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Fat in the Fossa and the Sphenoid Sinus: A Simple and Effective Solution to CSF Leaks in Transsphenoidal Surgery. Cohort Study and Systematic Review

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Abstract

Objectives Cerebrospinal fluid (CSF) leak following endoscopic transsphenoidal surgery (TSS) remains a challenge and is associated with high morbidity. We perform a primary repair with fat in the pituitary fossa and further fat in the sphenoid sinus (FFS). We compare the efficacy of this FFS technique with other repair methods and perform a systematic review.

Design, Patients, and Methods This is a retrospective analysis of patients undergoing standard TSS from 2009 to 2020, comparing the incidence of significant postoperative CSF rhinorrhea (requiring intervention) using the FFS technique compared with other intraoperative repair strategies. Systematic review of current repair methods described in the literature was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Results In all, there were 439 patients, with 276 patients undergoing multilayer repair, 68 patients FFS repair, and 95 patients no repair. No significant differences were observed in baseline demographics between the groups. Postoperative CSF leak requiring intervention was significantly lower in the FFS repair group (4.4%) compared with the multilayer (20.3%) and no repair groups (12.6%, $p < 0.01$). This translated to fewer reoperations (2.9% FFS vs. 13.4% multilayer vs. 8.4% no repair, $p < 0.05$), fewer lumbar drains (2.9% FFS vs. 15.6% multilayer vs. 5.3% no repair, $p < 0.01$), and shorter hospital stay (median days: 4 [3–7] FFS vs. 6 (5–10) multilayer vs. 5 (3–7) no repair, $p < 0.01$). Risk factors for postoperative leak included female gender, perioperative lumbar drain, and intraoperative leak.

Keywords
- transsphenoidal
- endoscopic
- CSF leak
- repair
- sellar
- fat graft

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Conclusion Autologous fat on fat graft for standard endoscopic transsphenoidal approach effectively reduces the risk of significant postoperative CSF leak with reduced reoperation and shorter hospital stay.

Background

The endoscopic transsphenoidal approach allows access to the anterior skull base with very low morbidity and has become the favored approach globally for the majority of pituitary adenomas and other sellar/suprasellar pathologies.[1] Although the access and visualization are excellent, cerebrospinal fluid (CSF) rhinorrhea remains a significant challenge.[2] Persistent CSF rhinorrhea is associated with meningitis in up to 20% of patients[3] and can cause tension pneumocephalus. Up to 50% of CSF leaks are not identified intraoperatively.[4] Further procedures are often required to address the leak and treat complications. There has been growing focus on minimizing the rate and incidence of CSF rhinorrhea after transsphenoidal surgery (TSS), yet no single effective solution has been identified.

Published rates for CSF leak following TSS range from 1 to 30%.[5,6] Methods used include combinations of autologous fat or fascial grafts, synthetic dural grafts, gelatin foam, fibrin glue, nasoseptal flaps, and use of intraoperative lumbar drainage. There is significant heterogeneity in the published literature and confounding factors include the proportion of microadenomas in a series, the pathologies addressed, the extent of resection, and heterogeneous patient populations. Furthermore, there is heterogeneity in the definition of a CSF leak.

We have recently changed our practice to perform a primary repair of suspected or confirmed intraoperative CSF leaks with fat in the fossa and more fat in the sphenoid sinus (FFS) at the first surgery, with no artificial dural substitutes or fibrin glues. As we had an increased incidence of postoperative CSF leaks with the multilayer repair technique, we decided to change our practice. Due to the high rate of CSF leaks, which go unrecognized intraoperatively and only present postoperatively, we have a low threshold for performing an FFS graft even in the absence of a clear intraoperative leak. This study assesses the efficacy of the FFS technique compared with previous techniques used in our institution and those reported in the literature. Risk factors such as patient demographics, previous TSS, size of tumor, and type of repair were also analyzed to address their impact on the rate of CSF leak.

Materials and Methods

Study Design

A retrospective analysis was performed of a prospectively collected database of all patients who underwent endoscopic TSS for sellar/suprasellar lesions at our tertiary neurosurgical unit between July 2009 and July 2020. All cases were analyzed according to repair type. We used our fat repair technique in the cases where there was a suspicion or confirmation of intraoperative leak. Due to the high rate of postoperative CSF leaks that are undetected at surgery, the effectiveness of the fat graft at reducing return to theater, and the low morbidity from the graft site, we have a low threshold for using a fat graft in those patients at risk of CSF leak, for example, those with a thin diaphragm.

Inclusion Criteria

All adult patients (≥18 years old) with complete surgical records of standard endoscopic TSS were included in the study.

Exclusion Criteria

Patients with incomplete surgical and medical records, pediatric patients (<18 years old), and patients who underwent an extended endoscopic transsphenoidal approach were excluded.

Surgical Technique

The purpose of this study was to evaluate the efficacy of the FFS intraoperative repair technique described below (►**Fig. 1–5**):

- Subcutaneous abdominal fat graft is harvested via a 1.5-cm paraumbilical transverse incision and placed in Ringer's lactate solution while awaiting placement in the sella. To avoid contamination of the graft site, the surgeon

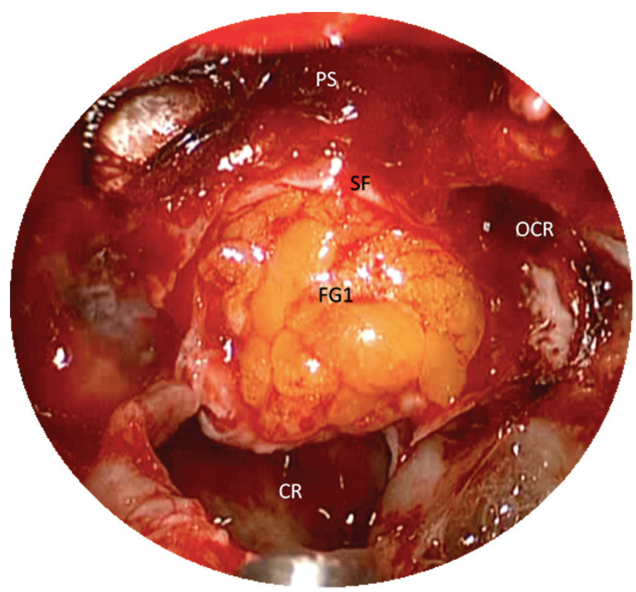

Fig. 1 Endoscopic photograph showing the first fat graft being used to fill the sellar floor without compressing the optic apparatus (CR, clival recess; FG1, fat graft 1; OCR, optic carotid recess; PS, planum sphenoidale; SF, sella floor).

