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Tissue Sealant Impact on Skull Base Reconstruction Outcomes: A Systematic Review and Meta-Analysis

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Objective: Despite significant advances in understanding of skull base reconstruction principles, the role of tissue sealants in modifying postoperative cerebrospinal fluid (CSF) leak outcomes remains controversial. We evaluate postoperative CSF leak incidence associated with tissue sealant use in skull base defect repair during endoscopic skull base surgery (ESBS).

Data Sources: Web of Science, PubMed/MEDLINE, Scopus, and Cochrane Library.

Review Methods: Systematic review and meta-analysis of risk differences (RD). A search strategy identified original studies reporting CSF leakage following ESBS with disaggregation by tissue sealant use and/or type.

Results: 27 non-randomized studies ($n = 2{,}403$) were included for qualitative and meta-analysis. Reconstruction with a tissue sealant did not significantly reduce postoperative CSF leak risk compared with reconstruction without sealant (RD[95% CI] = 0.02[−0.01, 0.05]). Sub-analyses of dural sealant (−0.02[−0.11, 0.07]) and fibrin glue (0.00[−0.07, 0.07]) compared with no sealant were similarly unremarkable. Postoperative CSF leakage was not significantly modulated in further sub-analyses of DuraSeal (0.02[−0.02, 0.05]), Adherus (−0.03[−0.08, 0.03]), or Bioglue (−0.06[−0.23, 0.12]) versus no dural sealant use, or Tisseel/Tissucol versus fibrin glue nonuse (0.00[−0.05, 0.05]). No significant association was seen comparing dural sealant use versus fibrin glue use on pairwise (0.01[−0.03, 0.05]) or network meta-analysis (−0.01[−0.05, 0.04]). Limitations in source literature prevented sub-analyses stratified by leak characteristics, defect size and location, and accompanying reconstruction materials.

Conclusion: Tissue sealant use did not appear to impact postoperative CSF leak incidence when compared with nonuse. Higher quality studies are warranted to thoroughly elucidate the clinical value of adjunct sealant use in endoscopic skull base reconstruction.

Key Words: cerebrospinal fluid leak, endoscopic endonasal approach, multilayer reconstruction, sealants, skull base surgery, tissue glue.

Level of Evidence: N/A

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INTRODUCTION

Endoscopic skull base surgery (ESBS) has, in many appropriate cases, replaced traditional open resection, providing improved visualization while avoiding external incisions and collateral injury to critical neurovascular structures.[1] Additionally, ESBS has shown to improve morbidity and mortality for some skull base pathologies, with decreased operative time, intraoperative blood loss, length of stay, and overall cost compared with open approaches.[2–5] As ESBS can entail intradural dissection leading to a skull base defect requiring repair, postoperative cerebrospinal fluid (CSF) leak is a major source of morbidity.[3,6] To reduce the risk of postoperative CSF leak, modern ESBS practices utilize combinations of free autografts, vascularized flaps, synthetic dural replacement grafts, and, frequently, a tissue sealant adjunct.[7,8]

Tissue sealants are absorbable agents designed to provide watertight closure by increasing burst pressure and supporting positional maintenance of grafts, as demonstrated in multiple *in vitro* studies.[9–12] Two major categories of adjunctive tissue sealants are fibrin glues, which are hemostatic agents that form insoluble fibrin mimicking the final phase of coagulation, and dural sealants, which polymerize into a cross-linked hydrogel solid.[7] Fibrin glue, dural sealant, or more rarely both, may be used to create a final watertight layer, an intervening adhesive in multilayer repairs, or even as packing for obliteration of dead space to help ensure an impermeable final product that effectively confines CSF.[7,13,14] Despite

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common use, however, there is lack of widespread consensus regarding the efficacy of fibrin glue and dural sealants in preventing postoperative CSF leaks. Several studies have found that neither fibrin glues nor dural sealants significantly reduced postoperative CSF leaks.[15–17] Moreover, the 2019 International Consensus Statement on ESBS assigned level D aggregate evidence for the use of tissue sealants, citing limited data in support of their utility.[18]

Overall, the use of tissue sealants for preventing CSF leaks in ESBS remains controversial. Due to the significant added cost they incur, it is imperative that thorough analysis be conducted to assess whether their continued use is supported by current evidence.[7] This systematic review and network meta-analysis aimed to evaluate rates of postoperative CSF leak associated with the use and nonuse of tissue sealants for repairing skull base defects during ESBS, as well as delineate whether specific sealants appear to impact reconstructive outcomes.

METHODS

Study scope was determined using the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework. Patients of any skull base pathology undergoing intradural ESBS comprised the population of interest. The intervention was tissue sealant use (vs. nonuse) for skull base reconstruction. Postoperative CSF leak was the primary outcome. Secondary variables included sex, pathology, intraoperative CSF leak flow (low vs. high), type of tissue sealant, and layer of sealant application. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines directed this systematic review with pairwise and network meta-analysis. As this review exclusively examined de-identified data from the literature, Institutional Review Board approval was waived.

Search Strategy

A literature search of four databases (Web of Science, PubMed/MEDLINE, Scopus, and Cochrane Library) was undertaken by a single author (J.C.P.) using the terms "(endoscopic OR endonasal) AND (reconstruction OR repair OR closure) AND (sealant OR glue OR adhesive)" in October 2022, with results limited to publication dates beginning in January 2001 to reflect the relevance of the endoscopic endonasal approach. Review articles were screened to identify eligible articles that may have been missed during the initial query using a hand-search approach.

Selection Criteria

Original studies reporting postoperative CSF leak incidence and use of a tissue sealant during ESBS were included for initial review. Each abstract was screened and full text assessed for inclusion using Covidence (Veritas Health Innovation, Melbourne, Australia) by two independent reviewers (J.C.P., M.M.N., A.B., C.H.N., T.I.H.) and conflicts were resolved via discussion with the senior author (E.C.K.). The following criteria were applied to exclude studies: (1) without full text, (2) not in English, (3) without primary data (i.e., reviews, meta-analyses, database studies, comments, letters to the editor, editorials, and errata), (4) reporting one case, (5) without reporting of the primary outcome, (6) without patients undergoing primary ESBS, (7) without reporting use of a tissue sealant, and (8) with unclear or absent disaggregation of surgical outcomes by tissue sealant status. Studies that met inclusion and exclusion criteria but described the application of tissue sealant based on explicit criteria related to intraoperative leak presence or severity were further excluded due to the confounding effects of such graded approaches.

