Effectiveness of Sealants in Prevention of Cerebrospinal Fluid Leakage after Spine Surgery: A Systematic Review

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Key words
- Cerebrospinal fluid leakage
- Dural sealant
- Durotomy
- Spinal surgery

Abbreviations and Acronyms
CI: Confidence interval
CSF: Cerebrospinal fluid
FG: Fibrin glue
PGA: Polyglycolic acid
RR: Risk ratio

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BACKGROUND: **Sealants are often used in spine surgery to prevent postoperative cerebrospinal fluid (CSF) leakage.**

OBJECTIVE: **To investigate the efficacy of sealants in preventing postoperative CSF leakage in spine surgery.**

METHODS: **The PubMed, Embase, and Cochrane databases were searched for articles reporting the outcome of patients treated with a sealant for spinal dural repair. The number of patients, indication of surgery, surgical site, applied technique, type of sealant used, and outcome in terms of postoperative CSF leakage were noted for each study. The primary outcome was CSF leakage in general and secondary outcome infection.**

RESULTS: **Forty-one articles were selected with a total of 2542 cases; there were 4 comparative studies with 540 sealed cases and 343 cases with primary suture closure only. The quantity of CSF leakage did not differ between the sealant group (50 of 540, 9.1%) and the group treated with sutures only (48 of 343, 13.8%) (risk ratio [RR], 0.58 [confidence interval [CI], 0.18–1.82]). The infection rate did also not differ between the sealant and primary suture groups (RR, 0.94 [CI, 0.55–1.61]). This result was found in both the intended and the unintended durotomy subgroups. Secondary analysis of all cases showed that endoscopic or minimally invasive surgery had lower CSF leakage rates compared with open surgery regardless of sealant use (RR, 0.18 [CI, 0.05–0.75]).**

CONCLUSIONS: **Currently available sealants seem not to reduce the rate of CSF leakage in spine surgery. In endoscopic and minimally invasive surgery, the CSF leakage rate is less frequent compared with open, conventional surgery regardless of sealant use.**

INTRODUCTION

Cerebrospinal fluid (CSF) leakage is a pervasive complication of spine surgery, after intradural surgery or unintended durotomy in extradural surgery. Persistent leakage of CSF can lead to secondary complications such as postural headache, durocutaneous fistula, meningitis, and even intracranial hemorrhage.[1,2] Unintended durotomy occurs in 1%–2% of all extradural cases, with higher rates in patients undergoing revision surgery and in elderly patients.[3-5] Despite repair, 10% of these patients experience CSF leakage. This rate is even higher in redo surgery. With more than one million spine procedures performed in the United States each year, more than 10,000 patients are annually at risk for CSF leakage.[6] The incidence of symptomatic CSF leakage for intradural surgery is 5%–13%, which is comparable to that for unintended durotomy.[7-10] Common management strategies such as bed rest, CSF drainage through a lumbar drain, or re-exploration have their own associated complications and can be ineffective in some cases.[11] Longer admissions and various interventions result in increased health care costs of nearly 50%.[12,13]

Sealants are often used in spine surgery to prevent postoperative CSF leakage after durotomy.[7,14] When primary closure is not feasible, a combination of sealant and graft can be used. Various sealants are applied to ensure a watertight closure in both intended and unintended durotomy.[15,16] No systematic review has been conducted on the effectiveness of sealants used in spine surgery. We therefore aimed to systematically review the efficacy of sealants in preventing postoperative CSF leakage after spine surgery.

METHODS

A systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[17] The search was performed in the PubMed, Embase, and Cochrane databases as per January 9, 2019. The search syntax is shown in **Appendix 1**. Two authors independently selected the relevant articles based on the title and abstract.

Only original articles in English were selected and no restrictions in terms of publication date were applied. Two authors (A.K. and T.P.C.v.D) identified the articles that met the eligibility criteria. The inclusion of articles was based on reading the full article. The reference lists of the included articles were screened for additional publications to include.

Study Criteria

Studies were included in which patients underwent spinal procedures and received a sealant for dural closure. Only cases in which disruption of the dural integrity led to intraoperative CSF leakage were included. Sealants could be applied on sutured as well as nonsutured dura. Only materials that have sealing properties stated by the manufacturer were selected. Studies were included when the CSF leakage rate for spinal cases could be extracted from the data. Cases in which a dural substitute was used were included only when it was used in combination with a sealant. Studies with <10 patients receiving a sealant were excluded. Chiari, pediatric, and spontaneous intracranial hypotension cases were excluded. Cases treated with percutaneous sealant injection were excluded. Cases in which patients received subarachnoid lumbar drainage immediately after surgery were excluded. Cases in which only the hemostatic effect of a sealant was examined were excluded.

