

# Dural Sealants Do Not Reduce Postoperative Cerebrospinal Fluid Leak after Endoscopic Endonasal Skull Base Surgery

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## Abstract

**Introduction** The application of cranial tissue sealants to assist with postoperative closure is widespread, but data are lacking regarding its utility in endoscopic endonasal surgery (EEA). A prospective study was conducted to assess the effect of sealant usage on postoperative cerebrospinal fluid (CSF) leak rate following standard reconstruction.

**Methods** A prospective trial of sealant usage after endoscopic endonasal skull base surgery was performed from May 2016 to June 2019 at a tertiary referral cranial base center. This study enrolled 300 consecutive adult and pediatric patients with skull base pathology who underwent EES in which an intraoperative CSF leak occurred. Patients were sequentially stratified into equally sized groups who did or did not receive sealant as part of their reconstruction.

**Results** Three hundred consecutive adult and pediatric patients were enrolled in the study and had a confirmed intraoperative CSF leak. The intervention cohort with sealant (first 150 patients) had 21 postoperative CSF leaks (14% rate) compared with 9 postoperative CSF leaks (6% rate) in the control group without sealant ( $p = 0.02$ ). On multivariate analysis, sealant usage was associated with a higher rate of postoperative CSF leak (odds ratio [OR] = 2.7;  $p = 0.025$ ). Male gender (OR = 2.4;  $p = 0.04$ ) and high-flow intraoperative CSF leak (OR = 3.1;  $p = 0.038$ ) were also found to be associated with postoperative CSF leak.

**Conclusion** Among all patients undergoing EES with an intraoperative CSF leak, the addition of sealant to standard closure techniques did not reduce the rate of postoperative CSF leaks.

## Keywords

- ▶ dural sealant
- ▶ fibrin glue
- ▶ cerebrospinal fluid leak
- ▶ endoscopic endonasal approach
- ▶ pituitary surgery
- ▶ skull base

## Introduction

With the increasing application of the endoscopic endonasal approach (EEA), postoperative cerebrospinal fluid (CSF) leak

has remained a significant complication associated with this approach.<sup>1–6</sup> Aggressive preventative measures using combinations of graft materials, repair techniques, lumbar drainage, and tissues glues, or dural sealants have all been used to address this complication.<sup>7–11</sup> In a prospective study of the utility of lumbar drainage after EEA procedures in preventing

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postoperative CSF leaks by Zwagerman et al, a significant benefit was found for high-risk cases only.<sup>12</sup> The results of this randomized controlled trial support a tailored approach to the utilization of adjuvant lumbar drainage for specific anatomical sites with high-flow leaks, reducing in postoperative CSF leaks.

There is consensus regarding the use of the nasoseptal flap as the primary reconstructive method for high-flow leaks,<sup>13,14</sup> but there is discordance on the efficacy of tissue glue to form a final sealant layer to reinforce the skull base closure. Sealants have potential side effects, including risks of infection and anaphylaxis,<sup>15–18</sup> as well as substantially increasing surgical cost.<sup>19</sup> In addition, the relative rapid reabsorption of sealants could result in dead spaces in the multilayered reconstruction which could promote a delayed CSF leak. Cost-effectiveness of these dural sealants has been studied in various open neurosurgical procedures, with Than et al, concluding that DuraSeal is effective at reducing incisional CSF leak after posterior fossa craniotomy or craniectomy, and Grotenhuis concluded that reduction of costs associated with CSF leaks can be achieved by augmentation of the dural closure with DuraSeal.<sup>20–22</sup> In Eloy et al, a retrospective analysis that compared the incidence of postoperative CSF leaks in patients undergoing EEA procedures with a pedicled nasoseptal flap with (42 patients) or without (32 patients) the addition of a dural sealant, the incidence of postoperative CSF leakage was not significantly different between the two groups.<sup>3</sup>

Given that the addition of dural sealant to complex endonasal reconstructive techniques has not been demonstrated to impact the rate of CSF leakage, this study sought to address the role of dural sealant usage in EEA procedures in a prospective study. It is hypothesized that dural sealants would not significantly reduce rates of postoperative CSF leaks when added to standard reconstruction techniques.

