The Risk of Meningitis Following Expanded Endoscopic Endonasal Skull Base Surgery: A Systematic Review

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Abstract

Objective To examine the risk of postoperative meningitis following expanded endoscopic endonasal skull base (EESB) surgery.

Setting A systematic analysis of publications identified through searches of the electronic databases from Embase (1980–July 17, 2012), Medline (1950–July 17, 2012), and references of review articles.

Main Outcome Measures Incidence of meningitis following EESB surgery.

Results A total of 2,444 manuscripts were selected initially, and full-text analysis produced 67 studies with extractable data. Fifty-two contained data regarding the frequency of postoperative meningitis. The overall risk of postoperative meningitis following EESB surgery was 1.8% (36 of 2,005). For those reporting a cerebrospinal fluid (CSF) leak, meningitis occurred in 13.0% (35 of 269). For those not reporting a CSF leak, meningitis occurred in 0.1% (1 of 1,736). The odds ratio for the development of meningitis in the presence of a postoperative CSF leak was 91.99 (95% confidence interval, 11.72–721.88; $p < 0.01$). There was no difference in reported incidence of meningitis or CSF leak between anterior and posterior cranial fossa surgery. There was one reported case of meningitis-related mortality following EESB surgery.

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

Keywords
- systematic review
- endoscopy
- endonasal
- skull base
- meningitis
- CSF rhinorrhea

Introduction

Advancements in endoscopic endonasal skull base (EESB) surgery continue to evolve with increasing surgical complexity.[1–10] The establishment of the endonasal route enables access and visualization to the ventral cranial base through the narrowest practical corridor with minimal trauma to surrounding tissue. Within anatomical limitations, the degree of tumor resection and vascular manipulation is often considered comparable with conventional microsurgical skull base techniques.[9–21]

Major concerns following an EESB surgery, however, are the risk of cerebrospinal fluid (CSF) rhinorrhea and meningitis. Much improvement has been made with the development of vascularized mucosal flaps to aid in the reconstruction of the skull base after EESB surgery.[7,22,23] These endoscopic reconstructions

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not only provide a reliable separation of the cranial and sinonasal cavity but are robust over time.[24] A recent systematic review demonstrated that the rate of CSF leak after true intradural EESB was 15.6% (representing 51 of 326 patients) with free graft techniques and 6.7% with vascularized flap reconstructions (representing 19 of 283 patients).[7] This is comparable with open craniofacial surgery,[25] but questions still arise due to the inability to formally provide a sterile field and connection with the upper aerodigestive tract.

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

Methods

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

Eligibility Criteria

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

Search Criteria

The Medline database was searched from 1950 to July 17, 2012, and the Embase database was searched from 1980 to July 17, 2012. The Cochrane Collaboration database and the National Health Service Evidence Health Information Resources Web site were also searched. The bibliographies of identified manuscripts were reviewed for additional data sources. No unpublished trials were included. We designed a search strategy to include manuscripts relevant to any aspect of endoscopic skull base surgery and skull base reconstruction. ►**Table 1** shows the search strategy used for Embase and Medline databases.

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

Data Extraction

Standardized data sheets were used for each study. The primary outcomes were recorded as the presence or absence of reporting on postoperative CSF leak and meningitis events. Secondary analysis of this outcome focused on the dichotomization of data for anterior cranial fossa (via a transcribiform or a transplanum route) and posterior cranial fossa surgeries (via a transclival route) to establish if a difference exists in the rate of meningitis following these two types of endonasal approaches. For each group, the number of patients, the type of approach, pathology, and perioperative morbidity relevant to the skull base surgery was recorded. The large range of methods, study aims, and pathologies were reported qualitatively in the data. Studies were deemed suitable for inclusion only if they documented the presence or absence of postoperative meningitis following EESB surgery or explicitly stated that patients had no further adverse events other than that reported. Where duplicate publication was anticipated from centers republishing updated reports on their EESB experience over time,[26–33] the most recent or largest published data were included for analysis in the current study.