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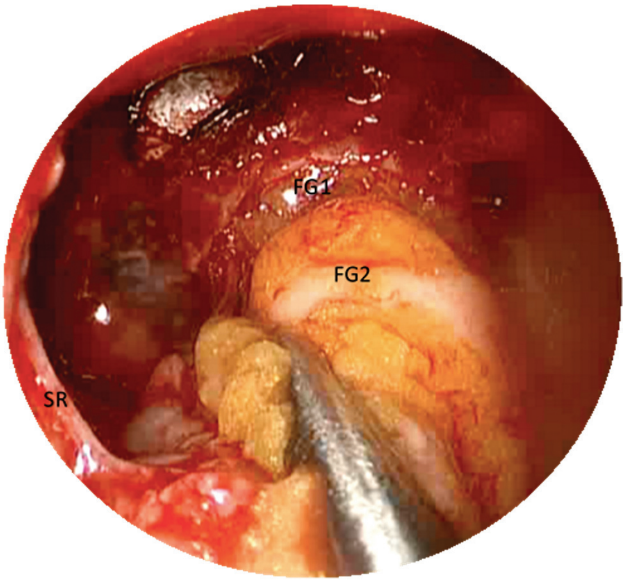

Fig. 2 Endoscopic photograph showing the second fat graph being inserted posterior and inferior to the sellar to support the first fat graph (FG1, fat graft 1; FG2, fat graft 2; SR, sphenoid rostrum).

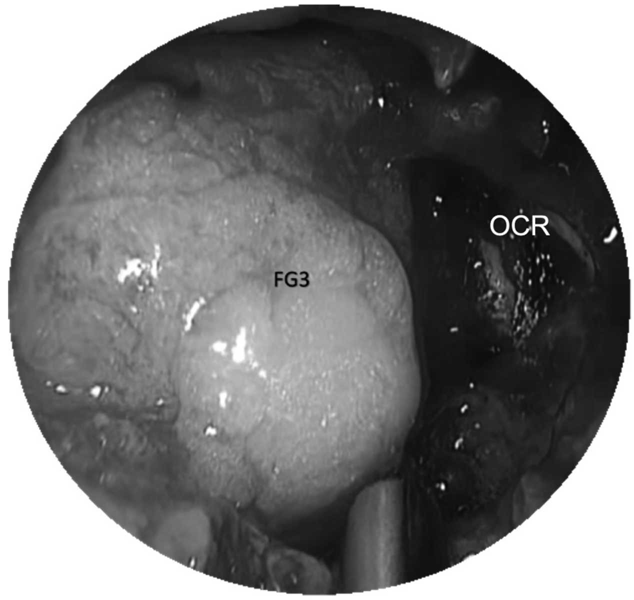

Fig. 3 Endoscopic photograph showing an optional third fat graft used to fill the sphenoid sinus depending on the pneumatization and the size of the sphenoid sinus (FG3, fat graft 3; OCR, optic carotid recess).

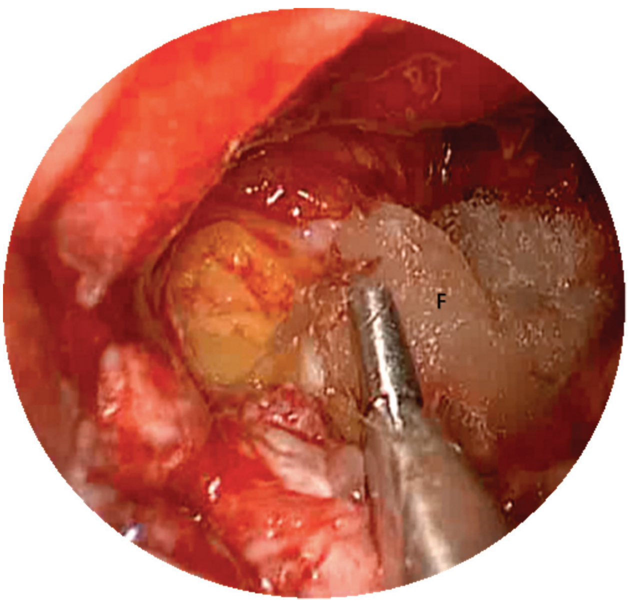

Fig. 4 Endoscopic photograph showing fibrillar surgicel (Johnson & Johnson Medical, N.V., Belgium) being used to cover the fat and support it against the sphenoid sinus wall (FG3, fat graft 3, F, fibrillar surgicel (Johnson & Johnson Medical, N.V., Belgium).

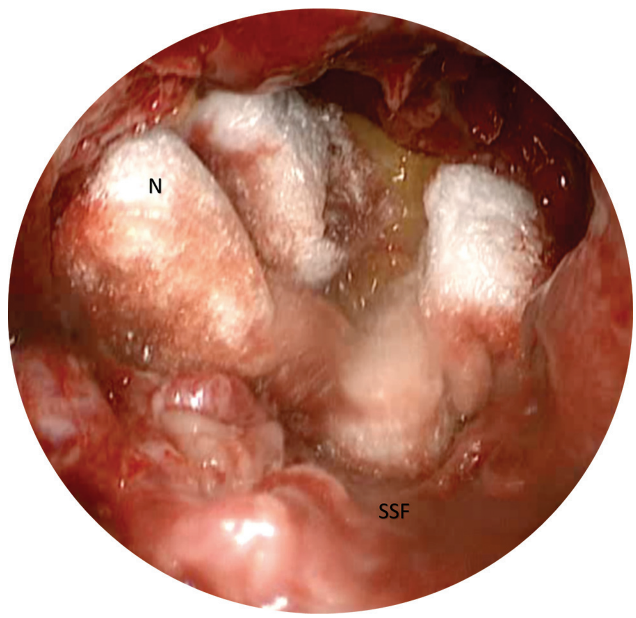

Fig. 5 Endoscopic photo showing absorbable nasopore by Stryker, Michigan, United States, being used to cover the fat and support it against the sphenoid sinus wall. (N, Nasopore by Stryker, dissolvable nasal packing; SSF, sphenoid sinus floor).

harvesting fat is not involved in performing the transsphenoidal approach. The majority of the mucosa is removed in our operative steps. The first piece of fat graft is measured according to the size of the sella and a second piece is taken according to the size of pneumatized sphenoid sinus. The closure is with a subcuticular absorbable suture after careful hemostasis.

- A single fat graft is placed in the sella. The size is judged to fill the sella but without any suprasellar extension, to avoid compression of the optic apparatus. The size is important as too small a graft risks being displaced intracranially or not covering the diaphragmatic defect and therefore being ineffective. This fat is supported by the dural edges and the remaining edges of the sellar floor (►**Fig. 1**).
- The second fat graft is placed in the clival recess to support the sellar fat graft (►**Fig. 2**). Further pieces of fat graft may be required to fill the sphenoid sinus depending on the pneumatization and the size of the sphenoid sinus. The sphenoid sinus fat graft is supported by the remaining lateral and anterior sphenoid wall (►**Fig. 3**).

