2489	1015	382	17	681
Total cases	38 817	27 788	9 991	2 795	181	5 380
Absolute change from 2010-19	+1393	-692	+229	+162	-25	+83
Percentage change from 2010-19	+39.0%	-21.8%	+29.1%	+73.6%	-59.5%	+13.9%

Table 1. The total number of sinus procedures performed in England between 2010-2019 as per the HES data. There is a breakdown in numbers for each specific sinus and year showing the overall change between 2010 and 2019 in terms of absolute numbers and percentage changes.

While there was an overall decrease in ethmoid sinus procedures in the last decade, the proportion of endoscopic cases making up the total ethmoid cases increased from 88.9% in 2010 to 95.2% in 2019 (representing an absolute increase of 6.3%). The number, and proportion of endoscopic frontal sinus procedures showed an increase from 2010 to its peak in 2014, from 744 to 1358 cases respectively, representing an increase from 94.7% to 97.8% of total frontal sinus procedures performed. However, this rise was not sustained and in 2019 during which the proportion of endoscopic frontal sinus work dropped to 96.6%.

The number of open and endoscopic procedures, and the change of percentage of endoscopic cases of total performed cases between 2010-2019 for maxillary, ethmoid and frontal sinuses is summarised in figures 2-4.

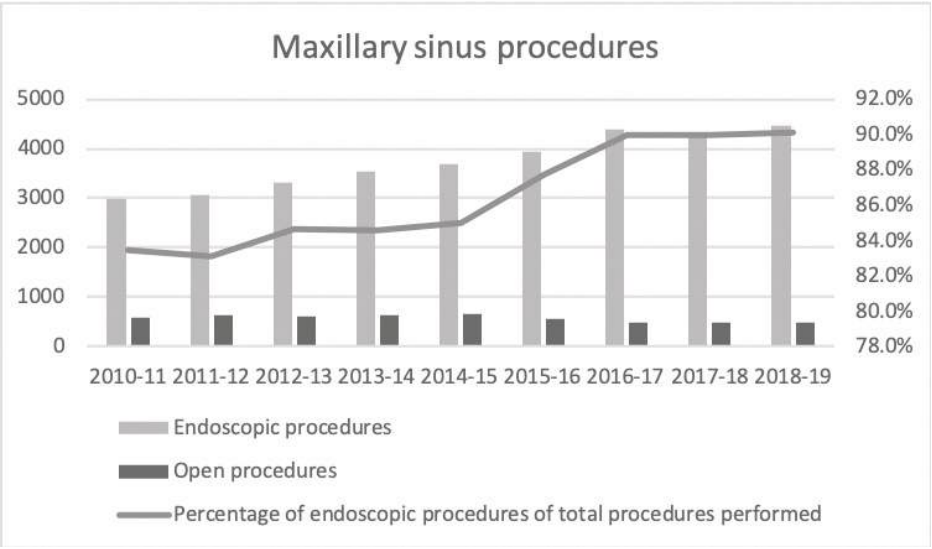

Figure 2. The change in the number of open and endoscopic maxillary sinus procedures over the last 9 years and the evolution of the percentage of endoscopic procedures with respect to the total number of maxillary sinus procedures performed

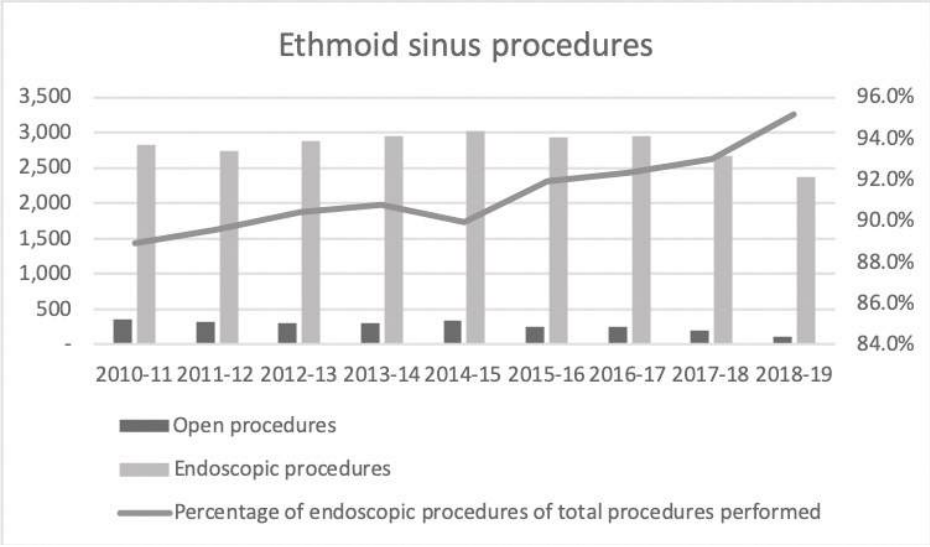

Figure 3. The change in the number of open and endoscopic ethmoid sinus procedures over the last 9 years and the evolution of the percentage of endoscopic procedures with respect to the total number of ethmoid sinus procedures performed.

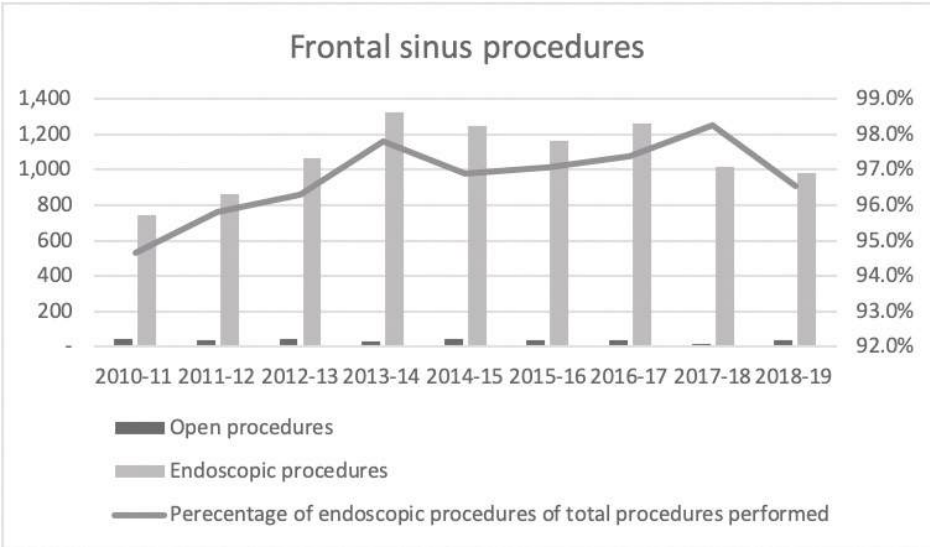

Figure 4. The change in the number of open and endoscopic frontal sinus procedures over the last 9 years and the evolution of the percentage of endoscopic procedures with respect to the total number of frontal sinus procedures performed.

Between 2010-2019, there was a 73.6% increase in endoscopic sphenoid sinus surgery (220 to 382), reaching a peak of 412 cases in 2017-18. This represented the largest increase of all sub-groups. During this time, there was a decrease in the number of "lateral rhinotomy into nasal sinus" procedures, from 42 to 17, representing a decrease of 59.5%. The trough was 13 cases in 2017-18. The evolution of sphenoid surgery procedures is illustrated in figure 5.

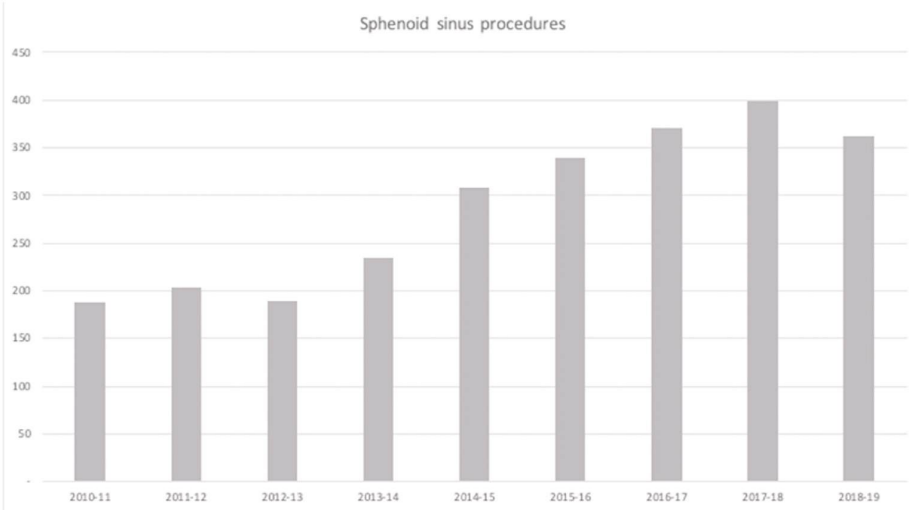

Figure 5. The change in number of sphenoid sinus procedures over the last 9 years

Discussion

Our results show an overall increase in sinus procedures from 2010 to 2019 from 7798 to 8865 procedures per year (figure 1). More interestingly, the proportion of endoscopic vs open procedures increased in this period from 86.8% to 92.5%. When looking at sinus specific procedures, there was an overall increase in maxillary, frontal and sphenoid sinus procedures, as well as procedures involving nasal sinus biopsy/excision. Although there was an absolute decrease in ethmoid sinus procedures, the proportion of endoscopic procedures in all sub-groups showed an increase over the last decade.

These findings expand upon previous studies that show similar results. In 2010, Venkatraman et al.[7] showed an increase in the rates of endoscopic sinus surgery in Medicare patients between 1998-2006, with a decrease in open sinus surgeries during the same study period, despite a similar number of

diagnoses of chronic rhinosinusitis (CRS). A study in 2014 by Pynonnen et al.[8] also demonstrated an increase in the total number of sinus procedures over 10 years in Florida, United States. They attributed this to an increased number of sinus procedures per patient and an overall increase in the number of patients undergoing sinus surgery. Similar results were also reported by Psaltis et al[9], who showed an increase in endoscopic sinus procedures, particularly in frontal sinusotomy and sphenoidotomy.

Our findings substantially build upon these previous studies, as we have analysed data from a whole country with no sampling, and over a 9-year study period. This contrasts with the Venkatraman[7] and Pyonnen[8] studies that looked at a specific population group, and area of the United States respectively. Furthermore, the long-term comparison of trends in our data set (9 years) allow more robust conclusions to be drawn when compared to the 3 and 8 year analysis reported by Psaltis[9] and Venkatraman[7] respectively.

Although our data set is comprehensive, it does not allow us to extrapolate a clinical explanation for the observed changes. This is due to a lack of data regarding patient factors such as disease severity and impact on quality of life. It is likely that the prevalence of CRS remains largely unchanged during the study period and is around 10% in the UK[10,11]. However, estimating the true prevalence of CRS is known to be difficult due to the combination of subjective and objective criteria in its diagnostic pathway. Observational studies used to estimate prevalence are often based on subjective criteria via questionnaires[12].

The changes therefore may be attributable to other factors such as increased patient acceptance of sinus surgery and improved surgeon training and confidence in endoscopic techniques. Indeed, this is a self-perpetuating cycle where an ever-increasing proportion of endoscopic surgery over time lends itself to the notion that more trainee surgeons will learn these techniques rather than traditional open approaches.

Another potential explanation for the results seen is dependent on disease processes. Historically, procedures that were performed open can now be performed endoscopically due to an increased knowledge of sinonasal anatomy, largely driven by CT guided navigation systems. Access to intranasal and paranasal sinus pathology has been significantly enhanced by a number of different endoscopic corridors described, including transethmoidal, transphenoidal, transpterygoid, prelacrimal and modified Denkers approach for laterally based lesions. This may explain the reduced need for extensive open access as demonstrated. In addition to this, endoscopic approaches to

the frontal sinuses have significantly increased. This was again reflected in the results by a reduction in open osteoplastic flap approaches to the frontal sinus.

External approach ethmoidectomy and frontoethmoidectomy both saw a 62% and 68% fall respectively over the 9-year period. There was an increase in "median drainage of frontal sinus" procedures from 96 in 2010-11 to 148 in 2018-19 with a change of 54%. However, when other frontal sinus procedure codes where included the global evaluation of all frontal sinus procedure codes did not demonstrate a significantly large increase over the last 9 years. This was partly down to coding limitation where 78.5% of frontal sinus procedures were coded as "other procedures on frontal sinus". This made it difficult to ascertain the approach taken and extent of surgery in the frontal sinus and is a limitation in using HES data. With regards to sphenoid sinus procedures, the expansion in endoscopic transsphenoidal approaches to sellar and clival lesions are likely to be a contributing factor to the increase in sphenoid sinus surgery seen over the years.

A major limitation of this study was lack of clarity provided by the coding parameters leading to variability and data identification bias. A large number of procedures were coded as "unspecified" or "other" approach to sinuses, making it difficult to identify the approach used. To minimise the effect of this bias, these procedures were subsequently excluded in subgroup analysis.

Furthermore, the operation codes do not include procedures that were converted to open from endoscopic approaches or similarly where combined approaches were used. Although, it is likely that these procedures will have been dual coded and therefore included correctly, this has not been explicitly stated in the HES database. The procedure codes themselves do not differentiate whether the approach was endoscopic and so there was a degree of bias interpreting the data. For example, biopsy/excision of sinus lesion may be open or endoscopically performed however we could not include this in the open vs endoscopic approach analysis.

The limitation with coding may also explain the overall decrease seen in ethmoid sinus procedures. One of the main purposes of coding is to generate income for hospitals in England. If an ethmoid sinus procedure has been conducted concurrently with a frontal or sphenoid procedure, then coders will generally only use the frontal or sphenoid code as this represents a higher tariff than an ethmoid code. Therefore, the use of coding may underrepresent the true number of ethmoid procedures. However, this would only likely affect the absolute numbers and not the trends or proportion of endoscopic surgery which are likely to still be accurate.

In addition, the same applied for procedures coded as "other unspecified" procedures for the frontal and sphenoid sinus. These were interpreted as being performed endoscopically. The data presented is very useful in presenting emerging trends in sinus surgery over the last decade, however the coding does not allow for analysis of underlying pathology being addressed or revision cases for example for inflammatory disease.

Conclusion

Overall, we see an increase in sinus surgery over the last 9 years from 2010 to 2019. These findings are in keeping with our initial hypotheses. Although our data set is limited by coding, and lack of patient factors, it represents most, if not all, of the data in England over a large study period. It is therefore useful to add to previous studies when demonstrating the increasing popularity of endoscopic sinus surgery over open procedures. With increasing novel medical therapies for inflammatory sinus disease and potential funding challenges in many countries, it will be interesting to see whether the upward trend of sinus surgery will be affected.

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3

Cone-Beam Computed Tomography Allows Accurate Registration to Surgical Navigation Systems: A Multidevice Phantom Study

Benjamin J Talks
Karan Jolly
Hannah Burton
Shahzada Khuram Ahmed

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Abstract

Background
Cone-beam computed tomography is a fast-imaging technique with a substantially lower radiation dosage than conventional multi-detector computed tomography for sinus imaging. Surgical navigation systems are increasingly being used in endoscopic sinus and skull base surgery, reducing mortality and morbidity.

Aims
To investigate cone-beam computed tomography as a low radiation imaging modality for use in surgical navigation.

Materials and methods
The required field of view was measured from the tip of the nose to the posterior clinoid process antero-posteriorly and the nasolabial angle to the roof of the frontal sinus supero-inferiorly on 50 consecutive multi-detector computed tomography scans (male=25; age 17-85 years). A phantom head was manufactured by 3D printing and imaged using three cone-beam systems (1. Carestream, 2. J Morita, 3. NewTom), a conventional multi-detector scanner (Siemens), and highly accurate laser scanner (FARO). The phantom head was registered to three surgical navigation systems (Brainlab, Stryker, Medtronic) using scans from each system.

Results
The required field of view (mean ± standard deviation) was measured as 107 ± 7.6 mm antero-posteriorly and 90.3 ± 9.6 mm supero-inferiorly. Image error deviations from the laser scan (median ± interquartile range) were comparable for multi-detector (0.19 ± 0.09 mm) and cone-beam computed tomography (1. 0.15 ± 0.11 mm; 2. 0.33 ± 0.18 mm; 3. 0.13 ± 0.13 mm). Fiducial registration error and target registration error were also comparable for multi-detector and cone-beam computed tomography-based navigation.

Conclusions
Cone-beam computed tomography is a low radiation pre-operative imaging modality suitable for use in surgical navigation.

Introduction

Chronic rhinosinusitis is a common condition with a prevalence of 10.9% in Europe (1), which is routinely managed with complex technically challenging endoscopic endonasal surgery (EES) (2). Anterior skull base surgery is another area frequently involving complex EES, with the aim of following the route to the pathology that results in the least possible morbidity.

Surgical navigation systems display the tracked position of surgical instruments on preoperative imaging, to help surgeons identify anatomical landmarks and pathological targets, reducing mortality and morbidity (3). Surgical navigation systems are becoming increasingly common in ear, nose and throat (ENT) theatres worldwide (4,5), with 94.6% of ENT surgeons reporting access to such systems in a 2010 survey of the American Rhinologic Society (5).

Preoperative imaging, typically multi-detector computed tomography (MDCT), plays a vital role in the diagnosis of sinonasal and anterior skull base pathology, and is further used to guide surgical navigation systems. Obvious requirements of preoperative imaging for surgical navigation are for it to be geometrically accurate, include all relevant anatomical structures in its field of view (FOV), and to have sufficient bony and soft tissue resolution to visualise required anatomical and pathological structures.

Cone-beam computed tomography (CBCT) is a fast, office-based imaging modality with a significantly lower radiation dosage than conventional MDCT, providing a dose reduction of 40-70% for sinus imaging (6,7). CBCT was first introduced to medicine by the Mayo Clinic Biodynamic Research Laboratory in 1982 (8), shortly after MDCT was first developed (9). Initially, CBCT was intended for use in angiography (8), although the focus of CBCT development shifted to dentistry in the late 1990s (10,11), and more recently ENT applications have been investigated (12). The first commercial maxillofacial CBCT scanner, the QR-DVT 9000 (NewTom, Verona, Italy) was approved by the Food and Drug Administration in 2001 (12).

In summary, CBCT involves the emission of X-rays from an X-ray tube that is rotated around the patient opposite to a detector to collect an isotropic volume of data, which can be assembled into both multiplanar and 3D reconstructions. CBCT scanners are cheaper than MDCT scanners, which in combination with their office-availability, provides a more cost-effective imaging option for use in ENT clinics (13). In CBCT images, voxels are isotropic providing high spatial resolution, which allows good visualisation of submillimetre bony structures comparable to high resolution MDCT (14). However, uncertainty exists regarding

the adequacy of CBCT FOV (15), geometric accuracy (16–19), and navigation accuracy (20,21) versus MDCT images for use in surgical navigation.

CBCT offers a lower radiation preoperative imaging modality than MDCT for use in EES (6). This study aims to provide a technical evaluation of the suitability of CBCT-based surgical navigation for EES by assessing the field of view, geometric accuracy, and navigation accuracy of CBCT and MDCT images.

Materials and Methods

Field of View

The minimum required FOV for EES on the sinuses and anterior skull base was investigated by measurements on 50 sequential MDCT sinus scans (1 mm slice thickness) requested by the ENT department of the Queen Elizabeth hospital Birmingham, between January and December 2017 (male=25, age=17-85 years; figure 1). The required anterior-posterior distance was defined from the tip of the nose to the posterior clinoid process. The required superior-inferior distance was measured from the nasolabial angle to the roof of the frontal sinus.

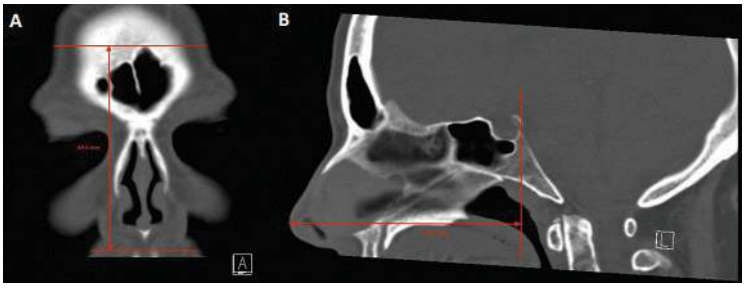

Figure 1. The measurements used to define a minimum FOV for EES on the sinuses and anterior skull base, shown on a MDCT scan: A) Anterior-posterior distance, measured from the tip of the nose to the posterior clinoid process, B) Superior-inferior distance, measured from the nasolabial angle to the roof of the frontal sinus.

Phantom head fabrication

A phantom head with a radio-density equivalent to skin was designed and manufactured by 3D-printing. Ten MDCT scans of the head (male=5; age=20-80 years) requested by the Queen Elizabeth Hospital Birmingham ENT department in January 2017 were reviewed. The radiodensity of the skin was measured at five sites per scan using the syngo FASTview (Siemens, Munich, Germany)

density tool: over the nasal bridge, right and left supraorbital regions, and right and left cheek. The mean density of skin of the head was 54.93 (± 27.25) HU. The literature was searched for published radio-densities of rapid prototyping materials; polylactic acid was the thermoplastic polymer found with a radio-density closest to that of skin of the head (66.34 ± 14.58 HU) (22).

A MDCT scan was taken of a FESS surgical trainer kit (Karl Storz, Tuttlingen, Germany). Image data was exported as DICOM files to Mimics v19 (Materialise, Leuven, Belgium). Radiodensity thresholding allowed isolation of the skin layer of the head, which was exported as a STL file to Freeform (Geomagic, Morrisville, United States) to add a posterior wall and 90 surface divots (2 mm diameter by 2 mm depth). Figure 2 shows the final phantom head design, which was 3D printed (Prusa, i3, Prusa Research, Praha, Czech Republic).

Figure 2. The final phantom head design, with 90 surface divots.

Computed tomography

Three CBCT scanners were evaluated in this study: the CS9300 (Carestream Health, New York, United States), 3D Accuitomo 170 (J Morita, Osaka, Japan), and 5G (NewTom, Verona, Italy). These CBCT scanners will be referred to as CBCT 1, CBCT 2, and CBCT 3 respectively. The three CBCT scanners were compared to a 64-slice MDCT scanner, SOMATOM Definition AS (Siemens, Munich, Germany). CBCT scans were performed according to each scanners' standard sinus protocol with its maximum FOV (table 1). MDCT scans were taken with the

standard navigation protocol used at the Queen Elizabeth Hospital Birmingham: 80 mAs, 120 KV, 15.3 s, and 1 mm slice thickness.

CBCT scanner	kVp	mA	mAs	FOV (mm)	Scan time (s)	Rotation	Voxel size (mm)	Volume size (voxels)
CBCT 1	85	5	56	170 x 135	11.30	360°	0.3	567 x 450
CBCT 2	90	5	87.5	140 x 100	17.5	360°	0.25	560 x 400
CBCT 3	110	0.57	2.04	180 x 160	3.6	360°	0.25	720 x 640

Table 1. CBCT sinus scanning protocol used in this study.

Geometric accuracy

The geometric accuracy of CBCT and MDCT scans was evaluated by comparison to a highly accurate laser scanner (FARO Quantum S, FARO, Lake Mary, United States), accurate to 0.025 mm (23), using an industrial inspection software (GOM inspect, GOM mbH, Braunschweig, Germany; figure 3).

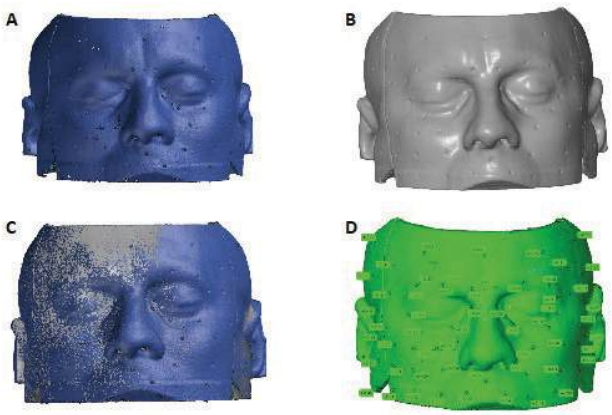

Figure 3. The stages of the deviation analysis between the highly accurate laser scan and CT data. A) The STL file of the laser scan was defined as the reference index. B) The CT scan data was converted from DICOM data to STL format. C) The CT scan and reference index were crudely aligned (pre-alignment). D) The CT scan and reference index were accurately superimposed and deviations were measured at 56 consistently visible points.

Surgical navigation systems

Three surgical navigation systems were used in this study: A) Kolibri (Brainlab, Munich, Germany), B) NAV3i (Stryker, Kalamazoo, United States), C) StealthStation

S7 (Medtronic, Minneapolis, United States). Each surgical navigation system has its own patient tracker, which was attached securely to the phantom before registration could begin. All three surgical navigation systems offer a range of registration techniques including paired-point touching and surface matching. Optical tracking and paired-point registration was used in this study to allow comparison between the surgical navigation systems. The same five fiducial points, on the phantom were used for registration of each of the surgical navigation systems. Five fiducials were used for registration, as previous work has demonstrated that the use of more fiducials to not significantly improve target registration error (TRE) (21).

Navigation accuracy

Fiducial Registration Error

Fiducial registration error (FRE) is the distance between matched fiducials in image and physical space following registration (24) and is commonly displayed by commercial surgical navigation systems following registration. The phantom head was registered 10 times to all three surgical navigation systems used in this study with scans from the MDCT scanner and three CBCT scanners being studied. The FRE of each registration was recorded and navigation accuracy was qualitatively assessed by touching pits on the phantom surface.

Target registration error

TRE is the best measure of registration accuracy, representing the overall accuracy of the navigation system (21). It is the distance between matched points, other than registration fiducials, in image and physical space after registration (24). An optical surgical navigation system (Kolibri, Brainlab, Munich, Germany) was used to assess the TRE of MDCT- versus CBCT- based surgical navigation for the scanners studied in this project. A surgical plan was prepared for each CT scan using iPlan Cranial 3.0 (Brainlab, Munich, Germany), the centre of 56 surface divots were selected as target landmarks, 5 of which were used to register the phantom to the navigation system by paired-point matching. The head phantom was registered to the surgical navigation system using MDCT and CBCT scans, and the TRE identifying 51 consistently visible pre-planned surface landmarks was measured twice for each scan.

Statistics

Statistics were carried out using GraphPad Prism 7. Significance level was determined at the level of alpha <0.05. A Bonferonni adjustment was calculated for multiple comparisons of the three CBCT scanners to MDCT ($\alpha = 0.05/3 = 0.017$).

Results

Field of View

The required dimensions of the FOV for EES on the sinuses and anterior skull base (mean ± standard deviation, range; figure 4) were measured antero-posteriorly (107 ± 7.6 mm, 106.1 – 120.1 mm) and supero-inferiorly (90.3 ± 9.6 mm, 73.1 – 114.8 mm).

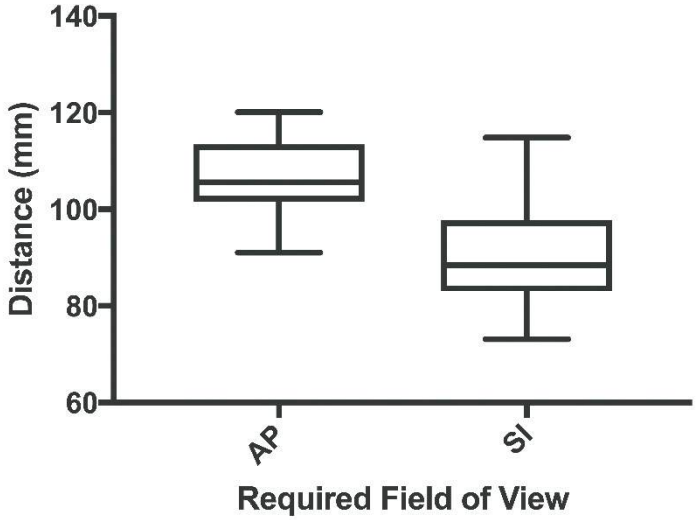

Figure 4. A graph of the required antero-posterior (AP) and supero-inferior (SI) FOV dimensions for EES on the sinuses and anterior skull base, defined as the distance from the tip of the nose to the posterior clinoid process and the nasolabial angle to the roof of the frontal sinus respectively.