Statistical Analysis

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

Results

Literature Review Results

The search of Embase and Medline produced a total of 2,429 studies written in English. Additional records identified through bibliographic and referencing resources yielded a further 15 studies that were included in the analysis, totaling 2,444 studies. After exclusion of duplicates, 1,985 studies remained. A title search found 293 articles on skull base

Table 1 Medline search strategy (similar modified version used in Embase)

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

surgery. Those studies captured in the search that described simple CSF leak repairs ($n = 49$; 16.7%), repairs for encephaloceles ($n = 14$; 4.8%), and microscopic skull base series ($n = 59$; 20.1%) were excluded from the analysis. This selection process is outlined in ►**Fig. 1**.

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

Perioperative outcomes were recorded for 67 EESB studies. An additional 15 studies were excluded due to duplicity of data ($n = 2$) and nonextractable outcomes for meningitis ($n = 13$). Fifty-two studies with reports of posttreatment meningitis were included in the final analysis (►**Table 2**).

Primary Outcome: Overall Risk of Meningitis following Expanded EESB Surgery

Quantitative analysis revealed a total of 2,363 patients, of which 2,005 were considered to have undergone an expanded EESB surgery. An attempt was made to exclude from the analysis all patients with pituitary adenomas in which a transellar approach was used. The mean age was 49.8 years (range: 3–91 years) and the mean follow-up was 21.8 months (range: 0.2–152 months). Of the studies that report on sex, females accounted for 49.8% of the cases (943 of 1,893).

The overall incidence of postoperative meningitis following EESB surgery was 1.8% (36 of 2,005). Of the total population, 269 experienced a postoperative CSF leak (►**Table 3**). This was represented as a 13.0% (35 of 269) risk of meningitis for those patients with CSF leak compared with 0.1% (1 of 1,736) for non-CSF leak cases (chi-square = 221.64; $p < 0.01$). Overall, the odds of developing meningitis in the presence of a postoperative CSF leak following an EESB procedure were 91.99 (95% confidence interval [CI], 11.72 to 721.88; $p < 0.01$).

One death related to postoperative meningitis was reported in a 42-year-old man following an endoscopic transsphenoidal supradiaphragmatic resection of a hypothalamic astrocytoma.[1] This patient underwent an uneventful subtotal resection of the tumor but experienced postoperative meningitis and died 2 weeks following surgery.

