Effectiveness of Dural Sealants in Prevention of Cerebrospinal Fluid Leakage After Craniotomy: A Systematic Review

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Key words
- Cerebrospinal fluid leakage
- Cranial surgery
- Dura mater
- Dural sealant

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
PEG: Polyethylene glycol
RCT: Randomized controlled trial
RR: Risk ratio

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OBJECTIVE: **Cerebrospinal fluid (CSF) leakage is one of the most challenging complications in neurosurgery. We sought to evaluate the efficacy of dural sealants in preventing CSF leakage after cranial surgery.**

METHODS: **A literature search was performed in the PubMed, Embase, and Cochrane databases. The inclusion criteria were defined to include articles describing regular cranial procedures combined with the use of any dural sealant reporting CSF leakage. The primary outcome was CSF leakage (pseudomeningocele formation or incisional CSF leakage), secondary outcomes were pseudomeningocele formation, incisional CSF leakage, and surgical-site infection.**

RESULTS: **Twenty articles were included. Ten of these were comparative studies (sealant vs. no sealant) including 3 randomized controlled trials. In the 20 articles, a total of 3682 surgical procedures were reported. The number of CSF leakages in general did not differ between the sealant group (8.2%) and control group (8.4%), risk ratio (RR) 0.84 (0.50–1.42), I^2 = 56%. Exclusion of non-randomized controlled trials did not alter the results. Meta-analyses for secondary outcomes showed no difference between number of incisional CSF leakage, RR 0.30 (0.05–1.59), I^2 = 38%. Also, no difference was found in the pseudomeningocele formation, RR 1.50 (0.43–5.17), I^2 = 0%. Surgical-site infection was seen less in the sealant group (1.0%) compared with the control group (5.6%), RR 0.25 (0.13–0.48), I^2 = 0%.**

CONCLUSIONS: **This systematic review showed that dural sealants did not reduce the number of CSF leaks in general, the number of incisional CSF leaks alone, or the number of pseudomeningocele formations alone. However, dural sealants reduced the risk of surgical-site infection.**

INTRODUCTION

Cerebrospinal fluid (CSF) leakage is one of the most challenging complications in neurosurgery. It is associated with delayed wound healing, meningitis, subcutaneous graft-bone or epidural infections, and pneumocephalus. These complications often lead to prolonged hospitalization, reoperation, and associated increased health care costs.[1-4] The incidence of CSF leakage may depend on the location and indication of surgery, as well as the size of the craniotomy and dural openings. Also, patient-related factors play a role, such as immune status, age, or medical history. Generally, CSF leakage in cranial surgery is reported in a wide range from 4% to 32%.[5,6]

Dural closure seems a critical step in neurosurgical procedures to avoid CSF leakage.[3] "Watertight" dural closure is an important adage within neurosurgery, although this is subject to debate.[7] Perfect watertight closure is a difficult task due to the biomechanical characteristics of the dura mater, where even a single needle piercing creates a pinhole that could cause leakage. In addition, dura mater tends to be fragile and shrinks due to dehydration during a prolonged operative procedure.

Commercially available dural sealants aim to reduce CSF leakage risk by augmenting the dural closure. Most currently available sealants were primarily developed as hemostatic agents.[8] The same biochemical qualities (e.g., tissue adhesion, barrier function, absorption over time) that make these products suitable for hemostatic purposes enable their potential dural sealing function. Over the years, many in vitro, animal, and clinical studies have been conducted to study the effect of sealants on CSF leakage in cranial and spinal surgery.

In general, there are 2 types of sealants: the synthetic absorbable sealant containing polyethylene glycol (PEG)-based polymers and the biological absorbable sealant containing allogenic or autogenic fibrogen in combination with (allogenic) thrombin. Both types are available in liquid forms, as well as in patches. The aim of this systematic review is to evaluate the efficacy of dural sealants in preventing CSF leakage after cranial surgery.