Quality Assessment

Included articles were assigned "Levels of Evidence" per the Oxford Centre for Evidence-Based Medicine (OCEBM)[19] and critically assessed for quality. All studies were assessed using the Methodological Index for Non-Randomized Studies (MINORS) criteria, with which each article was scored 0 if not reported, 1 if reported but inadequate, and 2 if reported and adequate.[20] Maximum possible scores for non-comparative and comparative studies were 16 and 24, respectively. All articles were independently appraised by two reviewers (A.B., C.H.N., T.I.H.) and conflicts resolved by a third reviewer (J.C.P.) or the senior author (E.C.K.). Of note, study inclusion did not require a minimum score per MINORS criteria, which was assessed for primarily observational purposes.

Data Extraction

Two authors (J.C.P., A.B., C.H.N., T.I.H.) independently extracted data from each study using a pre-standardized tool in Covidence. Discrepancies were raised to and resolved by a third author (B.F.B.). Characteristics for all included studies, including study location, period, design, OCEBM level of evidence, and MINORS assessment score were summarized in a table along with individual study cohort size, sex, age, follow-up length, adjunct tissue sealant used, and reconstruction layer of sealant application. Aggregate cohort demographic and clinicopathologic characteristics were reported in a separate table. Notably, only patients with intraoperative CSF leaks, where such disaggregation was reported, proceeded to quantitative meta-analysis; however, full study cohort numbers and demographics were reported in these summaries.

Statistical Analysis

Pairwise meta-analysis was performed using the Cochrane Review Manager (RevMan) Version 5.4.1.[21] A minimum of two distinct studies reporting the primary study outcome for the same tissue sealant was required for that sealant type to qualify as appropriate for meta-analysis. For comparison of dichotomous, categorical event data, risk differences (RD) and 95% confidence interval (CI) were calculated via the Cochran–Mantel–Haenszel method. As our primary outcome of interest represents a relatively rare occurrence in the literature where both-armed zero-event studies are common, RDs were deemed the most appropriate effect size measure for adequate capture of available data.[22,23] Fixed- and random-effects models were applied depending on the expectation of common effect size amongst the analyzed studies in conjunction with the effect size heterogeneity test.[24] The random-effects model was used in analyses with a significant I^2 heterogeneity test ($p < 0.05$). Where there was a lack of such significance in effect size heterogeneity, the fixed-effects model was utilized. Subgroup analyses were performed based on the two major tissue sealant types, dural sealants and fibrin glues, and their respective brand variations for comparisons of the primary outcomes. Of note, where studies reported use of multiple sealant types or brands but failed to specify exactly the number of patients receiving each specific sealant type or brand, such "unspecified sealant" data were included only in comparisons of any sealant use versus no sealant use and could not contribute to any comparisons of further granularity. Results of analyses were displayed in forest plots and p-values <0.05 were considered statistically significant. Finally, pairwise

comparisons drawing from 10 or more studies were visually assessed for publication bias via funnel plot asymmetry as well as Egger's regression test, where p-values <0.05 indicated evidence for publication bias.[25]

For further elucidation of the relative impact of dural sealant use versus fibrin glue use versus use of neither tissue sealant beyond pairwise relationships, network meta-analysis of RD using a frequentist approach was conducted in R (version 4.0.5; The R Foundation for Statistical Computing) in RStudio (version 1.4.1106) using the netmeta R-package[26–28] including studies that reported disaggregated primary outcome data by at least two of the three aforementioned tissue sealant treatments. Given some comparison of treatments A versus B, a direct estimate is generated from studies reporting direct comparisons. An indirect estimate is also generated based on extrapolated evidence from studies comparing A with a third treatment C and studies comparing B versus C. Direct and indirect evidence are then combined to produce a network estimate of the effect size. The common effects model was favored over a random-effects model unless the corresponding I^2 heterogeneity test is greater than 30%.[29]

RESULTS

Search Results and Study Characteristics

The search yielded 2,466 unique studies, of which 27 studies ($n = 2{,}403$) qualified for qualitative and quantitative synthesis (Fig. 1). On MINORS assessment, the 15 non-comparative studies averaged a score of 11.6 ± 1.8 out of 16 (range: 8–14) whereas the 12 non-randomized comparative studies scored 18.0 ± 3.4 out of 24 (range: 10–23) (Supplementary Table 1). Characteristics of all included studies were summarized in Table I.[30–34,15,17,35–44,16,45–47,10,48–52] Three studies reported level III evidence whereas the remaining 24 studies reported level IV evidence. Patients in the aggregate cohort were 49.0% female and, on average, 50.2 years (range: 1–87). Pituitary adenomas comprised the majority of skull base pathologies (61.1%) and, where reported, subsequent definitive ESBS resulted in intraoperative CSF leaks that were largely high-flow (59.3%) and located in the anterior cranial fossa (45.9%) and sellar (44.1%) regions. Where specifically named, dural sealant use ($k = 16$, $n = 767$) was reported as the adjunct sealant of choice in more patients but in fewer cohorts than fibrin glue ($k = 23$, $n = 500$) in our series of included studies. DuraSeal (Integra, Plainsboro, New Jersey, USA) was the most common dural sealant ($k = 15$, $n = 555$), followed by Adherus (Hyperbranch Inc, Durham, North Carolina, USA) ($k = 5$, $n = 202$) and BioGlue (Cryolife, Inc., Kennesaw, GA, USA) ($k = 2$, $n = 10$). Fibrin glue brand was often unspecified in the included literature ($k = 9$, $n = 307$); otherwise, Tisseel/Tissucol