## Materials and Methods

A prospective case control study of patients that underwent EEA was conducted at a high volume Center for Cranial Base Surgery from May 2016 to June 2019. This study was approved by the University of Pittsburgh institutional review board (PRO14080496). A sample size analysis was performed to detect a 10% difference in mean CSF leak rates with  $\beta = 0.2$  and  $\alpha = 0.05$ . Minimum sample size was calculated to be 140 in each group. The primary outcome measure was the identification of a postoperative CSF leak during the follow-up period. Given the short-term follow-up of the primary outcome measure with limited anticipated dropouts, the study was designed to have 150 patients in each cohort. Cohorts were divided chronologically with the first 150 patients undergoing reconstruction with a tissue sealant and the second 150 patients following the identical reconstruction algorithm without tissue sealant. Inclusion criteria included an intraoperative CSF leak during EEA to the skull base. Exclusion criteria included a secondary postoperative CSF leak.

Reconstruction was performed by an otolaryngologist and a neurosurgeon using a “standard” reconstruction protocol which included the variable use of intradural collagen inlay grafts, autologous and homologous fascial grafts, nasoseptal flaps, free mucosal grafts, fat grafts, Surgicel (Johnson & Johnson, New Brunswick, New Jersey, United States), Gelfoam (Pfizer, New York, New York, United States), and nasal packing, depending on the needs of the reconstruction. Lumbar drain utilization was based on the previously described protocol.<sup>12</sup> In all cases, tissue glue was applied external to all tissue grafts or flaps to avoid an impact on healing to underlying tissue. In this study, all postoperative CSF leaks were managed with revision surgery. Demographic variables such as age, sex, body mass index (BMI), smoking status, as well as surgical-specific variables, such as pathology, approach, need for revision surgery, and lumbar drain placement, were recorded for analysis.

Data were analyzed using Statistical Analysis System (SAS version 9.4; Cary, North Carolina, United States) software. Chi-square and Fisher’s exact tests were used for comparisons of categorical variables while the *t*-test was used for comparisons of continuous variables (e.g., age and BMI). Univariate and multivariate logistic regression analysis were used to assess the association between CSF leak and other factors. Association for inclusion into the logistic regression was defined as a *p*-value of 0.2 or less. Statistical significance was determined to be at  $p < 0.05$ .

## Results

Mean age at time of surgery was 51.6 (range: 4–87) years; 50% were male and 12% smoked at the time of operation. The mean BMI for the entire cohort was 31.1 kg/m<sup>2</sup>. The patients were divided evenly between control (no sealant used,  $n = 150$ ) and intervention (sealant used,  $n = 150$ ) groups. Demographic information for the two groups regarding cases by pathology and approach module is shown in ►Tables 1 and 2. There were no significant differences between the sealant and no sealant group composition in terms of rate of high flow leak, gender, age, BMI, and smoking status on univariate analysis (►Table 1). In comparison to the control group, the sealant group had a significantly higher incidence of chordoma pathology ( $p = 0.03$ ) and posterior fossa surgical approach ( $p = 0.049$ ).

There were 30 postoperative leaks (10% leak rate overall; ►Table 2). The sealant group had 21 (14%) postoperative CSF leaks compared with 9 (6%) leaks in the group without sealant ( $p = 0.03$ ; ►Table 1). There was no significant difference in age, BMI, or smoking status on univariate analysis in patients with a postoperative CSF leak overall; however, male gender ( $p = 0.02$ ), chordoma pathology ( $p = 0.04$ ), sealant usage ( $p = 0.03$ ), high-flow leak ( $p = 0.03$ ), and lumbar drain placement ( $p = 0.049$ ) were associated with postoperative CSF leak on univariate analysis (►Table 2). Malignant tumor type ( $p = 0.07$ ), BMI ( $p = 0.2$ ), and diagnosis of meningioma ( $p = 0.19$ ) trended toward association and were also included in the subsequent multivariate analysis. A spontaneous CSF leak diagnosis was

**Table 1** Comparison of relevant characteristics between the sealant and no sealant groups on univariate analysis

	Total	No sealant	Sealant	p-Value
Patient number	300	150	150	N/A
Male	149	69	80	0.20
Mean age (y)	51.6	51.6	51.6	0.99
Mean BMI (kg/m <sup>2</sup> )	31.1	31.7	30.5	0.22
Smoking	37	23	14	0.11
Malignant tumor diagnosis	74	36	38	0.79
Pituitary adenoma	89	39	50	0.16
Rathke's cyst	13	3	10	0.08
Craniopharyngioma	17	11	6	0.21
Meningioma	48	27	21	0.34
Chordoma	50	18	32	<b>0.03</b>
Sinonasal tumor	28	18	10	0.11
Other	15	8	7	0.99
Spontaneous CSF leak	40	26	14	0.06
Lumbar drain placement	120	65	55	0.24
High flow intraoperative leak	173	93	80	0.13
Sellar	138	68	70	0.82
Anterior	74	43	31	0.11
Posterior	64	25	39	<b>0.049</b>
Coronal	24	14	10	0.39

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; N/A, not available.