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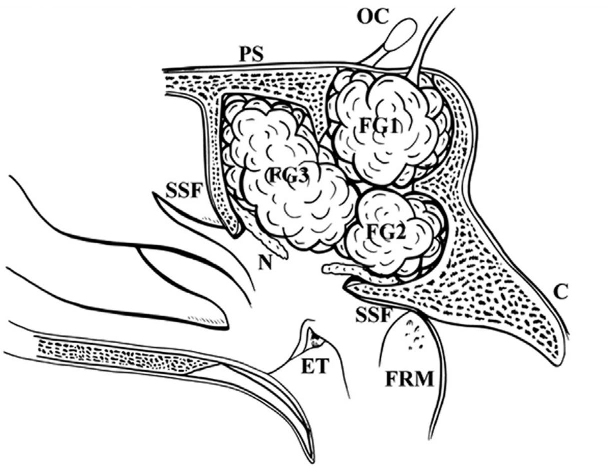

Fig. 6 Sagittal cross-section graphic of our FFS technique (C, clivus; ET, eustachian tube; FG1, fat graft 1; FG2, fat graft 2; FG3, fat graft 3; FRM, fossa of Rosenmüller; OC, optic chiasm; N, Nasopore by Stryker [dissolvable nasal packing]; PS, planum sphenoidale; SF, sella floor).

- The fat grafts are then covered with fibrillar surgicel (Johnson & Johnson Medical, N.V., Belgium, hemostatic agent) and/or nasopore (by Stryker, Michigan, United States, dissolvable nasal packing), which supports the fat grafts and is tucked in behind the sphenoid sinus wall (►**Figs. 4** and **5**).

A diagrammatic stylization of the finalized sagittal view of our technique is shown in ►**Fig. 6**.

Outcomes Measured

Significant CSF leak was defined as patients who had CSF rhinorrhea postoperatively, which required intervention (lumbar drainage or reoperation for CSF leak repair).

Patients were split into one of three groups:

- Multilayer: any patient who underwent repair via conventional methods described in the literature (including a combination of fascia lata, dural substitute, artificial glue, or only sealant or glue).
- Fat only: any patient in whom we performed the FFS technique only.
- No repair: any patient who did not receive any of the above methods of repair; hemostatic material (surgical fibrillar) alone may have been used in this group (usually due to the surgeon's assessment of whether a postoperative leak was likely).

The analysis consisted of demographics, histology of lesion, and risk factors for intra- and postoperative CSF leak (►**Table 1**). Tumor size in this study was defined as the following: microadenoma (<10 mm), macroadenoma (>10–40 mm), giant (>40 mm). Rate of postoperative leak and management thereof was analyzed as the primary outcome measure. Significant postoperative CSF leak was defined as any CSF leak requiring intervention, that is, lumbar drainage or reoperation. Specifically, reoperation for the purpose of this study was defined as any patient who required reoperation to repair CSF leak, rather than for hematoma or residual tumor.

Table 1 Factors for postoperative leak analyzed

	Factors
Patient	Age, gender, length of stay in hospital
Pathology	Size of lesion, number of previous transsphenoidal surgeries, previous transsphenoidal surgery, previous history of CSF leak, tumor apoplexy
Surgical	Perioperative use of lumbar drain inserted, number of days lumbar drain was inserted, use of neuronavigation, intraoperative repair type (multilayer, FFS, no repair), intraoperative CSF leak
Post-op	Postoperative CSF rhinorrhea, lumbar drain insertion, reoperation for formal CSF repair, readmission due to CSF leak

Abbreviations: CSF, cerebrospinal fluid; FFS, fat in the pituitary fossa and further fat in the sphenoid sinus.

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, Illinois, United States, 2013 and Microsoft Office Excel 2007. Inferential analyses were done for quantitative variables using Shapiro–Wilk test for normality testing. Quantitative normally distributed data were described using mean ± SD (standard deviation) for quantitative normally distributed data and compared using independent *t*-test in comparisons according to leak and analysis of variance (ANOVA) test in comparisons according to layers, whereas quantitative non-normally distributed data were described using median (1st – 3rd interquartile "IQ") and compared using Kruskal–Wallis test. Qualitative data were described using number and percentage (*n*, %) and compared using chi-squared test as well as Fisher's exact test for variables with small, expected numbers. Log-rank test compared rates among repair groups, Bonferroni test for post hoc analysis, and logistic regression model was used to find out independent factors affecting leak occurrence. The level of significance was taken at p value < 0.05.

Systematic Review

A systematic review of the literature was performed, following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (►**Fig. 7**). A systematic search was performed in November 2020 using EMBASE and MEDLINE for articles published between January 2000 and November 2020. Search criteria for these databases were all articles stating "transsphenoidal" and "endoscopic" plus either "CSF leak," "complications," or "outcomes." We limited results to journal articles in English, humans, adults, and published between 2000 and 2020. After duplicates were removed, the titles and abstracts of all identified articles

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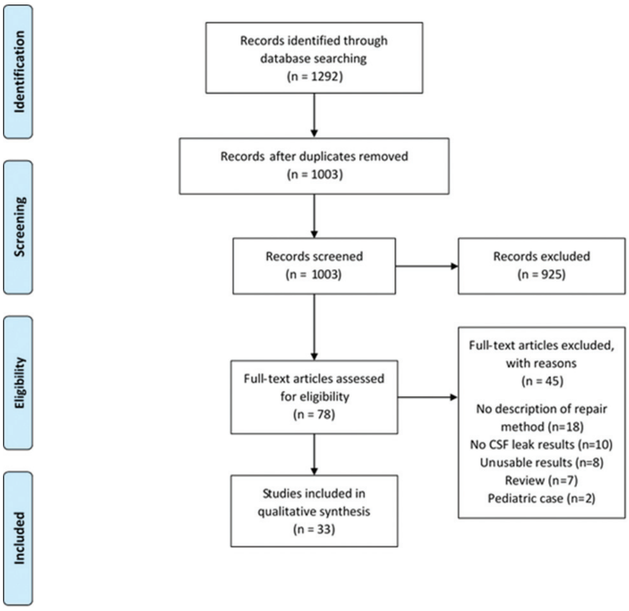

Fig. 7 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of our systematic search.

were screened by two reviewers. Screening inclusion criteria consisted of articles that reported information on endoscopic TSS performed on adults with details of surgical outcomes or complications, specifically looking at CSF leak. Articles including pediatric cases, fewer than 10 patients, nonendoscopic procedures, or studies not reporting TSS were excluded.