This measured minimum required FOV for EES on the sinuses and anterior skull base was compared to the FOV provided by the three CBCT scanners used in this study (table 2). All measured antero-posterior and supero-inferior distances fitted within the maximum FOV sizes provided by these three CBCT scanners.

FOV	Required FOV	CBCT 1	CBCT 2	CBCT 3
Anterior – Posterior	107 (± 7.6) mm	170 mm	170 mm	180 mm
Superior - Inferior	90.3 (± 9.6) mm	135 mm	120 mm	160 mm

Table 2. The required FOV for EES on the sinuses and anterior skull base compared to the maximum FOV of the three CBCT scanners used in this study.

Geometric Accuracy

The median (± interquartile range) of the error deviation measured at 56 pre-defined points on three sequential scans was 0.19 (± 0.09) mm for MDCT, 0.15 (± 0.11) mm for CBCT 1, 0.33 (± 0.18) mm for CBCT 2, and 0.13 (± 0.13) mm for CBCT 3 (figure 5). The error deviation of the three CBCT scanners studied was compared to that of MDCT by a Friedman test with Dunn's multiple comparison testing. The error deviation of CBCT 1 ($p=0.0996$) and CBCT 3 ($p=0.0256$) was not significantly different to that of MDCT. However, the error deviation of CBCT 2 was significantly higher than MDCT ($p<0.0001$).

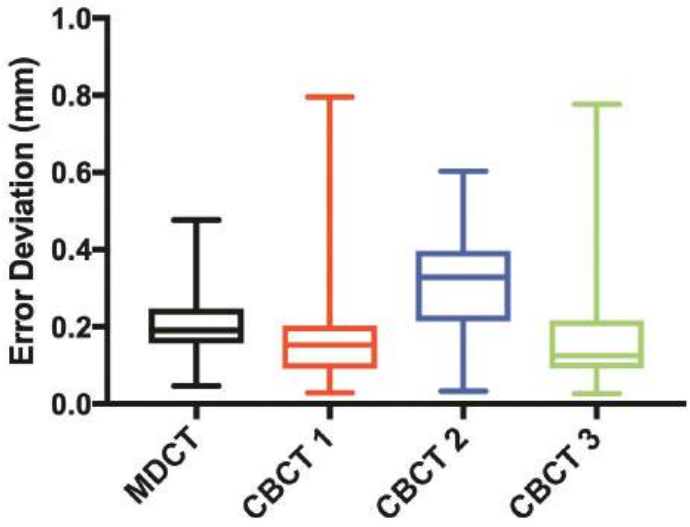

Figure 5. A graph of the error deviation of MDCT and CBCT scans compared to a highly accurate laser scanner, measured at 56 pre-defined points on three sequential scans.

Navigation Accuracy

Fiducial Registration Error

FRE was recorded for 10 registrations of the phantom head to three surgical navigation systems by paired point touching of five fiducials using optical tracking (table 3). All registrations using MDCT and CBCT scans were accepted as a 'good' accuracy by the surgical navigation systems, allowing surgical navigation to begin, and were qualitatively accurate.

Navigation system	MDCT	CBCT 1	CBCT 2	CBCT 3
Kolibri (Brainlab)	0.9 ± 0.1	1.4 ± 0.2	1.4 ± 0.1	1.0 ± 0.1
NAV3i (Stryker)	0.9 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.7 ± 0.1
StealthStation S7 (Medtronic)	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3

Table 3. The FRE of MDCT- and CBCT- based registration to three surgical navigation systems, calculated from 10 sequential registrations (mean ± standard deviation).

Target Registration Error

The mean (± standard deviation) TRE, measured at 51 pre-identified landmarks for two registrations, was calculated as 1.07 (± 0.35) mm for MDCT, 0.95 (± 0.21) mm for CBCT 1, 1.17 (± 0.31) mm for CBCT 2, and 0.89 (± 0.27) mm for CBCT 3 (figure 6). The measured TREs were compared using a one-way analysis of variance test, with an uncorrected Fisher's least significant difference test for multiple comparisons of the three CBCT scans to MDCT. CBCT 3 provided a significantly lower TRE than MDCT (p=0.0024), whilst the TRE using CBCT 1 (p=0.0372) and CBCT 2 (p=0.0749) was not significantly different from MDCT.

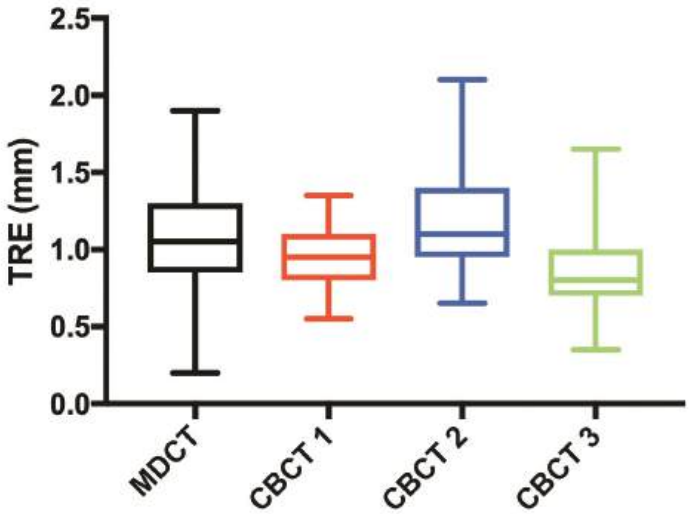

Figure 6. A graph of the TRE of MDCT- and CBCT- based surgical navigation, measured over 51 predefined points using an optical surgical navigation system (Kolibri, Brainlab, Munich, Germany).

Discussion

Field of View

For a preoperative scan to be used for surgical navigation, it must show all the anatomical landmarks of interest for the procedure within its FOV. The three commercially available CBCT scanners investigated in this study provided a FOV that is sufficient for EES on the sinuses and anterior skull base, based on the minimum FOV measurements made in this study.

The minimum antero-posterior dimension was defined as the distance from the tip of the nose to the posterior clinoid process of the sphenoid bone. The minimum supero-inferior dimension was defined as the distance from the nasolabial angle to the roof of the frontal sinus. The whole surface of the nose was included in the image, as it is required for patient-to-image registration by surface matching. The posterior clinoid process defines the posterior border of the sella turcica, ensuring the transsellar approach to the pituitary gland is visible. Pituitary adenomas are the most commonly encountered anterior skull base pathology, making up 49.8% of anterior skull base surgery cases (25), demonstrating the huge potential use of CBCT. Adequate visualisation of the frontal recess is essential for functional endoscopic sinus surgery, as operating on the frontal recess is classed as an advanced procedure and is often aided by use of surgical navigation systems (26). This is due to the complex and highly variable anatomy of the frontal recess, compounded by its close proximity to: the orbit laterally, olfactory fossa medially, anterior cranial fossa superiorly (27).

Geometric Accuracy

All of the CBCT and MDCT scanners were deemed highly accurate; with median error deviations ranging from 0.125 to 0.328 mm relative to a highly accurate laser scan. The error deviations of CBCT 1 and 3 were not significantly different from that of MDCT, although their means were slightly lower. The accuracy of CBCT 2 was significantly lower than that of MDCT, although its mean error deviation was only 0.138 mm greater, which is not clinically significant.

This study adds weight to a previous study showing that CBCT scanners can have an equivalent geometric accuracy to MDCT scanners (18), supporting the suggestion that CBCT systems have a suitable geometric accuracy for use by surgical navigation systems. However, as in other studies, there was variation in the accuracy of different CBCT systems (16); it may be of value for centres to independently evaluate the accuracy of their CBCT system, using the highly accurate approach demonstrated in this study, so that they may start to utilise it for surgical navigation.

This study is the first to have used the novel technique of determining image accuracy outlined by Wilmowsky et al. (28) to compare the accuracy of CBCT and MDCT scans. This technique involves using industrial inspection software to superimpose the CBCT or MDCT scan being evaluated onto data from a highly accurate laser scan and to measure deviation between the two data sets. This allows a 3D assessment of spatial accuracy of the CT scan, which is more appropriate than the 2D dimensional measurements made with digital callipers in previous studies (16,29,30).

Navigation Accuracy

Fiducial Registration Error

CBCT scans from all three scanners evaluated provided a comparable FRE (<1.4 mm) and qualitative accuracy to MDCT, demonstrating their compatibility with three commercially available surgical navigation systems. FRE is only a crude measure of navigation accuracy; however, it is the measure routinely reported by surgical navigation systems to allow surgeons to assess the accuracy of patient-to-image registrations in combination with qualitative assessments before their use intra-operatively.

Target Registration Error

The mean TRE for CBCT-based surgical navigation varied between 0.89 and 1.17 mm for the three CBCT systems evaluated, which was equivalent to or better than the measured TRE of MDCT-based surgical navigation. In this study, the mean TRE of MDCT- and CBCT-based surgical navigation was <2 mm, which has been suggested as the minimum accuracy required for surgical navigation systems to be clinically useful during surgery (31). This builds on evidence from a previous study that CBCT- and MDCT-guided surgical navigation systems are of comparable accuracy (20).

TRE is the best available measure of the registration accuracy of surgical navigation systems (24), taking into account errors in image accuracy, patient position tracking, and instrument position tracking. In this study, CBCT and MDCT scans were compared using the same optical surgical navigation system and image-to-patient registration was performed by paired-point matching using the same five fiducial points, to allow the effect of each preoperative imaging modality on TRE to be seen. The pits in the surface of the phantom had a diameter of 2 mm, which is similar to the diameter of the tracked probes of the surgical navigation systems, which tend to have a diameter of ~1.5 mm.

Image Quality

As well as the geometric accuracy of the preoperative imaging modality, the utility of surgical navigation also depends on its image quality. Few studies

have been done comparing image quality in CBCT and MDCT scans of the paranasal sinuses and anterior skull base. A major appeal of CBCT images are their submillimetric isotropic spatial resolution (14,32), a restriction is their limited soft tissue resolution (6,14). Consequently, CBCT is not appropriate for patients suspected of having primarily soft tissue pathology such as sinonasal tumours, mucoceles, or encephaloceles (6), unless it is only bony anatomy that needs to be defined. Most sinus surgeons rely on bony anatomy and not soft tissue anatomy for image guidance.

CBCT scans are deemed adequate for assessing sinonasal polyposis, despite extensive soft tissue swelling reducing the visibility of bony structures (33). Using CBCT to assess patients with rhinosinusitis has been estimated to result in only 3.3% of sinonasal abnormalities being missed, which would alter management in 1.1% of cases (34). Thus, with careful selection of patients, CBCT imaging offers an appropriate lower radiation imaging modality for sinus scanning.

Conclusion

Commercially available CBCT devices provide a sufficient FOV to assess sinus and anterior skull base pathology. Additionally, CBCT scans have comparable geometric accuracy to MDCT images, allowing image-to-patient registration by surgical navigation systems with an accuracy equivalent to or better than MDCT. Thus, CBCT presents a viable alternative to MDCT for accurate surgical navigation during EES on the sinuses or anterior skull base, with a substantially lower radiation dose than conventional MDCT. However, CBCT images are of more limited use when assessing primarily soft tissue diseases and many CBCT scanners do not allow the use of radiological contrast.

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4

Use of the Medial Canthal Point (MCP) as a reliable anatomical landmark to the frontal sinus

Karan Jolly
Theodoros Kontogiannis
Miran Pankhania
Khalid Hussain
Paresh Naik
Shahzada Khuram Ahmed

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Abstract

Objectives

Frontal sinus surgery is considered one of the more challenging aspects of Functional Endoscopic Sinus Surgery (FESS), due to the complex variations in normal sinus anatomy but also increased morbidity due to the close proximity of critical structures such as the anterior cranial fossa and orbits. We aim to investigate the Medial Canthal Point(MCP) as an anatomical landmark for safe frontal sinus access.

Methods

The MCP intranasally is identified during surgery with non-tooth forceps, with one limb just anterior to the medial canthus and the other intranasally in the same coronal plane along the skull base. This point was identified on 100 paranasal sinus Computed Tomography (CT) scan reconstructions. The distance between the anterior cranial fossa and MCP was measured on imaging- Medial Canthal Point Distance (MCPD). The maximal Anterior-posterior (AP) distance was measured on all scans.

Results

The average MCPD for males was 13.0mm(8.7-20.4mm) and for females 12.0mm(6.8-22.8mm). Mean AP distance for males was 12.0mm(4.5-20.2mm) and for females 10.4(3.8-15.9mm). Mean distance for all 100 patients was 12.6mm(range 7.5-22.8mm). In all cases, the MCP was anterior to the cranial fossa. Mixed effects modelling analysis showed a significant correlation between the MCPD and AP distance ($p=0.006$).

Conclusion

The medial canthal point (MCP) is a consistent anatomical landmark that can serve as an adjunct to safe frontal sinus access alongside the first olfactory fibre and CT navigation systems. However, patient selection continues to be very important, with larger well pneumatized frontal sinuses being ideal to tackle earlier in a surgeon's career.

Introduction

Frontal sinus surgery is considered one of the more challenging aspects of Functional Endoscopic Sinus Surgery (FESS), primarily due to the complex variations in normal sinus anatomy in this region but also increased morbidity due to the close proximity of critical structures such as the anterior cranial fossa and orbits. An increased understanding of sinonasal anatomy, optical advancements as well as improved powered instruments has allowed for an evolution in the management of complex frontal sinus pathology with better outcomes.

One of the fascinating aspects of FESS is the uniqueness of the fronto-ethmoidal air cell labyrinth. Our knowledge of the drainage pathways continues to expand as demonstrated recently by Bolger et al 2019, with the description of the anterior ethmoidal genu (1). Until recently the uncinate process and ethmoid bulla were considered separate entities, however the two appear to fuse superiorly forming a consistent landmark medial to which the frontal sinus drains in 77% of cases (1). The key to successful sinus surgery is the reliability and understanding of key anatomical landmarks which help guide the surgeon, especially in the presence of complex pathology that often distort common landmarks.

A number of different frontal sinus procedures have been classified by Draf depending on the access required to address the extent of underlying disease (2,3). These may involve an inside-out or an outside-in approach. The former involves identifying the natural frontal sinus drainage pathway whereas the latter involves a median approach with early identification of the floor of the frontal sinus and first olfactory filament. The approach taken is very much dependent on surgeon experience, anatomy of the sinuses and the pathology being managed.

Two important adjuncts to safely access the frontal sinus via the median approach have been the identification of the first olfactory filament and use of intraoperative image navigation systems. One study identified the first olfactory filament to be on average 4.0mm posterior to the frontal sinus (4). The authors proposed drilling at least 7mm rostral (anterior) to the first olfactory filament would allow safe access to the frontal sinus in 91% of patients (4). This important landmark continues to serve as a useful pointer especially when combined with image navigation. There are however limitations to this, including availability of and unpredictability of navigation systems as well as presence of disease obscuring anatomical landmarks. We aim to investigate the medial canthus and its correlation to the frontal sinus along the skull base, and assess the feasibility of using it as another fixed anatomical landmark to aid surgery to the frontal sinus. In addition, we will correlate this with different degrees of frontal sinus pnuematisation, by measuring the maximal anterior-posterior (AP) distances of each frontal sinus.

Methods

During frontal sinus surgery, the surgeon uses non-toothed surgical forceps to identify the level of the medial canthus coronally along the skull base. This is achieved by placing one limb of the forceps just anterior to the medial canthus with the other limb inserted intranasally. The tip of the limb of the forceps that is placed intranasally is painted with ink or methylene blue dye in order to mark the corresponding level of the medial canthus intranasally in the same coronal plane – Medial Canthal Point (MCP) (figure 1). This point is then used to elevate a mucosal flap along the skull base. We aimed to identify the distance between the point along the skull base in the same coronal plane as the medial canthus and the anterior cranial fossa using Computed Topography (CT) imaging. This point is demonstrated in figure 2 using CT navigation intraoperatively.

We analysed sequential CT sinus scans performed for 50 adult male and 50 adult female patients attending the rhinology clinic at a single centre. For each of the scans our radiologist performed 3D volume rendering to identify and mark a point at the medial canthus on the images in conjunction with the surgeon (figure 3). This point represents the position of the lateral arm of the forceps. This mark auto-registered on corresponding axial slices allowing us to mark a point in the same coronal plane within the nasal cavity paramedian to the septum (image 4). Sagittal images were used to extrapolate this point cranially to the skull base in the same coronal plane as the medial canthus as would be done intraoperatively with elevation of the mucosal flap. This represents the point of drilling to access the floor of the frontal sinus. The distance between the MCP and the inner table of the anterior cranial fossa was measured along the boney skull base – the medial canthal point distance (MCPD) (figures 4, 5). The angle at which this distance was measured depended on the slope of the skull base which varied from patient to patient. was Measurements were taken for both the right and left sides on each patient giving a total or 200 measurements. Alongside this, for each of the patients, the maximal anterior-posterior (AP) distance of the frontal sinus on both left and right sides were measured. Data were presented as mean (SD) by gender and position for each variable. Mixed effects models were used to estimate the mean of the pooled data and also to assess the relationship between the medial canthal distance and AP distance. The data were analysed using the statistical software Stata version 16.1.

Patients were excluded if they had a history of severe facial trauma that might have distorted the position of the medial canthus or if they had a hypoplastic frontal sinus.

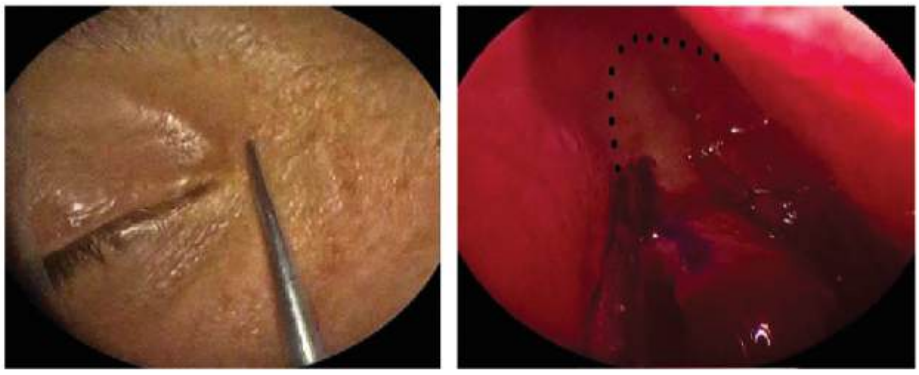

Figure 1. Endoscopic view of the lateral limb of the forceps on the medial canthus (left) and the medial limb stained with ink intranasally at the same coronal level along the skull base (medial canthal point). This landmark is also used in designing frontal sinus flaps (dotted line)

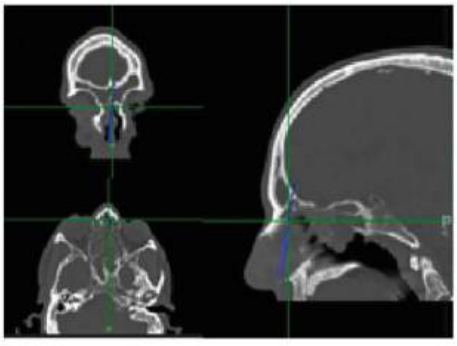

Figure 2. Computed tomography (CT) navigation image of the medial canthal point (MCP) along the skull base

Figure 3. 3D reconstruction with medial canthus

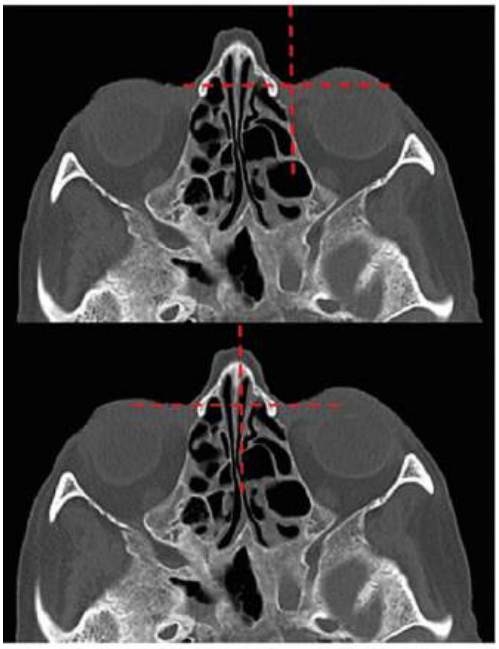

Figure 4 Medial canthal point (top) and corresponding intranasal point (bottom) illustrated by the intersection of the doted lines

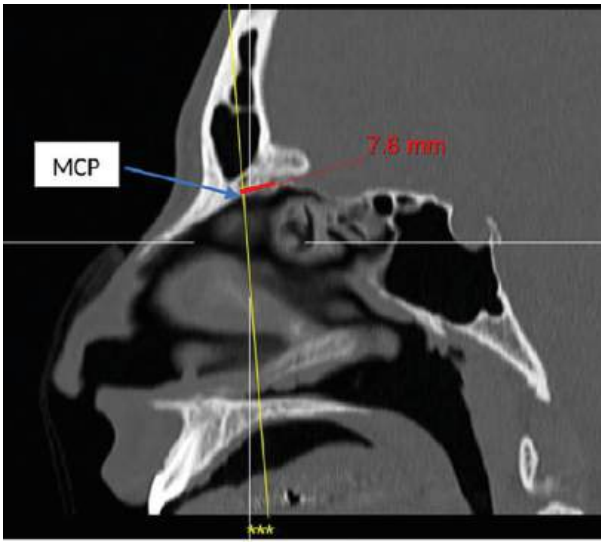

Figure 5. Medial canthal plane identified by yellow line (in asterisk) with arrow to medial canthal point (MCP) along skull base. Distance between ACF and MCP (red line)

Results

Of the 100 patients included, mean age was 50 (range 17-90yrs) with an average BMI of 29.7 (range 20.4-49.1kg/m^2). The average MCPD for males was 13.0mm (8.7-20.4mm) and for females 12.0mm (6.8-22.8mm). The mean AP distance for males was 12.0mm (4.5-20.2mm) and for females 10.4 (3.8-15.9mm). Our results demonstrate that the medial canthal point along the skull base point was sufficiently clear of the posterior table of the frontal sinus in all of the sample patients within 2 standard deviations (table 1 and table 2).

Mixed effects modelling was used to assess the relationship between the frontal sinus AP distance and the MCPD. Ignoring the effects of gender and side of frontal sinus, there was a significant relationship between AP distance and the MCPD (p=0.006) with the model suggesting that for every unit increase in AP distance the MCPD increases by 0.17mm. This also indicates a positive correlation between the 2 variables. The results therefore demonstrate that in patients with larger well pneumatized frontal sinuses, the MCPD will be larger and thus a more reliable marker for safe access into the frontal sinus

Variable	Position	Mean (mm)	SD	Minimum (mm)	Maximum (mm)
Male					
MCPD	Right	12.8	2.0	9.4	17.5
MCPD	Left	13.2	2.6	8.7	20.4
AP	Right	12.0	3.2	4.5	19.0
AP	Left	12.0	3.0	4.6	20.2
Female					
MCPD	Right	12.6	2.6	7.3	18.0
MCPD	Left	11.9	3.2	6.8	22.8
AP	Right	10.3	2.9	4.5	15.9
AP	Left	10.5	2.9	3.8	15.6

Table 1. Table showing the MCD and AP distances in both 50 males and 50 females for right and left frontal sinuses

Medial Canthal Point Distance (MCPD):	
	Mean (95% CI)
Male	13.0 (12.4, 12.4)
Female	12.0 (11.4, 13.5)
AP distance:	
	Mean (95% CI)
Male	12.0 (11.2, 12.7)
Female	10.4 (9.6, 11.1)

Table 2. Combined mean values for MCD and AP distance for males and females

Discussion

In recent years there has been an increase in the surgical management of frontal sinus pathology, owed to better anatomical and physiological understanding of the paranasal sinuses. Angled endoscopes accompanied by a wide range of angled instruments and powdered tools have allowed for better visualisation allowing more complex conditions to be tackled safely.

Frontal sinus surgery has been classified by Draf based on its approach for the underlying pathology (2). Extended frontal sinus drainage involves removal of the floor of the sinus between lamina papyracea and middle turbinate (Draf IIa) or nasal septum (Draf IIb), anterior to the anterior cranial fossa. More extensive drainage requires bilateral draf IIb procedures with resection of the superior nasal septum and the frontal intersinus septum. Sinonasal pathology can make identification of the frontoethmoidal recess challenging and inexperienced surgeons may find themselves struggling or performing an inadequate procedure in an attempt to avoid a complication. A systematic review by Scott et al reported the incidence of peri-operative CSF leak during modified Lothrop (Draf III) procedure to be higher than an osteoplastic flap approach, however postoperative outcomes were better with an endoscopic approach (5).

Historically, the first olfactory filament has been shown to be a useful landmark in identifying the posterior limit to drill into the floor of the frontal sinus, however a recent study demonstrated a wide degree of variability of this point from the posterior table of the frontal sinus, making it not as reliable as previously thought (4,6). As a result, this must be combined with image guidance to safely excise the floor of the frontal sinus. However, image guidance systems are not universally available and may not be accurate, so their reliability should be taken with caution. In addition, sinonasal and olfactory fossa pathology may distort

anatomy making it difficult to identify the first olfactory filament and other key anatomical landmarks such as the axilla of the middle turbinate. Branches of the anterior ethmoidal artery and nerve may also be mistaken for the first olfactory filament (4) which highlights the advantage in having another fixed reliable landmark (the medial canthus) for safe access to the frontal sinus.

Our study determined the medial canthus to be 12.5mm (6.8-22.8mm) anterior to the anterior cranial fossa along the skull base on 200 readings from 100 CT scans; with all registered points being clear of the anterior cranial fossa independent of gender and side of patient. The effects of age, BMI and height of patients on the MCPD were not explored in this study, however over the 100 patients studied across a wide range of ages and BMI, the MCP was clear of the anterior skull base in all cases as demonstrated. In addition to this there was a strong correlation between AP diameter of the frontal sinus and MCPD. A well pneumatized sinus with a larger maximal AP diameter will have a larger MCPD and thus improving the safety and reliability of the MCP. Similarly, a narrow frontal sinus will have a short MCPD and may therefore not be suitable for an endoscopic approach especially when less experience endoscopic surgeons are operating. Reliability of the MCP can be validated on preoperative imaging or intraoperatively with navigation imaging if available, or used alongside the first olfactory filament for increased accuracy to access the frontal sinus. Cautious drilling cranially at this point and just anterior to this point will allow for safe access into the frontal sinus. We recommend this is done with a high-speed drill and plenty of irrigation across a broad front until the frontal sinus is safely entered. Once the frontal sinus is entered, dissection can safely be continued with the posterior table under direct vision.

Conclusion

During parotid surgery, the facial nerve trunk can be safely identified by a number of different anatomical landmarks and often surgeons use a combination of these for increased reassurance. In a similar way, we propose the triad of first olfactory filament, medial canthal point (MCP) and navigation imaging to help identify the safest entry point for a frontal sinus drill out. We hope this landmark serves to be a useful consistent anatomical marker in expanded frontal sinus surgery and as with all cases, patient selection is very important, with larger well pneumatized frontal sinuses being ideal to tackle earlier in a surgeon's career.

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5.1

A novel technique for endoscopic repair of large anterior skull base defects: The PDS Wrap

Karan Jolly
Oke Okonkowo
Gerogios Tsermoulas
Shahzada Khuram Ahmed

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Introduction

During endoscopic skull base procedures, repair of the subsequent defect requires careful consideration and preoperative planning to reduce post-operative complications like Cerebrospinal fluid (CSF) leak, pneumocephalus and meningitis(1,2,3). Assessment of imaging before surgery will help identify the access required for such procedures and allow the surgeon to plan ahead. The site of surgery along the skull base, size and type of tumour, consideration for any post-operative treatment such as radiotherapy and also any previous surgery all need to be considered in order to help decide the best reconstruction strategy.