METHODS

This systematic review was conducted according to the protocol of the Preferred

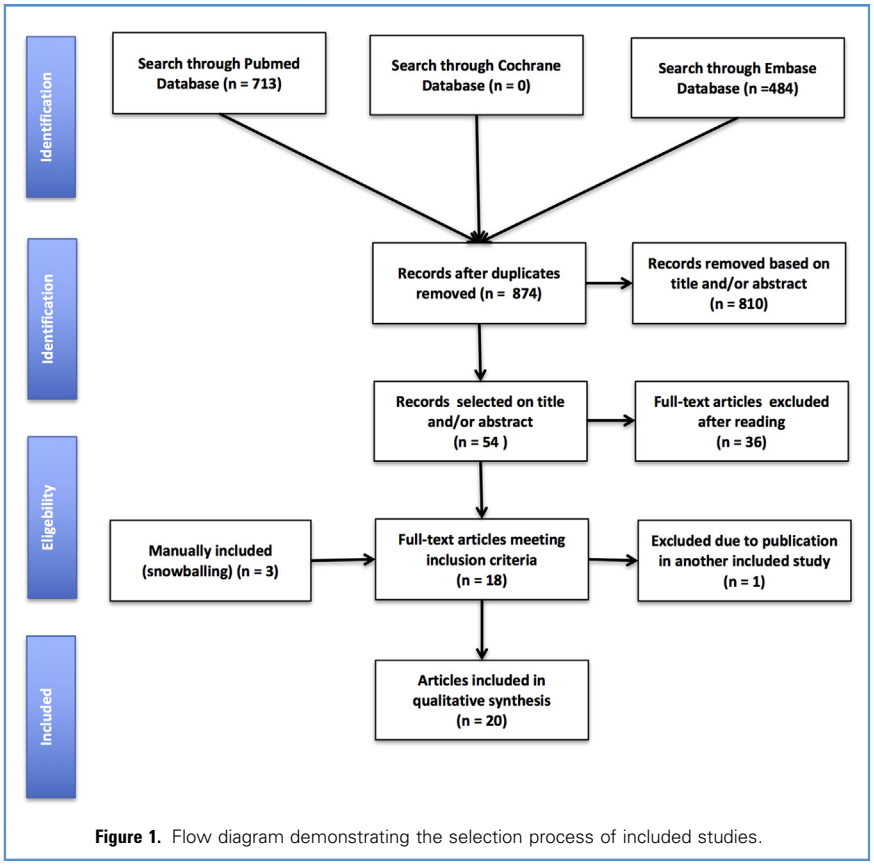

Figure 1. Flow diagram demonstrating the selection process of included studies.

Reporting Items for Systematic Reviews and Meta-Analysis.[9,10] Approval of the local ethical committee was not necessary for this literature review. Our search syntax is demonstrated in **Appendix A** and **B**. This search was performed in the PubMed, Embase, and Cochrane databases on September 26, 2017. All clinical articles in the English, Dutch, German, French, and Spanish language were selected for screening. No restrictions in terms of publication date were applied.

Study Selection

Two authors (A.K. and S.H.) independently selected the relevant publications based on the title and abstract. Subsequently, the full texts of the potentially relevant publications were screened for eligibility. Studies investigating dural substitutes in combination with sealants also were included. However, we included only studies investigating substitutes if they also reported a matched nonsubstitute control group since there are a wide variety of substitutes available (autograft, allograft, xenograft).

Studies were included when the rate of CSF leakage could be extracted from the data. Studies comparing 2 different sealants also were included and analyzed together since we were interested in the results of sealants in general. Also, case series were included. These series were analyzed separately. Laboratory studies, animal studies, cadaveric studies, pediatric studies, patients with confirmed hydrocephalus, and case reports were excluded. The 2 authors identified the articles that met the eligibility criteria. The final inclusion of articles was based on reading the full article. If disagreement regarding inclusion occurred, an agreement was reached by discussion between the 2 authors (A.K and S.H). Finally, the reference lists of the included articles were screened through "snowballing" for additional publications to include.

Outcome Definition

Primary outcome was CSF leakage of any origin. Secondary outcomes were incisional leakage, pseudomeningocele formation, and surgical-site infection. Incisional leakage was defined as CSF leakage through the skin, and pseudomeningocele formation was defined as subcutaneous or epidural collection of CSF determined by physical examination or imaging. Surgical-site infection was classified according to World Health Organization criteria for surgical-site infection, which is defined as infection that occurs after surgery in the part of the body where the surgery took place. Surgical-site infections can sometimes be superficial infections involving the skin only. Other surgical-site infections are more serious and can involve tissues under the skin, organs, or implanted material.[11]

Data Extraction

The following data were extracted from the included articles: year of publication, study design, type of patient selection (consecutively or after per-operative CSF leakage), location of procedure (infratentorial, supratentorial, or combined), indication for surgery (tumor, vascular, or other), number of patients included, brand of sealant, use of substitutes in the sealant group and control group if available, definition of leakage, rate of CSF leakage in general, rate of incisional CSF leakage, rate of pseudomeningocele formation, treatment of CSF leakage, and adverse events. CSF leakage was the primary outcome. Incisional leakage, pseudomeningocele formation, and surgical-site infection were secondary outcomes. Risk of bias assessment was done by authors' judgements for all randomized controlled trials (RCTs) and observational case-control studies according the Grading of Recommendations Assessment, Development, and Evaluation guidelines about methodologic quality.[12] The risk ratio (RR) with 95% confidence interval is used for outcome. The heterogeneity between studies is shown via the I^2 test.