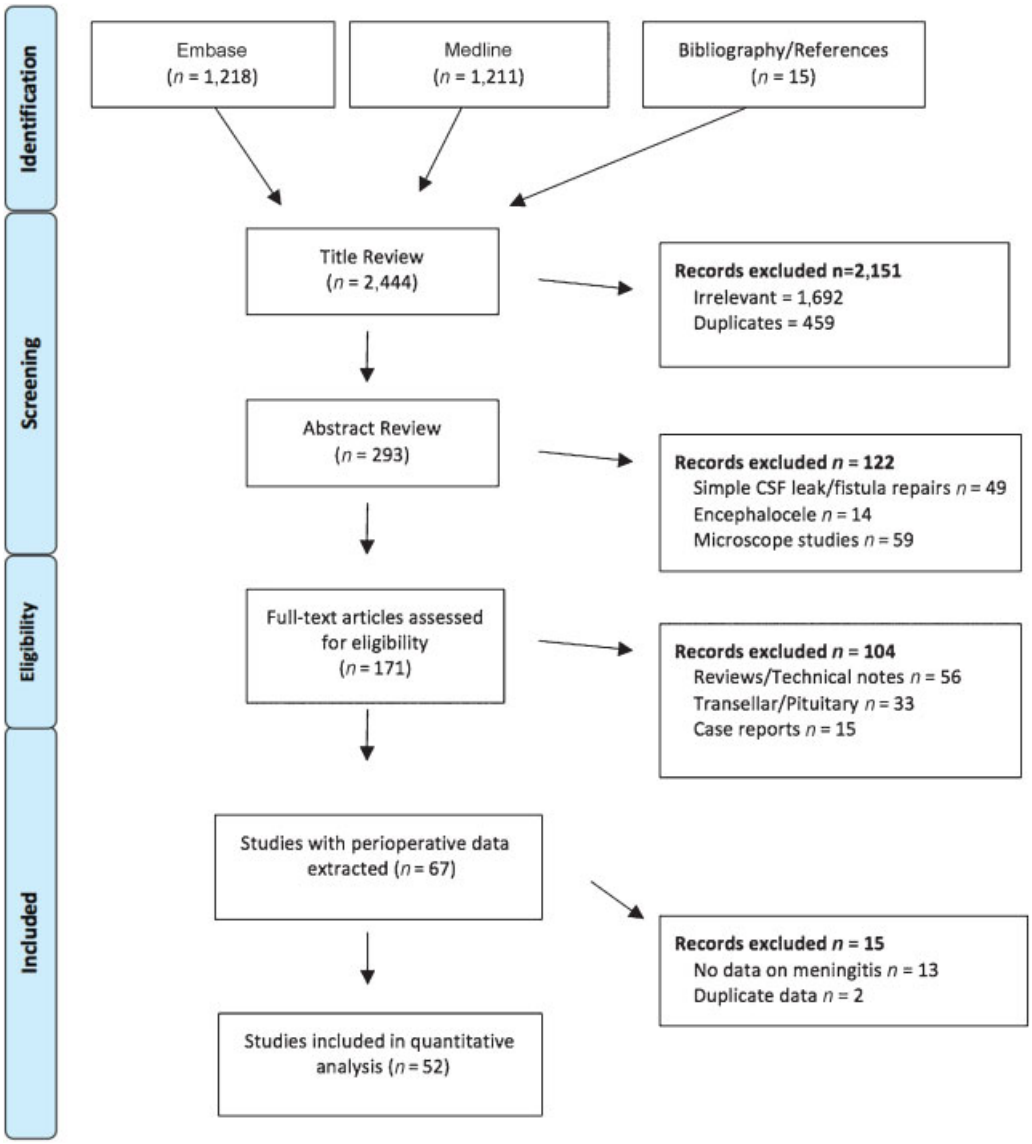

Fig. 1 Article selection process from the Embase and Medline database searches. CSF, cerebrospinal fluid.

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

Thirty-two studies described the endoscopic endonasal transcribiform or transplanum approach to the anterior skull base.[2,5,26,28,34–60] Of these 32 studies, 664 patients were considered to have undergone expanded EESB surgery of the ACF. The mean age was 51.9 years (range: 4–91 years), and the mean follow-up was 26.3 months (range: 0.8–152 months). Sinonasal malignancies with transcranial extension was accounted for in 409 cases (61.6%), craniopharyngioma in 112 cases (16.9%), meningioma in 66 cases (9.9%), Rathke cleft cyst in 43 cases (6.5%), chordoma in 7 cases (1.1%), metastasis in 5 cases (0.8%), glioma in 1 case (0.2%), and chondrosarcoma in 1 case (0.2%).

The risk of postoperative meningitis following EESB surgery to the ACF was 1.7% (11 of 664) and an 11.3% (75 of 664) CSF leak rate. The odds of developing postoperative meningitis among the ACF cases with a postoperative CSF leak were 90.46 (95% CI, 11.40–717.99; $p < 0.01$). In contrast, only 1 patient experienced meningitis (0.2%) among the 589 patients with no postoperative CSF leak.

Nine studies described the endonasal transclival approach to the PCF in 97 patients with a mean age of 48.6 years (range: 4–87 years).[4,30,32,33,61–65] There were 39 females (40.2%), and the mean follow-up was 14.9 months (range: 0.2–69 months). Chordoma was accounted for in 73 cases (75.3%), chondrosarcoma in 5 cases (5.2%), metastasis in 2 cases (2.1%), meningioma in 2 cases (2.1%), sinonasal malignancy with posterior cranial fossa extension in 1 case (1.3%), and vascular in 1 case (1.3%).