Data Extraction

The following data were extracted from the included articles: study design (randomized clinical trial, prospective, or retrospective), number of patients, location of procedure (cervical, thoracic, lumbosacral, or unknown), indication for surgery (degenerative, tumor, or others), conventional or endoscopic/minimally invasive surgery, intended or unintended durotomy, type and brand of sealant, use of substitutes, rate of CSF leakage, and infection (wound infection, spondylodiscitis, and meningitis).

Outcome Definition

Primary outcome was defined as CSF leakage in general (incisional leakage and pseudomeningocele) and secondary outcome as infection. The diagnosis of CSF leakage could be by either clinical examination or imaging. Further analysis was performed to determine location of surgery, indication of surgery, and surgical technique. The risk ratio (RR) was calculated using Review Manager version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark). For case series, the overall percentage of CSF leakage and confidence interval was calculated according to the binomial Clopper-Pearson method.[18] The heterogeneity between studies were shown using the I^2 test.

RESULTS

The search on January 9, 2019 yielded 1409 articles after duplicates were discarded. Seventy-six articles were deemed useful after title and abstract screening, 49 of which were excluded, because they did not meet the inclusion criteria. Of these articles, 2 randomized clinical trials and 1 retrospective study were excluded because they included Chiari surgeries and the leakage rate for spine cases could not be determined.[19-21] One randomized clinical trial was excluded because the primary outcome was drain output and CSF leakage rate could not be determined.[22] Eleven articles were included through screening of the reference lists of the included studies and were not found with the search strategy because the main aim of these articles was not sealant use (Figure 1).

Forty-one studies were included in the final analysis, of which 5 were prospective and 36 retrospective.[1,4,7,11,23-59] Extradural procedure cases without durotomy[43] and cases in which a dural tear did not lead to intraoperative CSF leakage were excluded.[39,41] Cases in which fibrin sealant was used for hemostasis only were excluded.[28] Cases in which lumbar drainage was received as part of the management of an unintended tear were excluded.[24] Chiari cases were excluded in 1 study.[50] Postoperative imaging was performed in all cases in 13 studies.[4,7,23,25,27,32-34,39,40,43,44,54] In 9 studies, postoperative imaging was available in some cases.[1,30,37,38,41,47,51,57,58]

A total of 2542 cases were included, in 1243 of which (48.9%) dural closure was performed for intended durotomy and in 1299 of which (51.1%) unintended durotomy was performed. In 2193 cases (86.3%), sealant was applied, and 349 cases (13.7%) underwent suture repair only. Fibrin glue sealants were the most common type of sealant used (1696 cases [66.8%]) in combination with a graft or alone. The most common indication for dural closure was degenerative surgery, in 1296 cases (51.0%), followed by tumor surgery in 920 cases (36.2%) and other indications in 326 cases (12.8%). Lumbosacral was the most frequent operative site, in 1286 cases (50.6%), followed by thoracic in 173 cases (6.8%) and cervical in 124 cases (4.9%). The operative site was indeterminable for 955 cases (37.6%). An open midline approach was the most common operative approach in 2416 cases (95.0%, whereas 126 cases (5.0%) were treated with endoscopic or minimally invasive techniques (Table 1).

Meta-Analysis

Five articles included a group with sealant and a group with primary closure only.[1,4,25,31,40] One study was excluded because patients were treated endoscopically for intradural tumors from this analysis because the surgical technique was profoundly different from the other studies.[25] One study included a group of patients in whom dural repair was performed with sutures and gelatin sponge. Because gelatin sponge has no sealing properties, this group was included with the group who received sutures only.[40]

The number of CSF leakages did not differ between the sealant group (50 of 540, 9.1%) and the group treated with sutures only (48 of 343, 13.8%) (RR, 0.58 [confidence interval [CI], 0.18−1.82]; I^2 = 71%) (Figure 2). No difference in infection was observed between the sealant group (26 of 540, 4.7%) and the group treated with sutures (23 of 343, 6.7%) (RR, 0.94 [CI, 0.55−1.61]). For intended durotomy cases, there was no difference in CSF leakage between the sealant group (8 of 215, 3.7%) and group treated with sutures only (17 of 70, 24.2%) (RR, 0.27 [CI, 0.07−1.13]). Also for the unintended durotomy cases, the rate of CSF leakage was not lower for the sealant group (45 of 325, 13.8%) compared with the suture only group (31 of 273, 11.4%) (RR, 1.05 [CI, 0.67−1.65]).