A variety of reconstructive options are available ranging from single layer to multilayer techniques using a combination of free autograft tissue, pedicled nasoseptal flaps and a range of synthetic dural grafts including fibrin based tissue glues; containing animal derivatives and requiring ethical consideration (4,5,6). In a small number of cases with large skull base defects, herniation of brain tissue into the sinonasal cavity can pose a challenge to reconstruction. Graft placement can be very challenging due to migration and lack of support. We describe a novel multilayer repair technique used to help reconstruct larger anterior skull base defects. The use of our PDS (Polydioxanone plate) wrap technique allows for easier handling and placement of dural graft material whilst providing structural support to the underlying brain parenchyma

Methods:

We demonstrate the use of this technique on a case of a patient presenting with a large olfactory groove meningioma measuring 40mm by 44mm in size (figure 1). Preoperative assessment of the imaging helped us identify the potential defect that would need repairing. The repair would need to be robust given the size and position of the tumour and a subsequent high risk of CSF leak. During the procedure a large nasoseptal flap was elevated and complete endoscopic craniectomy including the olfactory groove with planectomy was performed followed by tumour removal (figure 2). The subsequent defect measured approximately 4cm in length from the frontal sinus to the sella turcica and 2 cm in width from orbit to orbit. There was significant herniation of the brain into the sinonasal cavity making the duraplasty difficult. To repair the defect, initially a dural graft (DuraGen Plus® , Integra lifesciences corporation, USA) measuring approximately 30% larger than the size of the defect was used as an intradural underlay (figure 3) however the degree of brain herniation limited the amount of graft that could be placed between the native dura and brain as well as

increasing the surface area of the defect requiring a much larger graft. Then, a 0.5mm thickness Polydioxanone plate (PDS) (Ethicon inc, Somerville, NJ) was cut to the approximate size of the defect and placed on another dural graft (figure 4). The edges of the graft were then folded over and sutured to each other forming our "PDS wrap" (figure 4). This wrap is then introduced intranasally as an inlay, gently lifting the brain out of the sinonasal cavity and holding it in place by pushing the edges of the PDS plate under the bony defect extradurally. The sutures were then cut (figure 5), allowing the edges of the dural graft to unfold whilst held in place by the PDS plate (figure 6). The edges of the graft were subsequently unfurled and tucked under the bony defect extradurally with the use of the Castelnuovo double elevator (Karl Storz SE & Co, Tuttlingen, Germany) and a Cottle elevator (Karl Storz SE & Co, Tuttlingen, Germany), providing an additional layer of support. This was achieved much more ease due to the anchoring effect of the PDS plate reducing graft migration. The nasoseptal flap was then rotated over this reconstruction and additional layers of surgicel® and Tisseel® glue were placed on top. The nasal cavity was then packed with further absorbable and nonabsorbable packs to give additional support to the reconstruction for the first 3 days. The nonabsorbable packs were removed in 3 days whilst on the ward and the patient was seen in outpatient clinic 6 weeks after surgery. Postoperative imaging in 3 months showed adequate placement of the PDS plate as seen by a linear non-enhancing structure along the anterior skull base (figure 7).

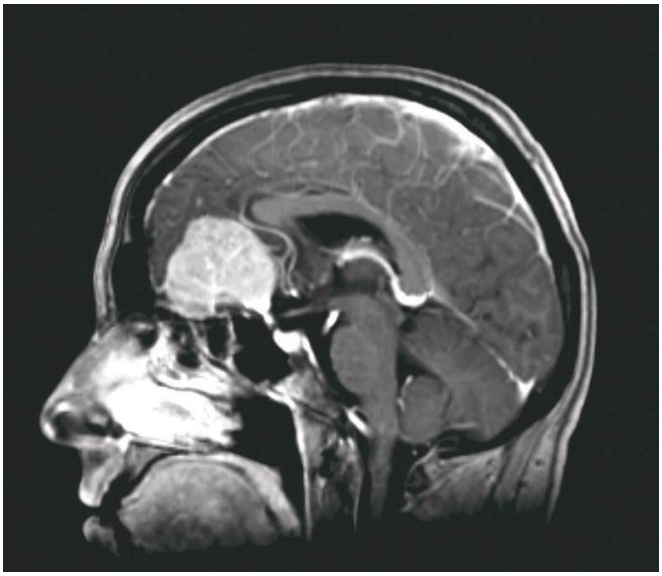

Figure 1. MRI image of Olfactory cleft meningioma

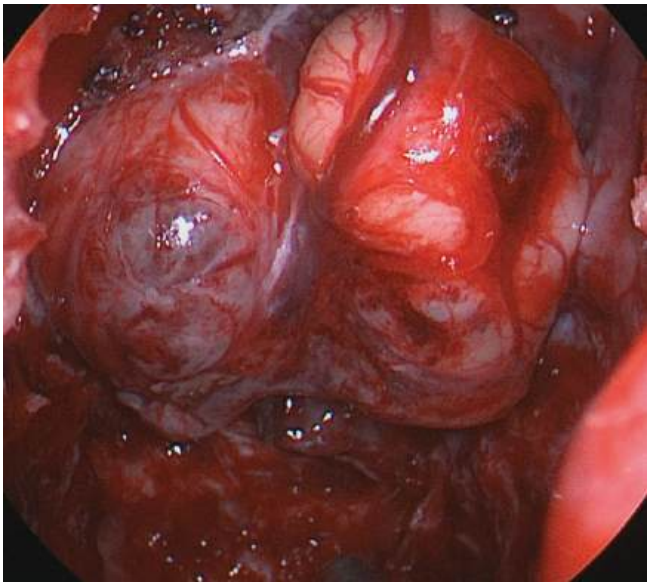

Figure 2. Base of skull defect with frontal lobe herniation

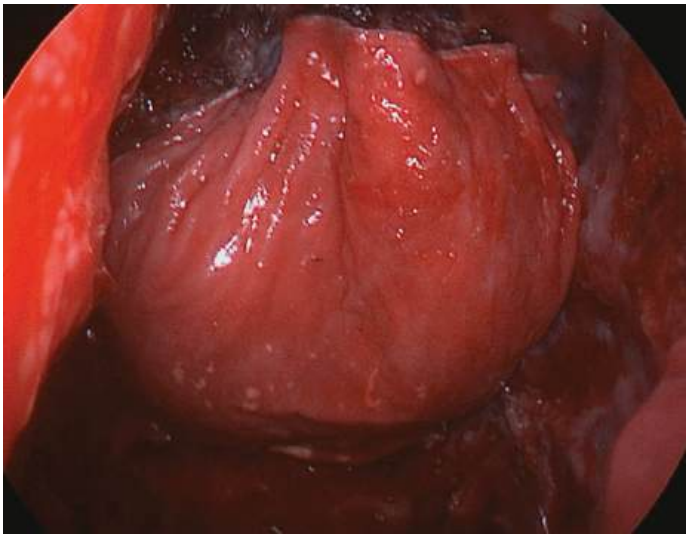

Figure 3. Dural graft underlay

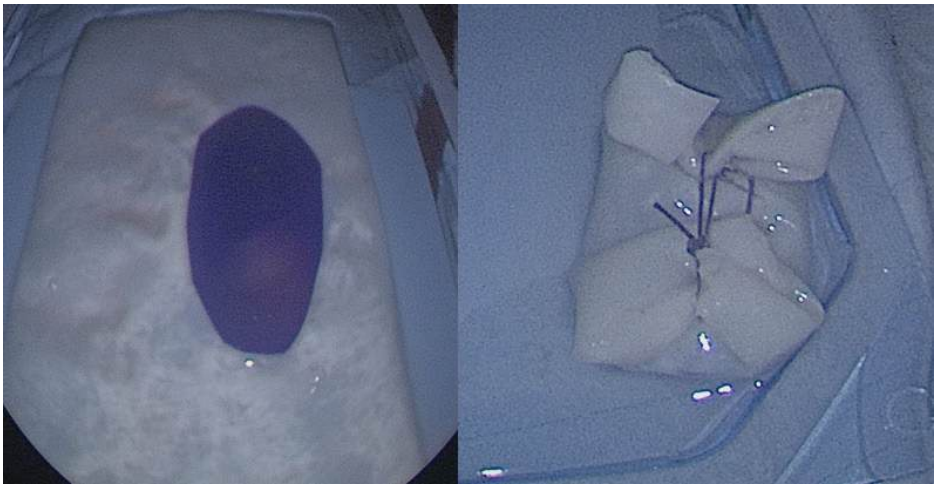

Figure 4. PDS sheet over dural graft and folded to make wrap

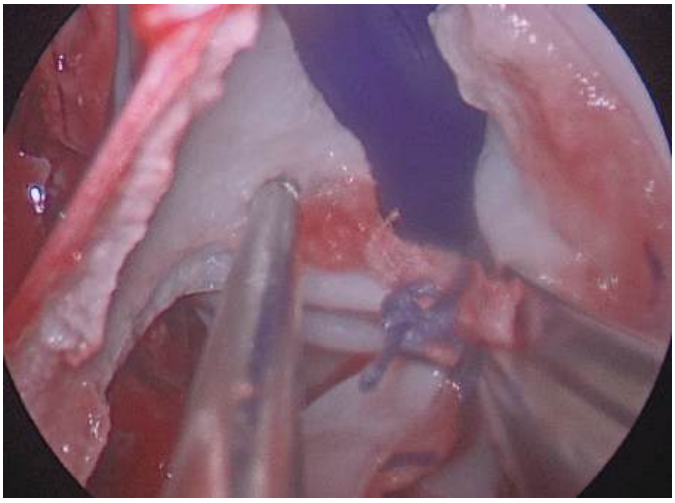

Figure 5. Sutures being cut to deploy the dural graft

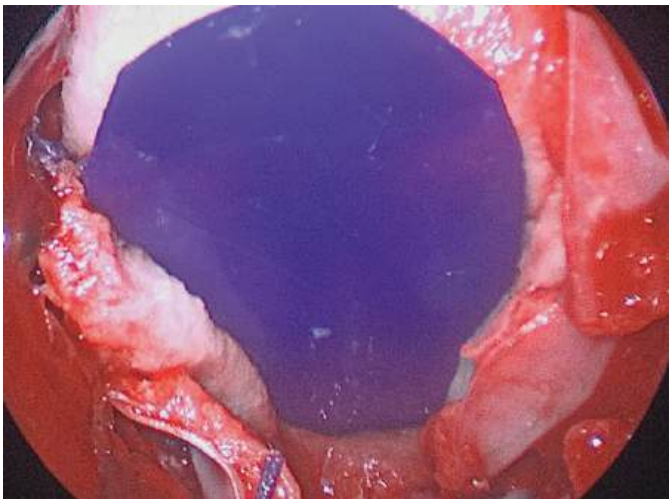

Figure 6. PDS wrap inserted under bone edges of defect with duragen placed as an additional underlay.

Discussion

PDS plates have been approved for the use of orbital floor and nasal septal repairs, with resorption taking 10-25 weeks following placement (7). The use of rigid materials for large defect repairs confers an advantage in that it prevents herniation of intracranial contents into the sinuses, which can make the reconstruction extremely challenging. Graft migration can also play a big factor in these cases as a result of brain pulsation. The long-term risk of brain herniation is not well documented in the literature however there are some case reports describing this problem (7, 8,9). Rigid repairs can be performed with autografts such as bone or cartilage (conchal or septal). We found the use of PDS to be advantageous as it can be trimmed to size and retains strength for a long period. In comparison to previous studies using PDS plates, the added advantage our wrap technique offers is easier placement of dural graft material due to the anchoring affect when introduced together as a parcel. This limits graft migration and allows better handling of the graft edges whilst reducing the herniated segment of brain. We have successfully undertaken this reconstruction in 3 patients to date, all of which have had good post-operative outcomes from their reconstruction. None of the 3 patients developed a CSF leak and flexible nasal endoscopy in clinic demonstrated a robust skull base repair with no brain herniation. Of the 3 cases 2 have been followed up to 12 months and discharged to the care of Neurosurgery.

We recommend the use of a PDS wrap in patients who have significant brain herniation at the time of surgery to support the repair in these larger skull base defects.

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5.2

The proper use of reconstructive material

Karan Jolly
Shahzada Khuram Ahmed
Anshul Sama

Book title: Cerebrospinal Fluid Rhinorrhea

Introduction

Over the last few decades Endoscopic Endonasal surgery has pushed boundaries, tackling a greater array of sinonasal, skull base and intracranial pathologies. A greater understanding of endoscopic anatomy has allowed development of new surgical corridors, enabling complex skull base resections. One of the challenges posed by this is the subsequent reconstruction required to prevent life-threatening morbidity, such as Cerebrospinal fluid (CSF) leak, meningitis, intracranial abscess and pneumocephalus. Advancements in reconstructive techniques has allowed for the evolution of endoscopic skull base techniques providing adequate separation of the sinonasal and intracranial compartments. The emergence of a range of flaps and biosynthetic materials have been pivotal in this journey. In this chapter we will discuss the use of reconstructive techniques and materials to allow for a robust skull base repair that seals the intracranial cavity from the nasal cavity.

Skull base repair requires meticulous replacement of the normal anatomical layers breached, the success of which can be measured by the absence of a post-operative CSF leak (1). CSF leak rates following endoscopic repair have fallen significantly from 30-40% to 6.7-11.5% (1,2); owed to better instrumentation, endoscopic technology and surgical materials and techniques such as vascularised nasoseptal flaps (3). Modern reconstructive techniques employ a combination of synthetic dural replacement drafts, autologous free grafts, vascularised flaps and synthetic tissue glues and sealants to achieve repair. Despite variations in techniques used, certain factors need to be considered in order to plan the most appropriate type of repair for each case. These include size of the defect, underlying pathology, tissue availability, flow rate of CSF, use of pre or post chemoradiotherapy and also patient and surgeon preference. We will aim to discuss these in an attempt to suggest optimal options for repair in different scenarios (4,5,6,7).

Materials

Free autografts

Free autografts include fat, mucosa, cartilage, bone and fascia (temporalis fascia or fascia lata) harvested from a donor site and implanted at the site of surgery; having the benefit of being readily available with no risk of tissue reaction (8). Fascial grafts serve to be an excellent underlay (subdural or extradural) and are the first option in a multilayer approach as well as an overlay graft (9). Intracranial fat graft can be used in combination to eradicate any dead space, for example in the sellar region. This provides an adequate

repair in low flow CSF leaks and smaller defects (<1cm) (9). The disadvantage of these grafts is the potential morbidity related to the donor site wound including infection, haematoma, scar and seroma. Free mucosal grafts from the turbinates or septum can be placed as an overlay for additional support, taking care to place it with the mucosal surface outwards to prevent formation of a mucocoele. The use of free cartilage or bone grafts provides rigid support in defects where there is high risk of herniation eg meningoencephaloceles arising from stenbergs canal (10). The use of this is again limited to smaller sized defects, in conjunction with dural underlay/overlay grafts. Free bone grafting is controversial where postoperative radiotherapy is to be considered due to risk of osteoradionecrosis and repair breakdown (4).

Intranasal	Extranasl
Mucosa (Inferior/middle turbinate/ nasal floor)	Fat (adipose)
Septal mucosa	Fascia (temporalis or fascia lata)
Bone (vomer)	
Cartilage (septum)	

Table 1. Free autologous graft material

Synthetic dural grafts

Over recent years there has been an increase in synthetic grafts that are used as dural substitutes for repair and have been used successfully during open middle and posterior fossa surgery (11,12). They can be used as alternatives to fascial/mucosal grafts for both intra and extra dural grafting, without additional donor site morbidity but at additional cost (8). These grafts are often made of a collagen matrix and come in many sizes, making them useful in larger defects as a single or multilayer repair or in combination with autologous tissue. A significant number of synthetic grafts contain animal extracts such as gelatin, which should be discussed with patients prior to their use. Polydioxanone plate (PDS) has been shown to be useful for rigid support in larger defects where bone or cartilage grafting may not be feasible. This has been demonstrated in the repair of large anterior skull base defects to prevent brain herniation (13). Use of synthetic grafts very much depends on surgeon preference, availability and cost implications. It is important to note, when using synthetic dural grafts, their enhancement in the early phases post-operatively can easily be confused with residual disease and radiologists should be made aware of this (14).

Vascularised flaps

Vascularised flaps can be divided into intranasal and extranasal in origin technical details of each has been discussed other chapters of this book. By

far the main workhorse of endoscopic skull base repair is the revolutionary Hadad-Bassagasteguy nasoseptal flap, first described in 2006 with several modifications since (9,15). Use of this flap however depends on the size of defect and availability of disease-free septal mucosa. It can be successfully used for defects anywhere from the posterior table of the frontal sinus to the clivus. Morbidity related to these flaps include nasal crusting and anosmia/hyposmia however its use encourages rapid healing (3,16). Studies demonstrate the use of vascularised flaps to be advantageous in larger defects measuring >3cm and with high flow CSF leaks, over free grafting especially if post-operative radiotherapy is planned (2,4,17,18). Nasoseptal flaps serve to be particularly useful in repair of ventral skull base lesions where CSF flow rates can be challenging (16). A review by Harvey et al analysing reconstructive techniques of the skull base demonstrated an overall 11.5 % CSF leak rate, 15.6% with free grafts and 6.7% with vascularised flaps respectively (2). Providing sufficient mucosa is available, bilateral non-adjacent nasoseptal flaps can be raised to cover almost 60% of the skull base (1). Where intranasal flaps are not possible, vascularised extranasal flaps can be utilised. These include the transfrontal pericranial flap for anterior defects and the temporoparietal fascial flap for middle and posterior fossa defects. Although very effective, these flaps have additional morbidity related to external approaches (16).

Absorbable sealants and glues

A wide range of sealants and glues are available as adjuncts to reinforce the primary reconstructive layers at the skull base. These are often applied at the end of the reconstruction again in a multilayer fashion. Commonly SURGICEL® (Ethicon inc, New Jersey, USA) is used to provide haemostasis and a scaffold onto which further glues are applied. Fibrin based adhesive glues such as TISSEEL**® (Baxter, Illinois, USA)** and Evicel® (Ethicon inc, New Jersey, USA) are used to hold the layers in place and prevent graft migration. Fibrin sealant patches such as TachoSil**®** (Baxter, Illinois, USA) can also be used as an overlay over the initial duraplasty instead of nasoseptal flaps or free mucosal grafts as an additional layer of support. The nasal cavity is then typically packed with absorbable (NasoPore**®** - Stryker, Michigan, USA) or non-absorbable (MEROCEL**®** - Medtronic Xomed, Jacksonville, FL, USA) products to provide further support and haemostasis. Whilst commonly used, it is very important for surgeons to familiarise themselves with the ingredients of these products. A significant proportion of them, including synthetic dural grafts, contain traces of animal or human derivatives which may conflict with patient's religious or personal beliefs. It is therefore worth discussing the use of these adjuncts with patients prior to surgery as there are many alternatives (19).

Reconstructive factors

When planning any endoscopic skull base procedure, the pre-operative scans must be carefully assessed to try and estimate the size and site of the defect. Depending on the underlying pathology and health of the sinonasal cavity, this can equip the surgeon with a range of potential reconstructive options.

Size and site

The size of the defect can be measured preoperatively with the benefit of images and intraoperatively. Intraoperatively, neuropatties can be used to estimate the size or more definitively a surgical paper ruler can trimmed and held next to the defect intranasally. The size of the defect is important for reconstruction dictating the grafts options that may be considered. In large resections where extranasal vascularised flaps are to be used, CT/MRI imaging can be used to measure the size of the flap. To achieve a successful duraplasty where segments of dura are resected/absent, the intradural inlay graft must be 30% larger than the defect size (3).

A recent study looking at factors affecting outcomes of skull base repair showed that the size and site of the defect did not affect the success of the repair (3). This being said, the authors used different repair techniques for each of the different locations based on their experience and patient factors. Heterogeneity of repair techniques between different case series in the literature makes analysis of these techniques very challenging. A well-established factor for repair strategies used at each location of the skull base is the rate of CSF flow (3,4).

Frontal sinus, ethmoidal roof and planum sphenoidale defects require adequate access with a frontosphenoethmoidectomy and can be successfully repaired with a multi-layered approach using an autologous or synthetic intradural graft 30% larger than the defect to allow adequate inlay followed by an extradural layer of the same material placed under the bony defect and finally a third overlay of free mucosal or synthetic dural graft. Small cribriform cleft defects (<1cm) may be repaired with one intradural and then a single extradural overlay technique using free autologous graft or synthetic dural graft. Care must be taken during extradural dissection to create a pocket for the graft as the dura is very thin in this region and can easily tear. Where there is a visible dural tear in this region, a free graft (fat, fascia or synthetic) can be tucked in as an intradural layer followed by the overlay layer for a more robust repair.

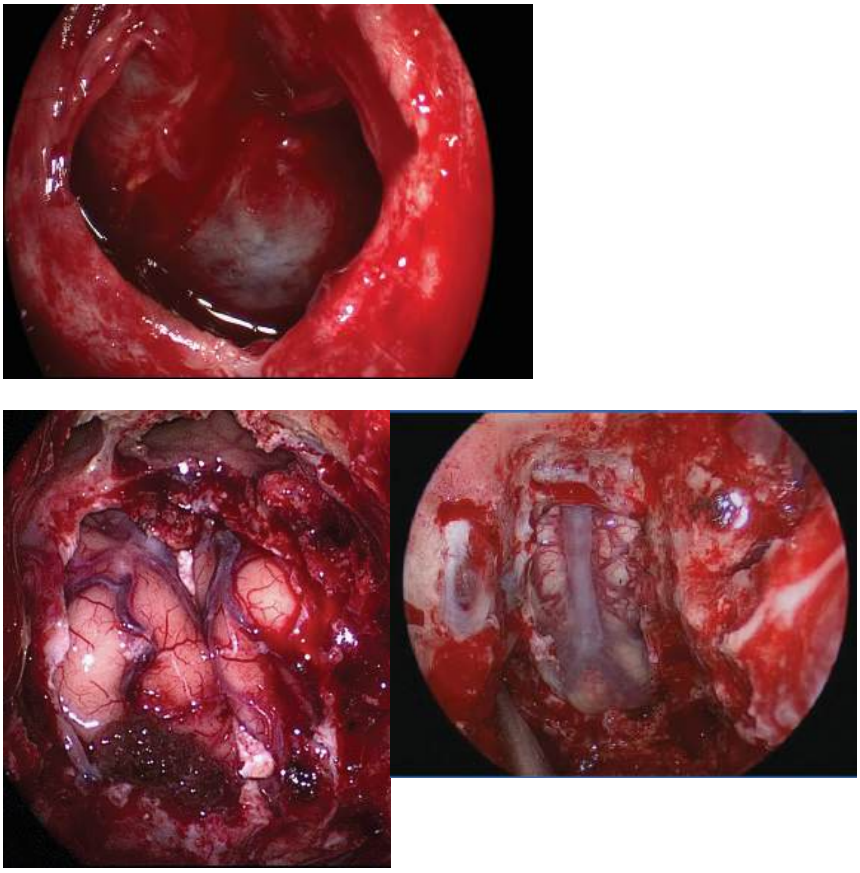

Figure 1 demonstrating sellar, cribriform and clival defects

Larger craniofacial resections are best repaired with a multi-layered approach with an intracranial intradural, intracranial extradural and then an extracranial overlay. For any of these layers free fascial or synthetic dural grafts may be used with a vascularised flap preferred as the final overlay, promoting faster healing of these larger defects. Often this will be a nasoseptal flap however in the absence of healthy mucosal flap, a pericranial flap can be used successfully. Anterior cranial fossa defects are often associated with low CSF flow and easier epidural dissection as well as having better bony support for reconstruction. In addition, the frontal lobes serve as extra support for the inlay grafts (20,21). However, large defects associated with brain herniation may occasionally need to be supported with a rigid repair layer as discussed earlier (13). Figure 2 demonstrates a multi-layered approach to repairing an anterior cranial fossa approach with a number of different materials available. These can be used alongside a range of tissue sealants/glues and absorbable packs.

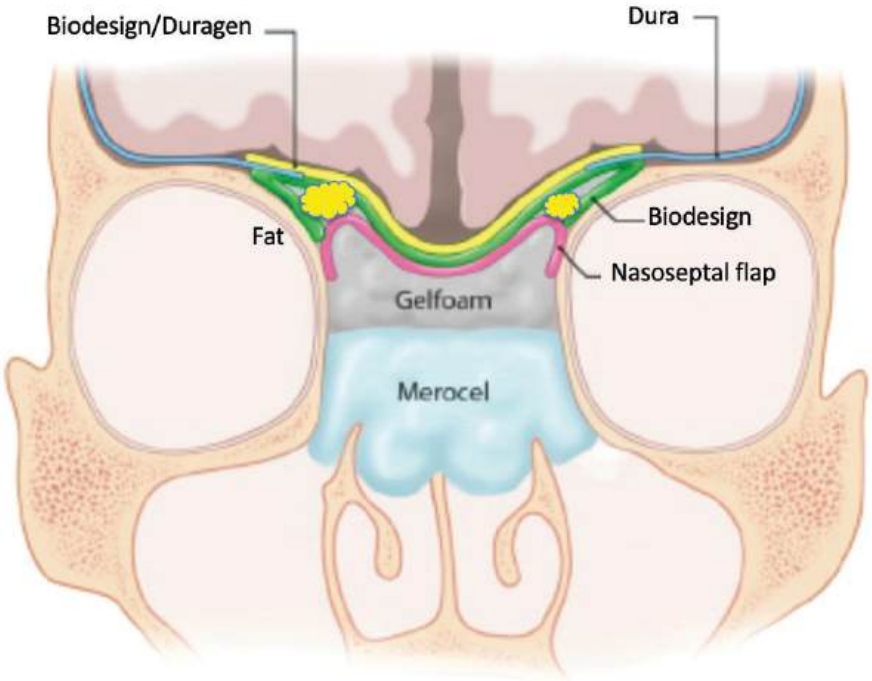

Figure 2: An image demonstrating a multi-layered approach to repairing an anterior cranial fossa defect

Large sellar and clival defects are also repaired with a multi-layered approach with an intradural and extradural duraplasty. A third mucosal or synthetic graft layer may be used if there is no breach of the arachnoid or a low flow CSF leak, however in the presence of a high flow leak a nasoseptal flap offers better outcomes of <5% leak rates in some studies (22).

Pathology

An understanding of the pathology can serve to be useful for appropriate repair. Certain lesions are associated with higher risks of postoperative leak, for which vascular flaps should be considered. These include meningiomas (extensive defect with dural and arachnoid disruption), craniopharyngiomas (breach of arachnoid) and patients who are morbidly obese or with high suspicion of Idiopathic Intracranial Hypertension (IIH). Malignant skull base lesions often require expanded approaches to gain negative resection margins and options for intranasal vascular flaps can be limited. In this case extranasal vascular flaps may be the best option. The use of preoperative or postoperative radiotherapy is also very important, as it is associated with a higher rate of failure (15). In these cases the use of bone grafts or synthetic grafts are usually avoided due to higher risk of infection and extrusion (4). Instead, vascularised flaps confer

an advantage in that they withstand the effects of radiation better, resulting in a better repair rate (9).

Advances in endoscopic skull base reconstruction are partly owed to implementation of improved and meticulous reconstructive techniques. This being said, reconstruction can be challenging and should be planned before the day of surgery with a range of different options available. Although there is a wide degree of heterogenicity in repair techniques used between surgeons, we propose a step wise approach. One of the most important factors for success of repair is the extent of CSF leak. Small (<1cm) uncomplicated defects with no or low CSF leaks may be repaired with a single layer approach but for other defects we recommend a multi-layered approach. We summarise our recommendations on the use of reconstructive materials for skull base repair (table 2).

	Exposed dura or vessels with no CSF leak	**Low flow CSF leak**	**High flow CSF leak**
No of layers	Single	Multiple	Multiple
Intradural intracranial	No dural defect, overlay technique with: Autologous (Fascia/Fat/ mucosa) or synthetic dural graft overlay technique or Fibrin sealant patch (Tachosil)	Autologus (fascia/ fat) or Synthetic dural graft	Autologous (fascia/ fat) or Synthetic dural graft
Extradural intracranial		Autologous (fascia/ fat) or Synthetic dural graft	Autologous (fascia/ fat/bone/ cartilage) or Synthetic dural graft
Extracranial overlay		*Optional:* Fibrin sealant patch or Autologous (Fascia/ mucosa)	*Recommended:* Nasoseptal flap or Extranasal vascularised flap if nasoseptal flap not available

Table 2: Recommendations on the use of reconstructive materials for skull base repair

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5.3

The intra-operative use of biological products: A multi-centre regional patient perspective of a potential consenting conundrum

Karan Jolly
Adnan Darr
Anna Alsandiou
Duncan Bowyer
Shahzada Khuram Ahmed

Clin Otolaryngol. 2019 Sep;44(5): 831835

Abstract

Introduction
An upward trend in the utilisation of human and animal derived products has been recently described within the literature, though religious consensus regarding their use remains sparse. Variations in inter-religious practice results in significant uncertainty and ethical conflict for patients undergoing surgical intervention. Our novel survey sought to explore patient opinion on the intra-operative use of a range of such products.