Eligible papers were analyzed to extract required variables. This included year of publication, date range, number of cases, and average age of the patient group. Rate of postoperative CSF leak was extracted and, where possible, intraoperative CSF leak as well. Finally, authors' descriptions of repair were extracted and standardized to similar language and terminology to aid the reader. During information extraction, as the majority of the studies were retrospective case series, we used the NHLBI Quality Assessment Tool for Case Studies to assess for low validity or bias.[7] If there were suspicion of bias, specifically looking for selective reporting of CSF leaks, then a third author would investigate and the study would then be excluded.

Results

A retrospective review of the last 10 years of patients who underwent direct TSS for sellar/suprasellar lesions yielded 439 patients (►**Table 2**). This included 246 females and 193 males with a mean age of 53 years (range: 18–86 years). Four patients (0.9%) had a history of spontaneous CSF leak (occurring after previous medical treatment for their adenoma) and 65 (14.8%) had undergone TSS at least 1 year previously.

Table 2 Comparison according to postoperative leak regarding demographic and clinical findings

Variables		Total (*N* = 439)	Multilayer (*N* = 276)	Fat only (*N* = 68)	No repair (*N* = 95)	*p*-value
Age (y), mean ± SD		53.0 ± 15.7	53.4 ± 16.0	53.5 ± 14.9	51.6 ± 15.5	^0.603
Gender (*n*, %)	Male	193 (44.0%)	133 (48.2%)	24 (35.3%)	36 (37.9%)	#0.064
	Female	246 (56.0%)	143 (51.8%)	44 (64.7%)	59 (62.1%)	
History of transsphenoidal surgery (more than 1 y prior; *n*, %)		65 (14.8%)	38 (13.8%)	13 (19.1%)	14 (14.7%)	#0.538
Tumor apoplexy (*n*, %)		43 (9.8%)	14 (5.1%)a	15 (22.1%)b	14 (14.7%)b	# < 0.001*
Tumor size (*n*, %)	Small	56 (12.8%)	36 (13.0%)a	1 (1.5%)b	19 (20.0%)a	# < 0.001*
	Large	224 (51.0%)	143 (51.8%)a	28 (41.2%)a	53 (55.8%)a	
	Giant	159 (36.2%)	97 (35.1%)a	39 (57.4%)b	23 (24.2%)a	
Lumbar drain perioperatively (*n*, %)		9 (2.1%)	9 (3.3%)	0 (0.0%)	0 (0.0%)	§0.081
Neuronavigation used operatively (*n*, %)		25 (5.7%)	11 (4.0%)a	3 (4.4%)ab	11 (11.6%)b	#0.020*
Fibrillary surgicel (*n*, %)		356 (81.1%)	232 (84.1%)a	37 (54.4%)b	87 (91.6%)a	# < 0.001*
Intraoperative CSF leak (*n*, %)		103 (23.5%)	75 (27.2%)a	28 (41.2%)a	0 (0.0%)b	# < 0.001*
Layers (*n*, %)	Fat	127 (28.9%)	59 (21.4%)	68 (100.0%)	0 (0.0%)	–
	Fascia lata	28 (6.4%)	28 (10.1%)	0 (0.0%)	0 (0.0%)	–
	Dural substitute	66 (15.0%)	66 (23.9%)	0 (0.0%)	0 (0.0%)	–
	Glue	238 (54.2%)	238 (86.2%)	0 (0.0%)	0 (0.0%)	–
	Flap	118 (26.9%)	118 (42.8%)	0 (0.0%)	0 (0.0%)	–
	No layer	95 (21.6%)	0 (0.0%)	0 (0.0%)	95 (100.0%)	–

Note: ^, ANOVA test; #, chi-squared test; §, Fisher's exact test; *, significant (<0.050). Fibrillary Surgicel by Johnson & Johnson Medical N.V. Belgium.

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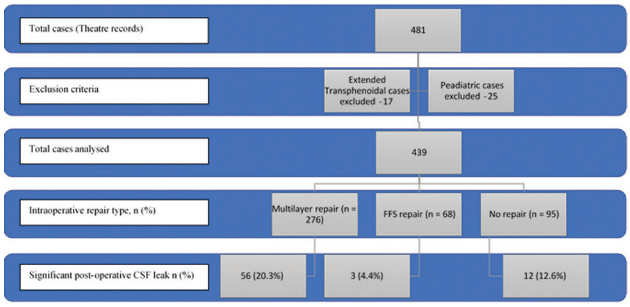

Fig. 8 Flow diagram of our patient cohort.

Multilayer versus Fat Only versus No Repair

Of our 439 patients, 276 underwent multilayer repair, 68 underwent FFS repair, and 95 had no repair (►**Fig. 8**). There were no significant differences between these repair groups regarding age, gender, history of leak, history of surgery, and lumbar drain insertion at our institution (►**Table 2**). The size of tumor and the presence of intraoperative CSF leak were investigated in our study, seen in ►**Table 2** and ►**Table 3**. Small tumor size was significantly less frequent (1.5%), whereas giant tumor size was significant most frequently (57.4%) in the FFS group with no significant difference between the groups. However, the size of the tumor did not reach significance in the logistic regression model as a factor affecting postoperative leak.

In total, 71 patients (16.2%) had a significant postoperative CSF leak following TSS surgery (►**Table 4**).

Across the series, there were 377 adenomas (85.9%), 20 craniopharyngiomas (4.6%), and 14 rathke's cleft cysts (3.2%). The rest of the pathologies included granulomas, hypophysitis, and metastasis; however, these were not compared across groups. Unfortunately, we did not examine the nature of the sella pathology and therefore were unable to analyze whether different pathologies affect rates of postoperative CSF leak.

Intraoperative leak occurred in 103 patients (23.5%) during TSS surgery across the study (►**Table 2**). There were 0 patients who had intraoperative leak who had no form of repair. In contrast, 75 patients (27.2%) in the multilayer repair group and 28 patients (41.2%) in the fat-only repair group had intraoperative leaks. Although there were significantly fewer patients in the no repair group, no significant difference was noted between the multilayer and fat-only groups.