Note: Bold p-values are statistically significant.

**Table 2** Factors associated with postoperative cerebrospinal fluid leak on univariate analysis

	Total	Post-op leak	No post-op leak	p-Value
Patient number	300	30	270	N/A
Male	151	21	128	<b>0.02</b>
Mean age (y)	51.6	48.9	51.9	0.38
Mean BMI (kg/m <sup>2</sup> )	31.1	32.9	30.9	0.20
Smoking	37	3	34	0.68
Malignant tumor diagnosis	74	11	63	0.07
Pituitary adenoma	89	10	79	0.64
Rathke's cyst	13	1	12	0.78
Craniopharyngioma	17	2	15	0.80
Meningioma	48	2	46	0.19
Chordoma	50	9	41	<b>0.04</b>
Sinonasal tumor	28	4	24	0.42
Other	15	2	13	
Spontaneous CSF leak	40	0	40	<b>0.02</b>
Sealant	150	21	129	<b>0.03</b>
Lumbar drain placement	120	17	103	<b>0.049</b>
High flow intraoperative leak	173	23	150	<b>0.03</b>
Sellar	138	13	125	0.76
Anterior	74	5	69	0.28
Posterior	64	10	54	0.09
Coronal	24	2	22	0.78

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; N/A, not available; Post-op, postoperative.

Note: Bold p-values are statistically significant.

**Table 3** Factors associated with postoperative cerebrospinal fluid leak on multivariate analysis

Category	OR	Confidence interval	p-Value
Male	2.4	1.04–5.8	<b>0.04</b>
BMI	1.04	0.99–1.1	0.08
Malignant tumor	1.01	0.26–3.9	0.99
Meningioma	0.22	0.04–1.1	0.07
Chordoma	0.81	0.13–5.1	0.82
Sealant	2.7	1.1–6.4	<b>0.025</b>
Posterior fossa	1.4	0.33–5.5	0.67
High-flow intra-op leak	3.1	1.1–8.9	<b>0.038</b>
Lumbar drain	1.7	0.65–4.3	0.29

Abbreviations: BMI, body mass index; intra-op, intraoperative; OR, odds ratio.

Note: Bold *p*-values are statistically significant.

associated with a reduced rate of postoperative CSF leak ( $p = 0.02$ ). In a multivariate analysis, male gender (odds ratio [OR] = 2.4;  $p = 0.04$ ), sealant usage (OR = 2.7;  $p = 0.025$ ), and high-flow intraoperative CSF leak (OR = 3.1;  $p = 0.038$ ) were significantly associated with an increased postoperative CSF leak rate (► **Table 3**). There were no significant differences on multivariate analysis of postoperative CSF leak with BMI, meningioma diagnosis, malignant tumor diagnosis, chordoma diagnosis, posterior fossa location, or lumbar drain placement.

## Discussion

The management and prevention of postoperative CSF leaks remain a priority in skull base surgery, the goal of which includes the development of a watertight closure, with total separation of the intra-arachnoid compartment from the sinonasal cavity.<sup>3</sup> Though dural sealants have been reported in conjunction with vascularized nasoseptal flaps, tissue grafts, and selective lumbar drainage, the utility of this practice remains undefined in the literature. Variations in materials and techniques make comparisons challenging, perhaps leading to this gap in the literature. The best evidence available is from Eloy et al, a retrospective analysis that compared the incidence of postoperative CSF leaks in patients undergoing EEA procedures with a pedicled nasoseptal flap with (42 patients) or without (32 patients) the addition of a dural sealant.<sup>3</sup> This study found the incidence of postoperative CSF leakage was not significantly different between the two groups. Tisseel (Baxter, Toronto, Ontario, Canada) and DuraSeal (Confluent Surgical Inc., Waltham, Massachusetts, United States) are the most commonly used sealants at our center. Our results of 300 patients studied prospectively in this article are similar to Eloy et al, suggesting that the addition of dural sealants is likely not necessary, and that selective lumbar drainage, tissue grafts, and vascularized flaps are sufficient in all cases.