Case Series Analysis

Thirty-six of the 41 studies were case series of durotomy, in which CSF leakage

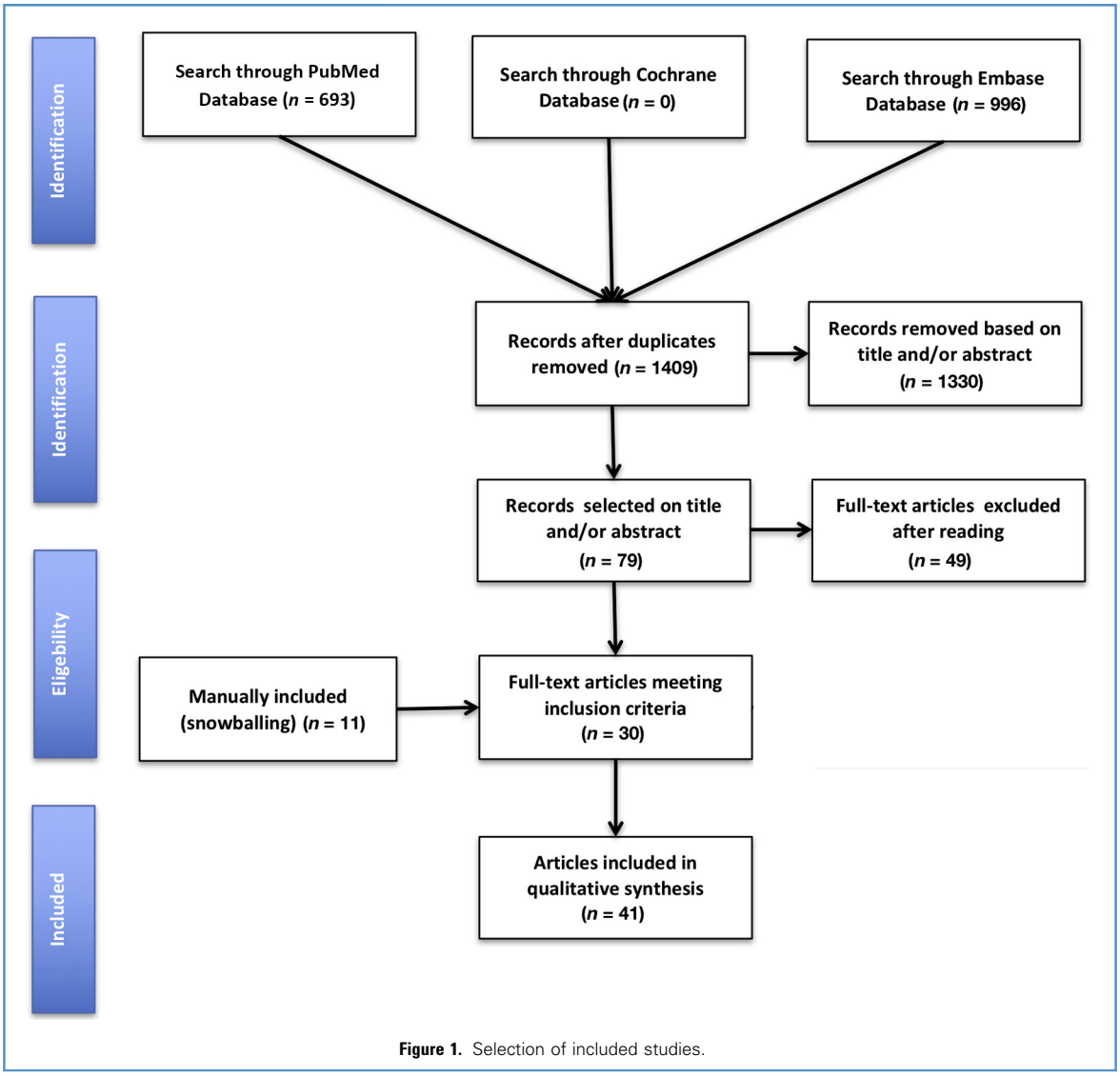

Figure 1. Selection of included studies.

occurred in 125 of 1641 cases (7.6%). This percentage was higher in comparative studies (98 of 883, 11.1%) (RR, 1.49 [CI, 1.13–1.97]). Therefore, case series studies were analyzed separately and not compared with the group treated with sutures only. For each study, the rate of CSF leakage for intended and unintended durotomy was determined (Figure 3).