Method
National ethical approval was obtained, and a questionnaire was devised, on the intra-operative use of biological products. Potential motives for objection if applicable, and circumstances where the use of such products could be deemed permissible were also ascertained. Questionnaires were distributed across three hospitals within the West Midlands, within Otolaryngology outpatient departments over a two-week capture period.

Results
560 questionnaires were distributed, of which 534 responses were received. Forty-four percent of respondents cited an importance of being informed of the potential use of biological products, with 17% actively objecting to their use intra-operatively. An overwhelming majority (91%) would permit the use of such products in emergency circumstances. Products of porcine origin were the most frequently objected to biological product. Eighty-one percent cited no objections to the ingestion of biological derivatives.

Conclusion
Objections to the intra-operative use of biological products can be multi-factorial in origin. Their potential use should be discussed pre-operatively, with concise documentation of acceptance or objection on the surgical consent form and within the patient casefile. Discussions around the availability of potential alternatives is also imperative in the decision-making process. Failure to routinely implement such clinical practice could have severe legal ramifications.

Introduction

In modern day medicine, the utilisation of human and animal derived products has become routine practice. Animal derived medications, dressings, implants and tissue grafts have been used across medical and surgical specialities for decades, but the ethical considerations around the consenting process is often overlooked by both healthcare professionals and patients (1-5). A general religious consensus regarding the use of biological products has been poorly described, mainly due to variations in inter-religious practice. Any uncertainty could be the cause of religious and/or ethical conflict for patients undergoing treatment with the use of such products. Many medications and implants contain compounds derived from porcine or bovine material, the most common of which is gelatin. Gelatin is a collagen protein, and due to its source of origin, its use within the field of medicine has been extensively debated amongst various religions (1). Previous studies demonstrated that Christians (inclusive of Jehovah's witnesses), Buddhists and Jews permitted the use of drugs, dressings or implants with animal or human derived content. Hindus and Sikhs objected to the use of products containing bovine material, with Muslims objecting to the use of porcine derived products (1,6). Despite this, the general consensus amongst religious leaders, in instances where alternatives are unavailable or life-threatening situations are encountered, is that the use of animal derived products is permissible in an attempt to preserve life (1,7). Such a belief can vary based on cultural diversity within each religion as well as personal beliefs and the interpretation of what is a life-threatening situation. The only caveat to this is amongst Jehovah's witnesses, where the use of blood derived products is strictly forbidden.

Within the field of surgery, a variety of synthetic surgical products are available, a significant proportion of which are derivatives of animal and human content. These can include dressings and material used to provide haemostasis, promote wound healing and reduce the potential for infection. Examples of such products within the field of otolaryngology have been listed in table *1*. Recent trends have shifted towards the use of implants and synthetic graft material to repair defects, whilst simultaneously promoting wound healing and reducing the need to take autologous grafts that may need additional skin incisions and potentially add to the theatre time taken. Although recommended, anecdotally, a significant proportion of surgeons do not fully discuss the use of biological products pre-operatively with patients, despite their wide use within the field of Otolaryngology. Patients may object, based on their religious and personal beliefs, to the use of such products, stressing the importance of raising the awareness of their potential use, whilst simultaneously presenting alternative solutions. The findings of our study will serve to identify whether informed consent for the intra-operative use of biological products should be

explicitly added to the standard surgical consent form which would facilitate the consenting process, thus altering current routine clinical practice.

Otology		**Use**
Gelfoam®	Porcine gelatin	Middle/outer ear dressing
Spongistan®	Porcine gelatin	Middle/outer ear dressing
Biodesign otologic graft	Porcine small intestine submucosa	Tympanic membrane repair
Rhinology / Skull Base		*Use*
Tisseel®	Human thrombin Human albumin	Tissue glue
Floseal®	Bovine gelatin	Haemostasis
Surgiflo®	Porcine gelatin + Human thrombin	Haemostasis
Biodesign® sinonasal graft	Porcine small intestine submucosa	Septal perforation repair
Biodesign® duraplasty	Porcine small intestine submucosa	Skull base repair
Tachosil®	Equine collagen + Human thrombin	Skull base repair
Duragen®	Bovine collagen	Skull base repair
Head and neck		*Use*
Tracheoesophageal valve cap – blomsinger®	Bovine gelatin	Introduction of valve
Dermal regeneration template – integra®	Bovine collagen Shark derivatives	Skin defect repair

Table 1: Synthetic biological products within the field of otolaryngology.

Method

Ethical consideration

Prior to starting the study, the local Research and Development team was approached with regards the how best to approach the topic. Firstly, National ethical approval (REC: 18/LO/0597) was obtained in order to approach patients with a questionnaire, aimed at exploring patient opinion on the intra-operative use of biological products. In addition to this questionnaire we handed out patient information leaflets informing them of the purpose of our study and whom they should contact if they had any further queries. We also highlighted

that should patients be going on to have surgery, they should discuss the use of biological products with their consultants if felt necessary. All consultants in the department were made aware of this should any patient wish to bring this up with them in preparation for their surgery.

Our questionnaire simultaneously assessed potential motives for objection where applicable, and circumstances where the use of such products could be deemed permissible. Demographic data including gender, age, religious and dietary background was collated, as well as the association of such beliefs with religious bodies. Questionnaires, along with patient information leaflets, were distributed to all patients attending the Otolaryngology outpatient department over a two-week capture period across three hospitals (two trusts) within the West Midlands, UK. Contact details were provided on the information sheet, for patients to discuss any concerns the study raised with the principal investigators. The lower age limit for inclusion was 16 years. Alongside this, at the study sites, we identified all elective Otolaryngology procedures over a 3-month period and reviewed the operation notes to ascertain cases where biological products had been used.

Results

Questionnaires were distributed and collected back from a total of 560 patients, of which 534 (95%) responded. Twenty-six patients abstained from partaking in the questionnaire, of which 22 cited no reasons, and the remaining 4 deeming the survey irrelevant for the purpose of their attendance.

Of patients that responded, there was an equal gender distribution (males=264 and females n=262). Eight respondents abstained from answering their gender. The largest cohort was in the 50-70yrs group (n=203), followed by 30-50yrs (n=150), >70yrs (n=105), and 16-30yrs (n=69). 7 respondents abstained from detailing their age group. Of the participants who objected to the use of biological products (n=92), the younger population felt more strongly against their use, with 33% being 30-50yrs and 21% 16-30yrs (figure 1). Seven percent of the cohort identified themselves as vegans/vegetarians.

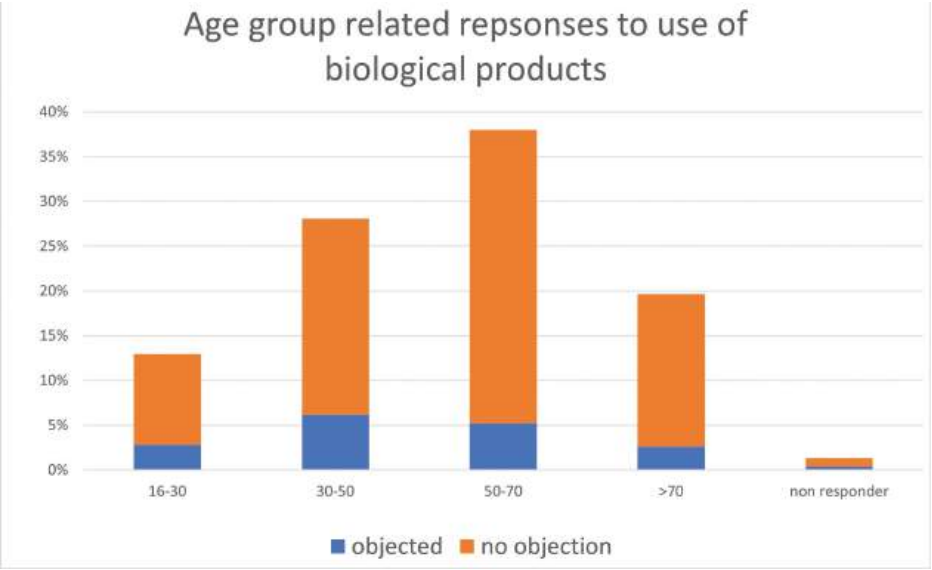

Figure 1

Amongst our surveyed cohort, Christianity (n=293) was identified as the most frequently adopted religious belief, followed by no beliefs (n=129), and Islam (n=45). Thirty-two patients abstained from commenting, and the remainder of the cohort comprised of Sikhism (n=9). Hinduism (n=7), Jehovah's witnesses (n=3), Judaism (n=2) and Buddhism (n=1). 13 (*table 2*).

Christianity	293
No beliefs	129
Islam	45
Not wish to disclose	32
Other	13
Sikhism	9
Hinduism	7
Jehovah's witness	3
Judaism	2
Buddhism	1

Table 2

Of the surveyed cohort, 44% (n=237) cited that they would like to be informed of the potential use of any biological products intra-operatively, should they undergo a surgical procedure. Seventeen percent of our cohort (n=92) actively

objected to the use of any biological products being used intra-operatively (figure 2). Of these there was a gender predominance (53 female: 35 male). Products of porcine origin were the most frequently objected to biological substance (n=44), followed by all animal derived products (n=39), bovine (n=28) and fish/ human (n=17) respectively (*figure 3*).

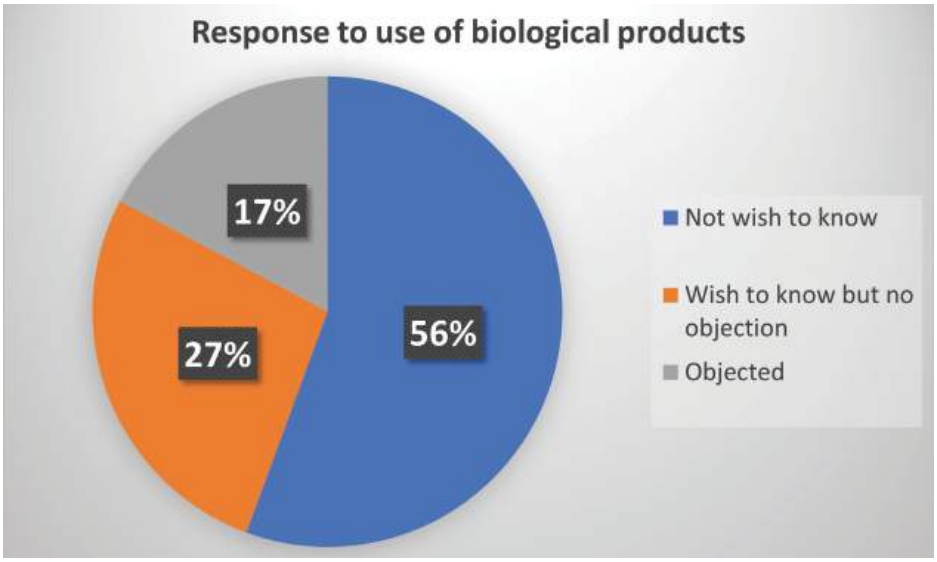

Figure 2

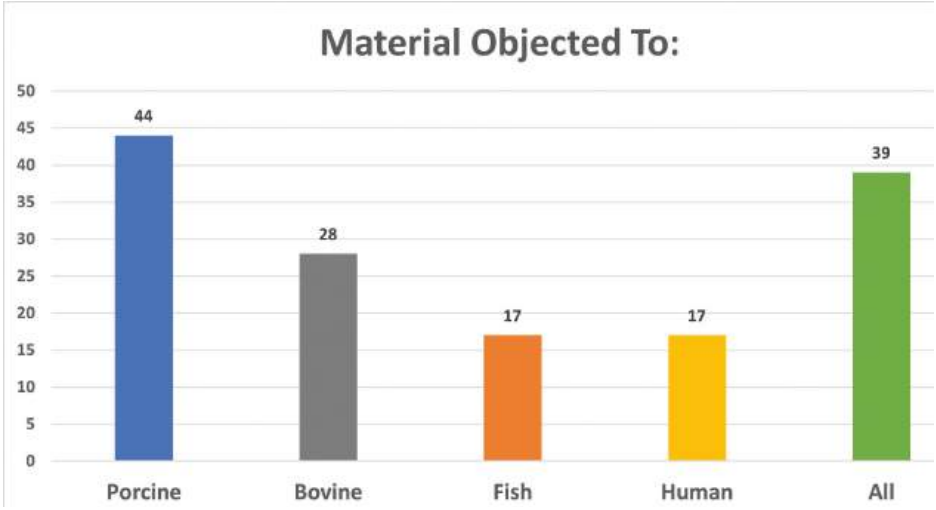

Figure 3

Our surveyed cohort were then asked about objections to ingested biological derivatives, of which 19% (n=100) cited an objection in comparison to the 17% (n=92) that initially objected to the use of biological products. We then asked respondents, whether they would object to the use of biological products intra-operatively if their condition was deemed life-threatening/ critical. An overwhelming majority of 92% would permit the use of biological products (n=490) under such circumstances.

Our cohort were finally questioned on whether any of their decisions were likely to be a reflection of a religious organisation linked to their religious beliefs, with 49% (260/534) stating that their religious body had no effect on their responses and 6% (31/534) of respondents stating that their religious body did have an impact on their responses. Religious beliefs of those objecting varied widely, with the largest group being Islam (37%, n=32) followed by Christianity (30%, n=28) and then no religious beliefs (15%, n=14). Due to fewer participants being captured from the remaining faiths, a subgroup analysis could not be undertaken. *Table 3* represents the percentage of respondents from individual religious groups who objected to the use of biological products. Of the 48 vegan/vegetarians captured, 46%, n=22 objected to the use of animal derived products.

Islam (n=34)	37%
Christianity (n=28)	30%
No-belief (n=14)	15%
Did not specify (n=8)	9%
Sikhism (n=4)	4%
Jehovahs (n=2)	2%
Hinduism (n=1)	1%
Other (n=1)	1%
Buddhism (n=0)	0%
Judaism (n=0)	0%

Table 3 Declared religious beliefs of patients objecting the use of biological products

Discussion

The use of biological products for medicinal purposes has been an area of contention for some time (6,8). The use of synthetically derived products across all surgical disciplines has gained prominence, to the extent where their use is now routine practice. In the hospitals surveyed, over a three month period,

557 elective otolaryngology procedures were performed, of which 120 (22%) used at least one biological product. These products were more likely to be used in otological procedures followed by skull base procedures. A detailed awareness of the constituents of such products can be lacking amongst surgical practitioners, despite their widespread use. Previous studies have demonstrated that amongst the largest religious faiths, Hindus and Sikhs most often did not consent to the use of bovine or porcine derivatives, whilst the Muslim community tended to refrain from the use of porcine derivatives alone. Christians, Jewish and Buddhist communities permitted the use of biological products, with Jehovah's witnesses solely objecting to the use of blood products (8). What such studies fail to ascertain are the widespread variations in religious practice amongst the religious subgroups accounting for geographical location, as well as individual beliefs. As such, general religious recommendations act as guidance, rather than strict protocol. A UK study within this subject area is lacking, despite the potential legal ramifications of using biological products without explicit consent. We believe that the use of biological products is now so frequent that a paragraph about this should be incorporated in the standard pre-printed hospital consent from to assist surgeons in discussing this topic during the consent process.

Our study highlights the importance of routinely informing patients on the potential use of biological derivatives in an era of increasing clinical transparency, and patient autonomy. A large number of our surveyed cohort (44%), formed of various religious beliefs and age groups expressed a preference to being informed of the potential intra-operative use of biological products. Although a smaller number of patients objected to their use (17%), not only must patient autonomy be maintained but all patients should be provided with sufficient information to permit both an informed and voluntary decision about the procedure they are consenting for.

One limitation of our study was the lack of representation from religious sects other than Islam, preventing detailed interfaith/ subgroup analysis. Our results suggest that objections to the use of biological derivatives is not solely dependent on religious beliefs, with a significant number of atheists also objecting (15%). An individual's perspective on such products could change depending on the severity of their condition and the urgency of any surgical intervention, which is difficult to assess within an outpatient setting. However, we still feel that it would not detract from good medical practice of respecting patient autonomy and the need for shared decision making.

Although our study was centered around products commonly used intraoperatively as surgical adjuncts, we are well aware of the wide spread use

of animal/ human derived products throughout all specialties both surgical and non-surgical. Studies have demonstrated the presence of gelatin in up to 80% of medicinal capsules, most of which patients may not be aware of, with certain drugs like Insulin known to be derived from animals (porcine/bovine), which could conflict with religious values (9). Vegans/ vegetarians may object to the use of drugs like Propofol, which contain egg. Consequently, this highlights the need for increased awareness of this topic across all healthcare workers, in order to align treatment options with patient's religious, ethical and personal beliefs.

Conclusion

The intra-operative use of biological derived products may conflict with religious or personal patient values, with objections to their use often being multi-factorial. The potential use of these products should be explicitly discussed incorporating alternatives where available. Clear documentation of acceptance or objection should be recorded within the patients' notes and on surgical consent forms. Failure to integrate such a protocol into routine clinical practice may not only result in patient dissatisfaction and distress, but could also potentially have legal ramifications. We outline some guidance on alternatives that may be considered for commonly used biological products in Otolaryngology (table 4).

Otology	
Gelfoam ® / spongistan®	Otopore
Biodesign® otologic graft	Perichondrium / Temporalis fascia
Rhinology / Skull Base	
Tisseel®	Nasopore/ Surgicel Bipolar/monopolar diathermy Adrenaline-soaked gauze Surgery to control bleeding vessels.
Floseal®	
Surgiflo®	
Biodesign® sinonasal graft	Tensor fascia lata Pericranium
Biodesign® duraplasty	
Tachosil®	
Duragen®	
Head and neck	
Tracheoesophageal valve cap – blomsinger ®	Provox vega valves
Dermal regeneration template – integra ®	Split thickness skin graft

Table 4 – alternatives to commonly used biological surgical products (in right column)

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5.4

Endoscopic transsphenoidal surgery reconstruction using the fibrin sealant patch Tachosil®

Karan Jolly
Keshav Gupta
Ofuchi egbuji
Paresh Naik
Shahzada Khuram Ahmed

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Abstract

Introduction

The incidence of CSF leak following endoscopic transsphenoidal surgery remains the most important measure in the success of any repair. The nasoseptal flap (NSF) has played a pivotal role in reconstructing defects. However, morbidity associated with the NSF includes bleeding, septal injury, altered smell and crusting. Tachosil® is an absorbable fibrin sealant patch that promotes haemostasis and wound healing. The purpose of this study was to evaluate the effectiveness of Tachosil® to repair intraoperative defects during an endoscopic transsphenoidal approach.

Materials and Methods

All patients who underwent an endoscopic transsphenoidal approach with the use of Tachosil® at the Queen Elizabeth Hospital Birmingham, between January 2013 and June 2020 were retrospectively analysed. Tachosil® was used as an overlay patch over of the bony defect, in a multi-layered repair depending on the defect and grade of CSF leak. The primary outcome measure was post-operative CSF leak.

Results

A total of 52 primary procedures where Tachosil® was used as the overlay were analysed. There were 23 (44.2%) intraoperative CSF leaks. The overall post-operative CSF leak rate was 7.8% (n = 4), with all cases having had a Tachosil® overlay reconstruction with no NSF. A formal NSF was harvested in only 5 cases alongside the Tachosil® patch, where a grade 2 or more leak was identified at the time of the primary procedure, none of which developed a post-operative leak. No patient had any post-operative adverse outcomes that were attributed to Tachosil®.

Conclusions

We believe this to be the largest case series evaluating the endoscopic use of Tachosil® in skull base reconstruction. Our data shows that in endoscopic transsphenoidal approach, Tachosil® may be used safely in a multi-layered approach as an effective alternative to the NSF in low flow CSF leak cases, or alongside a NSF in higher flow leaks.

Introduction

Endoscopic transsphenoidal surgery has become a favourable approach for sellar and para-sellar lesions with excellent outcomes and potentially better rates of normal pituitary gland function preservation compared to transfacial or microscopic approaches (1-3). The advent of powered instruments, surgical navigation systems and improved visual optics have allowed surgeons to tackle more complex skull base pathology. The success of these procedures has relied upon a robust repair and subsequent reduction in post-operative complications, such as cerebrospinal fluid (CSF) leak, meningitis and pnuemocephalus. The incidence of CSF leak post-operatively remains the most important measure in the success of any repair, over the years falling from 30-40% to between 6.7% and 11.5% for skull base defects (4, 5). Leak rates for purely sellar pathology has been reported to be up to 15% (0.8-15%), with more recently authors citing rates of between 1-4% in carefully selected patients (6-8).

Repair of skull base defects requires careful assessment on a case-by-case basis. It is dependent on the site and size of the defect but also the underlying pathology and CSF flow rate, requiring careful individualised assessment. The most methodical approach is that of a multi-layered reconstruction, replacing the layers of the skull base breached using a combination of autologous and synthetic grafts/materials. For transsphenoidal approaches, the description of the vascularised nasoseptal flap (NSF) has played a pivotal role in reconstructing large defects with high flow CSF leaks, significantly reducing post-operative leak rates (5, 9). Despite its effectiveness, morbidity associated with the NSF includes bleeding, septal injury with nasal saddling, altered smell and nasal crusting (9-11).

Tachosil® (TakedaPharma, Roskilde, Denmark) is an absorbable fibrin sealant patch made up of equine collagen coated with human fibrinogen and thrombin. It serves to provide haemostasis and promote wound healing. It has been demonstrated to be effective and safe to use in a variety of different surgical procedures with a decrease in post-operative complications and hospital stay (12, 13). In our centre, Tachosil® was mostly used in cases where there was no significant intra-operative CSF leak was identified or in low flow grade 1 leaks, in an attempt to preserve nasal septal mucosa and reduce associated morbidity.

The purpose of this retrospective study was to evaluate the effectiveness and safety of Tachosil® when used to repair defects during an endoscopic transsphenoidal approach in our experience.

Materials and Methods

Study design

All patients who underwent an endoscopic transsphenoidal, approach at the Queen Elizabeth Hospital Birmingham, between January 2013 and June 2020 were identified by the coding department. From this search result, cases where Tachosil® was used as part of reconstruction were identified. Case notes for these patients were analysed and data was extracted for patient demographics (age, sex), body mass index (BMI), prior irradiation and procedure details (primary procedure, intra-operative CSF leak, reconstruction technique and histology). The primary outcome measure was post-operative CSF leak.

Surgical technique

In all cases of transsphenoidal approach (TSA) to sellae or clival lesions, bilateral nasoseptal rescue flaps were raised first. This is done using a Colarado microdissection needle where the upper incision of the nasoseptal flap pedicle is made and the pedicle mucosa elevated inferiorly off the face of the sphenoid and rostrum on both sides. A limited posterior septectomy was then performed and a wide sphenoidotomy was made using a combination of Kerisons rongeurs and a high-speed diamond burr drill. After the primary pathology was addressed, the repair technique varied depending on the precise site and size of the defect as well as the CSF leak flow rate.

In sellar/parasellar lesions, identification of any intra-operative CSF leak after initial resection was graded (0-3), with the aid of a valsalva manoeuvre (table 1) (14). One layer of surgicel (oxidized cellulose, EthiconInc, Johnson&Johnson company; Somerville, NJ) was placed within the sella defect and, in the presence of a CSF leak, an extradural dural graft (Duragen®, Integra lifesciences, New Jersey, United States) was placed under the bony edges of the sellotomy defect. Where no CSF leak was identified, placement of Duragen® was omitted. A fibrin sealant patch (Tachosil®, TakedaPharma, Roskilde, Denmark) was then cut to size, making sure it was 30% larger than the bony defect, soaked in sterile saline and placed over the bony edges of the defect, previously denuded of mucosa.

The reconstruction was then tested with a valsalva manoeuvre and then held in place with further layers of Surgicel and tissue glue (EVICEL® fibrin sealant, Johnson & Johnson medical devices, New Jersey, United States) (figure 1). For other TSA to non-sellar lesions, reconstruction involved an underlay Duragen® graft with an overlay of Tachosil®. If there was evidence of a high flow CSF leak or in higher risk patients (high BMI, communication with suprasellar cisterns) a nasoseptal flap (NSF) was harvested and placed over the Tachosil®. The nasal cavity was then packed with absorbable Nasopore® (Stryker Corporation, Michigan, United States). Lumbar drains were not used in our practice post-operatively.

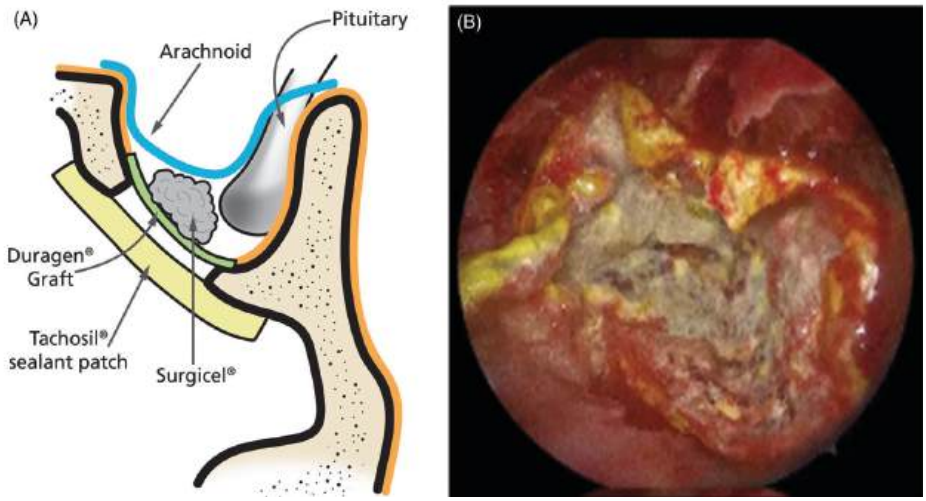

Figure 1. LEFT: Schematic to show multi-layered reconstruction of sella defect with Tachosil®. RIGHT: Intra-operative image of Tachosil® placement during endoscopic sella repair.

Results

A total of 52 primary procedures were performed on 51 patients (one patient required revision surgery for debulking of residual clival chordoma) between 2013 – 2020. Tachosil® was used as the overlay in all procedures. All procedures that used Tachosil® were performed by a single otolaryngology surgeon (S.K.A), with no neurosurgical involvement. The decision to use Tachosil® was based on the presence of an intraoperative grade 0 or 1 CSF leak. No patients were excluded. The mean age of included patients was 44 years with an average BMI of 29.8. There were 39 patients (76.5%) with a BMI greater than 25. Table 1 summarises the patient demographics.

Patient characteristic	
Mean age ± SD (range), years	44 ± 16.1 (18 – 83)
Male	21 (41.2%)
Female	30 (58.8%)
Mean BMI ± SD (range), kg/m^2	29.6 ± 7.5 (18.3 – 59.6)

Table 1. Patient demographics of included patients. SD = standard deviation.