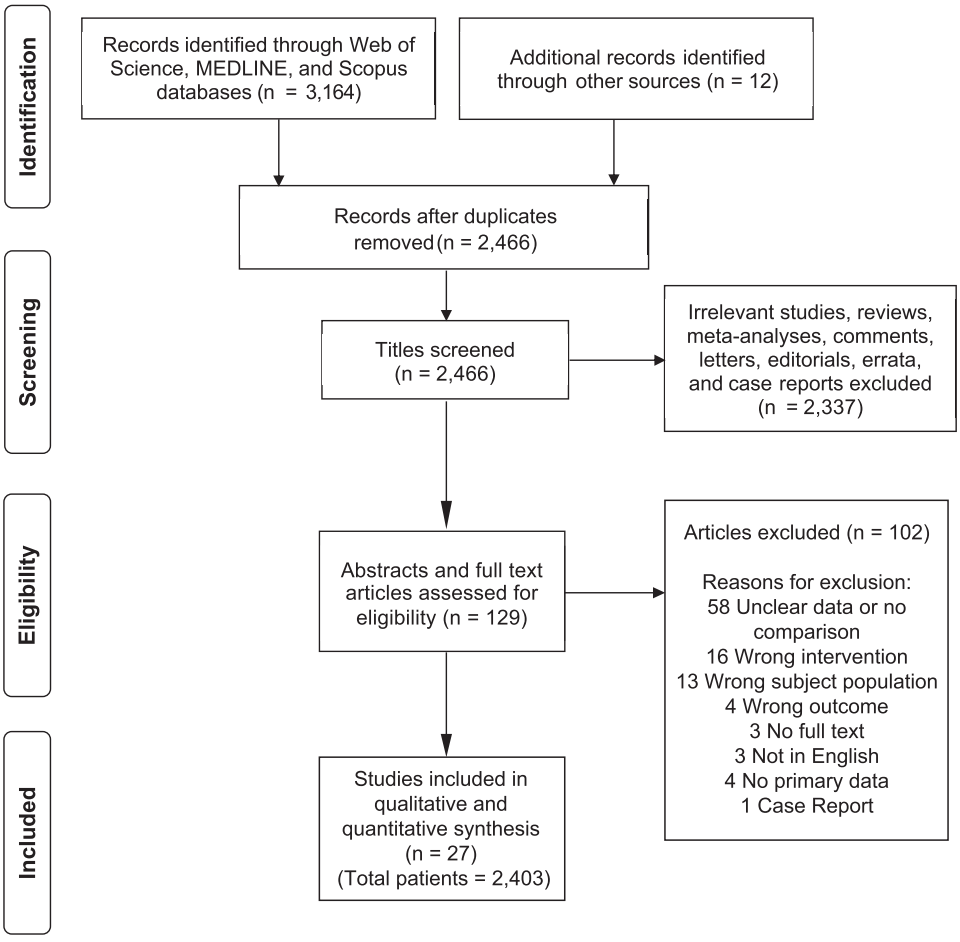


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection.

TABLE I.
Characteristics of included studies ($k = 27$).

Study	Country of study	Study period	Study design	Total patients (No.)	Female patients (No.)	Age (mean, median, range)	Follow-up in months (mean, median, range)	Adjunct sealant used (N)	Layer of sealant application (n)	OCEBM Level of evidence	MINORS score
Asmaro et al., 2021[30]	USA (Michigan)	2015–2019	Case series	73	47	54, NR, NR	NR, 8, NR	Adherus (46), Tisseel (15), DuraSeal (12)	Over onlay (73)	IV	14/16
Bosnjak et al., 2013[31]	Slovenia	2007–2011	Case series	8	4	61.8, 63, 47–73	31.5, 27, 10–69	DuraSeal (4), Beriplast (4)	Over flap (4), over inlay (3), over onlay (1)	IV	12/16
Burkett et al., 2011[32]	USA (Florida)	2000–2009	Retrospective cohort	204	111	52.0, NR, 15–83	52, NA, 14–120	Unspecified fibrin glue (107), DuraSeal (97)	Over inlay (204)	IV	18/24
Cappabianca et al., 2004[33]	Italy	1997–2003	Case series	56	NR	NR	NR	Tissucol (29)	Over inlay (29)	IV	8/16
CRANIAL, 2021[34]	United Kingdom	2019–2020	Prospective case–control	187	92	NR, 52, 7–84	NR	Tisseel (43), Adherus (36), DuraSeal (28), Evicel (16), Bioglue (9)	NR	III	19/24
Eloy et al., 2012[15]	USA (New Jersey)	2008–2011	Retrospective cohort	74	46	49.8, NR, 14–77	NR	DuraSeal, Tisseel, or Evicel (42)	Over flap (42)	IV	19/24
Ganesh et al., 2020[17]	India	2014–2018	Retrospective cohort	43	21	NR, NR, 27–70	6, 6, NR	Unspecified fibrin glue (26)	Over flap (26)	IV	17/24
Gruss et al., 2014[35]	USA (California)	2005–2012	Case series	121	57	NR, 50, 5–85	NA, 7.8, 1–55	DuraSeal (43)	Over flap (43)	IV	10/16
Horiguchi et al., 2010[36]	Japan	2005–2009	Retrospective cohort	32	12	55.9, NR, 20–79	NR	Unspecified fibrin glue (21)	Over flap (21)	IV	17/24
Hsu et al., 2015[37]	USA (New York)	NR	Case series	9	4	50.3, NR, 36–70	8.7, NR, 2.9–19.3	DuraSeal (5), Bioglue (1), unspecified fibrin glue (2)	Over onlay (7), over flap (1)	IV	10/16
Kitano and Taneda, 2004[38]	Japan	1998–2003	Case series	34	19	46.9, NR, 12–74	NR	Unspecified fibrin glue (2)	Over inlay (2)	IV	11/16
Laufer et al., 2007[39]	USA (New York)	NR	Case series	10		54, 52, 38–73	10, 9, 4–23	Tisseel (6), DuraSeal (4)	Over onlay (10)	IV	12/16
Lee et al., 2004[40]	Taiwan	1992–2002	Case series	39	17	36.8, NR, 18–59	30.6, NR, 9–112	Unspecified fibrin glue (23)	Over flap (23)	IV	14/16
Magro et al., 2016[41]	France	2002–2013	Case series	300	128	57, NR, 18–82	19, NR, 1–144	DuraSeal or Tissucol (77)	Over onlay (77)	IV	14/16
McDowell et al., 2022[42]	USA (Pennsylvania)	2016–2019	Prospective case–control	300	151	51.6, NR, 4–87	NR	DuraSeal or Tisseel (150)	Over flap (150)	III	19/24
Mohindra et al., 2013[43]	India	2005–2010	Retrospective cohort	27	5	7.8, 8, 2–15	54.3, NR, 34–75	Tisseel (13)	Over inlay (13)	IV	20/24
Peeters et al., 2020[44]	USA (California)	2014–2020	Case series	48	30	NR	NR	Adherus, DuraSeal, or Tisseel (23)	NR	IV	10/24
Pereira et al., 2017[16]	United Kingdom	2007–2010	Retrospective cohort	250	115	NR, 52, 14–83	NR	DuraSeal (180), Tisseel (16)	Over inlay (196)	IV	21/24
Pérez-López et al., 2020[45]	Spain	NR	Case series	100	45	54.8, NR, 18–84	NR	Adherus (94)	Over onlay or flap (94)	IV	9/16
Sautter et al., 2008[46]	USA (Ohio)	2002–2006	Case series	9	7	51.7, 54, 37–62	21.1, NR, 6–43	Tisseel (6)	Over flap (6)	IV	12/16
Solari et al., 2022[47]	Italy	2000–2021	Case series	84	28	30.6, NR, 4–78	63.5, NR, 3–240	Unspecified fibrin glue (39)	Over onlay (37), Over flap (2)	IV	11/16
Soneru et al., 2020[10]	USA (New York)	NR	Prospective case–control	50	29	51.4, NR, NR	NR	Adherus (26), DuraSeal (24)	Over flap (50)	III	23/24
Spitaels et al., 2022[48]	Belgium	2007–2018	Retrospective cohort	198	101	50.7, NR, NR	NR	DuraSeal (154), Tisseel (65)	Packing alone (154), over onlay (65)	IV	19/24
Tosaka et al., 2021[49]	Japan	2011–2020	Retrospective cohort	42	22	50.3, NR, NR	NR	Unspecified fibrin glue (28)	Over inlay (28)	IV	14/24
Yano et al., 2007[50]	Japan	2001–2005	Case series	56	NR	NR	NR	Bolheal (24)	Over onlay (18), alone (6)	IV	13/16