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

Table 2 Characteristics of included studies

Study	Study period	EESB cases	Age, y (SD or range)	Female, %	CSF leak,%	Meningitis, %	Mortality related to meningitis, %
Batra et al[2]	1995–2003	9	55 (26–77)	33	11	0	0
Solares et al[32]	2000–2004	6	50 (29–66)	33	0	0	0
Carrau et al[26]	NR	20	NR	55	15	5	0
Frank et al[61]	1998–2005	11	59.4 (32–76)	55	0	0	0
Frank et al[5]	1998–2005	10	41.5 (11–61)	60	30	10	0
Leong et al[34]	2000–2005	10	57.4 (26–84)	60	0	20	0
Cavallo et al[35]	2004–2006	16	NR	NR	13	0	0
Dave et al[36]	1997–2006	19	61.6 (39–81)	42	0	0	0
de Divitiis et al[37]	2005–2006	6	56.1 (44–77)	50	17	0	0
Santos Rde et al[38]	2001–2005	8	47.6 (9–79)	NR	25	25	0
Fortes et al[62]	NR	3	54 (51–57)	67	67	0	0
Kassam et al[74]	2000–2005	18	13.5 (3–18)	72	6	0	0
Laufer et al[39]	NR	10	54 (38–73)	NR	10	0	0
Cappabianca et al[75]	2004–2006	24	47.3	83	13	4	0
Carrabba et al[63]	2005–2008	17	48.0	41	24	0	0
de Divitiis et al[40]	1983–2006	7	NR	NR	29	0	0
de Divitiis et al[41]	2004–2007	11	55.3 (35–80)	64	27	0	0
Dehdashti et al[4]	2005–2007	12	49.4 (22–77)	33	33	0	0
El-Banhawy et al[42]	1997–2006	10	NR	NR	0	0	0
El-Sayed et al[43]	2006–2007	20	52 (18–56)	75	0	0	0
Gardner et al[44]	1999–2006	16	55 (36–80)	38	69	0	0
Gardner et al[31]	2002–2005	35	55 (39–79)	83	40	0	0
Kassam et al[29]	2006–2007	48	47 (4–80)	58	17	0	0
Kassam et al[28]	NR	10	44.4 (16–78)	30	50	0	0
Leng et al[76]	2005–2007	10	NR	NR	0	0	0
Nicolai et al[45]	1996–2006	134	58.7 (4–85)	50	3	1	0
Stamm et al[46]	2000–2007	7	23.4 (16.3)	14	29	0	0
Zhang et al[64]	2002–2006	9	35 (14–63)	44	0	0	0
Arbolay et al[1]	2006–2007	5	41.4 (25–60)	20	0	20	20
Cavallo et al[47]	2004–2008	22	49.4 (18–80)	32	14	0	0
Cohen et al[48]	2000–2006	18	53 (19–91)	50	17	0	0
Dehdashti et al[3]	2005–2007	19	44 (20–78)	37	21	5	0
Eloy et al[49]	1997–2006	18	61.2 (39–81)	44	6	0	0
Fatemi et al[50]	2000–2008	14	45 (8–79)	57	36	0	0
Folbe et al[51]	1994–2006	16	56.6 (15–79)	44	25	0	0
Harvey et al[22]	2007–2008	22	45.5 (20.2)	59	5	0	0
Liu and Di[52]	2004–2008	10	38.4 (20–58)	50	10	0	0
Stippler et al[33]	2003–2007	20	44.4 (4–76)	40	25	0	0
Vergez et al[53]	1994–2008	17	68 (44–82)	12	0	6	0
Batra et al[54]	2000–2008	31	57.5 (14–84)	42	6	3	0
Fraser et al[77]	NR	17	52.4 (22–87)	35	6	6	0
Greenfield et al[55]	2004–2009	43	55.4 (17–85)	63	7	0	0
Horiguchi et al[78]	2005–2009	19	55.9 (20–79)	63	26	0	NR
Jane et al[56]	2005–2009	12	50.8 (29–76)	58	0	8	NR
Madhok et al[57]	1998–2008	35	34 (12–67)	NR	0	0	0
Nyquist et al[79]	2008–2008	5	56.4 (31–72)	60	0	0	0
Prevedello et al[30]	NR	2	44.5 (42–47)	0	0	0	0
Villaret et al[58]	1996–2008	62	61.7 (25–84)	29	13	0	0

Table 2 (*Continued*)

Study	Study period	EESB cases	Age, y (SD or range)	Female, %	CSF leak,%	Meningitis, %	Mortality related to meningitis, %
Gallia et al[59]	2005–2010	8	56.9 (44–72)	38	0	0	0
Kono et al[69]	1998–2008	1000	49 (18.0)	50	14	2	0
Kurschel et al[80]	2004–2009	58	39.9 (4–78)	50	10	7	0
Carta et al[60]	2000–2009	16	59.0	NR	6	0	0