Ten of the 36 case series reported 221 patients with no postoperative CSF leakage. Ninety-four of these patients (42.5%) were treated endoscopically or with minimally invasive surgery. In most of these studies, fibrin glue was used, except in 1 study in which onlay collagen matrix was used. This same product was tested in 3 other studies in which CSF leakage occurred in 5.9% (15 of 256) of the cases.

Secondary Analysis

The rate of CSF leakage treated with endoscopic or minimally invasive surgery was 2 of 120 cases (1.7%). This rate was lower compared with the sealant group treated with conventional open surgery for the case series (173 of 2073, 8.3%) (RR, 0.18 [CI, 0.05–0.75]). No adverse events associated with the application of dural sealant were observed in any of the studies. We attempted to analyze whether the location of surgery and indication of surgery could influence CSF leakage rate. However, in most articles, these variables were not recorded consistently in relation to CSF leakage.

DISCUSSION

In this systematic review, we analyzed the effectiveness of sealants in preventing postoperative CSF leakage in spine surgery. Meta-analysis showed no difference in postoperative CSF leakage between the sealant group and the group treated with primary suturing. The infection rate did not show a difference between the 2 groups. Subanalyses showed no difference in CSF leakage between the 2 groups for intended or unintended durotomy. For

Table 1. Patient Characteristics

	Reference	Number of Patients		Location of Procedure				Type of Durotomy		Surgical Technique		Sealant Used (Brand Name)	Cerebrospinal Fluid Leakage		Infection	
		Sealant	Control	Cervical	Thoracic	Lumbosacral	Undeterminable	Intended	Unintended	Open	Endoscopic/ Minimally Invasive		Sealant	Control	Sealant	Control
1	Montano et al., 2019[59]	35		3	13	14	5	35	0	35	0	FSP (TachoSil) with FG	1		0	
2	Galarza et al., 2018[23]	62		0	0	62	0	0	62	62	0	FG (Tisseel) with or without FSP (TachoSil)	6	0	0	0
3	Yokogawa et al., 2017[26]	18		0	14	4	0	0	18	18	0	PGA mesh (Neoveil) and FG (Beriplast)	11		0	
4	Parihar et al., 2017[25]	12	6	4	7	7	0	18	0	0	18	FG (ReliSeal)	0	0	0	0
5	Jeon et al., 2017[24]	20		0	20	0	0	0	20	20	0	FG (Beriplast) or FG with DuraSeal	0		0	
6	Won et al., 2016[31]	184	47	0	0	0	231	231	0	231	0	FG (Tisseel)	5	2	1	0
7	Masuda et al., 2016[30]	75		0	0	0	75	53	22	75	0	PGA mesh (Neoveil) and FG (Bolheal)	3		1	
8	Kogias et al., 2017[29]	25		0	0	25	0	0	25	16	9	FSP (TachoSil), 1 case with FG	1		1	
9	Radcliff et al., 2016[11]	42		0	0	42	0	0	42	42	0	DuraGen and DuraSeal	2		1	
10	Graziano et al., 2016[28]	26		4	0	15	7	12	14	26	0	Autologous FG (Vivostat)	2		0	
11	Arnautovic et al., 2016[27]	40		13	13	14	0	40	0	40	0	Fat graft with FG	1		0	
12	Ito et al., 2015[32]	31		0	0	0	31	31	0	31	0	PGA mesh (Neoveil) and FG (Beriplast)	1		0	
13	Tan et al., 2014[34]	23		2	9	12	0	23	0	0	23	FG (Tisseel)	0		0	
14	Miscusi et al., 2014[33]	23		0	0	23	0	0	23	23	0	FG (Tissucol) or BioGlue	3		1	
15	Telera et al., 2014[35]	46		0	0	0	46	46	0	46	0	FSP (TachoSil)	3		0	
16	Sohn et al., 2013[37]	169		0	0	0	169	169	0	169	0	FG (Greenplast)	13		2	
17	Low et al., 2013[36]	61		0	0	61	0	0	61	61	0	FG	5		0	
18	Koechlin et al., 2013[7]	91		30	28	33	0	91	0	91	0	Various sealants	32		0	
19	Takahashi et al., 2013[38]	41		0	0	41	0	0	41	41	0	FG (Beriplast)	1		0	
20	Wolff et al., 2012[41]	15		0	0	15	0	0	15	15	0	FG (Tisseel) and Pangen (collagen)	0		0	
21	Guerin et al., 2012[1]	47	4	2	2	47	0	0	51	51	0	FG	9	0	2	0
22	Lei et al., 2012[39]	10		10	0	0	0	0	10	10	0	FG	4		1	