Yu et al., 2022[51]	USA (Pennsylvania)	2015–2021	Case series	19	9	10.6, 12, 1–15	18.2, 14, 1–36	DuraSeal (4)	Over onlay or flap (3), alone (1)	IV	12/16
Zeden et al., 2020[52]	Germany	2012–2016	Case series	30	17	55.2, 56, 16–80	15.7, 9.3, 2.8–67.5	Unspecified fibrin glue (15)	Over onlay (15)	IV	12/16

MINORS = Methodological Index for Non-Randomized Studies; NR = not reported; OCEBM = Oxford Centre for Evidence-Based Medicine.

TABLE II.
Pooled characteristics of the aggregate cohort ($n = 2,403$).

Variable	*N* (%) or Mean (range)
Sex	
Male	1,164 (51.0)
Female	1,117 (49.0)
Age	50.2 (1, 87)
Pathology	
Pituitary mass	1,467 (61.1)
Craniopharyngioma	150 (6.2)
Meningioma	108 (4.5)
Sinonasal mass	84 (3.5)
Rathke cleft cyst	68 (2.8)
Other	383 (15.9)
Not specified	90 (3.8)
Intraoperative CSF leak	
Low-flow	272 (40.7)
High-flow	396 (59.3)
Location of CSF leak	
Anterior cranial fossa	254 (45.9)
Sellar	244 (44.1)
Suprasellar	42 (7.6)
Posterior cranial fossa	13 (2.4)
Tissue sealant usage	
Total dural sealant used	767 (31.9)
DuraSeal	*555 (72.4)*
Adherus	*202 (26.3)*
BioGlue	*10 (1.3)*
Total fibrin glue used	500 (20.8)
Tisseel/Tissucol	*193 (38.6)*
Other (Evicel, Beriplast, Unspecified) fibrin glue	*307 (61.4)*
Unspecified tissue sealant used	292 (12.2)
No sealant used	845 (35.2)

CSF = cerebrospinal fluid leak.

(Baxter, Deerfield, Illinois, USA) ($k = 12$, $n = 193$), Evicel (Ethicon, Somerville, New Jersey, USA) ($k = 2$, $n = 16$), Bolheal (Teijin Pharma Ltd, Tokyo, Japan) ($k = 1$, $n = 24$), and Beriplast P (CSL Behring, King of Prussia, Pennsylvania, USA) ($k = 1$, $n = 4$) rounded out the fibrin glues represented. Notably, 292 patients from four cohorts received tissue sealants without disaggregated breakdown of specific type or brand (Table II).

Meta-Analysis

Pairwise meta-analysis demonstrated that reconstruction with a single tissue sealant did not significantly reduce risk of postoperative CSF leak compared with reconstruction without sealant ($k = 20$, RD[95% CI] = 0.02 [−0.01, 0.05]) (Fig. 2). Sub-analyses of dural sealant ($k = 4$, −0.02[−0.11, 0.07]) and fibrin glue cohorts ($k = 12$, 0.00[−0.07, 0.07]) compared with no sealant cohorts were similarly unremarkable. Postoperative CSF leakage was not significantly impacted in further sub-analyses of