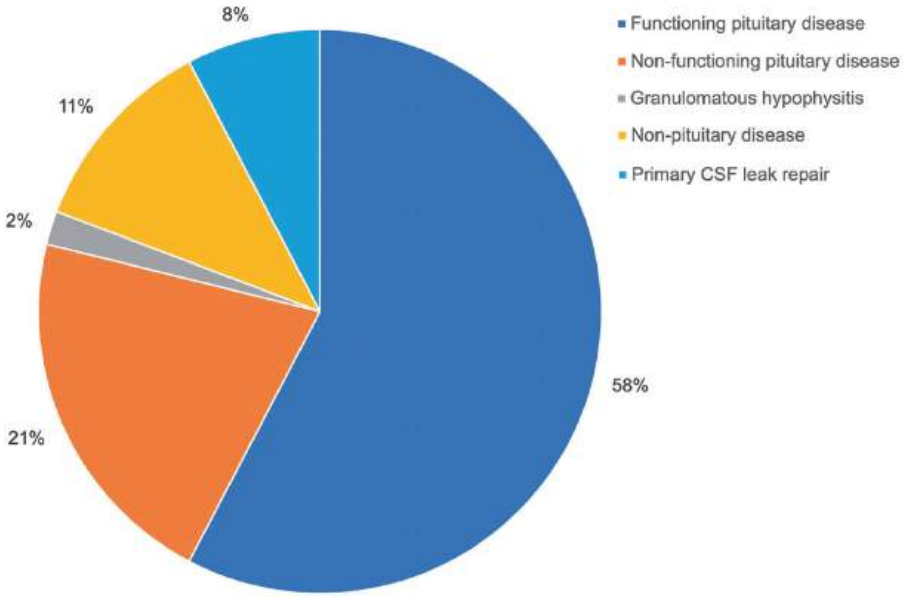

Figure 2. Distribution in pathology for patients who had endoscopic transsphenoidal surgery.

Of the procedures performed, 42 (80.8%) were pituitary lesions of which 30 (71.4%) were functioning adenomas and 11 (26.2%) were non-functioning adenomas and one (2.4%) case of granulomatous hypophysitis. Four (7.7%) patients underwent TSA repair of a primary spontaneous CSF leak (two lateral sphenoid defects and two planum sphenoidale defects) and the remaining six patients had other non-pituitary pathology (11.5%). There were three chordomas in two patients (one patient required revision surgery), one Rathke cleft cyst, one adenoid cystic carcinoma and one meningioma identified following biopsy of a cavernous sinus lesion. This distribution is summarised in figure 2.

Four (17%) were grade 2 and the remaining 16 (70%) were grade 1 leaks. The overall post-operative CSF leak rate was 7.8% (n = 4). Table 2 summarises the breakdown of CSF leaks according to pathology. All post-operative leak patients had a Tachosil® overlay reconstruction with no formal NSF harvested. These procedures were four endoscopic pituitary lesion excisions (two for functioning adenomas, two for non-functioning adenomas). Three of the pituitary cases were identified intra-operatively as having CSF leaks (1 grade 1 and 2 grade 2) and one of the four patients previously had stereotactic radiosurgery following 2 earlier procedures for acromegaly. From the total patient group, there were 5 (9.6%) cases where a NSF was harvested and used in addition

to Tachosil® based on an intra-operative finding of a grade 2 or more leak. These were for three cases of clival chordoma all of which had grade 3 leaks, one sphenoid meningoencephalocele and one revision pituitary lesion excision for acromegaly both having grade 2 leaks. A lumbar drain was used in two cases, both for excision of clival chordomas. No patient had any post-operative adverse outcomes that were attributed to Tachosil®.

	Cases	Intra-operative CSF leak	Post-operative CSF leak (%)
Functioning pituitary adenoma/lesion	30	13 (43.3%)	2 (6.7%)
Non-functioning pituitary adenoma/lesion	12	5 (41.7%)	2 (16.7%)
Non-pituitary disease	6	1 (16.7%)	0 (0.0%)
Primary CSF leak repair	4	4 (100.0%)	0 (0.0%)
Total	52	23 (44.2%)	5 (9.6%)

Table 2. Breakdown of intraoperative and post-operative CSF (cerebrospinal fluid) leaks.

Of the 52 total procedures, there were 23 (44.2%) intraoperative CSF leaks of which four were primary CSF leak repairs. Of the 23 cases, three (13%) were grade 3 (clival chordomas),

Discussion

Endoscopic endonasal approaches to ventral skull base pathology has become the gold standard across the world, with comparable if not better outcomes and significantly reduced morbidity in comparison with open or microscopic approaches (15). Despite increased experience in endoscopic skull base surgery, one of the major challenges remains reconstruction. The success of any procedure is determined not only by complete disease resection, but also adequate reconstruction of the defect and therefore a reduction in post-operative morbidity.

Endoscopic TSA remains very popular for management of primary pituitary lesions, lesions of the anterior cavernous sinus and also spontaneous CSF leaks. Depending on the extent of disease, intra-operative CSF leak in this region is not uncommon and ranges from 15-30% for pituitary pathology (16-18). One of the greatest advances in repairing skull base defects endoscopically came from the description of the vascularised NSF (4,5,10). Two systematic reviews

demonstrated that CSF leak rates with the use of the NSF fell significantly from 15.6% to in the region of 6.7%-8.5%, with more recent literature showing success rates as low as 5% (5, 19). The greatest advantage of using a NSF over avascular grafts was seen amongst clival defects and high flow CSF leaks (19,20). Despite this, skull base reconstruction remains varied partly due to the range of materials available but also individual surgeon experience and a range of patient factors including size, site of defect, flow of CSF leak, previous radiotherapy and pathology (10). The widely accepted practice is to repair defects in a multi-layered approach.

Tachosil® is a haemostatic sealant patch made from equine collagen coated with human thrombin and fibrinogen. When in contact with tissue and blood it triggers the coagulation cascade encouraging haemostasis and adherence to the wound. It originally gained popularity in vascular and cardiothoracic surgery, finally extending its use into abdominal surgery. As of 2017 it was approved for use as a dural sealant in open neurosurgical operations. Studies have demonstrated its use in open dural repair to be as effective as other conventional techniques currently used with low rates of CSF leak (21). More recently, its use in microscopic TSA has been investigated with positive outcomes but there was only one recent paper evaluating its use in endoscopic TSA surgery (22). In this particular paper, Tachosil® was used to repair sella diaphragm defects in 24 patients with only 1 patient developing a CSF leak post-operatively. In all these cases a NSF was used in addition to Tachosil®.

Our results demonstrate equivocal post-operative CSF leak rates with the use of Tachosil® to what is reported in the literature (5, 19). We believe this to be the largest case series evaluating the endoscopic use of Tachosil® in skull base reconstruction. Previous studies have alluded to the use of Tachosil® intradurally in a multi-layered approach to repair arachnoid defects. We promote its use as an overlay substitute in skull base defects as a potential alternative to the autologous fascia and NSF in ventral skull base lesions in the absence of intra-operative CSF leaks or in the presence of a low flow grade 1 leak. Of the 16 that had intra-operative grade 1 leaks in our series, 15 (94%) were successfully repaired with a Tachosil® overlay. The benefit being that it reduces morbidity associated with use of the NSF but also its use in scenarios where reconstructive options are limited. These include cases of sinonasal malignancy, mucosal inflammatory disease, iatrogenic injury to the pedicle of the NSF and post irradiation or revision surgery.

One of challenges of using Tachosil® is the handling of the patch when wet as it becomes very adherent. We found that introducing it intranasally whilst folded around a wet neruo-pattie allowed for easier placement over the defect.

A major limitation of Tachosil® will remain the additional cost over the use of autologous materials, which will need to be considered but is not prohibitive. As with all biological materials, it remains the responsibility of the operating surgeon to discuss and consent the patient for the use of this biological product in case there is a disagreement to its use (23). One of the limitations of our study was the cohort of cases in which we used Tachosil®. In our series a disproportionately large proportion of cases were functioning pituitary lesions where the dissection was more radical in an attempt to achieve biochemical remission. As a result, in these cases injury to the arachnoid and diaphragm is not uncommon resulting in higher rates of intra-operative CSF leak as demonstrated. Despite this, use of Tachosil® in our centre served to be safe and successful in repairing skull base defects.

Conclusion

Advancements in materials biotechnology have given rise to a variety of products which have expanded reconstructive options in endoscopic skull base surgery. In addition to arachnoid defect repair, endoscopic TSA Tachosil® may be used safely in a multi-layered approach to repair skull base defects. We found it particularly useful as an alternative to the NSF in case of grade 0 or grade 1 leaks, reducing the additional morbidity and negative impact on sino-nasal quality of life outcomes in patients (24). This alternative can be also particularly useful in post radiotherapy or revision cases where the NSF may not be viable. In defects with high flow CSF leaks or in clival defects, a NSF should still be considered with or without a lumbar drain, and can be used as an additional vascularised overlay graft alongside Tachosil® to reinforce the repair, however this is a decision that should be made on a case by case basis. That being said, we found Tachosil® and its excellent adhesive properties to be extremely valuable with regards to endoscopic skull base reconstructive options alongside more recent literature published on its use (16).

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5.5

The effectiveness and safety of intrathecal fluorescein in the management of cerebrospinal fluid leaks

Karan Jolly
Keshav Gupta
Abishek Banota
Shahzada Khuram Ahmed

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Abstract

Background
Cerebrospinal fluid (CSF) leaks can be associated with significant morbidity such as meningitis. Surgical management has proven effective, with endoscopic approaches having become the gold standard due to success rates >90%. Inability to localise the leak site prior to surgery is associated with surgical failure. The use of intrathecal fluorescein (IF) to localise CSF fistulae sites was first demonstrated in 1960. Despite this, its use in this context is unlicensed.

Objective
Evaluate the safety and efficacy of IF use in the management of CSF leak repairs in our centre.

Methods
All patients who underwent endoscopic repair of CSF fistula where IF was used between January 2010 – September 2019 at a single-centre (tertiary skull base referral unit in the United Kingdom) were retrospectively analysed. Primary outcome measures were localisation of CSF fistula with IF (efficacy) and peri-operative complications likely to be attributable to IF (safety).

Results
There were 55 patients included (60 procedures) with a positive localisation rate of 90.0% with IF. The overall peri-operative complication rate was 8.3% (n = 5). It is likely that none were related to IF use. However, three complications may be linked giving a complication rate potentially related to IF of 5.0%. There were no peri-operative mortalities.

Conclusion
Many studies have demonstrated IF to be safe at low doses (<50mg) with a high sensitivity, specificity and positive predicative value. Our results demonstrate that the use of IF in our centre is safe and effective at identifying CSF fistulae. While we have reported some complications in our cohort, these were unlikely to be directly attributable IF use. We have described no serious complications such as seizures, limb weakness or death. We believe this study adds to the growing body of evidence that IF use in the management CSF fistula repairs is safe and effective.

Introduction

Cerebrospinal fluid (CSF) is contained within the subarachnoid space and communication between the skull base and sinonasal cavity can result in a CSF leak. Common causes for CSF leaks include trauma, tumour, spontaneously sometimes in association with benign idiopathic intracranial hypertension or secondary to surgery. Advances in endoscopic skull base surgery have pushed the envelope in managing more complex pathology, with an evolution in reconstructive techniques leading to improved post-operative outcomes [1].

In the immediate post-operative phase, patient with cerebrospinal fluid (CSF) leaks generally present with unilateral rhinorrhoea, headaches or symptoms of meningitis or pneumocephalus [2,3]. CSF leaks are diagnosed through history and clinical examination with biochemical confirmation of β-2 transferrin. Repair of CSF leaks is crucial to minimise the risk of associated complications such as meningitis which occurs in 10-37% of cases managed conservatively [4]. Failing conservative measures, surgical management has been proven to be effective, with gold standard endoscopic approaches having success rates >90% [5-8]. Prior to surgical management, computed tomography (CT) or magnetic resonance imaging (MRI) have been proven to be highly effective in localising leak sites to aid subsequent planning of surgical approach and repair technique [9-11]. Inability to localise the site prior to surgery is associated with surgical failure [12]. In cases of iatrogenic CSF leaks following large skull base resections, early identification and robust multilayer reconstruction remains the mainstay of management.

Fluorescein dye was first introduced for medicinal use in the field of Ophthalmology in 1882 for diagnostic imaging [13]. Since then it continued to gain popularity expanding its use to angiography [14]. In 1960, Kirchner and Proud demonstrated the use of intrathecal fluorescein (IF) to localise the site of CSF fistulae, following which it gained popularity [15]. Despite IF being effective at localising the site of CSF leaks, its use is still not approved by the Food and Drug Administration (FDA) or the Medicines & Healthcare products Regulatory Agency (MHRA). Thus clinicians who use fluorescein intrathecally to localise a CSF leak must get prior approval for its unlicenced use locally and inform patients for off-label use. Although its use at doses of <50mg has been proven to be safe, higher doses are associated with seizures, limb weakness, cranial nerve deficit and death [16-18].

The purpose of this study is to present our experience of IF use in the management of CSF leak repairs in our centre in terms of its efficacy and safety.

Methods

Study design

This study was performed at a tertiary skull base referral centre, Queen Elizabeth Hospital Birmingham, United Kingdom. All patients who underwent an endoscopic repair of a confirmed CSF fistulae, based on a positive β-2 transferrin, by a single surgeon (S.K.A) were identified between January 2010 and September 2019 by our coding department. Of all the cases identified, only the cases having used IF intra-operatively were included. The primary outcome measures were two-fold; to assess efficacy (positive localisation of CSF fistula with IF) and safety (peri-operative complications) of IF use. Peri-operative complications were then evaluated to assess how likely they were to be associated to IF use based on clinical principles and any relevant investigations related to the complications where available.

Patient records were analysed retrospectively for demographics (gender, age, body mass index [BMI]), primary procedure, dose of IF, surgical outcome and peri-operative complications. Any complication was assessed for the likelihood of its relation to IF use based available on literature and whether this was a significant complication in terms of patient morbidity and mortality. Data analysis was conducted on MS Excel version 16.31. Patients were excluded if their data sets were incorrectly coded. Ethical approval was not required as this was a retrospective case series as per the National Code on Clinical Trials.

Peri-operative technique

A lumbar puncture (LP) was performed and 10mls of CSF withdrawn. Subsequently, 0.3mls of 10% preservative free fluorescein (representing a dose of 30mg) was mixed into the CSF and slowly injected back into the intrathecal space through the lumbar puncture port over 1 minute. The decision to use IF was surgeon specific, in primary cases where the site of the leak was not easily identifiable on imaging or in low flow leak sites for example at the fovea ethmoidalis or cribriform plate where defects are usually smaller, and in a post-operative leak setting in larger complex defects. Routine use of antihistamine or hydrocortisone was not used pre-operatively with administration of IF. Up to 30 minutes was allowed with the patient in 10-degree trendelenburg/head down position to allow the fluorescein which has a greater mass than CSF to mix with the intracranial CSF. A yellow light filter was attached to the endoscopic camera head and a blue light used to enable identification of the CSF fistula.

Results

Between January 2010 and September 2019, we identified 65 procedures where IF was used in the repair of a CSF fistula. This represented 60 patients as there

were 5 re-do surgeries for CSF re-leaks. Following exclusion of five patients that were incorrectly coded, there were 55 patients included in the final analysis (60 procedures). This cohort consisted of 32 females (58.2%) and 23 males (42.8%). The mean age of study population was 49.7 years which ranged from 17 to 80 years of age. The majority of patients were overweight at diagnosis with a body mass index (BMI) of greater than 25kg/m^2 (n = 43, 78.2%). These baseline characteristics are summarised in Table 1.

Baseline characteristics	
Gender	
Male (%)	23 (41.8%)
Female (%)	32 (58.2%)
Age (years)	
Median (range)	52.0 (17-80)
Body mass index (BMI) (kg/m^2)	n (%)
<20	2 (3.6)
20-25	11 (20.0)
25.1 – 30	20 (36.4)
>30	22 (40.0)

Table 1. Baseline patient demographics of included patients (n = 55).

There were five patients where an intra-operative CSF leak was not localised with fluorescein (with blue light assistance), resulting in a positive localisation rate of 90.0%. The first-time repair success rate was 91.7% (n = 55), with five patients requiring a single re-do procedure for re-leak (8.3%). The major cause of CSF leak in our cohort was iatrogenic (n = 38, 63.4%). The breakdown of iatrogenic causes can be found in Table 2. The other aetiologies were traumatic (n = 6, 10.0%) and spontaneous (n = 11, 18.3%) CSF leaks. The remaining five procedures were re-leaks. This is summarised in Table 2. The patients that re-leaked had the following initial primary pathologies; craniopharyngioma, spontaneous CSF leak, suprasellar meningioma, clival chordoma and parasellar chondrosarcoma.

Of the cases identified, there were two (3.3%) who reported intra-operative complications, however none of these were directly attributable to the use of IF (1 patient had intra-operative hypotension with a normal serum tryptase level and 1 patient had bradycardia and subsequent cardiac resuscitation however did not develop any adverse signs when IF was used in their re-do surgery at the same dose). Post-operative complications included three (5.0%)

patients with meningitis. Subsequent analysis of their LP results revealed the origin to be bacterial in all three cases. This gives a total peri-operative complication rate of 8.3% (n = 5). It is likely that none of the five complications were related to IF use. However, it cannot be unequivocally stated that IF and/or LP associated administration was not a contributing factor to the three patients who developed meningitis. Therefore, the peri-operative complication rate potentially related to IF was 5.0%. There were no peri-operative mortalities (0.0%).

Cause of CSF leak	n (%)
Iatrogenic	38 (63.4)
Pituitary	11
Meningocele/meningoencephalocele	6 (5 lateral sphenoid, 1 cribriform plate)
Craniopharyngioma	5
FESS	1
Clival chordoma	3
Meningioma	7 (4 suprasellar, 3 tuberculum sellae)
Osteoma (frontal)	1
Sinonasal malignancy	1
Cholesterol granuloma	1
Mucocele (frontal sinus)	1
Chondrosarcoma (parasellar)	1
Trauma	6 (10.0)
Spontaneous	11 (18.3)
Re-leak following initial leak	5 (8.3)

Table 2. Causes of CSF leaks in all included procedures (n = 60).

In addition to the above complications, two (3.3%) patients reported smell disturbance and one (1.7%) patient had epistaxis which are unlikely to be a consequence of IF use. Seventeen patients (28.3%) reported a post-operative headache. However, all symptoms related to these headaches resolved within 72 hours. These were not included in peri-operative complication rate as they were deemed to be non-significant and likely to be multi-factorial (sequalae of their skull base procedure, anaesthesia and/or lumbar puncture). When evaluating complications in terms of their morbidity, the only complications deemed 'high' morbidity risk were the intra-operative bradycardia and cardiac arrest, and the three meningitis cases. These findings are summarised in Table 3.

		Risk assessment	
	Complication	attributable to IF use	Significance
Intra-operative complications			
Hypotension	1	Unlikely	Medium
Bradycardia and subsequent cardiac arrest	1	Unlikely	High
Post-operative complications			
Meningitis	3	Unclear	High
Total mortality rate (%)			0 (0.0)
Total complication rate (%)			5 (8.3)
Total complication rate potentially related to IF use (%)			3 (5.0)

Table 3. Cohort complications in all included procedures (n = 60). Risk assessment to assess whether complication was likely attributable to the use of intrathecal fluorescein (IF) (proven, likely, unlikely or unclear) and to assess significance of complication in terms of associated morbidity or potential morbidity (high, medium, low)

Discussion

One of the major measures of success in any endoscopic skull base procedure is rate of CSF leak. Failure to complete a watertight closure of dura and arachnoid can predispose to post-operative CSF leak with a subsequent increased risk of meningitis, pneumocephalus and other intracranial complications [19]. Careful identification of intra-operative defects is paramount in ensuring a satisfactory result by influencing decision making in surgical repair. its use has been well documented since the 1960s for its value in localising CSF leaks due to its fluorescent properties that allow detection of translucent CSF when exposed to a white or fluorescent illumination [20, 21]. Despite not being FDA or MHRA approved, many studies have demonstrated IF to be safe at low doses (<50mg) [16, 22, 23]. Furthermore, it has been deemed to have a high sensitivity, specificity and positive predicative value [24]. A study in 2020 also demonstrated IF to have a superior diagnostic yield for identifying CSF leaks compared to CT in the presence of multiple leak sites [25].

Our results demonstrate that the use of IF in our centre is safe and effective at identifying CSF fistulae. We found that there was a 90.0% rate of positive localisation for CSF fistulae sites with IF use. It is unclear why IF was unable to identify the leak site in the remaining five patients. These were patients with low flow leak sites (confirmed with β-2 transferrin) with small defects and intermittent leaks which are all likely factors contributing to the absence of

positive identification. In addition to localisation, in our experience we found IF to be useful in assessing the robustness of the repair intra-operatively.

We have demonstrated a peri-operative complication rate of 8.3%, however, it is unlikely that the complications were attributed to the use of IF. The patient with intra-operative hypotension dropped their blood pressure over 1-hour post administration of IF and was likely to be related to anaesthetic agents. In addition to this, serum tryptase levels were normal which reduce the likelihood that the response was allergy driven. The patient with intra-operative bradycardia did not experience any adverse outcomes in their re-do surgery where the same IF dose was used. It is also therefore difficult to attribute this bradycardia to IF use.

All three patients who were diagnosed with post-operative meningitis also had positive bacterial cultures from LP analysis therefore giving a clear aetiology for their meningitis source that was unlikely to be due to direct meningeal chemical irritation from fluorescein use. Despite this, the aetiology may be related to the LP performed to enable IF administration, the surgery itself, or due to delays in surgical repair. We therefore cannot be sure if the meningitis, although bacterial in origin, was not associated in some way with IF and/or LP associated administration. All three patients had an history of CSF leak in excess of 6 months. The additional reports of headache and nasal symptoms are transient, may be due to other surgical factors such as skull base surgery, anaesthesia and LP and unlikely to represent any significant morbidity. When a risk-assessment is taken into consideration the possible peri-operative complication rate related to IF use is 5.0%.

It is important to note that adverse effects have been reported with IF use in the literature. These have been mainly related to usage at higher doses than that used in our centre. (500 to 1250mg). Reports of seizures, spinal cord injury and even death have been described with intrathecal injections at these doses [18]. There have been other reported side effects including mental status changes, status epilepticus and weakness of the lower limbs [17, 26], albeit in case reports and survey based data from the 1960s and 70s. In addition, serious reports of seizure, opisthotonos, weakness and death have mainly been described in case reports and at use with doses higher than those used in our centre [22]. Despite this, our data set has not revealed any gross adverse effects that can be directly attributable to IF use. No patient experienced any immediate or delayed seizure, altered mental status or lower limb weakness. Similar to our study findings, Placantonakis et al used a dose of 25mg and documented a localisation rate of 46.3%, post-operative leak rate of 9.3% and most side effects to be transient and likely unrelated to IF, with none of the 54

patients reporting seizures [19]. Of the more significant side effects described in their study, three patients described persistent post-operative limb weakness or numbness, however two of these had peri-operative lumbar drain insertions.

Importantly, there has been more recent research validating the safety of fluorescein at lower doses (<50mg), comparable to what was used in our centre (30mg). An Italian multicentre study in 2008 [16] revealed only three transient complications related to IF of <50mg administered to over 1900 patients. Other similar retrospective studies have demonstrated a comparable safety profile with low dose IF, where side effects such as malaise, headache, dizziness, hypotension, leak weakness and nausea were reported as transient and non-specific [19, 27-33]. Interestingly, Seth et al [34] reported no major or minor complications with 10mg IF use in 47 patients. The most recent study showed a 9% complication rate however all complications were attributed to other causes (such as bacterial meningitis and spinal headache related to LP) [25]. Therefore, although several side effects of IF are known, these have been generally described as transient and mild in the existing literature.

Our study is not without limitations. Although we have demonstrated a good safety profile with IF, this finding may be limited by the fact that our patients are all from one centre and of a relatively small data set. Despite this, our overall number of 60 procedures is comparable to other existing studies. Furthermore, the retrospective nature of our study, with no control group, may also impact the validity of conclusions drawn. Our study cohort was largely heterogenous, with a wide variety of operative indications and patient demographics. This may add strength to our findings, as it can be interpreted that IF is generally safe across a wider spectrum of disease and patient factors. However increased heterogeneity reduces the overall numbers in each theoretical subgroup.

Future research should ideally be as prospective designed trials in order to reduce heterogeneity and increase the validity of conclusions drawn. However, prospective trials with single surgical diagnostic adjuncts provides many challenges due to numbers regarding statistical power, costs and ethical issues in randomisation [35]. Meta-analyses could be conducted with the numerous similar retrospective studies but again may be invalidated due to wide heterogeneity between different surgical centres and methods. Furthermore, many of the reported side effects are from studies using different doses and in case reports.

Conclusion

In general, the use of IF in this study, and in the existing literature, at low doses has been shown to be both safe and efficacious in identifying CSF leaks. While we have reported some complications in our patient group, these were unlikely to be directly attributable IF use. We have described no serious complications such as seizures, limb weakness or death. The method by which fluorescein causes complications is not well understood. They are likely dose-dependent with most existing literature agreeing that low dose IF is safe. We believe this study adds to the growing body of evidence that IF use in the management CSF fistula repairs is safe and effective and look to follow up our findings with an up-to-date systematic review of the literature.

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5.6

The efficacy and safety of intrathecal fluorescein in endoscopic cerebrospinal fluid leak repair – a systematic review

Karan Jolly
Keshav Gupta
Jameel Muzaffar
Shahzada Khuram Ahmed

Auris Nasus Larynx. 2022 Dec;49(6):912-920

Abstract

Background
Effective management of cerebrospinal fluid (CSF) leaks can reduce significant associated morbidity. Intrathecal fluorescein (IF) may be a valuable intra-operative adjunct to localise leak sites. Recent reports have demonstrated low doses of IF to be safe, however, no internationally accepted dose of IF has been agreed.

Objective
To assess the efficacy and safety of IF used in the endoscopic management of anterior skull base CSF fistulae.

Methods
A systematic review and descriptive analysis were performed of all published data in accordance to PRISMA guidelines.

Results
There were 18 included articles giving a total of 335 procedures where IF was used. Doses of IF ranged from 10mg - 150mg. IF positively identified the site of CSF fistula in 88.7% of cases (n = 297). There was a total of 25 reported peri-operative complications in all included studies (7.5%) with 5.1% (n = 17) potentially related to IF use. Of these, the complication rate was 3.9% at low IF doses (<50mg) and 80.0% at higher doses (≥50mg).

Conclusion
Our review demonstrates that IF is effective at localising CSF fistulae with most significant complications being related to doses ≥50mg. We therefore propose that there is a potential for the licensing of IF in this field. Doses <50mg have consistently been shown to be safe while still maintaining effective localisation rates. Based on the most common doses used in this group, we recommend utilisation of a dosing below 50mg, with the most frequent range being between 10-30mg.

Introduction

Cerebrospinal fluid (CSF) fistulae typically present with rhinorrhoea and can be as a result of skull base tumours, trauma, surgery or occur spontaneously, typically associated with idiopathic intracranial hypertension (IIH). Management of this condition is crucial to reduce significant associated morbidity, such as meningitis; reported to be in the region of 10-37% per year of active leak[1]. Advances in skull base surgery have allowed for successful endoscopic repair of CSF fistulae with success rates in excess of 90%[2-5].

Localisation of CSF fistulae depends on positive biochemical findings of β-2 transferrin or tau protein, followed by radiological and endoscopic assessment to identify the potential site of the skull base defect or leak. Initial radiological assessment by means of Computed Tomography (CT) with Magnetic Resonance Imaging (MRI) can help identify the site of proven CSF fistulae in up to 90% of patients[6-7]. In cases of biochemically proven CSF fistulae where imaging fails to identify a skull base defect, or in low flow/intermittent CSF leak scenarios, surgical repair can be challenging. In these instances, intrathecal fluorescein (IF) is a valuable intra-operative adjunct in successfully localising the site of CSF fistulae with its use was first documented over 40 years ago[8-10].

Fluorescein dye was first introduced for medicinal use in the field of Ophthalmology in 1882 for diagnostic imaging and has since gained popularity, expanding its use to angiography[4]. In 1960, Kirchner and Proud[8] demonstrated the use of intrathecal fluorescein to localise the site of CSF fistulae and its use has been widely accepted despite it not being approved by the US Food and Drug Administration (FDA) or the UK Medicines & Healthcare products Regulatory Agency (MHRA). Prior studies of IF have demonstrated significant heterogeneity with reported doses ranging from between 10mg to 1250mg and subsequently varying degrees of side effects/ complications and rates of localisation[8,11-14]. Higher doses of IF have been associated with significant morbidity and neurological complications including seizures, limb weakness and death. More recent reported use has demonstrated lower doses of IF to be safer however, to date, no internationally accepted dose of IF has been agreed[8].