23	McMahon et al., 2012[57]	104		17	15	72	0	0	104	104	0	DuraGen	7		0	
24	Wang et al., 2012[40]	31	23	9	18	27	0	54	0	54	0	Medical glue	3	15	0	0
25	Ferroli et al., 2013[42]	18		0	0	0	18	18	0	18	0	TissuePatchDural	2		0	
26	Parlato et al., 2011[44]	14		2	0	0	12	14	0	14	0	TissuDura with FG	0		0	
27	Ruban and O'Toole, 2011[45]	53		2	0	51	0	0	53	0	53	FG	0		1	
28	Haji et al., 2011[43]	15		2	5	8	0	15	0	0	15	FG	1		0	
29	Teli et al., 2010[46]	10		0	0	10	0	0	10	2	8	FG	2		8	
30	Jankowitz et al., 2009[4]	278	269	0	0	547	0	0	547	547	0	FG (Tisseel)	33	31	23	23
31	Stendel et al., 2008[47]	30		0	0	0	30	12	18	30	0	DuraGen	0		0	
32	Narotam et al., 2007[58]	11		0	0	0	11	0	11	11	0	DuraGen	1		0	
33	Epstein, 2007[48]	10		0	0	10	0	0	10	10	0	FG	0		0	
34	Sin et al., 2006[52]	12		0	0	12	0	0	12	12	0	FG	0		0	
35	Shimada et al., 2006[51]	30		0	0	0	30	20	10	30	0	FG (Bolheal) or FG with PGA mesh (Neoveil)	5		0	
36	Hida et al., 2006[50]	137		0	0	0	137	129	8	137	0	FG (Bolheal) with PGA mesh (Neoveil)	7		0	
37	Narotam et al., 2004[49]	110		15	21	74	0	69	41	110	0	DuraGen	6	0	2	0
38	Black, 2002[53]	167		2	1	24	140	140	27	167	0	FG	2		0	
39	Reddy et al., 2002[54]	26		5	7	14	0	19	7	26	0	FG	0		0	
40	Hodges et al., 1999[55]	20		0	0	20	0	0	20	20	0	FSP (TachoComb)	1		0	
41	Shaffrey et al., 1990[56]	21		2	0	2	17	4	17	21	0	FG	2		0	
	Total	2193	349	124	173	1286	959	1243	1299	2416	126		175	48	44	23

FG, fibrin glue; FSP, fibrin sealant patch; PGA, polyglycolic acid.