RESULTS

Included Studies

On September 26, 2017, our search yielded 874 results after excluding duplicates. Of these reports, 20 clinical articles were included (**Figure 1**). One study, which met the inclusion criteria, was excluded

Table 1. Characteristics of the Included Studies

		Patient Selection,	Location of Prodecure			Indication		
Study	Study Design	Description	Supratentorial	Infratentorial	Combined	Tumor	Vascular	No Tumor or Vascular
Hutter et al., 2014[6]	RCT	Consecutive	184	45		164	31	34
Green et al., in press[4]	RCT	Per-operative spontaneous or after Valsalva CSF leakage	108	31		108	27	4
Osbun et al., 2012[15]	RCT	Per-operative spontaneous or after Valsalva CSF leakage	86	151		114	80	43
Ha et al., 2016[19]	Retrospective follow-up	Consecutive	301	62		166	172	22
Giovanni et al., 2014[3]	Retrospective follow-up	Consecutive	276	NA		187	76	13
Nishimura et al., 2012[22]	Retrospective follow-up	Consecutive	50	NA		0	50	0
Weinstein et al., 2010[21]	Retrospective and Prospective follow-up	ND	56	57	3	57	33	26
Litvack et al., 2009[17]	Retrospective follow-up	Consecutive	325	150		224	152	99
Kassam et al., 2003[18]	Retrospective follow-up	ND	200	53		70	173	10
Yoshimoto et al., 1997[24]	Prospective follow-up	Consecutive	183	NA		0	183	0
Tew et al., 2017[16]	Prospective follow-up	Per-operative spontaneous or after Valsalva CSF leakage	ND	ND		ND	ND	ND
Graziano et al., 2015[23]	Prospective follow-up	Consecutive	55	16		52	19	0
Schiariti et al., 2014[26]	Retrospective follow-up	Consecutive	NA	152		ND	ND	ND
Della Puppa et al., 2010[27]	Retrospective follow-up	Preoperative defined "high-risk" patients	10	2		10	1	1
Than et al., 2008[28]	Prospective and Retrospective follow-up	Consecutive	NA	200		111	ND	89
Cosgrove et al., 2007[29]	Prospective follow-up	Per-operative spontaneous or after Valsalva CSF leakage	58	53		127	99	50
Boogaarts et al., 2005[30]	Prospective follow-up	Per-operative spontaneous or after Valsalva CSF leakage	23	18		ND	ND	ND
Kumar et al., 2003[5]	Prospective follow-up	Per-operative spontaneous or after Valsalva CSF leakage	114	51		100	22	43
Sawamura et al., 1999[25]	Retrospective follow-up	Judgment of the neurosurgeon	295	NA		ND	ND	ND
Shaffrey et al., 1990[20]	Retrospective follow-up	Per-operative spontaneous or after Valsalva CSF leakage	ND	ND		ND	ND	ND
Total			2324	1041	3	1490	1118	434

RCT, randomized controlled trial; CSF, cerebrospinal fluid; NA, not applicable; ND, not descibed.

because the results were reported in another included study.[13]

One systematic review was identified, which included 2 RCTs comparing dural closure with a PEG hydrogel with conventional dural closure without a sealant in both cranial and spinal surgery.[14] The RCT assessing CSF leakage in cranial surgery of this review was included.[15] One study was an RCT comparing 2 different sealants. This study is included as a prospective cohort study taken both sealant groups together.[16] Three articles were manually selected by "snowballing."[17-19] One study was not found with our search strategy because this study compared different dural substitutes.[17] However, data about CSF