Rates of significant CSF leaks requiring intervention with repair surgery or lumbar drainage were significantly lower in

Table 3 Comparison according to postoperative leak regarding demographic and clinical findings

Variables		Significant leak (*N* = 71)	Nonsignificant/no leak (*N* = 368)	*p*-value
Age (y), mean ± SD		48.7 ± 16.0	53.9 ± 15.5	^0.010*
Gender (*n*, %)	Male	23 (32.4%)	170 (46.2%)	#0.032*
	Female	48 (67.6%)	198 (53.8%)	
History of previous transsphenoidal surgery (*n*, %)		10 (14.1%)	55 (14.9%)	#0.852
Tumor apoplexy (*n*, %)		4 (5.6%)	39 (10.6%)	#0.198
Tumor size (*n*,%)	Small	9 (12.7%)	47 (12.8%)	#0.939
	Large	35 (49.3%)	189 (51.4%)	
	Giant	27 (38.0%)	132 (35.9%)	
Lumbar drain (*n*, %)		4 (5.6%)	5 (1.4%)	§0.042*
Neuronavigation used operatively (*n*, %)		6 (8.5%)	19 (5.2%)	§0.267
Fibrillary surgicel (*n*, %)		56 (78.9%)	300 (81.5%)	#0.602
Intraoperative CSF leak (*n*, %)		24 (33.8%)	79 (21.5%)	#0.025*
Layers (*n*, %)	Fat	23 (32.4%)	104 (28.3%)	#0.485
	Fascia lata	10 (14.1%)	18 (4.9%)	§0.007*
	Dural substitute	21 (29.6%)	45 (12.2%)	# < 0.001*
	Glue	45 (63.4%)	193 (52.4%)	#0.090
	Flap	26 (36.6%)	92 (25.0%)	#0.043*
	No layer	12 (16.9%)	83 (22.6%)	#0.290
Repair (*n*, %)	Multilayer	56 (78.9%)	220 (59.8%)	#0.004*
	Fat only	3 (4.2%)	65 (17.7%)	
	No repair	12 (16.9%)	83 (22.6%)	

Note: ^, independent *t*-test; #, chi-squared test; §, Fisher's exact test; *, significant (<0.050). Homogenous groups had the same symbol "ab" based on post hoc Bonferroni's test. Fibrillary Surgicel by Johnson & Johnson Medical N.V. Belgium.

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Table 4 Comparison according to postoperative leak regarding leak occurrence and its management

Variables	Total ($N=439$)	Multilayer ($N=276$)	Fat only ($N=68$)	No repair ($N=95$)	*p*-value
Persistent CSF leak (*n*, %)	71 (16.2%)	56 (20.3%)a	3 (4.4%)b	12 (12.6%)ab	#0.004*
Reoperation for CSF leak (*n*, %)	46 (10.5%)	37 (13.4%)a	2 (2.9%)b	8 (8.4%)ab	#0.032*
Time till reoperation (d) Median (1st – 3rd IQ)	4.0 (2.5–7.0)	3.5 (2.0–7.0)	5.0 (5.0–5.0)	4.0 (3.0–8.0)	¤0.830
Repeated reoperation (*n*, %) *"Among operated"*	5 (10.9%)	5 (13.5%)	0 (0.0%)	0 (0.0%)	§0.615
Lumbar drain for CSF leak (*n*, %)	50 (11.4%)	43 (15.6%)a	2 (2.9%)b	5 (5.3%)b	#0.001*
Time till drain (d) Median (1st – 3rd IQ)	4.0 (2.0–7.0)	3.0 (2.0–6.0)	4.5 (4.0–5.0)	7.0 (4.5–15.0)	¤0.103
Reoperation and drain (*n*, %)	26 (5.9%)	24 (8.7%)a	1 (1.5%)ab	1 (1.1%)b	#0.006*
Length of stay (d) Median (1st – 3rd IQ)	6.0 (4.0–9.0)	6.0 (5.0–10.0)a	4.0 (3.0–7.0)b	5.0 (3.0–7.0)b	¤ < 0.001*
Readmission due to CSF leak (*n*, %)	9 (2.1%)	8 (2.9%)	0 (0.0%)	1 (1.1%)	§0.379

Note: ^, independent *t*-test; #, chi-squared test; §, Fisher's exact test; ¤, Kruskal–Wallis test; *, significant (<0.050). Homogenous groups had the same symbol "ab" based on post hoc Bonferroni test.

the FFS group (20.7% multilayer vs. 4.4% FFS vs. 12.0% no repair; $p=0.004$). There were significantly fewer reoperations required in the FFS group compared with the multilayer group (2.9 vs. 13.4%; $p=0.032$; ►**Fig. 9A**). The multilayer group was the only group requiring more than one formal CSF repair (13.5% multilayer vs. 0% FFS vs. 0% no repair). Postoperative lumbar drain was most frequently required in the multilayer group (15.6% multilayer vs. 2.9% FFS vs. 5.3% no repair; $p=0.001$; ►**Fig. 9B**). Length of hospital stay was longest in the multilayer group, with no significant difference in the fat-only and no repair groups (6 days in the multilayer group vs. 4 days in the FFS group vs. 5 days in the no repair group; $p=0.001$; ►**Table 4**; ►**Fig. 9C**).

There were significantly more leaks in younger patients (≤50 years; $p=0.010$) and female patients ($p=0.032$). A higher rate of significant postoperative leaks was noted in the patients in whom an intraoperative leak had been identified ($p=0.025$), in patients who required lumbar drainage at the time of the original procedure ($p=0.042$), and in patients who underwent repair using fascia lata ($p=0.007$), dural substitute ($p=0.001$), nasoseptal flaps ($p=0.043$), or multilayered repair ($p=0.004$; ►**Table 3**).

Logistic regression analysis of these results showed an age of ≤50 years (►**Table 5**) and multilayer repair were significant risk factors for significant postoperative leak.

Complications of FFS

In our FFS cohort, we did not experience a fat graft hematoma or an overpacked sella that required a return to the theater. There was a graft site hematoma; however, this was managed

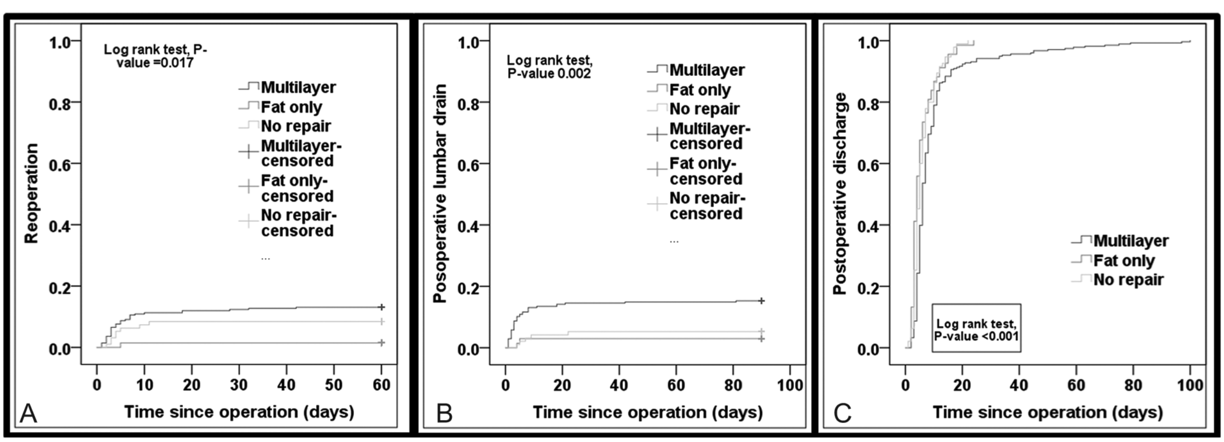

Fig. 9 **(A)** The Kaplan–Meier curve for reoperation rate in repair groups. Significant difference was seen between the multilayer and fat-only groups only. **(B)** The Kaplan–Meier curve for postoperative lumbar drain rate in repair groups. The rate was significantly higher in the multilayer group with no difference between the other groups. **(C)** The Kaplan–Meier curve for postoperative discharge rate in repair groups. The postoperative discharge rate was significantly lower in the multilayer group (meaning longer hospital stay). There was no significant difference in the other two groups.