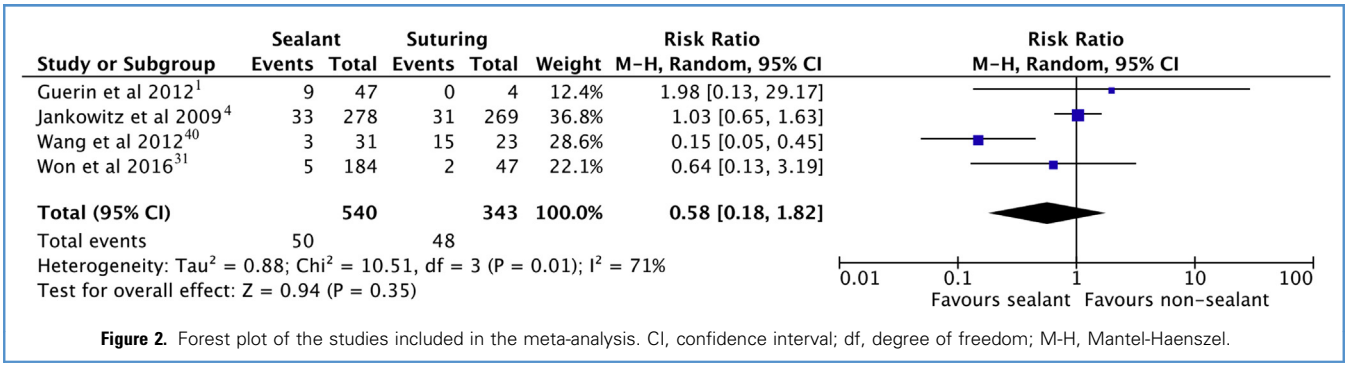

Figure 2. Forest plot of the studies included in the meta-analysis. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

endoscopic and minimally invasive surgery, a lower rate of CSF leakage was observed compared with an open approach.

Fibrin glue sealants, not approved for dural sealing, were the most commonly used sealants in case series as well as comparative studies. Three of the 4 comparative studies included in the meta-analysis used fibrin glue sealant for dural closure and showed no reduction of CSF leakage. Jankowitz et al.[4] evaluated the effect of fibrin glue on the prevention of CSF leakage after incidental durotomy in spine surgery. No reduction of postoperative CSF leakage was seen with the use of fibrin glue sealant. These investigators contradicted the possibility of selection bias, whereby theoretically only the difficult durotomies are repaired with fibrin glue, because they reviewed all operative notes and found no correlation between the length and complexity of the dural tear and use of fibrin glue. They concluded that the prophylactic use of fibrin glue sealants should be avoided when primary repair is deemed adequate. Guerin et al.[1] investigated the management of incidental dural tears after spine surgery. Fibrin glue was used, either with or without sutures, and a few patients were treated with primary suturing. There is a high possibility that selection bias is present in this study, because some incidental durotomies could not be sutured and only fibrin glue was applied. The investigators stress the necessity of primary suture closure, if possible, of unintended durotomies. Won et al.[31] reviewed the effect of fibrin glue sealant on postoperative CSF leakage after primary intradural spinal cord tumor surgery. Extra treatment with fibrin glue of the sutured dura did not lead to less postoperative CSF leakage. The investigators therefore concluded that the use of fibrin sealants might not be necessary with primary spinal intradural tumor surgery. Extensive in vitro studies on the dural sealing properties of fibrin glue sealants[60,61] have been performed that showed mean burst pressures <12 mm Hg. Resisting high burst pressures is essential in spine surgery, because the intraspinal pressure in an erect person is approximately 30 mm Hg and can increase up to 45 mm Hg during coughing.[62] This factor could suggest why fibrin sealants are not effective in clinical studies.

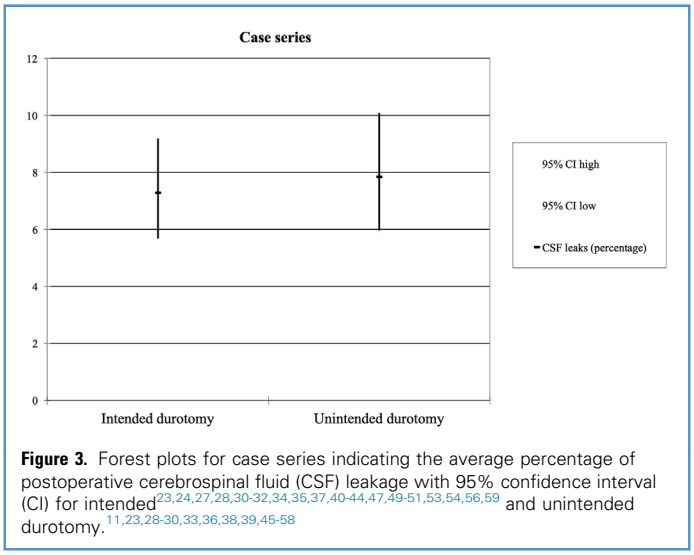

Figure 3. Forest plots for case series indicating the average percentage of postoperative cerebrospinal fluid (CSF) leakage with 95% confidence interval (CI) for intended[23,24,27,28,30-32,34,35,37,40-44,47,49-51,53,54,56,59] and unintended durotomy.[11,23,28-30,33,36,38,39,45-58]

Wang et al.[40] investigated the use of medical glue, composed of cyanoacrylates, for dural sealing after intradural spinal tumor surgery. These investigators concluded that using the sandwich method, in which the dura is closed with interlocking sutures and covered with 2 layers of medical glue separated by gelatin sponge, led to less CSF leakage compared with closure with interlocking sutures and gelatin sponge only. However, these substances are not approved for dural sealing and although no short-term complications were noted in this study, it has been reported[63] that internal application of cyanoacrylates might inhibit collagen remodeling and thus wound healing.