Table 2. Use of Sealants and CSF Leakages

Study	Number of Patients		Name of Sealant(s)	Definition CSF Leakage	CSF Leakage		Incisional Leakage		Pseudomeningocele	
	Sealant	Control	Brand		Sealant	Control	Sealant	Control	Sealant	Control
Hutter et al., 2014[6]	113	116	Tachosil*	Incisional or pseudomeningocele	11	20	Unclear	Unclear	Unclear	Unclear
Green et al., in press[4]	89	50	Evicel†	Incisional	2	1	2	1	0	0
Osbun et al., 2012[15]	120	117	DuraSeal‡	Incisional or pseudomeningocele	1	2	ND	ND	ND	ND
Ha et al., 2016[19]	117	246	Duraform§	Unclear	6	31	ND	ND	ND	ND
Giovanni et al., 2014[3]	184	92	Tisseel,‖ Tutopatchdural†† + sealant	Incisional	7	2	0	0	7	2
Nishimura et al., 2012[22]	24	26	DuraSeal‡	Incisional	2	2	0	0	2	2
Weinstein et al., 2010[21]	66	50	DuraSeal‡	Unclear	5	3	ND	ND	ND	ND
Litvack et al., 2009[17]	155	320	DuraSeal,‡ Tisseel‖	Incisional or pseudomeningocele	18	14	ND	ND	ND	ND
Kassam et al., 2003[18]	72	181	Tisseel‖	Incisional	0	10	0	10	0	0
Yoshimoto et al., 1997[24]	138	45	Bolheal and Fibroplast¶	Unclear	36	19	ND	ND	ND	ND
Tew et al., 2017[16]	231	—	Adherus,# Duraseal‡	Incisional	17	NA	2	NA	15	NA
Graziano et al., 2015[23]	71	—	Vivostat**	Unclear	3	NA	3	NA	ND	NA
Schiariti et al., 2014[26]	152	—	Tisseupatchdural,†† DuraSeal‡	Incisional	7	NA	2	NA	5	NA
Della Puppa et al., 2010[27]	12	—	Tissuepatchdural††	Incisional	0	NA	0	NA	0	NA
Than et al., 2008[28]	200	—	DuraSeal,‡ fibrin glue; fibrinogen with Trombostat	Incisional	25	NA	12	NA	13	NA
Cosgrove et al., 2007[29]	111	—	DuraSeal‡	Incisional	5	NA	2	NA	3	NA
Boogaarts et al., 2005[30]	41	—	DuraSeal‡	Incisional	1	NA	0	NA	1	NA
Kumar et al., 2003[5]	165	—	Bioglue‡‡	Incisional	0	NA	0	NA	0	NA
Sawamura et al., 1999[25]	295	—	Bolheal¶	Incisional	7	NA	0	NA	7	NA
Shaffrey et al., 1990[20]	83	—	Fibrin glue; fibrinogen with Trombostat	Unclear	4	NA	ND	NA	ND	NA

CSF, cerebrospinal fluid; ND, not described; NA, not applicable.
*Baxter, Deerfield, Illinois, USA.
†Ethicon US, LLC, Somerville, New Jersey, USA.
‡Covidien, Inc., Bedford, Massachusetts, USA.
§Codman & Shurtleff, Inc., Raynham, Massachusetts, USA.
‖Baxter, Deerfield, Illinois, USA.
¶Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan.
#HyperBranch Medical Technology, Durham, North Carolina, USA.
**Vivostat A/S, Alleroed, Denmark.
††Tissuemed Ltd, Leeds, United Kingdom.
‡‡Cryolife, Inc., Kennesaw, Georgia, USA.