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Table 5 Logistic regression models for factors affecting postoperative leak

Factors	β	SE	*p*-value	OR (95% CI)
Fascia lata	1.36	0.45	0.002[a]	3.90 (1.62–9.37)
Dural substitute	1.36	0.33	<0.001[a]	3.89 (2.02–7.49)
Age ≤50 y	0.93	0.28	0.001[a]	2.52 (1.46–4.35)
Nasoseptal flap	0.85	0.30	0.005[a]	2.35 (1.30–4.23)
Male	−0.60	0.29	0.038[a]	0.55 (0.31–0.97)
Constant	−2.49	0.28	<0.001[a]	

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; β, regression coefficient.
[a]Significant.

conservatively without the need for surgical intervention. Where there was radiological extension of fat graft into the suprasellar space, a decision was made that if vision improved then no action was required. Long-term follow-up confirmed resorption and reduction of fat graft size. Long-term complications of a transsphenoidal approach is the formation of a delayed mucocele; this, however, was not identified in our retrospective review of clinical notes.

Systematic Review

A systematic review was conducted using the PRISMA guidelines as per methods. Initial database search using our limitations yielded a total of 1,292 articles. After exclusion of duplicates, this was reduced to 1,003 articles, all of which went through screening. Screening the title and abstract of these articles resulted in 925 articles being excluded. Common reasons for exclusion during screening included article topics being off topic (nonendoscopic or transsphenoidal surgeries), pediatric cases, or case reports/series containing fewer than 10 patients.

The remaining 78 articles had their full text analyzed, resulting in further exclusions. A total of 45 articles were excluded on full text analysis with reasons detailed in ►**Fig. 1**. This yielded 33 articles for inclusion in our study (►**Table 6**).[4,6,8–38] One article had two separate groups of TSS surgeries[12] producing a total of 34 sets of patients, totaling 9,141 patients altogether. The rate of postoperative CSF leak varied between 0 and 14.6%. Twenty-one articles also included rates of intraoperative leak, which ranged from 7.7 to 62.6%.[9–13,17,18,20,22,23,26,28–33,35–37] The authors used a variety of techniques, and both autologous and synthetic materials. The use of autologous fat was mentioned specifically in 12 articles,[6,9,10,13,15–17,19,22,26,31,38] nasoseptal flaps in 10 articles,[4,14,21,22,25,29,32,33,36,37] and specific mention of a multilayered repair method in 5 articles.[8,21,24,26,29]

Discussion

Endoscopic TSS is widely recognized as the gold standard for sellar and some suprasellar pathology. However, postoperative CSF rhinorrhea may lead to morbidity including meningitis, reoperation, prolonged hospital stays, and may even result in mortality. In addition, not repairing or packing the sellar can lead to prolapse or ptosis of the sellar, which can result in empty sellar syndrome and further complication in the future.[39,40] Many CSF leak repair techniques have been described in the literature, yet the optimal method of repair remains a matter of debate. In this study, we evaluated a simple autologous fat graft technique and demonstrated it to be superior to multilayer techniques previously used in our institution and described in the literature.

Comparing Repair Techniques

Intraoperative leaks are generally dealt with in two ways: (1) packing the sella or (2) reconstruction of the sella. Sellar packing involves filling of space in the sellar and sphenoid sinus to seal any fistulae, whereas reconstruction aims to provide a seal across the front of the defect, supported by other materials. Autologous materials such as fat, fascia lata, mucosa from the septum or the middle turbinate, or muscle have been used.[6,8–10,13,15–17,19–22,24,26,27,30,31,36,38] Numerous synthetic materials have also been proposed in the form of dural substitutes, collagen sponges, and fibrin glues.[12,23,29,33–35,37] No single technique has been found to deliver consistently good results. Sellar packing can produce positive results, although overpacking can result in compression of the optic chiasm.[41] It has been suggested that a multilayer repair technique using a mixture of different autologous tissues and synthetic materials provides a more robust repair and thus reduces the likelihood of postoperative leaks.[8,20,24,26,29,37] Generally, multilayered approaches have reported low rates of postoperative leaks, ranging between 2.4 and 6.0% of patients.[8,20,24,26,29,37,42] However, in the current study, multilayered techniques were associated with significantly increased rates of persistent postoperative CSF leaks (20.3%) compared with using the fat-only repair (4.4%; ►**Table 4**). The use of synthetic materials, specifically dural substitutes, was also associated with a greater postoperative leak rate with higher rates of postoperative lumbar drainage. Patients who underwent fat-only repair had significantly lower lumbar drainage requirements compared with our other multilayer and no repair groups (15.6% multilayer vs. 2.9% FFS vs. 5.3% no repair; $p = 0.001$). This is also seen in other studies.[43,44] It is likely that this is due to the simplicity of the FFS repair.

The use of the Hadad–Bassagasteguy vascularized pedicled nasoseptal flap[45] is now well established, and was the sole use of repair in four studies.[4,25,32,36] In three of these

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Table 6 Literature review of endoscopic transsphenoidal surgeries, CSF leak rate (intra and post op) and repair method