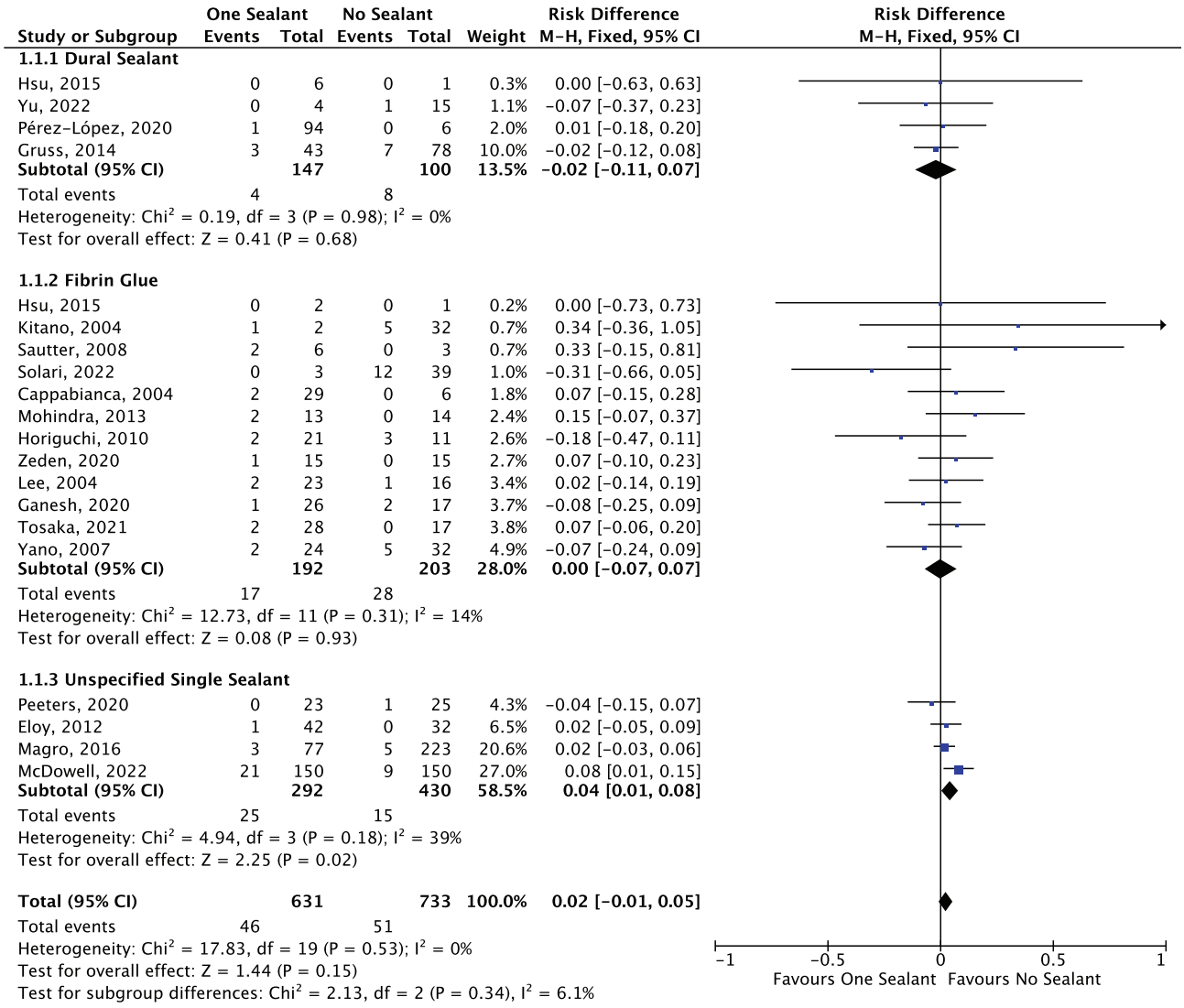


Fig. 2. Assessing postoperative cerebrospinal fluid leak risk differences (RD) between tissue sealant use versus nonuse with sub-analyses by tissue sealant type. 95% CI of each study is represented by horizontal lines whereas point estimates are represented by squares. Summary effects are represented by diamonds and bolded values. Horizontal axis favors population with lower relative risk. M-H = Cochran–Mantel–Haenszel method; Fixed = fixed-effects model; CI = confidence interval; df = degrees of freedom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

DuraSeal ($k = 10$, 0.02[−0.02, 0.05]), Adherus ($k = 3$, −0.03[−0.08, 0.03]), or Bioglue ($k = 2$, −0.06[−0.23, 0.12]) versus no dural sealant use (Fig. 3), or Tisseel/Tissucol versus fibrin glue nonuse ($k = 8$, 0.00[−0.05, 0.05]) (Fig. 4). No significant RD was seen in a comparison of dural sealant versus fibrin glue use ($k = 8$, 0.01[−0.03, 0.05]) (Fig. 5A). Finally, a comparison of two dural sealant types also revealed no significant relationship with postoperative CSF leak risk ($k = 3$, −0.00[−0.06, 0.05]) (Fig. 5B). Funnel plots describing any tissue sealant use versus nonuse (Supplementary Figure 1A), dural sealant use versus nonuse (Supplementary Figure 1B), and fibrin glue use versus nonuse comparisons (Supplementary Figure 1C) displayed relative visual symmetry, and corresponding analysis using Egger's regression test corroborated a lack of evidence for small study effects due to publication bias ($p = 0.374$, 0.713, and 0.923, respectively). Unfortunately, despite methodological goals to stratify outcomes based on pathology, intraoperative leak characteristics, and defect size and location, the primary literature did not provide sufficient granularity for further sub-analyses. In an aggregate cohort of exclusively patients with pedicled flap reconstruction, however, tissue sealant use did not significantly impact postoperative CSF leak incidence ($k = 6$, $n = 261$, RD[95% CI] = 0.02[−0.05, 0.09]). Similarly, sealant use did not modify postoperative CSF leakage in patients with reconstruction using free grafts ($k = 3$, $n = 81$, RD[95% CI] = −0.04[−0.19, 0.12]).

Studies reporting direct comparisons of dural sealant use versus no tissue sealant use ($k = 2$), fibrin glue use

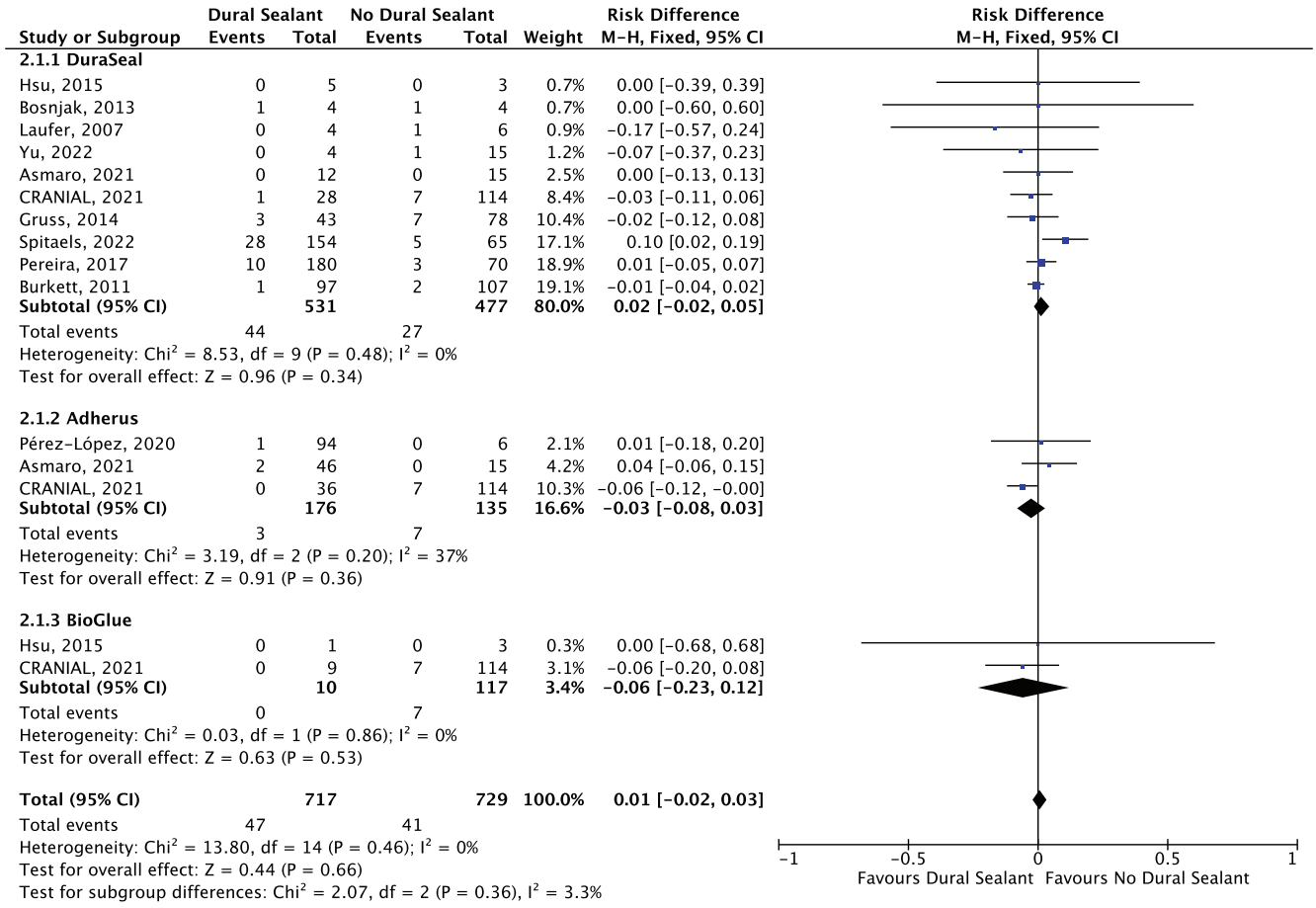


Fig. 3. Postoperative cerebrospinal fluid leak risk differences (RD) comparing dural sealant use versus nonuse with sub-analyses by dural sealant type. 95% CI of each study is represented by horizontal lines whereas point estimates are represented by squares. Summary effects are represented by diamonds and bolded values. Horizontal axis favors population with lower relative risk. M-H = Cochran–Mantel–Haenszel method; Fixed = fixed-effects model; CI = confidence interval; df = degrees of freedom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