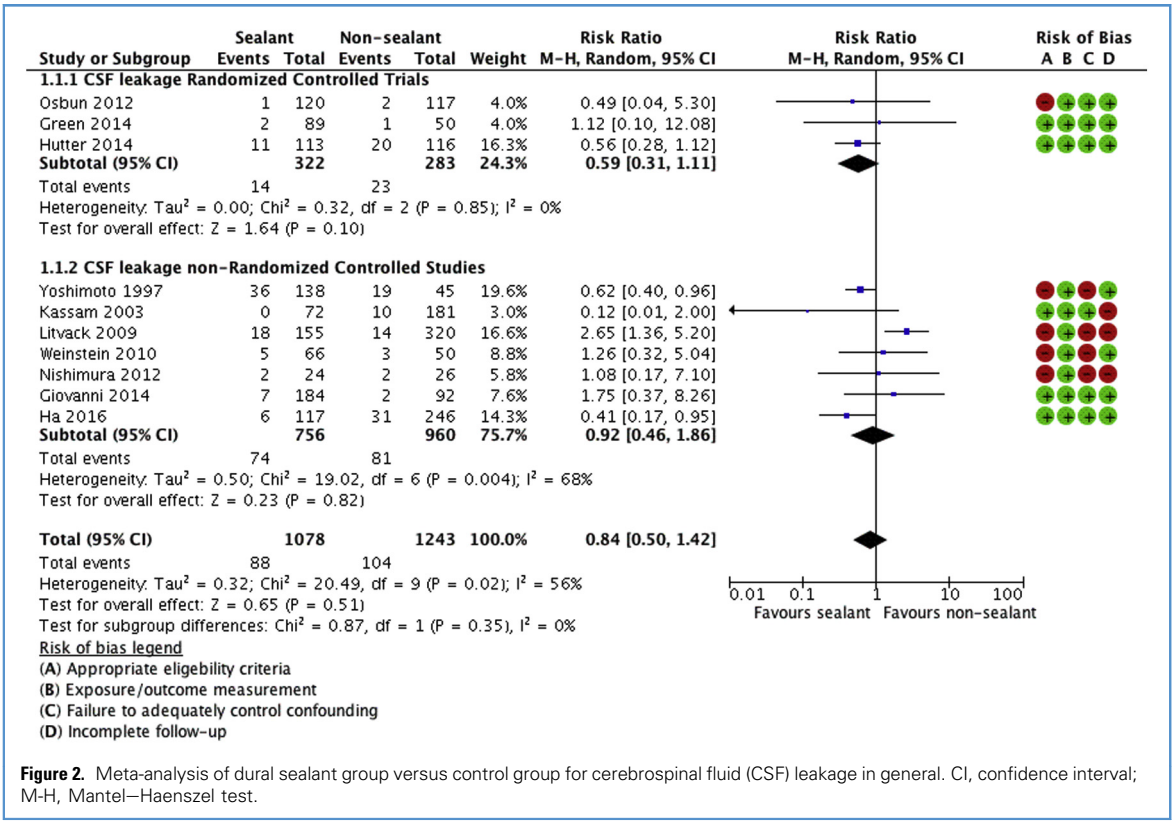

Figure 2. Meta-analysis of dural sealant group versus control group for cerebrospinal fluid (CSF) leakage in general. CI, confidence interval; M-H, Mantel–Haenszel test.

leakage with and without dural sealant could be extracted and therefore it was included in this review. A second study did not meet our search criteria because the term "dura" was not mentioned in the abstract or title and not included as MeSH term.[18] The last study was not indexed in Medline or Embase indexed.[4,6,15-17,18,20-24] Two studies that also included patients younger than the age of 18 were included. However, the average ages were far older than 18 years without a large standard deviation.[18,25]

Ultimately 20 articles were included in this systematic review (Table 1).[3-6,15-30] Three studies were RCTs, 6 studies were prospective cohort studies, 9 studies were retrospective cohort studies, and 2 were prospective cohort studies with a retrospective control group. Ten studies were comparative, including 3 RCTs. Three studies compared 2 different types of sealants without a reference aim with no sealant.[16,26,28] Both sealant groups were taken together in the analyses. In 2 studies, 2 different sealants were investigated and compared with a control arm.[3,17]

In all studies, watertight closure was pursued regardless of the use of dural substitutes. A total of 3682 surgical procedures was reported. In 1490 procedures, an intracranial tumor was the indication of surgery; in 1118 procedures, it was a vascular disease. In 434 procedures, another indication was described. In 640 procedures, the indication was not described. A total of 2324 supratentorial, 1041 infratentorial, and 3 combined supra- and infratentorial procedures were included. In 314 cases the exact location of surgery was unknown.

No consistent definition of CSF leakage was used in the included papers. Twelve of 20 studies defined CSF leakage as incisional leakage. In 3 studies CSF leakage was defined as a combination of incisional leakage and pseudomeningocele formation. In 5 of 20 studies the definition was unclear (Table 2).

Sealant Techniques and Substitutes

Sealants used in the included studies were either liquid glue or dry patch sealants. In 9 studies, patients were included consecutively and received a dural sealant. In 7 studies patients received dural sealants only when CSF leakage occurred after primary closure (spontaneous or after Valsalva maneuver). In most studies, dural substitutes were additionally used to help close the dural defect. A wide variety of substitutes was used in combination with sealants. In 3 studies the use of sealants was compared with primary closure. In 10 studies, there was no control group. Dural sealants were used in a total of 2439 patients. In the control group, the number of patients was 1243. Most studies did not report how many patients received dural substitutes and its indication generally was at the judgment of the surgeon. The numbers of patients, the types of sealant, and the usage of dural substitute are shown in Table 2.