Study	Years assessed	No. of cases	Average age (y)	Surgical approach	Repair	CSF leak	
						Intra-op (%)	Post-op (%)
Thakur et al[32]	2010–2019	123	All $\geq$65	Endoscopic TSS	Nasoseptal flap	77 (62.6)	2 (1.6)
Ahn et al[9]	2008–2018	216	53	Endoscopic TSS	Autologous abdominal fat	53 (24.5)	2 (0.93)
Vimawala et al[33]	2005–2019	658	N/A	Endoscopic TSS	Dural substitute + duraseal (+ nasoseptal flap if severe leak)	178 (27.1)	11 (1.7)
Hannan et al[22]	2006–2015	270	50.1	Endoscopic TSS	Autologous abdominal fat + glue; nasoseptal flap + glue; fascia lata graft	109 (40.4)	24 (8.9)
Xue et al[37]	2017–2018	216	46.5	Endoscopic TSS	Collagen sponge; multilayered; nasoseptal flaps; fibrin glue	65 (30.1)	13 (6.0)
Pablo et al[27]	2011–2014	140	48.5	Endoscopic TSS	Tissue graft + glue	N/A	3 (2.1)
Wengier et al[36]	2008–2014	77	48	Endoscopic TSS	Nasoseptal flap; nasoseptal flap + fat or fascia lata graft	25 (32.5)	5 (6.5)
Agam et al[8]	1992–2017	160	N/A	Endoscopic TSS	Multilayered with fascia lata	N/A	4 (2.5)
López-García et al[25]	2011–2016	86	54	Endoscopic TSS	Nasoseptal flap	N/A	0 (0)
Patel et al[29]	2004–2016	806	48.5	Endoscopic TSS	Multilayer; dural substitute; nasoseptal flaps; fat only	205 (25.4)	38 (4.7)
Faraj et al[19]	2011–2016	94	N/A	Endoscopic TSS	Abdominal autologous fat + gelfoam	N/A	3 (3.1)
Caggiano et al[13]	2008–2017	773	N/A	Endoscopic TSS	Autologous abdominal fat	295 (38.2)	14 (1.8)
Akbari et al[4]	2012–2014	16	N/A	Endoscopic TSS	Nasoseptal flap	N/A	3 (18.8)
Kim et al[24]	2010–2016	331	53	Endoscopic TSS	Multilayer absorbable fibrin sealants	N/A	8 (2.4)
Magro et al[26]	1996–2002	300	57	Endoscopic TSS	Multilayer repair with autologous fat, tissue glue, and LD; Titanium mesh, Medpor	104 (34.6)	8 (2.7)
Gondim et al[21]	2000–2012	374	72.5	Endoscopic TSS	Fat graft, fascia lata, nasoseptal flap, and fibrin sealant	N/A	14 (3.7)
Dallapiazza et al[16]	2004–2008	80	56.6	Endoscopic TSS	Autologous fat graft	N/A	2 (2.5)
Wang et al[34]	2006–2013	1166	40.3	Endoscopic TSS	Duragen, Duraform, BioGlue; fascia lata graft	N/A	7 (0.6)
Zhan et al[38]	2012–2014	384	44	Endoscopic TSS	Autologous fat or fascia lata graft with syn dural graft; vascularized PNSF with fibrin glue, Gelfoam	N/A	33 (8.6)

(*Continued*)

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Table 6 (*Continued*)

Study	Years assessed	No. of cases	Average age (y)	Surgical approach	Repair	CSF leak	
						Intra-op (%)	Post-op (%)
Cavallo et al[14]	1997–2012	103	50.36 and 10.1	Endoscopic TSS	Gasket seal, pedicled nasoseptal flap, dural substitute, fibrin glue	N/A	15 (14.6)
Patel et al[28]	2010–2013	209	49.4	Endoscopic TSS	Fat graft, Medpor, NS flap, DuraSeal, Gasket seal, DuraGuard & lumbar drain[a]	125 (60)	0 (0)
Bokhari et al[11]	1998–2010	79	56.7	Endoscopic TSS	Fat graft + lumbar drain	15 (19)	2 (3)
Berker et al[10]	2006–2011	570	N/A	Endoscopic TSS	Autologous fat; fascia graft; nasal packing	44 (7.7)	8 (1.3)
Burkett et al[12]	2000–2005	107	51	Endoscopic TSS	Fibrin sealant, gelfoam, abdominal fat graft	40 (37.3)	2 (1.9)
Burkett et al[12]	2005–2009	97	53	Endoscopic TSS	Polyethylene glycol (PEG) hydrogel dural sealant + collagen dural graft	29 (29.9)	1 (1)
Messerer et al[6]	2006–2009	82	57	Endoscopic TSS	Autologous fat; fascia graft using synthetic dural graft	N/A	10 (12.1)
Hobbs et al (2011)[23]	2002–2008	120	N/A	Endoscopic TSS	Gelatin sponge, fibrin glue; sinus packing with bismuth iodoform paraffin	28 (23.3)	2 (1.7)
Gondim et al[20]	1998–2009	301	42.44	Endoscopic TSS	Multilayer closure with muscle, fat and fibrin glue; nasoseptal flap	31 (10.3)	8 (2.6)
Wang et al[35]	2005–2010	255	52	Endoscopic TSS	Gelatin sponge, hydrogen sealant	74 (29)	2 (2.7)
Charalampaki et al[15]	2004–2007	150	57	Endoscopic TSS	Autologous fat and muscle; fibrin glue	N/A	5 (3.3)
Dehdashti et al[17]	2004–2007	200	49.9	Endoscopic TSS	Autologous fat + fascia graft	42 (21)	7 (3.5)
Tamasauskas et al[31]	1995–2005	99	N/A	Endoscopic TSS	Autologous fat + bone graft	26 (26.3)	4 (1.1)
Dusick et al[18]	2003–2006	282	45	Endoscopic TSS	BioGlue; collagen sponge; intrasellar titanium mesh buttress; autologous fat graph	124 (44)	2 (1.6)
Shiley et al[30]	1994–2001	217	45.6	Endoscopic TSS	Autologous fat packing, fibrin glue, surgicel	32.7%	13 (12.7)

Abbreviations: LD, lumbar drain; NSF, nasoseptal flap; PNSF, pedicled nasoseptal flap; TSS, transsphenoidal surgery.
[a]All patients had LD perioperatively; two required repeat drainage.

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studies, rates of postoperative leak have been extremely low,[25,32,36] with one study quoting 0%.[25] In the current study, the leak rate was higher in patients who had nasoseptal flap repair. This may have been due to nasoseptal flap repairs being part of the multilayer repair group, which was associated with more postoperative leaks and therefore may have been due to case selection (►Table 5). Akbari et al also found a high leak rate (18.8%) in patients who had nasoseptal flaps alone.[4] It is important to note the morbidity associated with nasoseptal flaps; as the vascular nutrient supply to the nasal septum is compromised, it prolongs the procedure and there are concerns about its use in the pediatric population.

The current study confirms that using fat in the fossa and the sphenoid is an effective technique, which, when compared with the traditional multilayered approaches, produced better results in our hands. This is supported by recent studies that have also found low rates of postoperative CSF leaks with a fat-only technique, along with little need for lumbar drainage or reoperation.[9,13] We also demonstrated a reduction in mean postoperative hospital stay. Despite our relatively long mean length of stay of 4 to 6 days in the no postoperative CSF leak cohort, the postoperative needs for patients varied from inpatient ophthalmology for visual assessment or endocrine input for diabetes insipidus. Patients who underwent fat-only repair were discharged, on average, 2 days earlier than those who had a multilayer repair ($p = 0.001$). This improves patient satisfaction as well as improving patient flow and can reduce pressures on already overwhelmed health care systems. The reduction in hospital stay is likely to be due to the reduced need for lumbar drainage.[32,33] When comparing our FFS group with those patients who did not have a repair and did not leak, there was no additional length of stay associated with the FFS group.