Secondary analysis for location and indication of surgery was not possible, because it was not reported consistently with CSF leakage. However, we identified a lower rate of CSF leakage in endoscopic or minimally

invasive surgery compared with open surgery. This result is most likely caused by a combination of less soft tissue disruption, decreased dead space, and selection bias in endoscopic spine surgery.[25,64]

The current study has several limitations. First, there was a lack of prospective controlled studies assessing the effectiveness of sealants in spine surgery. Two prospective randomized clinical trials were excluded because they included Chiari cases; however, these studies also did not show better outcome with the use of a sealant.[19,20] Second, most studies were retrospective and the use of sealant depended on the discretion of the surgeon in studies with a control group. Therefore, selection bias was inevitable. Third, there was a high variety of indications for sealant use, varying from pinhole dural defects to complex dural defects. The closure technique was also profoundly different; for example, some cases did not receive suture closure at all. Fourth, there was a wide variety of sealants and application methods, with or without substitutes or grafts. Most of the sealants were fibrin sealants, but medical adhesives and polyethylene glycol sealants were also used. Moreover, some surgeons paid extra attention to eliminating dead space with sealants and/or substitutes.[40] The diagnosis of CSF leakage was made by clinical examination or by magnetic resonance imaging. In the studies with clinical examination, there could be an underestimation of CSF leakage because pseudomeningoceles could not be detected.

In this study, no sealant used in the included articles showed clear superiority in terms of preventing postoperative CSF leakage. Although some articles reported no postoperative CSF leakage rates for a sealant, other comparable studies failed to note this same effect. Therefore, the heterogeneity of the meta-analysis was very high ($I^2 = 71\%$).

Given the continuing high number of CSF leaks and its associated complications with high economic and patient burden, there is a strong need for a dural sealant applicable for spinal use. Spinal dura is flexible and has to endure high pressures, and therefore, sealants have to be developed that can maintain their sealing properties in these conditions.[62,65] Special care should also be given for a no-swell formula, because spinal cord and nerve compression have been described with use of some sealants.[66-68]

CONCLUSIONS

This systematic review shows that currently available sealants do not reduce the rate of CSF leakage after spine surgery. However, high-quality studies of dural sealant use in spinal surgery are warranted. In endoscopic and minimally invasive surgery, the rate of CSF leakage is significantly lower than in open surgery regardless of sealant use.

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APPENDIX 1

SEARCH STRATEGY SYNTAX (JANUARY 9, 2019)

PubMed

((Cerebrospinal Fluid Leak[Mesh] OR dural tear*[tw] OR durotom*[tw] OR durectom*[tw] OR dural repair[tw] OR duraplast*[tw] OR csffistul*[tw] OR cerebrospinal fistul*[tw] OR pseudomening*[tw] OR intradural[tw] OR extradural[tw]) AND ("Adhesives"[Mesh] OR "Fibrin Tissue Adhesive"[Mesh] OR "Polyethylene Glycols"[Mesh] OR "Autografts"[Mesh] OR "Allografts"[Mesh] OR substitute[tw] OR sealant*[tw] OR glue*[tw] OR fibrin*[tw] OR hydrogel[tw] OR collagen[tw])).

Embase

(('dura mater'/exp OR 'dura mater':ab,ti OR 'dura':ab,ti OR 'dural':ab,ti OR 'dural and tear':ab,ti OR 'liquorrhea':ab,ti OR 'durectomy':ab,ti OR 'dural and repair':ab,ti OR 'pseudomeningocele':ab,ti OR 'cerebrospinal fluid fistula':ab,ti OR 'spine surgery':ab,ti) AND ('sealant':ab,ti OR 'tissue adhesive':ab,ti OR 'hydrogel':ab,ti OR 'macrogol derivative':ab,ti OR 'fibrin glue':ab,ti OR 'glue':ab,ti OR 'autograft':ab,ti OR 'allograft':ab,ti))