versus no sealant use ($k = 10$), and dural sealant use versus fibrin sealant use ($k = 6$), as well as multi-arm studies reporting all three treatment cohorts ($k = 2$), were included in a network meta-analysis; studies that failed to specify their usage of tissue sealants by type were unqualified for inclusion (Fig. 6A). Network estimates revealed no significant RDs in dural sealant use versus no tissue sealant use (RD[95% CI] = 0.00[−0.10, 0.10]), fibrin glue use versus no sealant use (0.01[−0.09, 0.11]), or dural sealant use versus fibrin sealant use (−0.01 [−0.05, 0.04]) comparisons (Fig. 6B).

DISCUSSION

This meta-analysis evaluated postoperative CSF leak incidence in 2,403 ESBS patients and demonstrated a lack of evidence supporting tissue sealant use for mitigating postoperative CSF leaks, regardless of sealant type or brand. Our analysis revealed no significant differences in postoperative leak rates with versus without using tissue sealants. Similar observations were made in sub-analyses by brand within the dural sealant (DuraSeal, Adherus, and BioGlue) and fibrin glue (Tisseel and other) categories. Additionally, network meta-analysis demonstrated no differences in likelihood of postoperative leak when comparing dural sealants, fibrin glues, and tissue sealant nonuse groups. Although these findings should motivate discussion on the value of adjunct sealants, the current review should also highlight a general lack of high-level evidence reported in the primary literature on tissue sealant use, with a further lack of data granularity preventing critical sub-analyses stratified by adjacent reconstructive factors such as intraoperative leak characteristics, defect size and location, and accompanying reconstruction materials.

Dural sealants comprised 49.2% of all tissue sealants used compared with 32.0% and 18.7% for fibrin glues and unspecified sealants, respectively. DuraSeal was the most common tissue sealant (35.6%) and represented 72.4% of all dural sealants used. Although fibrin glues and dural sealants are used for the same purpose in skull base reconstruction, their basic composition and mechanisms of action are different. Fibrin glues are generally comprised of thrombin and fibrinogen to mimic the final steps of the coagulation cascade in forming a fibrin clot.[53] They are derived from animals or humans and therefore pose a risk

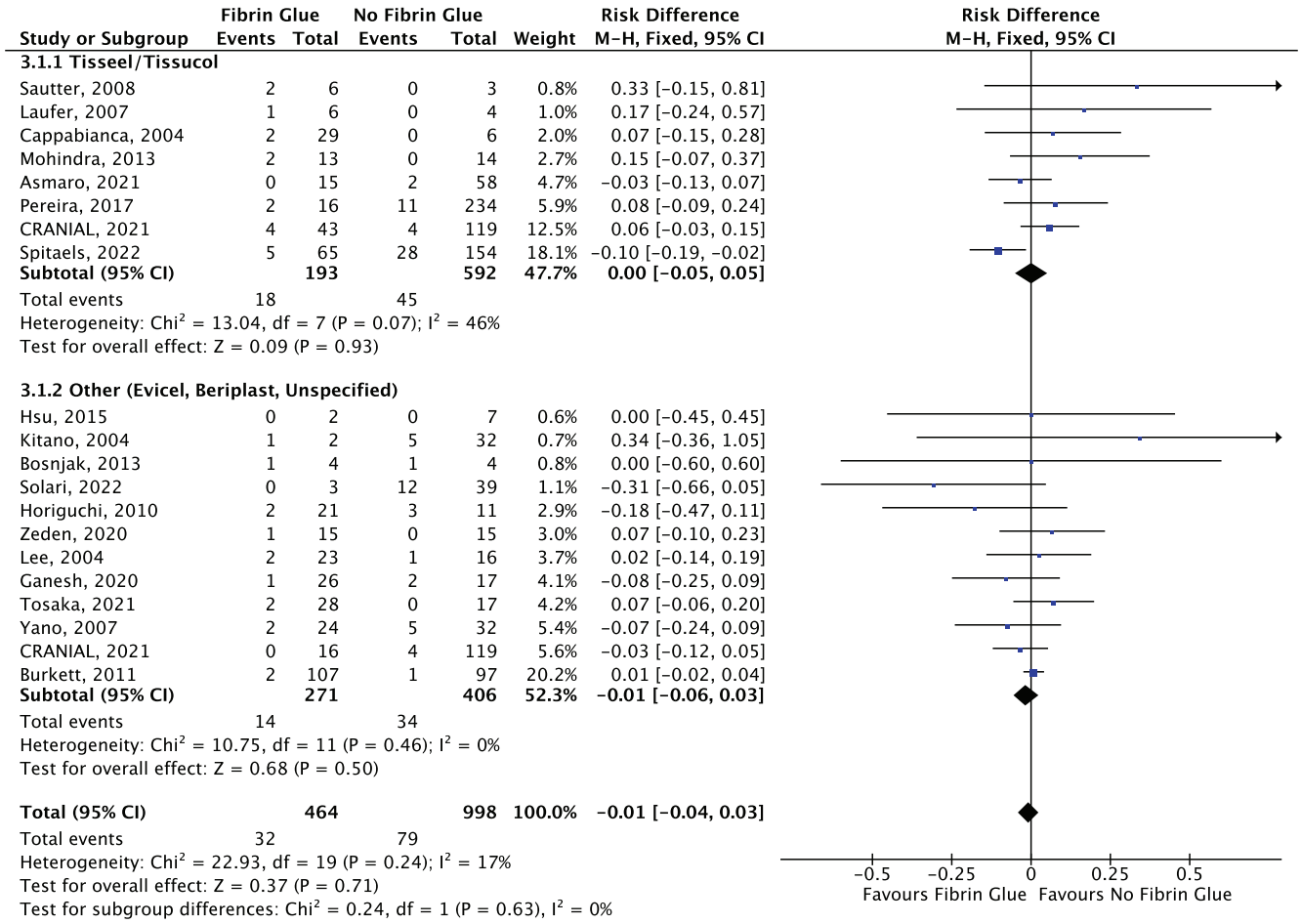


Fig. 4. Comparing differences in cerebrospinal fluid leak risk (RD) associated with fibrin glue use versus nonuse with sub-analyses by fibrin glue type. 95% CI of each study is represented by horizontal lines whereas point estimates are represented by squares. Summary effects are represented by diamonds and bolded values. Horizontal axis favors population with lower relative risk. M-H = Cochran–Mantel–Haenszel method; Fixed = fixed-effects model; CI = confidence interval; df = degrees of freedom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

of transmitting infectious viral agents.[16,54] Additionally, use of animal or human derivatives may be of ethical concern to some patients. In contrast, dural sealants are synthetic and pose no risk of transmitting infectious agents.[16]