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

Table 3 Risk of meningitis following expanded endoscopic endonasal skull base surgery

	Overall meningitis risk	Meningitis with associated postoperative CSF leak	Meningitis with no associated postoperative CSF leak	*p* value
All studies ($n = 52$)	1.8% (36/2,005)	13.0% (35/269)	0.1% (1/1,736)	< 0.01
EESB to the anterior cranial base studies ($n = 32$)	1.7% (11/664)	13.3% (10/75)	0.2% (1/589)	< 0.00
EESB studies to the posterior cranial base ($n = 9$)	1.0% (1/97)	6.3% (1/16)	0% (0/81)	< 0.00

Abbreviations: EESB, expanded endoscopic endonasal skull base; SD, standard deviation; CSF, cerebrospinal fluid.

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

Discussion

In the past decade, the application of EESB surgery to midline cranial base pathologies has been established through various cadaveric and clinical studies.[9,10,21,66–68] The rapid expansion of this technique, however, carries with it a particular concern for the infectious ramifications of operating through the "clean-contaminated" field of the sinonasal cavities.[69] Problems with closure of the dura mater and prevention of CSF leaks remain a challenge and a significant source of postoperative morbidity following an endoscopic transnasal craniotomy.

In the current study, a systematic analysis of the literature was performed to establish the incidence of meningitis following expanded EESB surgery. Our results indicated an overall 1.8% risk of postoperative meningitis. The risk, however, was not substantially different for an endoscopic endonasal approach to the anterior cranial base (1.7%) or a posterior cranial base (1.0%) ($p = 0.64$). These rates are comparable with conventional transcranial or transfacial surgical approaches that harbor a reported infectious risk ranging from 0.9 to 2.5%.[70,71] Mortality related to meningitis was reported in 1 patient among the 36 reported cases of postoperative meningitis following an EESB procedure.[1]

As expected, the presence of postoperative CSF leak was associated with subsequent meningitis (OR: 91.99; 95% CI, 11.72–721.88; $p < 0.01$). In a large retrospective series of 1000 endoscopic skull base patients treated at the University of Pittsburgh, Kono and colleagues identified several risk factors for subsequent meningitis.[69] Included among the factors that were recognized to predispose to meningitis were male sex, a history of prior craniotomy or endonasal surgery, the presence of ventriculoperitoneal shunt or an external ventricular drain at the time of surgery, and higher complexity intradural surgeries. The presence of a postoperative CSF leak was, not surprisingly, considered by many as an important factor in predisposing to the subsequent development of meningitis. The incidence of meningitis without an associated CSF, as demonstrated in this study, was very low (0.1% [1 of 1,736]).

Although it is considered that endonasal surgery to the PCF is associated with a higher risk of both CSF leak and meningitis, the data presented in this study demonstrate no difference across 761 patients in which a comparison of approach could be made. Over the past few years, the application of multilayer reconstructions and the routine use of vascularized mucosal flaps in expanded endonasal surgery have drastically decreased the risk of postoperative CSF complications and meningitis.[72,73] Harvey and colleagues reported a 0.9% risk of subsequent intracranial complication with a delayed CSF leak rate of 1.9% in 106 endoscopic skull base repairs over a 5-year period.[22] In a systematic review of endoscopic skull base reconstruction of large dural defects, postoperative CSF leak following vascularized endonasal reconstruction for expanded endoscopic skull base surgery was estimated to be 6.7%.[7] The dramatic effect of vascularized dural closure techniques

for EESB procedures was also emphasized in several studies.[7,22,43] In particular, Kono and colleagues observed a fivefold reduction in postoperative infections among intradural EESB patients from 11.5 to 2.4% following the introduction of vascularized endonasal flap reconstruction.[69]

Study Limitation

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

In the current review, there is an overrepresentation of the 2005 published cases by one group.[69] The University of Pittsburgh Medical Center (UPMC) data accounts for 1,000 of the total 2,005 included cases (49.9%). However, in a subanalysis, the meningitis rate was similar for the UPMC experience of 1.8% (18 of 1,000) as compared with the remaining publications: 1.8% (18 of 1,005). The bias of a single large center publishing report does not appear to alter significantly the published reports for other centers.

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

Conclusion

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

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