The FFS repair is therefore safe and effective and does not significantly increase the morbidity of the procedure. Worldwide literature confirms that a significant number of postoperative CSF leaks are not detected intraoperatively. Our rationale is therefore to have a low threshold to perform an FFS repair even if no clear CSF leak is appreciated intraoperatively. As the FFS group had lower rates of persistent CSF leak, reoperations, lumbar drain requirements, and readmissions, this prophylactic-type repair is likely to provide a more definitive management option in these cases compared with no repair.

General Risk Factors for CSF Leak

Risk factors associated with CSF leak (summarized in ►Table 3 and ►Table 5) have been divided into three main categories: (1) patient factors, (2) surgical factors, and (3) tumor factors.

Patient Factors

There are three main patient factors reported in the literature: age, gender, and body mass index (BMI). Age as a risk factor is seldom reported in the literature although a few studies have reported age as a predictor of post-op CSF leak with one study suggesting leaks are more common in younger age groups[46] and another study purely focusing on elderly patients (minimum age 65), reporting very low rates of postoperative leak.[32] One study concluded that postoperative complications following TSS generally have a higher incidence in older age groups, but postoperative CSF leak alone is specifically more common in younger generation.[47] We found that the mean age of those who had postoperative CSF leak was significantly lower than those who did not leak ($p = 0.010$). Logistic regression analysis of our patient cohort confirmed these findings, showing that patients ≤50 years were at increased risk of developing postoperative CSF leaks.

When looking at gender as a risk factor, our study found postoperative leaks occurred significantly more frequently in female patients ($p = 0.032$). Prior to this study, only two studies had reported any significant findings associated with gender, both of which found similar findings of increased postoperative leaks in females.[46,48]

Although age and gender are not modifiable risk factors, this knowledge allows us to counsel patients more accurately in terms of their postoperative CSF leak risk.

BMI, on the other hand, is a modifiable risk factor and has been investigated separately as a risk factor for postoperative CSF rhinorrhea in five studies.[29,46,48,49] These studies have noted that patients who developed CSF leak in the early postoperative period had a higher BMI than those who developed it later. Furthermore, an abnormal BMI is also a risk factor for developing meningitis and an independent risk factor for not only postoperative but also intraoperative leaks.[29] In one study, the authors stressed upon meticulous sellar reconstruction for patients with a higher BMI.[48] Unfortunately, we were not routinely capturing BMI data at the time of this study but have since changed our practice to include this important index value.

Surgical Factors

Surgical factors identified in the literature as risk factors for CSF leak include a previous surgery,[12,30,50–52] radiation,[52,53] and intraoperative CSF leak.[29,50,54] Previous surgery can increase the risk of CSF leak due to scarring, adhesions, and altered anatomy.[52] The current study found no significant increase in the rate of CSF leaks with previous surgery.

In line with current literature, our study showed that intraoperative leaks were noted in 55.3% of all patients with postoperative leaks ($p = 0.025$). Only 33.8% of them required postoperative intervention. The fat-only technique described in the current study has low morbidity and therefore we can adopt a low threshold for using this repair technique even when no intraoperative CSF leak has been identified.

The role of lumbar drainage in the management of CSF leak remains controversial.[12,38,55,56] It is hypothesized that CSF diversion reduces the risk of CSF fistula formation[56] and any measure sought to reduce intracranial pressure postoperatively will reduce the chances of leak.[38] One study has attributed rapid sellar floor healing to LD placement since it reduces intracranial pressures.[12] However, some surgeons

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argue that placing lumbar drains prolongs operative time as well as hospital stay, is associated with a risk of CSF infection, and is uncomfortable for the patient. In the current study, lumbar drainage was associated with longer hospital stay. Further analysis of lumbar drain data will be presented in a separate publication.

Tumor Factors

In our study, we investigated two main tumor factors: tumor size and apoplexy. There was no significant difference in incidence of postoperative CSF leak across these groups. Previous studies have shown higher leak rates in macroadenomas versus microadenomas,[2] functioning versus nonfunctioning,[35] and specifically in ACTH-secreting microadenomas compared with other functioning tumors.[30,51] We did not analyze the rate of CSF leak in functioning versus nonfunctioning tumors but recognize that this is an important area for study and would propose a lower threshold for primary FFS repair in patients with functioning tumors, especially in Cushing's disease where the tissues are known to be friable. Few studies have investigated apoplexy as a risk factor. Zhan et al reported 45 patients with apoplectic tumors and only 2 cases of postoperative CSF leak.[57]

We did not analyze the leak rate according to tumor morphology in terms of parasellar and suprasellar extension as the focus of our study was to establish whether FFS was an effective repair for all tumors accessed via a standard transsphenoidal approach. Literature establishing the effect of tumor extension on the postoperative CSF leak is scarce. Extension of the tumor can be described in three ways: (1) cavernous sinus/parasellar extension,[20,29] (2) suprasellar extension,[20,29,58] and (3) intraventricular extension.[46] The postoperative complication rate was found to be similar regardless of cavernous sinus involvement by pituitary adenoma in one study.[59] Suprasellar extension is associated with a greater risk of leak, as one would expect.[20,29] Intraventricular extension is known to be a risk factor for postoperative leak.[46,47,49]

Limitations

Further useful information regarding risk factors for CSF leak could have been obtained by analyzing the data on patient BMI and tumor pathology. Similarly, the grade of CSF leak was not analyzed and may have impacted the choice of repair, in particular the use of nasoseptal flaps. We recognize that lack of data on suprasellar extension is a limitation to this study. In practice, the extent of suprasellar extension does not alter our approach to management. If the tumor is resected via a standard approach, the fat graft is effective as the bony borders of the sella remain intact. If the suprasellar component is not accessible with a standard approach, our practice is to consider a supraorbital craniotomy rather than an extended transsphenoidal approach. Another limitation is that our FFS repair technique was used later in the learning curve, so it is indeed possible that the identification of leaks improved. The study provides data on a useful technique for primary CSF leak repair in TSS that can be widely adopted without the need for specialist adjuncts. These limitations do not impact the relevance of this study in day-to-day practice.

Conclusion

CSF leak remains a common complication following endoscopic TSS. In the current study, the rate of postoperative CSF leak in patients undergoing a standard transsphenoidal approach over 10 years ($n = 439$) was 16.2%. CSF leak rates reduced to 4.4% when the primary repair was fat in the fossa and more fat in the sphenoid without any dural substitutes or glues. This repair is simple, and the data presented show it to be an effective method to protect against postoperative CSF leak in TSS. Having a low threshold to use this technique intraoperatively, even when no CSF is seen, it can significantly reduce the incidence and rate of significant postoperative CSF leak and thus decrease the length of stay and the requirement for reoperation. We therefore advocate using this technique in TSS.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
For this type of study formal, consent is not required.

Conflict of Interest
None declared.

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