The aim of this study was to systematically review the literature with regards to the use of IF in adults for endoscopic management of anterior skull base CSF fistulae according to the PRISMA guidelines. The outcome measures of interest were reported rates of success for identification (efficacy) and reported complications (safety).

Methods

Study design

A systematic review and descriptive analysis were performed of all published data regarding the use of IF in endoscopic CSF leak repairs. This was carried out in accordance with the PRISMA guidelines [15]. The protocol for this systematic review was prospective registered on the PROSPERO database of systematic reviews in January 2021. (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021230924).

Search strategy

Electronic searches of the following databases; EMBASE (1974 – January 2021), MEDLINE (1946 – January 2021), PubMed, Cochrane Library, ClinicalTrials.gov (via Cochrane) and ClinicalKey (1946 – January 2021), were systematically conducted in January 2021 for articles written in English. Conference abstracts were excluded from the search. Databases were accessed through the University of Hospitals Birmingham NHS Trust library. The full search terms can be found in Table 1. The reference lists of any relevant articles were also manually searched in order to identify any additional articles. Corresponding authors were contacted to obtain missing data in January 2021 with no responses received by June 2021.

Study selection

Following the initial search, all abstracts were assessed for eligibility against the inclusion and exclusion criteria with any duplicates removed. This initial screening was performed by two authors independently (K.J and K.K.G) with any discrepancies reviewed by a third author (J.M). We included all studies that reported data on the efficacy (positive localisation rate of leak with IF) and safety (side effect profile) of IF in endoscopic CSF leak repairs in adults, including case reports. Exclusion criteria were where IF was not used intra-operatively, the dose of IF or complications were not reported, number of patients exposed to IF was not reported, or where IF was administered any route other than intrathecally. Ongoing trials, systematics reviews, narrative reviews, opinion letters or technical notes that did not report novel data were also excluded.

#	Search term
1	(intrathecal ADJ3 fluorescein).ti,ab
2	("Cerebrospinal fluid" ADJ2 leak).ti,ab
3	("Cerebro spinal fluid" ADJ2 leak).ti,ab
4	("CSF leak").ti,ab
5	"CEREBROSPINAL FLUID LEAK"/
6	("CSF fistula").ti,ab
7	("Cerebrospinal fluid" ADJ2 fistula).ti,ab
8	("Cerebro spinal fluid" ADJ2 fistula).ti,ab
9	(2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	(endoscop*).ti,ab
11	ENDOSCOPY/
12	(10 OR 11)
13	(1 AND 9 AND 12)
14	13 [DT 2005-2021]
15	("Cerebrospinal fluid" ADJ2 rhinorrhea).ti,ab
16	("Cerebro spinal fluid" ADJ2 rhinorrhea).ti,ab
17	("CSF rhinorrhea").ti,ab
18	(15 OR 16 OR 17)
19	(9 OR 18)
20	(1 AND 12 AND 19)
21	20 [DT 2005-2021] [Publication types Article OR Report OR Review]

Table 1. Search strategy.

Data extraction and analysis

Extracted data was analysed on a standard spreadsheet (Excel version 16.31, Microsoft Corp, WA, USA). Once tabulated, the data was rechecked against the original data source to correct any clerical data entry errors. Primary outcome measures were two-fold; (1) positive localisation rate of CSF fistulae with IF use (efficacy endpoint) and (2) peri-operative complications (safety endpoint). All reported complications in each paper were included in the analysis. Subgroup analysis was performed with respect to complications likely attributable to IF use and for high doses (≥50mg) and low doses (<50mg). Full data extraction terms are summarised in Table 2. Data extraction was performed independently by two authors (K.J and K.K.G), with any discrepancies resolved by a third author (J.M).

	Output
1	Study and year
2	Study design
3	Total number of participants included in trial (population)
4	Number of patients exposed to IF (n)
5	Mean age
6	Gender
7	Cause of CSF leak
8	Dose of IF
9	Pre-operative medications administered with doses (not including anaesthesic)
10	Use of lumbar drain (yes/no)
11	Primary efficacy endpoint (% of positive localisation rate with IF)
12	Primary safety endpoint (reported peri-operative complications)
13	Mean follow-up

Table 2. Extracted data from included articles.

Risk of Bias Scoring

Two reviewers (K.J & K.K.G) independently classified each included study according to the Oxford Centre for Evidence Based Medicine (OCEBM) grading system[16]. Discrepancies in assessment were resolved by discussion between reviewers and if required arbitration by a third reviewer (J.M).

Results

Search results

Figure 1 illustrates our study selection process. The literature search identified a total of 205 records. After removing duplicates and screening of titles and abstracts, 35 full-text records remained for assessment of eligibility against our inclusion and exclusion criteria. Of these, we identified 17 articles published between 2002-2020 and our own case series (published in 2021), giving a total of 18 included data sets for analysis [7,12,17-32]. This gave a total of 335 procedures where IF was used and outcomes were reported in terms of efficacy and safety.

Table 3 summarises the study design and baseline characteristics of all included studies and participants. The majority of included studies were retrospective case-series (n = 11, 61.1%)[7,12,17,18,20,21,23,,28-31], one study reporting retrospective and prospective data (5.6%)[24], and six case-reports (33.3%) [19,22,25-27,32].The number of participants to whom IF was administered

ranged from one (case reports) to 102[18]. Mean age ranged from 33.7 to 71.8 with a mean of 61.3% females included. The weighted mean age was 40.2 years. The range of IF doses used was 10mg to 150mg. Pre-operative medications were administered in two studies (11.1%)[22,24] and lumbar drains (LD) were used in some form in seven studies[7,12,18,20,24,30,31]. Mean follow-up ranged from 2 weeks[15] to 31.6 months[24] but was only reported in 13 studies (72.2%)[7,12,19,21-26,28-31].

Outcome measures

From the included studies, there were a total of 297 cases where IF positively identified the site of the CSF fistula (88.7%). There was a total of 25 reported peri-operative complications in all included studies (7.5%). These results are summarised in Table 4.

Study and year	Study design and OCEBM grade	Total population	Number of procedures with IF (n)	Mean age	Female (%)	Cause of CSF leak*	IF dose	Pre-operative medication	Lumbar drain	Mean follow up
Jolly et al. (2021)[17]	Retrospective case series, IV	55	60†	49.7	58.2	Multi	30mg	No	No	Not reported
Flynn et al. (2020)[18]	Retrospective case series, IV	102	56	49.5	73.5	Multi	10mg	No	Yes	Not reported
Keshri et al. (2019)[7]	Retrospective case series, IV	43	15	36.7	74.4	Spontaneous	12.5mg	No	Yes (n = 21)§	18 months
Ramalingam et al. (2018)[19]	Case report, IV	1	1	40	100.0	Spontaneous	10mg	No	No	6 months
Englhard et al. (2018)[20]	Retrospective case series, IV	24	24	Not reported	62.5	Spontaneous	50mg max	No	Yes (n = 16)	Not reported
Borsetto et al. (2017)[21]	Retrospective case series, IV	110	62	49	Not reported	Multi	15mg	No	No	24 months
Rodríguiez-Navarro et al. (2017)[22]	Case report, IV	1	1	67	100.0	Traumatic	50mg	Dexamethasone 0.1mg/kg and dexchlorpheniramine 5mg	No	12 months
Emanuelli et al. (2015)[23]	Retrospective case series (patients >65 years), IV	20	8	71.8‡	62.5	Multi	50mg max	No	No	3-24 months (range)

Table 3.Continued

Study and year	Study design and OCEBM grade	Total population	Number of procedures with IF (n)	Mean age	Female (%)	Cause of CSF leak*	IF dose	Pre-operative medication	Lumbar drain	Mean follow up
Banu et al. (2014)[24]	Prospective and retrospective case series, IV	41	50†	50.3	63.4	Multi	25mg	Dexamethasone 10mg and diphenhydramine 50mg	Yes (n = 26)	31.6 months
Javadi et al. (2013)[12]	Retrospective case series, IV	20	20	33.7	25.0	Multi	25mg	No	Yes (n = 16)	6 months
Jacob et al. (2008)[25]	Case report, IV	1	1	59	100.0	Iatrogenic	50mg	No	No	6 months
Anari et al. (2007)[26]	Case report, IV	1	1	57	100.0	Iatrogenic	50mg	No	No	2 weeks
Park et al. (2007)[27]	Case report, IV	1	1	41	0.0	Trauma	50mg	No	No	Not reported
Silva et al. (2006)[28]	Retrospective case series, IV	24	24	39	45.8	Multi	50mg max	No	No	26 months
Landeiro et al. (2004)[29]	Retrospective case series, IV	10	4	Not reported	30.0	Multi	50mg max	No	No	12 months
White et al. (2003)[30]	Retrospective case series, IV	13	3	36	25.0	Iatrogenic	10mg	No	Yes (n = 9)§	21.4 months
Gendeh et al. (2002)[31]	Retrospective case series, IV	3	3	51	100.0	Spontaneous	10mg	No	Yes (n =1)	16 months
Wallace et al. (1972)[32]	Case report, IV	1	1	69	0.0	Iatrogenic	150mg	No	No	Not reported

Table 3.Continued

Study and year	Study design and OCEBM grade	Total population	Number of procedures with IF (n)	Mean age	Female (%)	Cause of CSF leak*	IF dose	Pre-operative medication	Lumbar drain	Mean follow up
Total/Average		471	335	40.2II	61.3					

Table 3. Study design and baseline characteristics of included articles and patients.

* leak cause – 'mulit' can include spontaneous, iatrogenic, tumour, trauma, congenital
† number of procedures with IF is greater than the number of participants due to re-do procedures
‡ study only included patients >65years (range 65-83 years)
§ not reported how many lumbar drains were used in patients who were exposed to IF
II weighted average
OCEBM = Oxford Centre for Evidence Based Medicine, IF = intrathecal fluorescein, CSF = cerebrospinal fluid

Study	n, procedures	IF dose	Positive localisation rate, n (%)	Complications, n (%)	Details of peri-operative complications
Jolly et al. (2021)[17]	60	30mg	54 (90.0)	5 (8.3)	1 = intraoperative hypotension with normal serum tryptase level 1 = bradycardia and cardiac resuscitation 3 = bacterial meningitis
Flynn et al. (2020)[18]	56	10mg	40 (73.0)	6 (10.7)	3 = post-operative headache 3 = seizures
Keshri et al. (2019)[7]	15	12.5mg	15 (100.0)	2 (13.3)	2 = bacterial meningitis
Ramalingam et al. (2018)[19]	1	10mg	1 (100.0)	0 (0.0)	

Table 4. Continued

Study	n, procedures	IF dose	Positive localisation rate, n (%)	Complications, n (%)	Details of peri-operative complications
Englhard et al. (2018)[20]	24	50mg max	21 (87.5)	0 (0.0)	
Borsetto et al. (2017)[21]	61	15mg	61 (100.0)	1 (1.6)	1 = transient lower limb flap
Rodríguiez-Navarro et al. (2017)[22]	1	50mg	1 (100.0)	0 (0.0)	
Emanuelli et al. (2015)[23]	8	50mg max	8 (100.0)	0 (0.0)	
Banu et al. (2014)[24]	50	25mg	40 (80.5)	2 (4.0)	1 = transient leg weakness 1 = hydrocephalus
Javadi et al. (2013)[12]	20	25mg	18 (90.0)	4 (20.0)	2 = meningitis (1 bacterial, 1 aseptic) 1 = tension pneumocephalus 1 = pseudoaneurysm
Jacob et al. (2008)[25]	1	50mg	1 (100.0)	1 (100.0)	1 = multiple seizures and decerebrate posturing
Anari et al. (2007)[26]	1	50mg	0 (0.0)	1 (100.0)	1 = multiple seizures likely secondary to chemical reaction
Park et al. (2007)[27]	1	50mg	1 (100.0)	1 (100.0)	1 = myelopathic changes in lower thoracic spinal cord, weakness and numbness in lower extremities, confusion, paraparesis, and two grand mal seizures
Silva et al. (2006)[28]	24	50mg max	24 (100.0)	0 (0.0)	

Table 4. Continued

Study	n, procedures	IF dose	Positive localisation rate, n (%)	Complications, n (%)	Details of peri-operative complications
Landeiro et al. (2004)[29]	4	50mg max	4 (100.0)	0 (0.0)	
White et al. (2003)[30]	3	10mg	3 (100.0)	1 (33.3)	1 = meningitis
Gendeh et al. (2002)[31]	3	10mg	3 (100.0)	0 (0.0)	
Wallace et al. (1972)[32]	1	150mg	1 (100.0)	1 (100.0)	1 = local neural irritation and status epilepticus
Total/average	335		297 (88.7)	25 (7.5)	

Table 4. Outcome measures from included articles.

The data from our own case series [17] demonstrated two intra-operative complications (one patient had hypotension and one became bradycardic requiring cardiac resuscitation). However, these were unlikely to be attributable to IF use as serum tryptase level was normal in the hypotensive patient suggesting that anaphylaxis was unlikely, and the patient requiring cardiac resuscitation had no adverse side effects when IF was used at the same dose in their re-do procedure. Three patients had meningitis but were all found to be bacterial in origin giving a clear aetiology that is unlikely to be due to direct chemical meningeal irritation from fluorescein administration. Despite this, the aetiology may be related to the steps required to administer IF, such as the lumbar puncture (LP) itself, or due to delays in surgical repair.

Flynn et al[18], described three post-operative headaches which the authors attributed to the use of LDs and three seizures. One seizure was related to anoxic brain injury and the others to post-operative meningitis. Keshri et al[7], reported two patients with post-operative meningitis which were both found to be bacterial in origin. Borsetto et al[21] reported one complication where a patient exhibited a flapping tremor in the lower limbs that spontaneously resolved with no long-term complications. This was thought to be due to an overdose of IF. Banu et al[24], reported two complications with one patient requiring a ventrico-peritoneal shunt for hydrocephalus and transient lower limb weakness thought to be related to LD placement. Javadi et al[12], described two patients with post-operative meningitis (one bacterial in origin and the other aseptic), one patient with tension pneumocephalus and one patient with a pseudoaneurysm. White et al[30], reported one patient developing meningitis 36 hours after repair that required treatment with intravenous antibiotics and a lumbar drain.

In the six case-reports, complications were reported in four. Jacob et al[25], used IF in a patient that subsequently had seizures and decerebrate posturing that required intubation and intensive care admission. There was resolution of seizure activity and return to baseline cognitive and functional status by 6 months post-operatively. The case report by Anari et al[26], reported that their patient had three short absence seizures followed by two grand-mal seizures requiring intravenous sedation and likely to be chemical in origin as a neurology review, CT scan and LP showed no evidence of bacterial involvement. Park et al[27], described a case with post-operative pain and numbness in the lower extremities at the end of IF injection with subsequent confusion, paraparesis and two grand-mal seizures. Two days later, the patient had lower limb weakness and an MRI showed myelopathic changes in the lower thoracic spinal cord. The earliest included study was in 1972 and showed a patient with local neural irritation and status epilepticus requiring steroid and anticonvulsant therapy after 150mg of IF administration [32].

Sub-group analysis

Sub-group analysis was performed to assess a more accurate complication rate likely attributable to IF use. When assessing all papers, eight complications were excluded as these were unlikely to be attributable to the use of IF. These were the patients with intra-operative hypotension with a subsequent normal serum tryptase level, intra-operative bradycardia, and cardiac arrest with no adverse effects with subsequent re-use of IF[17]. There were three patients with headaches that was reported to be likely due to LD rather than IF administration. In addition, the patients with hydrocephalus [24], tension pneumocephalus and pseudoaneurysm[12] were unlikely to be as a result of IF administration. Those patients with bacterial meningitis were not excluded as although the origin of meningitis is unlikely to be related to IF use, it cannot be unambiguously stated that IF and LP administration were not contributing factors to the development of bacterial meningitis. This gives a total complication rate potentially attributable IF use of 5.1% (n = 17).

When breaking this down further according to high dose (≥50mg) and low doses (<50mg). The complication rate potentially attributable to IF was 3.9% (n = 13) in lower doses and 80.0% (n = 4) in higher doses. In addition, the specific complications observed at higher doses included multiple seizure activity, myelopathic changes in the lower spinal cord with paraparesis and status epilepticus and are therefore likely to represent more serious morbidity compared to the complications observed at lower doses. The localisation rate was 88.8% (n = 293) at low doses and 80.0% (n = 4) at high doses. These findings are summarised in Table 5

Risk of Bias Assessment

All included studies were graded IV according to the OCEBM levels of evidence

Dose	n	Total complications (%)	Complications potentially attributable to IF (%)	Localisation rate (%)
Low (<50mg)	330	21 (6.4) • Intra-operative hypotension, n = 1 • Intra-operative bradycardia and cardiac arrest, n = 1 • Headache, n = 3 • Bacterial meningitis, n = 7 • Aseptic meningitis, n = 1 • Transient leg weakness, n = 1 • Hydrocephalus, n = 1 • Tension pneumocephalus, n = 1 • Pseudoaneurysm, n = 1 • Single seizure, n = 3 • Transient lower limb flap, n = 1	13 (3.9) • Bacterial meningitis, n = 7 • Aseptic meningitis, n = 1 • Transient leg weakness, n = 1 • Single seizure, n = 3 • Transient lower limb flap, n = 1	293 (88.8)
High (50mg)	5	4 (80.0)* • Multiple seizures/status, n = 4 • Decerebrate posturing, n = 1 • Myelopathic changes in spinal cord, n = 1 • Lower limb weakness and numbness, n = 1 • Confusion, n = 1 • Paraparesis, n = 1	4 (80.0)* • Multiple seizures/status, n = 4 • Decerebrate posturing, n = 1 • Myelopathic changes in spinal cord, n = 1 • Lower limb weakness and numbness, n = 1 • Confusion, n = 1 • Paraparesis, n = 1	4 (80.0)
Total	335	25 (7.5)	17 (5.1)	297 (88.7)

Table 5. Sub-group analysis for doses of Intrathecal fluorescein ≥50mg and <50mg and detailing specific complications and likelihood of relation to IF adminsitration.

*One patient exhibited myelopathic changes in the spinal cord with lower limb weakness and numbness, confusion, paraparesis and multiple seizures so is included in all categories. One patient had multiple seizures and decerebrate posturing so is included in both categories.

Discussion

The ability to reconstruct and repair complex defects is one of the major reasons for advancements in endoscopic skull base surgery. CSF is a colourless fluid and intra-operative identification can be difficult, especially in the presence of low flow leaks associated with small defects. Intrathecal fluorescein has allowed for improved visualisation and localisation of CSF leaks intra-operatively, and subsequent assessment of persistent leaks following repairs. Despite its use since the 1960s, IF has not been FDA or MHRA approved, and use remains off licence.

The use of IF in the endoscopic management of CSF fistulae has been reported in the literature by several case series and smaller multicentre reviews that we have included in this systematic review. Our results demonstrate that rates of CSF fistulae localisation was 88.7%, similar to rates quoted by recent studies [18]. The majority of included studies used doses of IF that were less than 50mg, with only four case reports using higher doses of 50mg or more. IF is used primarily for localisation of CSF fistulae in cases where radiological imaging has failed to identify the site of a defect or in low-flow fistulae with intermittent leaks. One of the limitations of this review is the heterogenous population of leaks with differing aetiologies and a range of site/size of defects which was variably reported. In addition, there is likely to have been slight differences in the method of IF administration, although this was not specified by all included studies. When the method of IF administration was described, this typically involved performing an LP and withdrawing 10mls of CSF. This would then be diluted with the required dose of IF, before a slow injection of the solution into the intrathecal space over 1-10 minutes. Despite these factors, we found IF serves to be an outstanding adjunct in identifying the site of CSF fistulae, especially in anterior cranial fossa defects where they tend to be smaller and low flow in nature where prior imaging was unequivocal. This excellent localisation rate was maintained at lower doses of IF use (88.8%).

Complications associated with IF used have been documented since its first use in 1960. These include minor symptoms such as headaches and dizziness, to more severe neurological complications including seizures, limb weakness, neurological deficit and death[9]. Of the studies reviewed in our search, the peri-operative complication rate was 7.5%. When examining the complication rate in more detail, the overall complication rate potentially related to IF use was less, at 5.1%.

When inspecting this further, our subgroup analysis reveals a higher proportion of complications that are potentially related to IF use to be with higher doses (≥50mg) compared to lower doses (<50mg). There were only

3.9% of such complications reported at low doses compared to 80% at higher doses. In addition, all complications at higher doses are likely to represent significant morbidity. Despite this, it should be noted that our interpretation of complications at higher doses is limited due to the low total numbers (n = 5) of included studies using higher doses. In addition, there may be reporting bias since all studies in which complications are reported at higher doses were case reports, and therefore more likely to report specifically on complications.

The significant complications observed at lower doses were meningitis (n = 8) and single seizures (n = 3). While these may be related to IF administration, they may also be explained by numerous other factors related to the surgical procedure such as LP and instrumentation of the anterior skull base. There was only one case of meningitis where the origin was found to be aseptic (and not bacterial) in nature. This may therefore be related to direct meningeal irritation by fluorescein. The remaining two complications observed at lower doses were transient (leg weakness and lower limb flap) and resolved with no long term sequalae.

As our review was evaluating the use of IF in the endoscopic management of CSF fistulae in adults, there were several larger studies we had to exclude due to a variety of reasons including, localisation rates not being documented, IF being used in the primary setting for tumour resection, use in a paediatric population and administration of IF via a sub-occipital approach. Of these, 2 of the largest series documented use of IF via an LP of doses <50mg to be very safe with minimal associated complications [8,11]. A large Italian multi-centre study by Felisati et al, observed no adverse events in a sample size of 53 patients at a dose of 50mg or less [11].The authors also conducted a meta-analysis of 1940 administrations of IF at a dose of <50mg and identified only 3 complications[11]. Older studies documented higher more severe complications associated with IF which were likely to be attributed to higher doses of IF (50mg -1250mg), occipital approaches of administration as well as preparations of fluorescein contaminated by irritative preservatives [8].

There are limitations associated with this review with regards to the efficacy and safety of IF. Firstly, all included studies were graded as level IV evidence according to OCEBM. Therefore, there is a clear limitation with the quality of evidence available to be included in this systematic review. In addition, the studies included looked at mixed aetiology of CSF fistulae of varying sizes and so localisation may be affected by this, however it was not possible to correlate this due to lack of information. With regards to the safety of IF, we had to exclude a number of studies which had larger patient samples, however the results from this have been taken into account within our discussion and are not dissimilar from the findings of our study. Symptoms such as headaches and nausea although

recorded, are deemed very non-specific as they may be associated with general anaesthesia, endoscopic skull base procedures, LP or even IF. That being said, the symptoms are transient and not associated with any significant morbidity.

Conclusion

The results of our review demonstrate that IF is effective at localising CSF fistulae during endoscopic approaches in adults. Our data shows a total complication rate of 7.5%, with those potentially being attributable to IF being in the region of 5.1%. The highest proportion of significant complications related to use at doses of 50mg or greater. Large studies not included in this review also found dose-dependent relationship with complications, with lower doses being generally safe and associated with little morbidity while still allowing for an effective localisation rate. Based on the available data, we propose that there is a potential for the licensing of IF in this field. Doses <50mg have consistently been shown to be safe while still allowing an effective localisation of CSF leak site. Based on the most common doses used in this group, we recommend utilisation of a dosing below 50mg, with the most frequent range being between 10-30mg.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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5.7

Reconstruction and Cerebrospinal Fluid Leaks in Endoscopic Endonasal Approach for the Management of Clival Chordomas

Keshav Gupta
Edward Balai
Adnan Darr
Karan Jolly

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Abstract

Aims
The success of the endoscopic endonasal approach (EEA) to surgically manage clival chordomas (CC) relies on robust repair methods to reduce complications, such as cerebrospinal fluid (CSF) leaks. Our study aims to evaluate the existing literature to assess reconstructive techniques utilised and post-operative CSF leak rates in this cohort.

Materials and Methods
A systematic review and analysis was performed of all published data related to CC patients managed with an EEA.

Results
A total of 24 articles were included, representing 363 patients and 396 procedures. A variety of reconstruction methods were used with 95.9% of studies using an intracranial repair graft, 70.8% using a nasoseptal flap (NSF), 62.5% using glue/haemostat, 58.3% using nasal packs and 75.0% employing multi-layered reconstruction. Post-operative CSF leak rate was 10.1%. The leak rate was less in subgroups where a NSF was used (9.4%) although this was not statistically significant (p=0.273). There were no differences in leak rates when glue/haemostat (p=0.139) or nasal packs (p=0.550) were used.

Conclusion
Our review is the most up-to-date synthesis of the existing literature surrounding the EEA to CCs assessing reconstruction and post-operative CSF leaks. It demonstrates most authors employ a multi-layered reconstruction method. The lack of statistical significance observed for CSF leaks in subgroups is likely due to a variety of cofounding surgeon and patient factors. Higher quality prospective randomised multi-centric studies, with reporting of specific repair techniques will enable future systematic reviews to provide a more accurate consensus regarding optimal methods of reconstruction in this field.

Introduction

Chordomas are rare tumours derived from notochordal remnants with an incidence of 0.08 per 100,000[1]. They are classified as low-grade malignancies, although their infiltrative nature means a high rate of recurrence, and a median survival of 7.7 years[2]. Clival chordomas (CC) account for up to 40% of chordomas[3], with anatomical location posing a significant barrier to adequate resection and post-operative outcomes. Medical therapies such Imatinib or Erlotinib have been trialled in the treatment of CCs but have failed to demonstrate adequate tumour control[4].

Tumour extension is highly variable, ranging from restricted infiltration of the clival bone, to intra-cranial extension extending to the posterior fossa. For this reason, gross tumour resection (GTR) is surgically challenging[5]. Recent advances in the endoscopic endonasal approach (EEA) have largely superseded the more traditional aggressive transcranial approaches, providing superior visualisation, limiting retraction of neurovascular structures, permitting ventral exposure to deep lesions[6], but crucially permitting the use of vascularised mucosal flaps[7]. This has been made possible by improved endoscopic instrumentation as well as improved reconstructive understanding over recent years.

Although there are a variety of descriptions of techniques and approaches for resection of CCs, the rarity of presentation (0.1% of all skull base malignancies) [8] and the paucity of data at our disposal by means of either retrospective or prospective studies have been limited. This has led to no clear consensus regarding the ideal reconstructive technique that minimises post-operative complications. The success of these procedures relies on robust repair methods to reduce such complications, such as cerebrospinal fluid (CSF) leaks, meningitis and pneumocephalus. The incidence of CSF leak post-operatively remains the most important measure in the success of any repair.

Our study aims to evaluate existing literature through a systematic review to assess the current reconstructive techniques utilised and post-operative CSF leak rates using an EEA for resection of CCs.

Methods

Study design

A systematic review and analysis was performed of all published data related to CC patients managed with an EEA where articles reported a detailed account of their reconstructive techniques and post-operative CSF leak rates. This was

undertaken in accordance with the PRISMA guidelines[9]. The protocol for this review was registered on the PROSPERO database in March 2021.

Search strategy

Electronic searches of the following databases were systematically undertaken in March 2021; EMBASE (1974 – March 2021), MEDLINE (1946 – March 2021), and the Cochrane Library. Limits used in the search included articles only published in English and conference abstracts and duplicates were excluded. Databases were accessed through the University of Hospitals Birmingham NHS Trust library. The search was conducted using Medical Subject Heading (MeSH) terms (Table 1). The reference lists of any relevant articles and systematic reviews were manually searched to identify any additional articles. Relevant articles already known to the authors were also included if not identified in the search.