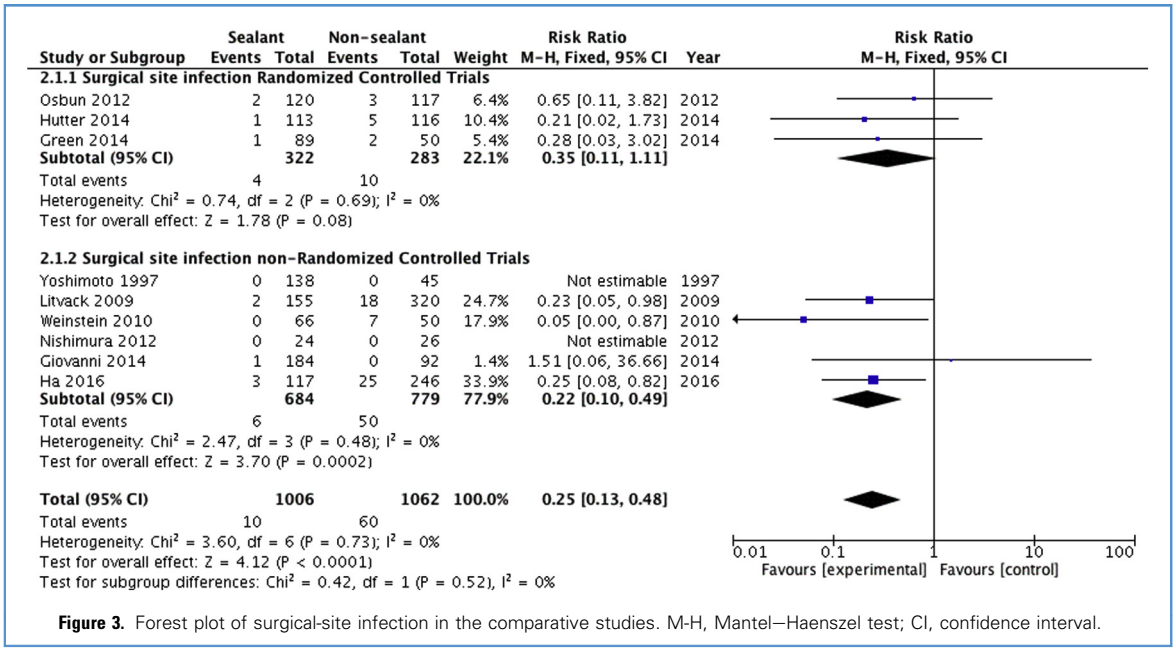

Figure 3. Forest plot of surgical-site infection in the comparative studies. M-H, Mantel–Haenszel test; CI, confidence interval.

Meta-Analysis

Ten comparative studies were included in this analysis with in total 2321 patients. The risk of bias of these studies is shown in Figure 2. The risk of bias in the RCTs was low. The other studies had a greater risk of bias, especially for appropriate eligibility and adequately control of confounding. The number of CSF leakages in general did not differ between the sealant group (88 of 1078 patients, 8.2%) and control group (104 of 1243, 8.4%), RR 0.84 (0.50–1.42), I^2 = 56% (Figure 2). Exclusion of non-RCTs did not alter the results. Meta-analyses for secondary outcomes showed no difference between number of incisional CSF leakage in both groups, RR 0.30 (0.05–1.59), I^2 = 38%. Also, no difference was found in the pseudomeningocele formation in both groups RR 1.50 (0.43–5.17), I^2 = 0%. Surgical-site infection was less seen in the sealant group, RR 0.25 (0.13–0.48), I^2 = 0% (Figure 3). The number of patients with surgical-site infection in the sealant group was 10 of 1006 (1.0%) versus 60 of 1062 (5.6%) in the control group.