Surprisingly, our study found that sealants were associated with an increased rate of postoperative CSF leaks. This finding may be attributed to the presence of the sealant creating a nonhealing barrier between the tissues at the

reconstruction site and adjacent nasal tissues during the critical period of early healing. Since the study groups were sequential over the time period of the study, it is possible that reconstructive techniques improved over time; however, the study was performed at a high volume, highly experienced center with no obvious changes in surgical repair technique or algorithm between either of the cohorts over the study period. Differences in composition of the study groups (chordoma and posterior approach) would predispose to a higher leak rate in the sealant group due to the difficulty in obtaining watertight closure after extensive clival resection, but sealant usage was found to be independent of both of these variables. Not surprisingly, patients with a high-flow intraoperative leak had an increased risk for postoperative CSF leaks ( $p = 0.03$ ). When controlling for other factors such as high-flow leak, chordoma pathology and posterior fossa location were not associated independently with leak. The use of the sealant could also have subtly influenced intraoperative decision-making regarding the reconstruction in a way that predisposed to a higher leak rate. Regardless, these data suggest that there is no benefit for tissue sealants in the setting of complex reconstructive protocols. Male gender was associated with CSF leak rate overall, suggesting a possible treatment bias in the management of these patients. BMI has been found to be a risk factor for postoperative CSF leak in past reports from this center investigating larger numbers of CSF leaks.<sup>23</sup> In this study, BMI trended toward significance but was not a significant independent contributor to CSF leak rate in multivariate analysis. The majority of patients in both study groups were obese, however, confounding the use of this variable for analysis.

There is a significant economic cost associated with the usage of dural sealants; however, this was not offset by the economic benefit of preventing a CSF leak in our prospectively collected data. These findings differ from a retrospective study which examined the costs associated with CSF leaks in 412 consecutive elective neurosurgical procedures in a Dutch tertiary care hospital, 44 of which were endoscopic transsphenoidal procedures.<sup>21</sup> Given the 10.7% (44 patients) postoperative CSF leak rate in that cohort (which accounted for 21.7% of total costs of all 412 procedures) compared with

the 4% postoperative CSF leak rate that had been achieved at the same institution using the addition of DuraSeal, the authors extrapolated that prophylactic DuraSeal usage in the 412 patients would have saved the institution a total cost of €226,600. Interestingly, transsphenoidal procedures had a lower rate of clinically significant CSF leaks, and thus it can be argued that this cost savings would not be present in the most comparable portion of their cohort relative to our own.

### Limitations

A weakness of the present study is the fact that it only uses data from a single institution with standardized reconstruction technique. Varying reconstructive techniques may generate different results, and therefore may not have the same effect with presence or absence of a dural sealant. Despite differences in composition between the study groups, it is unlikely that a significant benefit of dural sealant was missed.

### Conclusion

The addition of a dural sealant to tissue graft placement, vascularized reconstruction, and selective lumbar drainage does not decrease the risk of postoperative CSF leak. Therefore, its routine use in the prevention of postoperative CSF leaks is not supported. This study can be utilized to both guide and standardize postoperative care in endoscopic endonasal surgery patients.

#### Conflict of Interest

None declared.