#	MeSH search term	Database
1	("clival chordoma*").ti,ab	Medline
2	("clivus chordoma*").ti,ab	Medline
3	("skull base chordoma").ti,ab	Medline
4	(1 OR 2 OR 3)	Medline
5	(endoscop*).ti,ab	Medline
6	(4 AND 5)	Medline
7	("clival chordoma*").ti,ab	EMBASE
8	("clivus chordoma*").ti,ab	EMBASE
9	("skull base chordoma").ti,ab	EMBASE
10	(7 OR 8 OR 9)	EMBASE
11	(endoscop*).ti,ab	EMBASE
12	(10 AND 11)	EMBASE
13	12 [Publication types Article OR Editorial OR Letter OR Note OR Report OR Review] [English language] [Languages English]	EMBASE

Table 1. Search strategy

Study selection

Primary screening was performed by two authors independently (K.K.G and E.B) with any discrepancies resolved by the senior author (K.J). Articles were initially excluded if their titles or abstracts were clearly irrelevant. The full texts of remaining articles were sought for eligibility screening. We included all articles that met the inclusion and exclusion criteria. Inclusion criteria were all articles that reported data for patients with CCs managed surgically with an EEA and

reported data for their reconstructive methods and post-operative CSF leaks. Exclusion criteria were alternate surgical approaches (for example transcranial or combined approaches where data and outcomes were not separated for EEA), other pathologies (for example clival xanthoma), articles not in English and articles not reporting details regarding reconstruction methodology or post-operative CSF leak rates. Meta-analyses/systematic reviews and case reports were excluded as well as articles reported duplicated data.

Data extraction and analysis

Data was extracted from included papers by all four authors independently to a standard spreadsheet. Following tabulation, the data was re-evaluated against the original data source to avoid any clerical errors related to data entry. Extracted data included study characteristics (year, design, number of patients and procedures, follow-up) and patient characteristics (age, gender, GTR). Primary outcome measures were (1) reconstructive techniques used in terms of repair used (for example fat/fascia/duragen), nasoseptal flap (NSF), glue/haemostat, nasal packing, lumbar drain (LD) utilisation, whether these repairs were multi-layered or not, and (2) post-operative CSF leak rate. Other post-operative complications were also recorded.

Basic descriptive statistics were used where applicable and percentage values were calculated in each individual study for gender, GTR, LD utilisation, post-operative CSF leak and other complications. An overall percentage was calculated for each of these parameters. Sub-group analysis was performed for reconstruction methods used. This was used to compare the post-operative CSF leak rate between studies that utilised a NSF and those that did not. This was repeated for other reconstructive methods – i.e. glue/haemostat and for nasal packs. Statistical comparison between groups was achieved using chi-squared tests (χ^2). A p-value of <0.05 was deemed statistically significant in all applicable analysis. All calculations were completed using SPSS Statistics version 27.0.1.0 (IBM, Armonk, NY) and MS Excel® version 16.31 (Microsoft, Redmond, WA)

Results

Search results

The study selection process is illustrated in Figure 1. The literature search identified 213 articles after which 61 underwent eligibility screening following exclusion of duplicates and articles based on their titles and abstracts. A total of 24 full-length articles met our inclusion criteria published between 2005 – 2020[6,10-32]. This included a total of 363 patients (396 procedures) where CCs

were treated with an EEA and details were reported in terms of post-operative CSF leak rate and reconstructive methods.

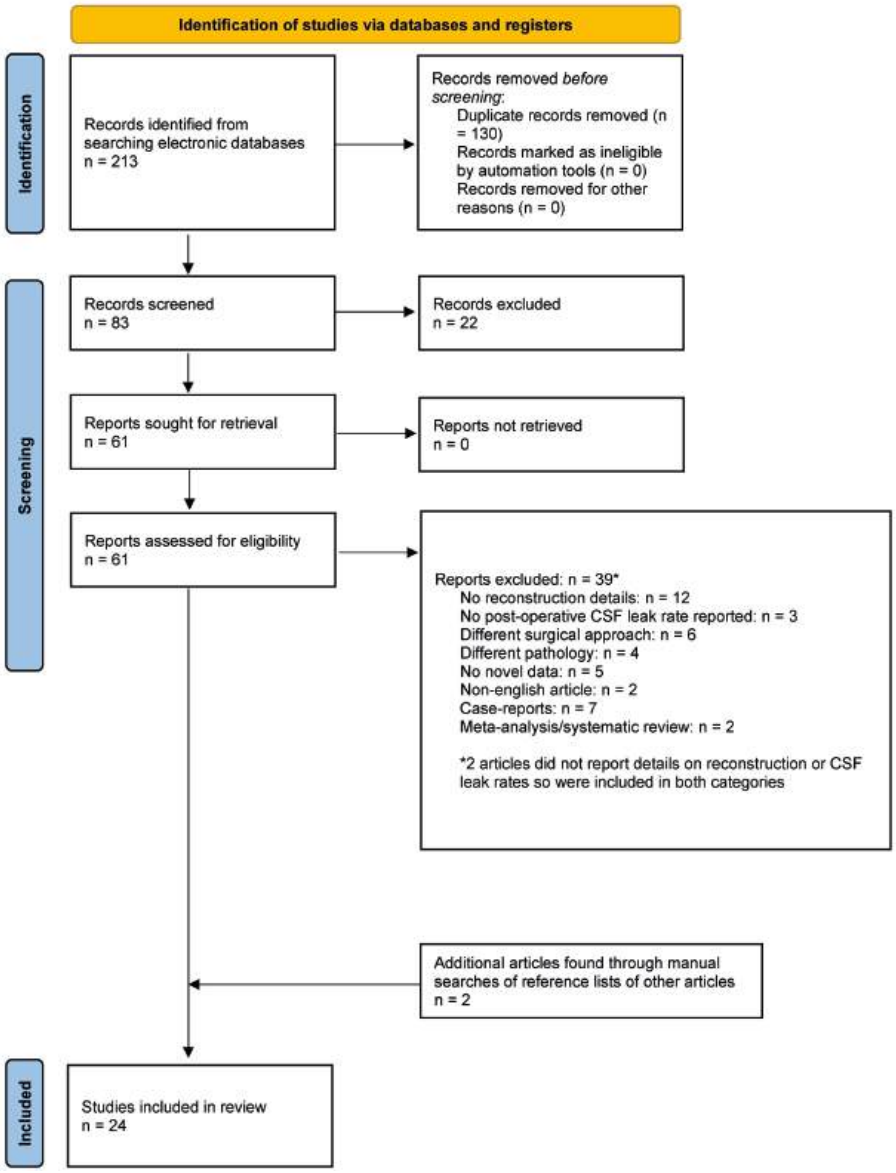

Figure 1. Study selection process of included articles.

Table 2 summarises the study design and baseline characteristics of all included studies and participants. The majority of included studies were retrospective case series (n = 22, 91.7%)[6,10-16,19-32], with two studies reporting prospective data (8.3%)[17,18]. The number of participants ranged from 2[19,20] to 65[6]. Mean age ranged from 31[27] to 62[31] with reported GTR rates ranging from 0%[30] to 100%[24] with an average GTR of 55.1%. Mean follow up ranged from 6[19,20,27] to 68[10] months.

Outcome measures

From the included studies, the post-operative CSF leak rate was 10.1% (n = 40). There were a wide variety of reconstruction methods used with 95.8% studies (n = 23) using an intracranial repair graft[6,10-14,16-32], 70.8% (n = 17) using a NSF[6,10-14,16-18,20-26,28], 62.5% (n = 15) using a glue/haemostat[6,10,13,14,16,17,19,21-23,25,38-30,32], and 58.3% (n = 14) using a nasal pack[6,10,12,14,16,21-26,28-30]. There were 20 studies (80%) using a multi-layered reconstruction technique[6,10-14,16-26,28,29]. Nine studies reported the use of a LD in a total of 55 patients (13.9%)[13,15,16,18,23-26,29] The results from all outcome measures are summarised in Table 3. The overall number of other post-operative complications was 63 (15.9%). These were a variety of complications, the most common being cranial neuropathies and diplopia (n = 19, 30.2%), and meningitis (n = 15, 23.8%). The breakdown of all other post-operative complications, excluding CSF leaks, is summarised in Table 4.

Study and year	Study design	Patients (n)	Procedures (n)	Mean age (years)	Male (%)	GTR (%)	Follow up (months)
Oishi, 2020[10]	Retrospective	17	17	Not reported (NR)	10 (58.8)	5 (29.4)	68
Wang, 2020[11]	Retrospective	49	49	NR	28 (57.1)	32 (65.3)	NR
Soloperto, 2019[12]	Retrospective	8	8	61	4 (50.0)	2 (25.0)	25
Yousaf, 2019[13]	Retrospective	15	15	49	NR	4 (26.7)	40
Rahme, 2018[14]	Retrospective	17	23	48	10 (58.8)	9 (52.9)	63
Zoli, 2018[6]	Retrospective	65	80	48	34 (52.3)	47 (72.3)	52
Shimony, 2017[15]	Retrospective	15	17	53	10 (66.7%)	4 (26.7)	20
Catapano, 2016[16]	Retrospective	7	7	NR	NR	2 (28.6)	39
Garzaro, 2015[17]	Prospective	9	9	57	9 (100.0)	6 (66.7)	9
Chibbaro, 2014[18]	Prospective	54	58	NR	33 (61.1)	35 (64.8)	34
Iacoangeli, 2014[19]	Retrospective	2	2	NR	NR	NR	6
Ishii, 2014[20]	Retrospective	2	2	NR	NR	NR	6
Shidoh, 2014[21]	Retrospective	9	9	56	4 (44.4)	3 (33.3)	NR
Saito, 2012[22]	Retrospective	6	6	59	3 (50.0)	3 (50.0)	16
Tan, 2012[23]	Retrospective	14	14	NR	8 (57.1)	7 (50.0)	41
Taniguchi, 2011[24]	Retrospective	4	4	57	2 (50.0)	4 (100.0)	21
Fraser, 2010[25]	Retrospective	8	8	50	5 (62.5)	4 (50.0)	9
Holzmann, 2010[26]	Retrospective	13	13	46	7 (53.8)	11 (84.6)	18
Arbolay, 2009[27]	Retrospective	2	2	31	1 (50.0)	1 (50.0)	6
Stippler, 2009[28]	Retrospective	20	26	44	10 (50.0)	9 (45.0)	13
Dehdashti, 2008[29]	Retrospective	12	12	49	8 (66.7)	7 (58.3)	16
Hwang, 2007[30]	Retrospective	3	3	52	3 (100.0)	0 (0.0)	40
Frank, 2006[31]	Retrospective	9	9	62	3 (33.3)	3 (33.3)	27

Table 2. Continued

Study and year	Study design	Patients (n)	Procedures (n)	Mean age (years)	Male (%)	GTR (%)	Follow up (months)
Solares, 2005[32]	Retrospective	3	3	50	2 (66.7)	2 (66.7)	13
Totals/averages	**-**	**363**	**396**	**51**	**194 (53.4)**	**200 (55.1)**	**26**

Table 2. Baseline characteristics of included studies and participants.

Study and year	Reconstruction				Multi-layered reconstruction (Y/N)	Lumbar drain (%)	CSF leak (%)	Other complications (%)
	Repair	NSF (Y/N)	Glue/ Haemostat	Nasal pack				
Oishi, 2020[10]	Fascia	Y	Oxidised cellulose, fibrin glue	Foley catheter	Y	0 (0.0)	2 (11.8)	2 (11.8)
Wang, 2020[11]	Fascia	Y	Nil	Nil	Y	0 (0.0)	6 (12.2)	5 (10.2)
Soloperto, 2019[12]	Fascia	Y	Nil	Foley catheter	Y	0 (0.0)	0 (0.0)	1 (12.5)
Yousaf, 2019[13]	Artificial dura	Y	Glue	Nil	Y	15 (100.0)	2 (13.3)	2 (13.3)
Rahme, 2018[14]	Fat	Y	Sealant	Foley catheter	Y	0 (0.0)	6 (26.1)	5 (21.7)
Zoli, 2018[6]	Fat, fascia, bone/ cartilage	Y	Gelofoam	Merocel	Y	0 (0.0)	2 (2.5)	9 (11.3)
Shimony, 2017[15]	Nil	N	Nil	Nil	N	9 (52.9)	0 (0.0)	5 (29.4)
Catapano, 2016[16]	Fat, fascia	Y	Fibrin glue	Anterior nasal pack	Y	7 (100.0)	1 (14.3)	2 (28.6)

Table 3. Continued

Study and year	Reconstruction							
	Repair	NSF (Y/N)	Glue/ Haemostat	Nasal pack	Multi-layered reconstruction (Y/N)	Lumbar drain (%)	CSF leak (%)	Other complications (%)
Garzaro, 2015[17]	Fat, fascia	Y	Fibrin and gelatin glue	Nil	Y	0 (0.0)	2 (22.2)	2 (22.2)
Chibbaro, 2014[18]	Fat, fascia	Y	Nil	Nil	Y	4 (6.9)	4 (6.9)	8 (13.8)
Iacoangeli, 2014[19]	Fat, fascia	N	Bone dust, fibrin glue, sutures	Nil	Y	0 (0.0)	0 (0.0)	0 (0.0)
Ishii, 2014[20]	Fat, fascia	Y	Nil	Nil	Y	0 (0.0)	0 (0.0)	0 (0.0)
Shidoh, 2014[21]	Fascia	Y	Oxidised cellulose, fibrin glue	Foley catheter	Y	0 (0.0)	1 (11.1)	4 (44.4)
Saito, 2012[22]	Fat, fascia	Y	Oxidised cellulose, fibrin glue	Foley catheter	Y	0 (0.0)	0 (0.0)	3 (50.0)
Tan, 2012[23]	Fat, fascia	Y (n=5)	Gelofoam paste	BIPP ribbon	Y	2 (14.3)	3 (21.4)	3 (21.4)
Taniguchi, 2011[24]	Fat, fascia	Y	Nil	Sinus balloon	Y	1 (25.0)	0 (0.0)	1 (25.0)
Fraser, 2010[25]	Fat, duraseal, gasket seal	Y	Floseal	Tefla nasal splints	Y	2 (25.0)	0 (0.0)	1 (12.5)

Table 3. Continued

Study and year	Reconstruction							
	Repair	NSF (Y/N)	Glue/ Haemostat	Nasal pack	Multi-layered reconstruction (Y/N)	Lumbar drain (%)	CSF leak (%)	Other complications (%)
Holzmann, 2010[26]	Fascia	Y (n=12)	Nil	Nasal pack	Y	11 (84.6)	1 (7.7)	2 (15.4)
Arbolay, 2009[27]	Fat	N	Nil	Nil	N	0 (0.0)	0 (0.0)	0 (0.0)
Stippler, 2009[28]	Duragen	Y	Surgicel	Gelatin foam, nasal pack	Y	0 (0.0)	5 (19.2)	5 (19.2)
Dehdashti, 2008[29]	Fat, fascia	N	Fibrin glue	Gelofoam balloon	Y	4 (33.3)	4 (33.3)	3 (25.0)
Hwang, 2007[30]	Fat	N	Fibrin glue	Anterior nasal pack	N	0 (0.0)	0 (0.0)	0 (0.0)
Frank, 2006[31]	Fat	N	Nil	Nil	N	0 (0.0)	1 (11.1)	0 (0.0)
Solares, 2005[32]	Fat	N	Collagen, gelofoam, thrombin	Nil	N	0 (0.0)	0 (0.0)	0 (0.0)
Totals/ averages	**-**	**-**	**-**	**-**		**55 (13.9)**	**40 (10.1)**	**63 (15.9)**
N of studies reconstruction method used in (%)	**23 (95.8)**	**17 (70.8)**	**15 (62.5)**	**14 (58.3)**	**18 (75.0)**	**9 (37.5)**	**-**	**-**

Table 3. Results from outcome measures in terms of reconstruction, post-operative CSF leaks and other complications.

Complication	n (%)
Cranial nerve palsy and diplopia	19 (30.2)
Meningitis	15 (23.8)
Endocrinopathies (including diabetes insipidus)	7 (11.1)
Major haemorrhage	6 (9.5)
Paresis (quad/hemi)	4 (6.3)
Hydrocephalus	2 (3.2)
Pneumocephalus	1 (1.6)
Brain infarction	2 (3.2)
Haematoma	2 (3.2)
Epistaxis	1 (1.6)
Craniocervical fixation	1 (1.6)
Medical complications *Hypokalaemia* *Pulmonary embolus* *Pneumonia*	3 (4.7) 1 1 1
Total	**63 (100.0)**

Table 4. All post-operative complications excluding CSF leaks from all included studies.

Subgroup analysis

Subgroup analyses were performed to compare post-operative CSF leak rates according to reconstruction methods. Analysis for patients with LD was omitted as seven studies using LDs did not stratify post-operative CSF leak rates according to whether a LD was used or not. Where studies reported data where CSF leak rates were stratified according to reconstruction methods, these data were separated accordingly into each subgroup [23,26].

The CSF leak rate was less than the overall CSF leak rate (10.1%) in subgroups where a NSF was used (9.4%), where no glue/haemostat was used (7.4%) and where no pack was used (9.0%). In terms of comparison between groups, there was a lower rate of CSF leak when a NSF was used compared to when one was not used (9.4% vs. 13.8%), but this was not a statistically significant difference ($p = 0.273$). There were higher rates of CSF leaks seen when glue/haemostat was used compared to not used (12.0% vs. 7.4%) and when nasal packs were used compared to not used (10.9% vs. 9.0%). Both differences were not statistically significant ($p = 0.139$ and 0.550 respectively). These findings are summarised in Table 5.

Reconstruction method	n	CSF leak n	CSF leak %	*p*-value
NSF	331	31	9.4	0.273
No NSF	65	9	13.8	
Glue/haemostat	234	28	12.0	0.139
No glue/haemostat	162	12	7.4	
Pack	230	25	10.9	0.550
No pack	166	15	9.0	
All	**396**	**40**	**10.1**	**-**

Table 5. Subgroup analysis comparing post-operative CSF leak rate in terms of reconstruction methods. P-values are calculated from chi-squared (χ^2) statistical tests.

Discussion

Since the advent of endoscopic endonasal skull base surgery, multiple methods for reconstruction of the cranial base have been described. Generally, there are four aspects that surgeons may consider using within a multi-layer reconstruction: graft repair of the intra-cranial defect, utilisation of a pedicled NSF, utilisation of tissue adhesive glue or haemostatic agents, and packing of the nasal cavity. We found that whilst the majority of studies evaluated in our study initiated their reconstruction with an intra-cranial graft. The material utilised was varied and ranged from autologous fat, fascia or cartilage, to synthetic collagen matrix with or without sealant systems such as DuraSeal® [Integra LifeSciences Corporation, Plainsboro, NJ].

There was also heterogeneity in the use of tissue glue, haemostatic agents, and packing within the nasal cavity. Hadad et al first described the use of a vascularised pedicle NSF for skull base reconstruction following endoscopic endonasal approaches, demonstrating that addition of this to a multi-layer reconstruction could reduce post-operative CSF leak rate to just 5%[7]. However, we found that a NSF was used in only 70.8% of studies, with a multi-layer reconstruction being employed in 75.0% of studies.

Our systematic review found an overall post-operative CSF leak rate of 10.1%. This is comparable with previous literature comparing open and endoscopic management of clival chordomas, where open transcranial CSF leak rate ranged from 9.5% - 10.7% and endoscopic 5.0 – 10.3%[33,34]. Whilst not reaching statistical significance, there was a higher rate of CSF leak in cases that did not adopt a NSF in their reconstruction (9.4% vs. 13.8%).

This lack of statistical significance may be explained by the inclusion of a number of studies where the overall incidence of CSF leak was somewhat higher than the average of 10.1%, ranging from 14-33%[16,17,23,28,29]. Dehdashti et al reported a case series of 12 patients undergoing endoscopic resection of a clival chordoma, where four patients had a post-operative CSF leak (33%). They used a multi-layer reconstruction technique in the entire cohort, but adopted a NSF in the final five patients. The CSF leaks they encountered occurred in patients where a NSF was not utilised, although this was hypothesised to be secondary to the underlying patient anatomy, with the presence of large pre-mesencephalic and pre-pontine cisterns[29].

Rahme et al reported results from a series of 23 endoscopic endonasal chordoma resections where a NSF was utilised for reconstruction in all cases[14]. There were six CSF leaks in total (26%). They found that patients who developed a CSF leak had a significantly higher mean tumour volume than those that did not and were more likely to have had intra-dural extension at presentation. Three of these were in cases of resection of a recurrent tumour. These findings would suggest that tumour size, level of invasiveness, and technicality of dissection due to scar tissue formation are all potentially important factors in predicting risk of a CSF leak.

These included studies with higher observed leak rates are likely to have skewed our overall average in favour of higher CSF leaks and therefore influenced the lack of statistical significance observed when comparing the use of an NSF to without. Furthermore, in all 11 individual studies where the CSF leak rate was greater than our mean of 10.9%, the rate of other observed complications in these studies accounted for 52.4% of the overall post-operative complication rate (excluding CSF leaks). This suggests that in studies where a higher leak rate was observed, there was an overall higher complication rate, perhaps related to tumour complexity and/or surgeon experience rather than reconstructive methods.

Tissue glue and nasal packing are utilised by some centres in an attempt to create a seal at the edge of the graft material and to provide additional support to the reconstruction. The foley catheter balloon can be utilised to tamponade graft material against the defect, counteracting gravity and the pulsations of the brain. We found however that there was actually a higher non-statistically significant rate of CSF leak in the studies where glue/haemostat (12.0% vs. 7.4%, $p = 0.139$) and/or nasal packs (10.9% vs. 9.0%, $p = 0.550$) were utilised. This is somewhat contradictory to what one might expect but may be related to the multitude of both surgeon and tumour-specific factors involved in determining occurrence of CSF leak as described previously. In addition, there may be large variance in how glue is used. There may be misuse for example being placed

between layers which may contribute to greater leak rates compared to no glue. Furthermore, we have assumed nasal packs were not used unless explicitly stated given the methodology of our review. There were also no studies that differentiated between absorbable and non-absorbable packs. There may have been studies using packs without documenting them, which may contribute to the lack of observed statistical significance.

Approximately one third of the included studies provided details regarding the use of a LD. Authors varied in their approach with some preferring to pre-emptively insert a LD either in all patients or based on intra-operative findings, whilst others adopted LDs only in the case of a confirmed post-operative CSF leak. However, in the studies where LDs were utilised following a pre-emptive approach, they did not provide specific data on patient drain status in relation to post-operative CSF leaks that they encountered. We were therefore unable to undertake any subgroup analysis on this particular subset of patients.

There are several limitations of this systematic review that should be kept in consideration. In terms of the quality of the evidence available, this was limited to case series and case reports and thus is a synthesis of level 3 and 4 evidence only. It therefore will represent data from a variety of treatment approaches, adjuvant therapy regimens and patient characteristics. These original reports may also be subject to selection and publication biases. Our search was also limited to the English language only, there may therefore be some degree of linguistic bias in our systematic review.

We found there was significant variation between studies in terms of the data reported and the level of detail included. Multiple studies did not report data on demographic points such as patient gender and age, or operative outcomes such as GTR. A number of studies also lacked a specific and comprehensive breakdown of their reconstruction method and its justification, and even fewer disclosed complete data relating to the use of LDs. This limited our ability to include these variables within our subgroup analysis of CSF leak rates.

In addition, there were many other cofounders that would affect CSF leak rates. Such examples include patient age, tumour size and extent, surgeon experience and any adjuvant treatment. While we evaluated and compared many baseline characteristics between studies (Table 2), we were not able to account for many other cofounders as described. Indeed, even within the baseline charactersitcs we have reported, there is heterogeneity with respect to patient demographics such as age and tumour factors such as GTR. This likely impacts on our overall effect estimate of 10.1% as an overall CSF leak rate. Despite this, we have synthesised all the available evidence pertaining to the

endoscopic resection of CC. In addition, our value of 10.1% is in keeping with other reported estimates of CSF leaks in this patient cohort [33,34].

As with all endoscopic skull base procedures, a variety of materials and repair strategies can be utilised and vary based on surgeon preference. As eluded to previously, most studies did not provide detailed accounts for the individual approach taken but it was clear in most cases, a multi-layered reconstruction was best suited to large clival defect repairs. The NSF has revolutionised skull base repair, especially in endoscopic clival approaches, however it may not necessarily be indicated in the absence of intra-operative CSF leaks. Again, it was not always clear which cases had intra-operative leaks and which did not, and whether a tailored approach to reconstruction was utilised on this basis. The length of patient follow-up also ranged significantly (6 - 68 months), and in multiple studies details on follow up were omitted.

Conclusion

In conclusion, our data is the most up-to-date synthesis of the existing literature surrounding the EEA to CCs with respect to reconstruction and post-operative CSF leaks. It demonstrates that EEA to CCs provides comparable outcomes to open approaches, with most authors employing a multi-layered reconstruction method. Although not statistically significant, the majority of authors prefer to use a NSF due to improved outcomes from repair, especially in higher flow site areas [35].

To date, the evidence does not demonstrate any statistically significant difference in CSF leak rate between all reconstruction methods used. However, this is likely due to a variety of surgeon and patient factors such as tumour size and invasiveness. Our results were somewhat limited by the reporting of reconstruction in the available literature. Higher quality prospective randomised multi-centric studies, with reporting of specific repair techniques need to be conducted to be enable more valid subgroup analyses in order to draw statistically significant conclusions. This will enable future systematic reviews and analyses to provide a more accurate consensus regarding optimal methods of reconstruction in this field.

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6

General Discussion

Endoscopic sinus surgery has evolved significantly since its first inception in the early 1900's to what we consider modern rhinology practice today (1). Invention of the Hopkins rod in the 1960's enabled for more detailed analysis of the sinonasal cavities and an improved understanding of natural drainage pathways (2,3,4). This coupled with greater anatomical awareness, superior radiological technology and both cold and powered instrumentation paved the path for what we today call endoscopic Anterior Skull Base (ASB) surgery (4,5). Prior to endoscopic endeavours of the anterior skull base, open approaches to the anterior skull base were being described as early as 1940's for sinonasal tumours and tumours involving the orbit (6,7). The combined transcranial and transfacial approach in 1963 quite possibly marked the beginning of ASB surgery as its own discipline (7,8). This fast became the gold standard approach by head and neck surgeons to deal with malignant paranasal sinus pathologies involving neighbouring key critical structures (9).

The value of the endoscope in ASB surgery was recognised before the start of the 20th century as endoscopic sinus surgery was being popularised for inflammatory sinonasal disease. In 1999 Thaler et al described endoscopic assisted anterior craniofacial resections for sinonasal tumour with intracranial extension (10). It was found that direct visualisation through the nasal cavity allowed for more accurate, safer resections whilst preserving major neurovascular structures (10,11,12). Not long after in 2001, Casiano et al published the first purely endoscopic ASB resection for esthesioneruoblastoma pathology (13). From here this approach fast became the gold standard for sinonasal tumours involving the ASB (14).

As our anatomical understanding of the ASB grew from an endoscopic approach, so did our will to take on larger, more complex pathologies. This forged a unique working relationship between the Otolaryngology and Neurosurgical teams, today known as the skull base team (15). Advantages of using minimally invasive sinonasal corridors mitigated the morbidity that came with extensive open approaches previously employed to tackle complex ASB lesions (16,17,18,19). Since Casiano et al's publication, many skull base teams developed over the world and adopted their techniques in an attempt to tackle larger more complex pathologies via different approaches. The work of other great world leaders like Aldo Stamm and Paolo Cappabianca further popularised endoscopic techniques far beyond the anterior cranial fossa and sella to more ventrally based lesions at the clivus and ones extending into the suprasellar space (20,21).

One of the biggest criticisms for endoscope ASB approached to malignant pathology is the inability to provide oncologically margin free en bloc resection

(22). However, it has been challenged on the basis that the idea is not to provide an en bloc resection but to excise tumours with negative surgical margins whilst reducing excessive morbidity from other open approaches, similar to Mohs micrographic surgery which delivers a margin-controlled excision (21). Other complications of endoscopic ASB approaches include cerebrospinal fluid (CSF) leak, epistaxis, meningitis, pneumocephalus and intracranial haemorrhage (22,23). Despite this, studies have demonstrated faster recovery, shorter length of hospital stay and decreased blood loss with endoscopic approaches in comparison to more traditional open approaches. In addition, endoscopic procedures allow for better tumour visualisation and improved cosmetic outcomes (25,26).