Routine use of tissue sealants in ESBS may be attributed to early *in vitro* studies that demonstrated improved stability of skull base reconstruction and an increase in burst pressure with certain tissue sealants.[9,11,55] de Almeida *et al*. were the first to study tissue sealant burst pressure in a porcine skull model and found that Tisseel reduced CSF leakage by improving repair strength and graft adherence. Burst pressure in controls was 4.6 ± 3.1 pounds per square inch (PSI) compared with 13.8 ± 5.4 PSI in the test group, both of which were above physiologic intracranial pressure (ICP). Fandiño *et al*. later utilized the same porcine model to compare burst pressures for reconstructions using Tisseel or DuraSeal in combination with three types of soft tissue grafts—porcine pericranium, AlloDerm (Life-Cell Corporation, Branchburg, NJ), or Durasis (Cook Biotech, West Lafayette, IN). They found Tisseel applied over a pericranium graft produced the strongest repair, with a burst pressure of 95.5 ± 86 mmHg. Notably, burst pressures were not significantly different between reconstructions using fibrin glue versus dural sealant regardless of the type of soft tissue graft they were paired with, suggesting that tissue sealant type may factor less strongly into burst pressure than the accompanying soft tissue graft's composition. However, this study did not include a control group comparison for soft tissue graft use, making it difficult to isolate the specific impact of each sealant on burst pressure. In 2018, van Doormaal *et al*. examined nine common tissue sealants in a modified in vitro model and found Tachosil (71 ± 71 mmHg), Adherus (87 ± 47 mmHg), and DuraSeal (51 ± 42 mmHg) showed burst pressures well above physiologic ICP, whereas the remaining six sealants—Duraform (Codman, Raynham, Massachusetts), Tissudura (Baxter, Deerfield, Illinois), Hemopatch (Baxter), TissuePatchDural (Tissuemed, Leeds, United Kingdom), Tisseel, and Duragen Secure (Integra, Plainsboro, New Jersey)—burst below 20 mmHg. Nonetheless, critical limitations to in vitro burst pressure modeling exist, and whether such findings translate reliably to clinical practice remains unclear.

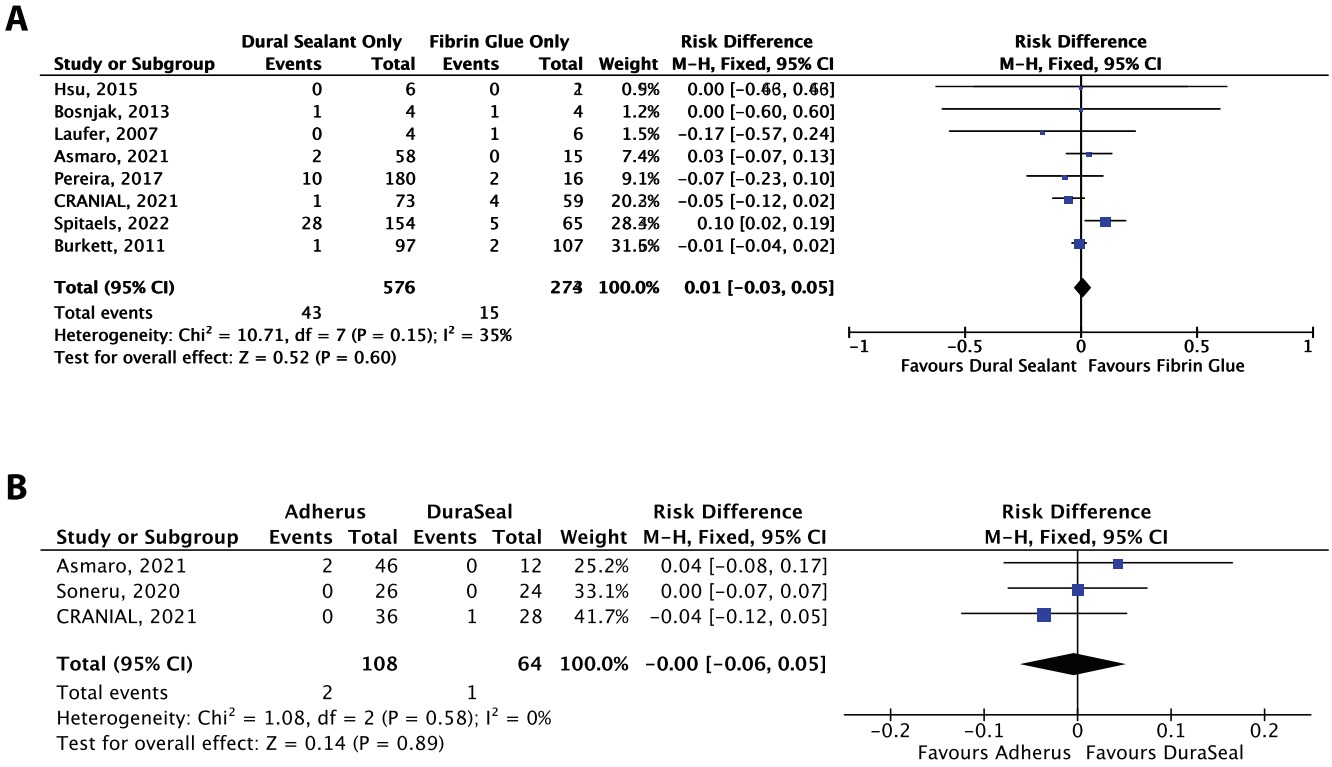
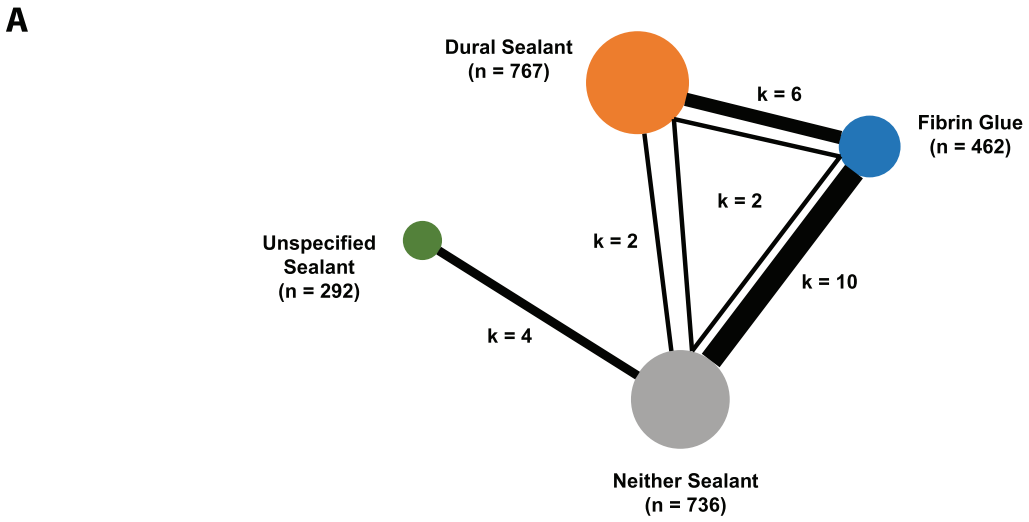