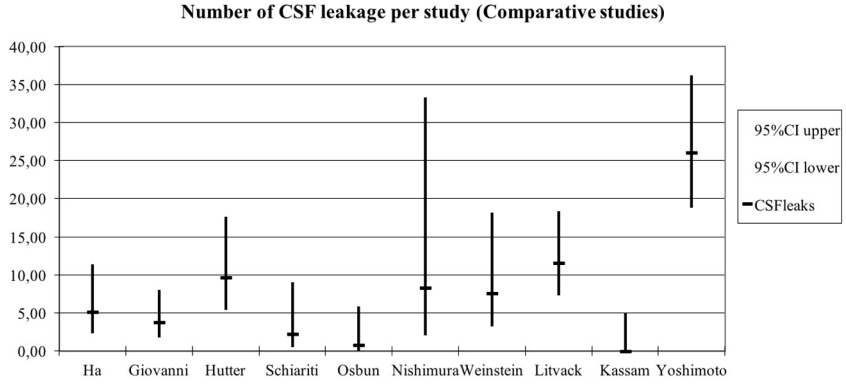

Figure 4. Forest plot of cerebrospinal fluid (CSF) leakage in the comparative studies. CI, confidence interval.

Total Sealant Group Analysis

Ten studies of the included 20 studies were case series. In the case series, the number of CSF leakage, including pseudomeningocele formation, occurred in 69 of 1361 (5.1%) patients, whereas the CSF leakage in the sealant group of the comparative studies was 88 of 1078 (8.2%) patients. Since the number of CSF leakages differed between the comparative cohort studies and case series (RR 0.56 [0.40–0.79]), the studies were analyzed separately. Therefore, also no statistical analyses were done comparing the total sealant group with the control group. A forest plot of the number of leakages per study was made. Figure 4 shows a forest plot of CSF leakage according to study for case series and Figure 5 does so for comparative studies. Both forest plots show a high heterogeneity (I^2 > 80%). There was no difference between liquid sealants and patch sealant for CSF leakage. There was also no difference between fibrin sealants and PEG sealants.

No adverse events associated with the application of dural sealant were observed in any of the studies. We attempted to analyze whether location of surgery (supra vs. infratentorial), indication of surgery, sex, or/and age could influence CSF

leakage rate. However, these variables were not recorded in relation with CSF leakage in the articles.

DISCUSSION

In this systematic review, we identified 3 RCTs, 7 comparative cohort series, and 10 case series. The percentage of CSF leakage in general (both incisional and pseudomeningocele) was not different in the sealant group compared with the control group, neither in the RCTs nor comparative cohort studies. We also did not find differences in incisional leakage or pseudomeningocele formation. Liquid sealants did not differ from sealant patches regarding CSF leakage. Neither difference was found when divided sealants in fibrin glue and PEG sealants. In contrast, surgical-site infection was less seen in the sealant group. A suggestion for less-frequent infections is that optimal sealing of the intradural compartment after surgery avoids bacterial migration to the meningeal layer or intradural compartment.[6] Another reason might be that sealants fill the layer between the dura and bone flap. This reduces the volume of air and fluid collection necessary for (aerobic) bacterial growth.

None of the included studies reported adverse events in patients who received a dural sealant. Specific adverse events related to the use of dural sealants were systematically reported only sporadically. We found 5 cases who reported adverse events, which included 2 allergic reactions,[31,32] 1 case of cervicomedullary compression,[33] 1 case of suspected air embolism with the use of a spray device,[34] and 1 case of obstruction of epidural drain.[35] However, in these case reports, the direct relationship between sealant use and adverse event was never confirmed objectively.

The current systematic review has some limitations. First, the number of randomized controlled trials was limited to 3 studies. Even in 2 of these studies, in more than the one half of the control patients, rescue therapy was used in the control group with other types of sealants or grafts to obtain watertight closure.[4,15] We contacted the authors of these 2 studies to find out which patients of the control group had CSF leakage, since we aimed to exclude the patients with rescue therapy.

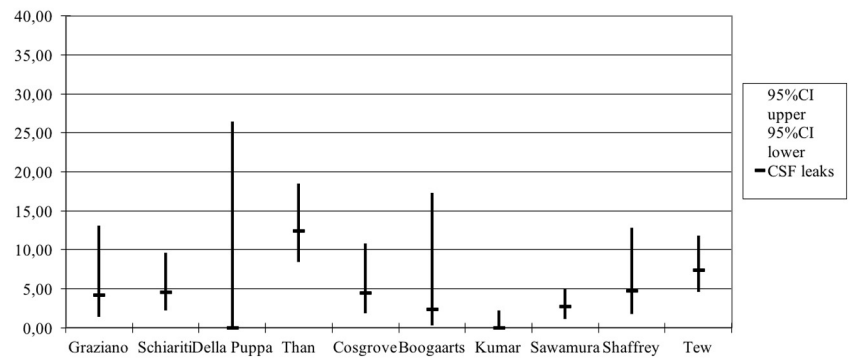

Figure 5. Forest plot of cerebrospinal fluid (CSF) leakage in the case series studies. CI, confidence interval.