Resection of skull base tumours often leads to the creation of large skull base defects with open communication between the intracranial content and the sinonasal cavity (26). In cases where dura has been breached or dural resection is required, this leads to CSF fistulae with a potential for postoperative CSF leaks, meningitis and intracranial abscesses. Whilst there have been a variety of techniques described to reconstruct these defects, the pericranial flap had historically been the work horse for open cranial base resections since described first in 1978 (27,28,29). With the transition from open to endoscopic ASB resections, reconstruction of large endonasal defects remained the largest challenge to success of surgery. In a study published by Kassam et al, CSF leak was found to be the highest complication following expanded endoscopic approaches to skull base lesions – as high as 16% (30). With time as newer expanded corridors were developed to take on larger more complex pathologies, reconstruction became the limiting factor, especially in areas of high flow CSF cisterns. Over the years, a better understanding of endoscopic CSF leak repair and skull base reconstruction has allowed for reduced morbidity and improved outcomes from endonasal endoscopic approaches to ASB lesions.

Cerebrospinal Fluid rhinorrhea:

CSF rhinorrhea, which occurs due to an abnormal connection between the subarachnoid space and sinonasal cavity through a skull base defect, can be categorized as traumatic nontraumatic. Traumatic cases, which make up 80-90% of CSF rhinorrhea cases, are typically caused by head injuries or iatrogenic factors resulting from endoscopic endonasal surgery (31,32). Nontraumatic causes include skull base tumors, raised intracranial pressure, and congenital skull base defects. The management of CSF rhinorrhea is crucial due to the risk of meningitis, ranging from 10% to 37%, if left untreated (33,34,35). Traditionally, this was a limiting factor in large endoscopic skull base resections due to

poor reconstructive techniques and understanding. The traditional approach for managing CSF rhinorrhea involved open intracranial surgery. However, advances in endoscopic endonasal surgery have transformed the treatment of CSF rhinorrhea by reducing morbidity and achieving higher success rates ranging from 87% to 100% and allowing for the evolution of anterior skull base surgery (36).

Traumatic CSF leaks can arise from head injuries that involve fractures of the anterior skull base. This occurs in 15 to 30% of skull base fracture cases, with a higher prevalence in comminuted fractures (37). These leaks often occur through the cribiform plate of the ethmoid sinus roof due to the tight adhesion of the dura in these regions. Most patients (80%) will experience CSF rhinorrhea within the first 48 hours, and 95% of these patients will exhibit symptoms within 3 months (37). In such instances, leaks seldom require treatment as up to 85% heal spontaneously with conservative management (37). Surgical intervention is typically reserved for patients who do not respond to conservative measures due to the risk of meningitis. Iatrogenic CSF rhinorrhea makes up 16% of all traumatic CSF leak cases (36). This type of leak can occur after both routine endoscopic sinus surgery and more complex skull base surgery. The most common site of iatrogenic injury is the lateral cribiform plate, with other potential sites being the sphenoid sinus and posterior ethmoid fovea. The risk of a CSF leak following functional endoscopic sinus surgery is estimated to be 0.5%, but it increases with more complex skull base procedures such as clival approaches and revision surgery (38). Most of these leaks will be repaired immediately at the time of injury, or the patient will be transferred to a specialized skull base centre for surgical repair.

Spontaneous CSF leaks, those occurring without any apparent trauma, account for the majority of nontraumatic cases. The exact mechanism behind spontaneous CSF rhinorrhea remains unclear, but it's believed to be linked to elevated intracranial pressure (ICP), often from idiopathic intracranial hypertension (IIH) (39). Patients with IIH typically present as middle-aged, overweight women experiencing headaches, visual disturbances, and papilledema. This condition has seen a rising prevalence in the western world over recent decades, likely attributed to the obesity epidemic.

Spontaneous leaks arising from prolonged elevated ICP are thought to result from increased dural pulsation, leading to remodelling and thinning of the skull base and the formation of osteodural defects in pneumatized areas of the skull base (36). However, while elevated ICP has been implicated in spontaneous leaks, it's not the case for all patients with this condition (40,41). Historically, nontraumatic spontaneous leaks accounted for around 4% of all CSF leaks.

However, more recent data suggests a higher incidence, ranging from 20.8% to 40% (40). Other causes of nontraumatic leaks include tumors, mucoceles, or infectious processes that erode the skull base. Congenital causes, which can occur with or without elevated ICP, include encephaloceles, persistent craniopharyngeal canal (with or without a tumour), and congenital widening of the diaphragma sella (41).

Maintaining a high degree of suspicion based on the patient's history is crucial for accurate diagnosis. This includes considering recent trauma or surgery, which is a common factor in CSF rhinorrhea cases. The most prevalent clinical symptom is persistent clear rhinorrhea, often affecting one side of the nose, and worsening when bending over or performing a valsalva manoeuvre (40). Some patients may report a history of headaches associated with elevated intracranial pressure (ICP) or intracranial lesions. A quick bedside test for CSF fluid involves observing the formation of a "double ring sign" when drops of the fluid are placed on absorbent filter paper or the "halo sign" on a pillowcase. The definitive test for CSF fluid is Beta 2 transferrin detection using immunofixation electrophoresis, which offers a sensitivity of 94% to 100% and a specificity of 98% to 100% (41). If there is a strong suspicion or once the nasal discharge is confirmed as CSF, imaging is necessary to pinpoint the exact location of the leak.

High resolution Computed tomography (CT) scans are typically the first line imaging modality offering detailed osseous anatomy to pinpoint a site of dehiscence with a sensitivity of 88-95% (42). CT myelograms have largely been replaced by Magnetic Resonance Imaging (MRI) to detect sites of dural rupture, especially where CT findings are negative but biochemical markers of CSF are positive (such as β-2 transferrin) [43,44]. Better soft tissue enhancement with MRI can also help identify the presence of co-existing meningoencephalocoeles and any potential vascular loops within the defect. Other imaging methods less frequently used now include radioisotope cisternography with 111-Indium-DPTA as well as CT cisternography. Combined CT and T2 weighted CISS (constructive interference in steady state) MRI has shown to localise leak sites in 90-100% of cases (45). In cases where CT and MRI fails to localise the site of the leak, Intrathecal Fluorescein has been shown to be a safe effective technique in visualising the leak site intra-operatively (46). Based on previous studies and data, doses <50mg have consistently been shown to be safe while allowing for effective localisation of CSF leak site (45,46).

Skull base reconstruction:

Advancements in reconstructive methods and materials have led to the evolution of endoscopic skull base techniques, effectively separating sinonasal and intracranial compartments. The pivotal role played by a variety of flaps and biosynthetic materials in this evolution cannot be overstated. The principle of skull base repair lies in the accurate restoration of breached anatomical layers, with success gauged by the absence of post-operative CSF leaks (47). Notably, the rates of CSF leaks subsequent to endoscopic repair have markedly decreased, dropping from 30-40% to 6.7-11.5%, owing to advancements in instruments, endoscopic technology, and surgical materials and techniques, including the adoption of a vascularized nasoseptal flap (24,47,48). Contemporary reconstructive approaches integrate synthetic dural replacement grafts, autologous free grafts, vascularized flaps, as well as synthetic tissue glues and sealants to achieve effective repair. While techniques may vary, certain factors must be considered to determine the most suitable repair type for each case. These factors encompass the size of the defect, underlying pathology, tissue availability, CSF leak flow rate, the utilization of pre or post-treatment chemoradiotherapy, and patient preferences. (49,50,51,52).

Free autologous grafts such as free mucosa, fat, and fascia lata, continue to be a robust workhorse for a significant number of skull base reconstruction techniques and emerged as primary choices for reconstruction. The first report of an endoscopically applied free graft to repair a CSF leak was made by Wigand in 1981 (53). Free mucosal grafts remain easily accessible with low morbidity and can be obtained from the septum, nasal floor, inferior or middle turbinates (36,54,55). These are meticulously prepared by removing the turbinate bone and stripping the mucosal tissue. Free mucosal grafts prove to be extremely versatile and can be sized according to the size of the defect. Large free mucosal grafts can be obtained from the entire one side of the septum with extension onto the nasal floor if required (56). Often in small defects (<10mm) and low flow CSF leaks of the anterior cranial fossa, a single overlay free mucosal graft is sufficient at providing an excellent repair, providing the repair site has been adequality prepared to receive the graft (53,54,57). For higher flow leaks or larger defects involving the ventral skull base with significant dural loss, single onlay mucosal grafting is usually not adequate and a multi-layered approach is necessary (58). Care must be taken when applying free mucosal grafts to ensure that the graft is applied with the mucosal side outward to prevent the development of a mucocele. In cases of a multi-layered reconstruction approach, free mucosal grafts can serve as an excellent superficial bio-dressing layer to reduce nasal morbidity such as crusting and promote improved healing (56). Harvesting free mucosal grafts from turbinates carries the additional

risk of intra and postoperative bleeding due to injury to the branches of the sphenopalatine artery (59). In addition, donor site dysfunction is usually seen whilst remucosalisation occurs within 90 days, which is managed by regular debridement and saline irrigation (50).

For larger more complex defects in areas of high-volume CSF leaks, it is widely accepted to adopt a multi-layered reconstruction approach for a more robust watertight closure. This usually involves replacement of the layers breached using a variety of different graft materials. This includes intracranial layers (intradural and extradural) and extracranial layers overlying the bony defect (60,61,62). For the final overlay layer, extensive work and agreement has emerged with regards to the utility of a vascularised local pedicled flap like the Nasoseptal Flap (NSF), which we will discuss later, however there continues to be a significant amount of heterogeneity and little agreement on the ideal material for inlay grafting of large defects (51,62,63,64). In the context of autologous grafts, fascia lata (FL) harvested from the lateral thigh region has been recognized as a viable option for dural reconstruction, as both an inlay and onlay graft (65,66,67). Its advantageous characteristics, such as flexibility, durability, easy adaptation to the nasal cavity, and minimal donor-site complications, make it a valuable choice (65). More recent studies have shown success rates of 92% where a combination of FL inlay/onlay grafting was to reconstruct large, complex skull base defects endoscopically. Large sheets of FL can be harvested from the leg to provide enough material for a multi-layered approach (68). The pliability and adherence properties of FL has proven to be advantageous when reconstructing, with its ability to drape over complex skull base geometries whilst not easily being displaced (68).

Autologous fat grafts can also be used in the setting of skull base reconstruction to eradicate surgical dead space or In areas of low flow leaks with small dural defects as a plug to seal the hole. Typically sourced from the abdominal or leg dural FL harvesting, fat serves as a suitable subdural inlay substance, ideally employed to fill substantial cavities resulting from resection of tumors. Both fat and fascia lata can be synergistically utilized, with a fat graft applied to the resection cavity and fascia lata positioned over it, secured with packing and sealant (52, 54). In cases requiring rigid repair, free bone grafts can be relevant, particularly in morbidly obese patients where there is a potential risk of brain or meningeal herniation over time. These grafts can be harvested as split calvarial grafts or from the vomer and perpendicular plate of the ethmoid during septectomy (62,69). However, the use of bone grafts is a subject of controversy, as patients undergoing postoperative radiation therapy may face the risk of osteoradionecrosis and graft breakdown (70).

In recent years, there has been a rise in the utilization of synthetic grafts as substitutes for dural repair, proving successful in open middle and posterior fossa repairs (71,72). These grafts serve as effective alternatives to fascial/mucosal grafts for both intra and extra dural grafting, minimizing donor site morbidity albeit at an increased financial cost (73). Typically composed of a collagen matrix and available in various sizes, these grafts are particularly valuable for addressing larger defects through single or multilayer repairs. It's noteworthy that a considerable number of these grafts incorporate animal extracts, such as gelatin, necessitating discussion with patients before use. In cases where bone or cartilage grafting is impractical for larger defects, polydioxanone plates (PDS) have proven useful for providing rigid support, as seen in repairing significant anterior skull base defects to prevent brain herniation (74). The decision to employ synthetic grafts is contingent on surgeon preference, availability, and cost considerations. A diverse array of synthetic sealant and adhesive products serves as supplementary components to reinforce the primary reconstructive layers at the skull base. Typically, these are applied towards the end of the reconstruction process. SURGICEL® (Ethicon Inc, New Jersey, USA) is commonly utilized to ensure hemostasis and fill cavities, eliminating dead space. Fibrin-based adhesive glues like TISSEEL® (Baxter, Illinois, USA) and Evicel® (Ethicon Inc, New Jersey, USA) are employed to secure the layers in place and prevent graft migration. Fibrin sealant patches, such as TachoSil® (Baxter, Illinois, USA), can also function as an overlay for the initial duraplasty, serving as an alternative to nasoseptal flaps or free mucosal grafts for an additional layer of support (75). Following this, the nasal cavity is typically packed with absorbable (NasoPore® - Stryker, Michigan, USA) or non-absorbable (MEROCEL® - Medtronic Xomed, Jacksonville, FL, USA) products to enhance support and haemostasis. While these products are widely used, it is imperative for surgeons to acquaint themselves with the ingredients as a significant number of them may contain traces of animal or human derivatives, potentially conflicting with a patient's religious or personal beliefs and necessitating the need to avoid such materials should this be the case (76).

Contemporary endoscopic skull base repair techniques primarily rely on the Hadad-Bassagasteguy flap, or the pedicled nasoseptal flap (NSF), introduced in 2006 (77). This flap has significantly reduced postoperative cerebrospinal fluid (CSF) leak rates, expanding the scope of endoscopic intervention for various lesions and locations, especially in areas of high flow CSF cisterns (52, 70, 77). The NSF's key attributes include consistent vascularity, a long and robust pedicle, ease of harvest, and adaptability. It serves as a great overlay option as the final layer of the reconstruction, in large complex defects with high flow leaks. In the original article by Hadad and colleagues, the creation of the flap involves three incisions in the nasal septal mucosa, performed using needle-tip

monopolar cautery or cold steel techniques. The first superior cut commences along the sphenoid os and extends anteriorly along the septum, maintaining a distance of 1 to 2 cm below the cribriform plate to preserve olfaction. The second inferior cut starts from the superior margin of the choana, extends across to the posterior margin of the vomer, and then proceeds along the junction of the septum and the nasal floor over the maxillary crest. While this inferior incision can be extended laterally for wider defect coverage, caution is needed to avoid incising over the soft palate. The incision can also be extended anteriorly to the junction between the septal mucosa and the vestibular skin depending on the size of the flap required. These two incisions are connected anteriorly by a vertical incision (77). Subsequently, the flap is carefully freed from the underlying bone/cartilage, whilst preserving the posterior vascular pedicle where the postural septal branch of the sphenopalatine artery supplies the flap. In instances where the nasoseptal flap (NSF) is not viable due to reasons such as interrupted pedicle or blood supply from prior surgeries, alternative local pedicled flaps must be considered such as a posterior pedicled inferior turbinate flap or middle turbinate flap, however these can be technically more challenging to elevate. Importantly, pedicled intranasal flaps can sometimes be moved and reused, particularly in cases of recurrent surgeries, reducing the need for additional reconstruction. Prior to the advent of endoscopic procedures, open skull base approaches utilised several different reconstruction techniques, some of which included the use of the robust precranial flap. Till date, the pericranial flap serves to be a useful extranasal pedicled flap in the armamentarium of a skull base surgeon for large anterior cranial fossa defects, especially where intranasal flaps are not available for use or in the setting of previously failed reconstruction (52,70,74). The flap when harvested is delivered intranasally via a small incision through the bony anterior table of the frontal sinus. Though it is associated with increased morbidity whilst harvesting, it is an excellent backup option to have. An example of another extranasal pedicled flap is the temperoparietal fascial flap, supplied by the superficial temporal artery (52,53,70, 78). Once raised, the flap is tunnelled from the temporal fossa through into the infratemporal fossa and eventually intranasally through the posterior aspect of the maxillary sinus after exposure of the pterygopalatine fossa (78).

The use of lumbar drains (LD) in skull base surgery and reconstruction remains a controversial topic (79). Use of LD are not without increased complications and morbidity and so the benefits of its use must outweigh the risks. The risk of a complication is in the region of 5-8% and includes headaches, persistent leak, meningitis, pain and rarely tension pneumocephalus and subdural haematomas (78,79). Since the advent of pedicled nasoseptal flaps, the incidence of post-operative CSF leak rates significantly reduced to below 5% (77). Thus, the use of

a LD is not routinely recommended for low flow, low volume leaks. Numerous studies have failed to show a clear benefit with the use of LD in reducing post-operative leak rates, with a large review by Tien et al identifying 2049 skull base cases with a leak rate of 7.5% in the CSF diversion group vs 3.4% in the non-CSF diversion group (79). The reality of the situation is that skull base reconstruction is very heterogeneric with several factors influencing the repair outcome, making like for like comparisons very difficult. In summary the authors concluded that LD were useful in 2 scenarios, one of these being in early post-operative leaks where CSF diversion may aid the repair and reconstruction. The second scenario is in high flow intra-operative leaks with other high-risk factors such as complex anatomy with large defects eg trauma, revision cases, previous radiotherapy, cases of suspected intracranial hypertension and in cases with limited vascularised reconstructive options (78,79).

Conclusion

Endoscopic skull base surgery continues to advance in the modern era of surgery, with forever expanding indications and surgical corridors to approach complex pathologies. More recently, Transorbital Neuroendoscopic Surgery (TONES) has utilised the orbital corridor to tackle lesions lateral to the internal carotid artery and optic nerve. As our endoscopic anatomical understanding improves and with technological advancements, we may continue to see an increased trend towards minimally invasive endoscopic procedures for sinonasal and skull base pathologies. Sound anatomical awareness, skilled surgical team proficiency and meticulous watertight reconstruction will continue to underpin the successes of endoscopic skull base surgery and time will show how much more this specialty will evolve.

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7

Summary
Samenvatting

Summary

Skull base surgery has undergone a significant evolution over the years, marked by advancements in technology, surgical understanding and techniques, and interdisciplinary collaboration. This has resulted in transformative journey from high-risk procedures to more sophisticated minimally invasive endoscopic techniques employed today.

Chapter 2 looks at the trend and evolution of endoscopic sinus surgery as we know it today. The introduction of the Hopkin rod in 1945 transformed visualisation of the surgical field and the enable pioneers of Rhinology to explore sinonasal anatomy and physiology, giving birth to Functional Endoscopic Sinus Surgery. This, accompanied with other technological advancements has enabled us to perform complex sinus/skull base procedures via more favourable minimally invasive approaches with significantly less morbidity and complications. Over the years, we have seen a shift from open to endoscopic procedures with comparable if not better outcomes and faster patient recover.

Chapter 3 illustrates another key pillar of anterior skull base surgery, which gave surgeons the confidence to develop novel endoscopic surgical corridors to the skull base and tackle complex pathologies. Advancements in neuroimaging techniques such as CT and MRI provided a better understanding of both the bony anatomy of the skull base and the complex vascular anatomy near lesions commonly encountered at the skull base. Alongside this, the inception of image Guided Systems has truly allowed for safer surgery, whilst facilitating better surgical planning. This chapter specifically identified how lower radiation Cone Beam CT (CBCT) scans can be used to successful navigate the skull base during surgery.

Chapter 4 discusses highlights the importance of fixed anatomical landmarks to safely approach the skull base. In particular, the anatomical study demonstrates the Medial Canthal Point (MCP) as a safe consistent landmark to the frontal sinus, posterior to which is the anterior skull base. Through superior endoscopic visualisation and neuroimaging, our understanding of the anatomy of the skull base improved vastly, enabling minimally invasive surgical corridors to be invented.

The final **chapters 5.1-5.7** focus solely on another one of the key pillars of skull base surgery – reconstruction. One of the biggest obstacles in undertaking complex skull base pathologies was the ability to reconstruct the skull base and reduce the risk of post-operative CSF leaks. Over the years through more meticulous techniques, a variety of reconstructive materials and a multi-layered

approach with vascularised tissue options, our ability to reconstruct and repair complex skull base defects as significantly improved. In this section of the thesis we comprehensively explored a variety of aspects of skull base reconstruction from materials used through to adjuncts that can be implemented to help localise and repair defects (fluorescein) successfully, that has enabled anterior skull base surgery to be where it is today

Overall, I hope this thesis has provided some insight into the journey of anterior skull base surgery and the key pillars that have enabled it to evolve to where it stands today. With more novel minimally invasive approaches to the skull base continuing to be developed, such as Transorbital Neuroendoscopic Surgery (TONES), I am excited to see how this fascinating subspeciality will continue to evolve go over the next decade, whilst improving both patient and surgical outcomes.

Samenvatting

Chirurgie van de schedelbasis heeft door de jaren heen een aanzienlijke evolutie ondergaan, gekenmerkt door vooruitgang in technologie, chirurgisch begrip en technieken, en interdisciplinaire samenwerking. Dit heeft geresulteerd in een transformatieve reis van hoog-risico procedures naar de meer verfijnde minimaal invasieve endoscopische technieken die tegenwoordig worden toegepast.

Hoofdstuk 2 kijkt naar de trend en evolutie van endoscopische sinuschirurgie zoals we die vandaag de dag kennen. De introductie van de Hopkin-rod in 1945 transformeerde de visualisatie van het chirurgische veld en stelde pioniers van de rhinologie in staat om de anatomie en fysiologie van de neusbijholten te verkennen, wat de geboorte gaf aan

Functionele Endoscopische Sinuschirurgie. Dit, in combinatie met andere technologische vooruitgangen, heeft ons in staat gesteld om complexe procedures aan de sinussen/schedelbasis via gunstigere minimaal invasieve benaderingen uit te voeren met aanzienlijk minder morbiditeit en complicaties. Door de jaren heen hebben we een

verschuiving gezien van open naar endoscopische procedures met vergelijkbare, zo niet betere resultaten en snellere herstel van patiënten.

Hoofdstuk 3 illustreert een andere belangrijke pijler van de voorste schedelbasischirurgie, die chirurgen het vertrouwen gaf om nieuwe endoscopische chirurgische corridors naar de schedelbasis te ontwikkelen en complexe pathologieën aan te pakken. Vooruitgangen in neuro-imaging technieken zoals CT en MRI zorgden voor een beter begrip van zowel de benige anatomie van de schedelbasis als de complexe vasculaire anatomie nabij laesies die vaak bij de schedelbasis worden aangetroffen. Daarnaast heeft de introductie van beeldgestuurde systemen werkelijk veiliger chirurgie mogelijk gemaakt, terwijl het betere chirurgische planning faciliteerde. Dit hoofdstuk identificeerde specifiek hoe lage straling

Cone Beam CT (CBCT) scans succesvol kunnen worden gebruikt om de schedelbasis tijdens de chirurgie te navigeren.

Hoofdstuk 4 bespreekt het belang van vaste anatomische oriëntatiepunten om de schedelbasis veilig te benaderen. In het bijzonder toont de anatomische studie het Mediale Canthale Punt (MCP) als een veilig consistent oriëntatiepunt naar de frontale sinus, waarachter de voorste schedelbasis ligt. Door superieure

endoscopische visualisatie en neuro-imaging is ons begrip van de anatomie van de schedelbasis enorm verbeterd, waardoor minimaal invasieve chirurgische corridors konden worden uitgevonden.

De laatste hoofdstukken 5.1-5.7 richten zich uitsluitend op een andere belangrijke pijler van schedelbasischirurgie – reconstructie. Een van de grootste obstakels bij het aanpakken van complexe schedelbasis pathologieën was het vermogen om de schedelbasis te reconstrueren en het risico op postoperatieve CSF-lekken te verminderen. Door de jaren heen, door meer nauwgezette technieken, een verscheidenheid aan reconstructieve materialen en een gelaagde benadering met gevascullariseerde weefselopties, is ons vermogen om complexe defecten van de schedelbasis te reconstrueren en te herstellen aanzienlijk verbeterd. In dit deel van het proefschrift hebben we uitgebreid verschillende aspecten van schedelbasisreconstructie onderzocht, van gebruikte materialen tot adjuncten die kunnen worden geïmplementeerd om defecten (fluoresceïne) succesvol te lokaliseren en te herstellen, wat de voorste schedelbasischirurgie heeft gebracht waar het vandaag de dag staat.

Over het geheel genomen hoop ik dat dit proefschrift enig inzicht heeft gegeven in de reis van voorste schedelbasischirurgie en de belangrijke pijlers die het in staat hebben gesteld om te evolueren naar waar het vandaag de dag staat. Met meer nieuwe minimaal invasieve benaderingen van de schedelbasis die blijven ontwikkelen, zoals Transorbitale Neuroendoscopische Chirurgie (TONES), ben ik benieuwd hoe deze fascinerende subspecialiteit zich in het komende decennium zal blijven ontwikkelen, terwijl zowel de patiënt- als chirurgische resultaten verbeteren.

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Curriculum Vitae

Karan Jolly was born on August 27, 1988, in Wolverhampton, UK, where he grew up with his parents and two brothers. During his time at Queen Mary's Grammar School in Walsall, he quickly realised his aspiration to pursue a career in surgery. Following his schooling, he studied Medicine at the University of Birmingham, graduating in 2011.

Karan completed all his postgraduate training locally in the West Midlands, where he decided early on to specialize in Otolaryngology. At a conference where he was presenting his work, he was inspired by a talk from Mr. Shahzada Ahmed on Anterior Skull Base surgery. This encounter was pivotal, as Karan later had the privilege of being mentored by Mr. Ahmed, collaborating closely with him on numerous clinical and research projects. During the final phase of his higher surgical training, Karan spent 18 months at Queen Elizabeth Hospital Birmingham, gaining significant experience in Anterior Skull Base surgery under the mentorship of Mr. Ahmed. During this period, he also began working towards his PhD through published work.

After completing his higher surgical training in 2011, Karan was awarded a fellowship in Rhinology and Anterior Skull Base surgery with Professor Arif Janjua in Vancouver, Canada. He spent a year abroad before achieving his goal of returning to Queen Elizabeth Hospital Birmingham as a consultant, working alongside Mr. Ahmed.

Karan feels fortunate to have had excellent training opportunities and supportive mentors throughout his journey. He has published over 60 peer-reviewed papers, contributed to 20 book chapters, edited 4 books, and presented more than 100 posters and oral presentations both nationally and internationally. Over the years, Karan has received several awards for his dedication to research and published work. With the support of his mentor, he became the first UK trainee to successfully complete the European Diploma of Skull Base Surgery in Paris.

Currently, Karan lives in Birmingham with his wife and their two young sons, Vihaan and Viraj. He remains committed to collaborating with Mr. Shahzada Ahmed and his colleagues to enhance the skull base service at his hospital and provide the highest level of care.

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No endeavour or achievement is complete without acknowledging the people who have made it possible and been part of the journey. Without their motivation, guidance and support, none of this would be possible.

Family forms a significant proportion of my support system and motivation. My parents have been a constant pillar of support throughout my training years and supported me through all the challenges in my life and been there to celebrate every success and achievements. They forever remain proud of what I have achieved till date, and I am grateful for their support and blessings. My amazing wife Pawanjit has allowed me to pursue all my career ambitions and supported me throughout and understood the time and commitment required to achieve all I have today. She has sacrificed a lot for me to be able to be where I am today. She has also given me two beautiful boys, of whom I am immensely proud and deeply in love with. I look forward to growing together as a family and for many adventures to come and hope to be a great role model for them both.

Aside from my family, the credit for a significant proportion of what I have achieved today and what I continue to achieve goes to Mr Shahzada Ahmed, my mentor. His passion and commitment to his craft was from the start infectious to me and never failed to impress me. I have always admired his work ethic and how he always goes above and beyond for his patients to deliver the highest level of care – something that I also hope to emulate. Without his ongoing support, guidance, mentorship and inspiration, none of what I have achieved today would be possible. To me, he has been my Guru (teacher), and I can only hope to follow in his footsteps.

None of the publications and work submitted in this PhD is a product of one or two individuals. There is always a team behind every research work and contributes to the success of every publication. There are too many people to name who have helped me in all my achievements, but I would like to take the time to thank each and every one who has helped me in all my academic endeavours and made today possible.

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Research data management

The thesis is based on the results of human studies which were conducted according to the guidelines for Good Clinical Practice and ethical principles stated by the Declaration of Helsinki. Where relevant, local ethical committee approval was sought and none of the studies were subject to the medical research involving human subjects acts (WHO).

There are no conflicts of interest to declare, including financial and personal, that could influence the results and data of the published thesis. No institution or individual provided financial support to conduct the studies and research included in this thesis.

All original data obtained for the relevant studies was anonymised and stored on a password protected electronic file and stored securely on a hospital computer, with access granted to only those involved in the individual research projects.