### References

- Borg A, Kirkman MA, Choi D. Endoscopic endonasal anterior skull base surgery: a systematic review of complications during the past 65 years. *World Neurosurg* 2016;95:383–391
- Dehdashti AR, Stofko D, Okun J, Obourn C, Kennedy T. Endoscopic endonasal reconstruction of skull base: repair protocol. *J Neurol Surg B Skull Base* 2016;77(03):271–278
- Eloy JA, Choudhry OJ, Friedel ME, Kuperan AB, Liu JK. Endoscopic nasoseptal flap repair of skull base defects: is addition of a dural sealant necessary? *Otolaryngol Head Neck Surg* 2012;147(01):161–166
- McCoul ED, Anand VK, Singh A, Nyquist GG, Schaberg MR, Schwartz TH. Long-term effectiveness of a reconstructive protocol using the nasoseptal flap after endoscopic skull base surgery. *World Neurosurg* 2014;81(01):136–143
- Thorp BD, Sreenath SB, Ebert CS, Zanation AM. Endoscopic skull base reconstruction: a review and clinical case series of 152 vascularized flaps used for surgical skull base defects in the setting of intraoperative cerebrospinal fluid leak. *Neurosurg Focus* 2014;37(04):E4
- Wang EW, Zanation AM, Gardner PA, et al. ICAR: endoscopic skull-base surgery. *Int Forum Allergy Rhinol* 2019;9(Suppl 3):S145–S365
- Esposito F, Dusick JR, Fatemi N, Kelly DF. Graded repair of cranial base defects and cerebrospinal fluid leaks in transsphenoidal surgery. *Oper Neurosurg (Hagerstown)* 2007;60(04, Suppl 2):295–303, discussion 303–304
- Germani RM, Vivero R, Herzallah IR, Casiano RR. Endoscopic reconstruction of large anterior skull base defects using acellular dermal allograft. *Am J Rhinol* 2007;21(05):615–618
- Lanza DC, O'Brien DA, Kennedy DW. Endoscopic repair of cerebrospinal fluid fistulae and encephaloceles. *Laryngoscope* 1996;106(9 pt. 1):1119–1125
- Leong JL, Citardi MJ, Batra PS. Reconstruction of skull base defects after minimally invasive endoscopic resection of anterior skull base neoplasms. *Am J Rhinol* 2006;20(05):476–482
- Lorenz RR, Dean RL, Hurlley DB, Chuang J, Citardi MJ. Endoscopic reconstruction of anterior and middle cranial fossa defects using acellular dermal allograft. *Laryngoscope* 2003;113(03):496–501
- Zwagerman NT, Wang EW, Shin SS, et al. Does lumbar drainage reduce postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery? A prospective, randomized controlled trial. *J Neurosurg* 2018;131(04):1172–1178
- Harvey RJ, Parmar P, Sacks R, Zanation AM. Endoscopic skull base reconstruction of large dural defects: a systematic review of published evidence. *Laryngoscope* 2012;122(02):452–459
- Zanation AM, Carrau RL, Snyderman CH, et al. Nasoseptal flap reconstruction of high flow intraoperative cerebral spinal fluid leaks during endoscopic skull base surgery. *Am J Rhinol Allergy* 2009;23(05):518–521
- Boogaarts JD, Grotenhuis JA, Bartels RH, Beems T. Use of a novel absorbable hydrogel for augmentation of dural repair: results of a preliminary clinical study. *Neurosurgery* 2005;57(1, suppl)146–151, discussion 146–151
- Cosgrove GR, Delashaw JB, Grotenhuis JA, et al. Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair. *J Neurosurg* 2007;106(01):52–58
- Kacher DF, Frerichs K, Pettit J, Campbell PK, Meunch T, Norbash AM. DuraSeal magnetic resonance and computed tomography imaging: evaluation in a canine craniotomy model. *Neurosurgery* 2006;58(1, suppl)ONS140–ONS147, discussion ONS140–ONS147
- Preul MC, Bichard WD, Spetzler RF. Toward optimal tissue sealants for neurosurgery: use of a novel hydrogel sealant in a canine durotomy repair model. *Neurosurgery* 2003;53(05):1189–1198, discussion 1198–1199
- Kus LH, Rotenberg BW, Duggal N. Use of tissue glues in endoscopic pituitary surgery: a cost comparison. *Can J Neurol Sci* 2010;37(05):650–655
- Chin CJ, Kus L, Rotenberg BW. Use of duraseal in repair of cerebrospinal fluid leaks. *J Otolaryngol Head Neck Surg* 2010;39(05):594–599
- Grotenhuis JA. Costs of postoperative cerebrospinal fluid leakage: 1-year, retrospective analysis of 412 consecutive nontrauma cases. *Surg Neurol* 2005;64(06):490–493, discussion 493–494
- Than KD, Baird CJ, Olivi A. Polyethylene glycol hydrogel dural sealant may reduce incisional cerebrospinal fluid leak after posterior fossa surgery. *Neurosurgery* 2008;63(01, Suppl 1):ONS182–ONS186, discussion ONS186–ONS187
- Fraser S, Gardner PA, Koutourousiou M, et al. Risk factors associated with postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery. *J Neurosurg* 2018;128(04):1066–1071