Fig. 5. Postoperative cerebrospinal fluid leak risk differences (RD) between tissue sealant types. (A) Comparison of dural sealant use versus fibrin glue use. (B) Comparison between two types of dural sealant. 95% CI of each study is represented by horizontal lines whereas point estimates are represented by squares. Summary effects are represented by diamonds and bolded values. Horizontal axis favors population with lower relative risk. M-H = Cochran–Mantel–Haenszel method; Fixed = fixed-effects model; CI = confidence interval; df = degrees of freedom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Importantly, tissue sealant use for skull base repair is not without drawbacks. McDowell *et al.* studied 300 ESBS patients with intraoperative CSF leak, in which half of the multilayer skull base reconstructions were supported with either Tisseel or DuraSeal.[42] Postoperative CSF leak was observed in 14% of patients with sealants and in only 6% of control patients. They posited that this difference may be due to poor wound healing from the potential barrier created between the tissues at the skull base defect and the surrounding soft tissue. This theory has been supported by multiple studies evaluating inflammatory responses to tissue sealants followed by poor wound healing, especially with the use of BioGlue.[56–62] Additionally, introducing foreign materials into a surgical field despite sterile technique may pose a risk for surgical site infection (SSI) in ESBS. Gaberel *et al.* and Klimo *et al.* both found an increased risk of SSI in cranial surgery following intradural application of BioGlue.[59,60] However, Hannan *et al.* studied extradural application of the same dural sealant during endoscopic endonasal pituitary surgery and avoided similar risks.[56] They concluded that prior concerns of infection with BioGlue use may not extend to extradural applications. Further investigation into postoperative sinonasal morbidity including infection associated with tissue sealant use is warranted.

Costs associated with tissue sealant use must also be considered as a common reason certain sealants are adopted over others. Many currently available tissue sealants are expensive.[10,12,15,42,63] van Doormaal *et al.* estimated that the average cost of one tissue sealant in the United States in 2018 was over $300 and estimated an annual cost of $300,000–$400,000 for the average neurosurgical department.[12] Eloy *et al.* noted DuraSeal was historically the most costly tissue sealant used at their institution at $597/mL in 2012, compared with Evicel ($128.91/mL) and Tisseel ($55.91/mL).[15] Though specific costs have fluctuated since, from an economic standpoint, given a lack of evidence supporting tissue sealant use for the reduction of CSF leak complications, potentially unnecessary costs without clear clinical benefit should urge careful deliberation amongst stakeholders prior to routine adoption.

Despite care taken to analyze and interpret the data, there exist limitations inherent to systematic reviews and we encourage cautious interpretation of the results in this study. Most of the included studies were retrospective, which introduces potential publication bias skewing reporting toward an over-representation of favorable outcomes and potentially affecting the overall incidence of CSF leak regardless of tissue sealant use. The lack of randomization further limits the quality of evidence, allowing for the influence of potential implicit and explicit biases in individual authors' choices regarding sealant use versus nonuse in included literature. Notably, lack of granularity in reporting of outcomes in the available



B

Comparison (A vs. B)	Studies (k)	Direct evidence	I^2	Common effects model	RD [95%–CI]
				Postoperative CSF Leak	
Dural Sealant vs. No Sealant					
Direct estimate	4	0.39	0		−0.02 [−0.18; 0.15]
Indirect estimate					0.02 [−0.11; 0.14]
Network estimate					0.00 [−0.10; 0.10]
Fibrin Glue vs. No Sealant					
Direct estimate	12	0.67	0		0.02 [−0.10; 0.14]
Indirect estimate					−0.01 [−0.19; 0.16]
Network estimate					0.01 [−0.09; 0.11]
Dural Sealant vs. Fibrin Sealant					
Direct estimate	8	0.95	0		−0.00 [−0.05; 0.04]
Indirect estimate					−0.04 [−0.24; 0.17]
Network estimate					−0.01 [−0.05; 0.04]

Fig. 6. Network meta-analysis of postoperative cerebrospinal fluid leak risk differences (RD). (A) Network plot of multi-arm studies comparing use of dural sealant, fibrin glue, unspecified sealant, and/or neither tissue sealant. B) Network meta-analysis estimates of postoperative cerebrospinal fluid leak RD in three tissue sealant treatment comparisons. 95% CI of each study is represented by horizontal lines, whereas point estimates are represented by squares. Summary effects are represented by diamonds. Horizontal axis favors population with lower relative risk. CI = confidence interval. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

literature limited our ability to produce sub-analyses of sealant use versus nonuse based on patient pathology, intraoperative leak characteristics, defect size or location, accompanying reconstruction materials such as use of pedicled flap versus free graft or absorbable versus nonabsorbable packing, or postoperative management strategies, despite methodological intent. Finally, there is a possibility that qualified studies may have erroneously not been included despite our vigilant search and comprehensive review processes.

CONCLUSION

Pairwise and network meta-analyses of 27 nonrandomized studies revealed that use of tissue sealants in ESBS may not significantly reduce risk of postoperative CSF leakage either in absolute comparisons with nonuse or relative comparisons among tissue sealant types and brands. However, lack of granularity in primary literature prevented robust sub-analyses stratified by leak characteristics, defect size and location, and accompanying reconstruction materials, despite methodological intent. Further investigation of prospective randomized design may be warranted to thoroughly elucidate the clinical value of adjunct sealants in ESBS.

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