However, they did not record in which patient (rescue therapy or not) CSF leakage occurred. Therefore, we did not exclude any of these patients. Second, the comparative cohort studies had a relatively high risk of bias based on the Grading of Recommendations Assessment, Development, and Evaluation guidelines and showed a moderate heterogeneity ($I^2 = 68\%$). This heterogeneity was even larger in the total sealant group analyses. Both the heterogeneity of the sealant group in the comparative cohort study as well as in the case series was $I^2 > 80\%$. This heterogeneity may be caused by bias, especially selection bias in the case series. The number of CSF leakages in the comparative cohort studies was greater than that in the case series, pointing toward more bias in the case series.

A third limitation was the fact that different sealants were used between studies. All dural sealants were pooled because we were interested in the overall effect of dural sealants in preventing CSF leakage. However, different sealants may have different characteristics and therefore different outcomes. The fourth limitation of this study is that we could not differentiate between supra- and infratentorial craniotomies because the studies did not show the number of CSF leakage for each location. It is known that infratentorial craniotomies are evidently associated with greater CSF rates (odds ratio 5.84) regardless the use of dural sealants.[36,37] Therefore, the ratio of supra- and infratentorial craniotomy may influence the number of CSF leakages. Ideally, these 2 locations should be analyzed separately. The final limitation was the wide use and variety of dural substitutes that may have influenced the outcome. Primary closure is not always possible, which makes the use of a dural substitute inevitable. In more than one half of the included studies, dural substitutes were used if needed. To overcome this bias, we included only comparative studies with use of substitutes in both groups under the assumption that the ratio in use of substitutes was comparable.

This review showed that studies of greater methodologic quality are warranted. Ideally, these would be RCTs comparing the use of sealant with no sealants with exclusion of other type of intervention like grafts. The development of a dedicated and effective sealant is thereby still recommended. Until an RCT has shown clear benefit of such a future sealant, focus should be on watertight closure with sutures whether or not in combination with autologous material like fat, muscle of fascia. An ideal future sealant should have the following properties: it should be easy to prepare, sterilize, and handle. It should be capable of rapidly producing a true watertight seal and maintain the seal for the time it takes the dura to regenerate. Moreover, it should be shaped for intracranial use, be flexible, yet durable; chemically inert, nontoxic, and capable of producing minimal or no inflammatory reaction. Ideally it should be cost-effective and should induce neither adhesions nor infections.[30,38]

CONCLUSIONS

This systematic review showed that dural sealants did not reduce the number of CSF leakages, both incisional CSF leakage and pseudomeningocele formation. Dural sealants reduced the risk of surgical-site infection.

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APPENDIX A

SEPTEMBER 26, 2017, MEDLINE

((((("Dura Mater"[Mesh:noexp]) OR dura [Title/Abstract] OR dural[Title/Abstract]) OR cranial surgery[Title/Abstract])) AND ((((((((((("Fibrin Tissue Adhesive"[Mesh]) OR glue*[Title/Abstract]) OR seal*[Title/Abstract]) OR Duraseal[Title/Abstract]) OR Adherus[Title/Abstract]) OR Tachosil [Title/Abstract]) OR TissuePatchDural[Title/Abstract]) OR Duragen[Title/Abstract]) OR Hemopatch[Title/Abstract]) OR Tissucol[Title/Abstract]) OR Tissudura[Title/Abstract]) OR Duraform[Title/Abstract])

APPENDIX B

SEPTEMBER 26, 2017, EMBASE

'dura mater'/exp OR 'dura mater':ab,ti OR 'dura':ab,ti OR 'dural':ab,ti OR 'cranial surgery':ab,ti AND ('tissue adhesive'/exp OR 'glue*':ab,ti OR 'seal*':ab,ti OR 'duraseal*':ab,ti OR 'adherus*':ab,ti OR 'tachosil*':ab,ti OR 'tissuepatchdural':ab,ti OR 'duragen':ab,ti OR 'hemopatch':ab,ti OR 'tissucol':ab,ti OR 'tissudura':ab,ti OR 'duraform':ab,ti) AND [embase]/lim NOT [medline]/lim