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Risk factors for postoperative CSF leakage after elective craniotomy and the efficacy of fleece-bound tissue sealing against dural suturing alone: a randomized controlled trial

Clinical article

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Object. Cerebrospinal fluid leakage is an immanent risk of cranial surgery with dural opening. Recognizing the risk factors for this complication and improving the technique of dural closure may reduce the associated morbidity and its surgical burden. The aim of this paper was to investigate whether the addition of TachoSil on top of the dural suture reduces postoperative CSF leakage compared with dural suturing alone and to assess the frequency and risk factors for dural leakage and potentially related complications after elective craniotomy.

Methods. The authors conducted a prospective, randomized, double-blinded single-center trial in patients undergoing elective craniotomy with dural opening. They compared their standard dural closure by running suture alone (with the use of a dural patch if needed) to the same closure with the addition of TachoSil on top of the suture. The primary end point was the incidence of CSF leakage, defined as CSF collection or any open CSF fistula within 30 days. Secondary end points were the incidence of infection, surgical revision, and length of stay in the intensive care unit (ICU) or intermediate care (IMC) unit. The site of craniotomy, a history of diabetes mellitus, a diagnosis of meningioma, the intraoperative need of a suturable dural substitute, and blood parameters were assessed as potential risk factors for CSF leakage.

Results. The authors enrolled 241 patients, of whom 229 were included in the analysis. Cerebrospinal fluid leakage, mostly self-limiting subgaleal collections, occurred in 13.5% of patients. Invasive treatment was performed in 8 patients (3.5%) (subgaleal puncture in 6, lumbar drainage in 1, and surgical revision in 1 patient). Diabetes mellitus, a higher preoperative level of C-reactive protein (CRP), and the intraoperative need for a dural patch were positively associated with the occurrence of the primary end point (p = 0.014, 0.01, and 0.049, respectively). Cerebrospinal fluid leakage (9.7% vs 17.2%, OR 0.53 [95% CI 0.23–1.15], p = 0.108) and infection (OR 0.18 [95% CI 0.01–1.18], p = 0.077) occurred less frequently in the study group than in the control group. TachoSil significantly reduced the probability of staying in the IMC unit for 1 day or longer (OR 0.53 [95% CI 0.27–0.99], p = 0.048). Postoperative epidural hematoma and empyema occurred in the control group but not in the study group.

Conclusions. Dural leakage after elective craniotomy/durotomy occurs more frequently in association with diabetes mellitus, elevated preoperative CRP levels, and the intraoperative need of a dural patch. This randomized controlled trial showed no statistically significant reduction of postoperative CSF leakage and surgical site infections upon addition of TachoSil on the dural suture, but there was a significant reduction in the length of stay in the IMC unit. Dural augmentation with TachoSil was safe and not related to adverse events. Clinical trial registration no. NCT00999999 (http://www.ClinicalTrials.gov).
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Key Words • **cerebrospinal fluid leakage** • **dural sealant** • **surgical quality** • **surgical site infection** • **surgical technique**

While performing cranial surgery, it is of utmost importance to achieve a tight and reliable closure of the dura mater. Cerebrospinal fluid leakage leads to increased morbidity, prolongation of hospital stay, surgical revision, and enhanced costs as well as possible surgical revisions.[15,19] The incidence of CSF leakage is reported to depend on the location of surgery (for example, more likely in the posterior fossa)[15] but may also depend on the size of the craniotomy and dural opening or on patient-related factors such as immune status, age, or the underlying pathological process. Dural closure is usually achieved with an intended watertight suture and the addition of hemostyptic or hemostatic agents such as fibrin glue or cellulose collections.[2,4,12] Several studies have described the use of sealants as useful in avoiding CSF leakage in supratentorial,[4,20,28,33] infratentorial,[15] transsphenoidal,[5,10,21] skull base,[23] and spinal[18,20] procedures. According to the literature, CSF complications vary from 4% in transsphenoidal procedures to 32% in posterior fos-

Abbreviations used in this paper: CRP = C-reactive protein; GLM = generalized linear model; ICU = intensive care unit; IMC = intermediate care.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

sa procedures.[20] After sealant application, the percentages of CSF leaks vary from 0.9%[20] to 10.7%.[15] Dural sealants have been described to be safe when used in combination with autologous dural substitute material.[8,19,35]

However, there is no consensus on a standardization of dural closure, and only a few clinical studies assessed outcomes of various closure methods in a randomized and controlled manner. Kim and Wright[19] and Osbun et al.[25] prospectively assessed the addition of polyethylene glycol hydrogel sealant (DuraSeal, Covidien) in spinal and cranial surgery for dural closure in comparison with standard techniques that included various dural augmentation methods according to the surgeon's choice. However, suturing alone was only used in a small percentage of the control cases. The preparation of the dural augmentation with DuraSeal was faster in the study group, but the frequency of clinically overt postoperative CSF leaks remained similarly low in both groups. In the spinal study, intraoperative water tightness was significantly better with DuraSeal.[19] In recent years, TachoSil (Takeda Pharma), a ready-to-use, fixed combination of a collagen sponge coated with a dry layer of the biologically active human coagulation factors fibrinogen and thrombin, was introduced into the market and was used mainly as a hemostatic agent in visceral, thoracic, gynecological, and urological surgery.[9,13,16,17,29–31] In liver surgery, TachoSil was superior to argon-beam laser hemostasis in a controlled parallel group trial.[13] Several animal studies could prove a beneficial effect of TachoSil in hemostasis compared with other sealant techniques.[11,16] Other studies analyzed the capacity of TachoSil to seal visceral organ anastomoses (such as small bowel or esophageal anastomosis) compared with standard techniques and indicated a safe and additional sealing effect of the agent.[24,26,34] However, a recent animal study showed marked inflammatory reaction around the anastomized region covered with TachoSil and a higher postanastomotic complication rate, resulting in an unfavorable recommendation for this agent.[7] Indeed, foreign body reactions to hemostatic agents such as Oxycel, SPONGOSTAN (Ethicon), and TachoSil are also described in the clinical literature as rare events.[1] Another animal study involving TachoSil could identify enhanced fibroblastic activity at the sealed site but failed to identify an inflammatory reaction.[34] Clinical feasibility studies in aortic[22] and bowel[27] anastomosis in 12 patients could not relate an adverse event to the application of TachoSil.

In convexity and posterior fossa neurosurgery, TachoSil is used in an individualized and unstandardized way based on the surgeon's preference. A recently published laboratory study found a significant positive effect on water tightness of diverse dural sealants including TachoSil over suturing alone, whereas the use of running versus interrupted sutures had no differentiating effect.[6] The authors found a superiority of TachoSil over Tissucol (Baxter) or BioGlue (CryoLife). An equal effect of TachoSil was found in a retrospective study of transsphenoidal surgery, where it completely eliminated postoperative CSF leaks compared with just fat packing of the dural defect.[32]

The occurrence of CSF leaks is especially critical in posterior fossa surgery. Arlt et al.[2] found no difference when retrospectively comparing dural closure with a "sandwich technique" (TachoSil applied epi- and subdurally) versus epidural TachoSil alone. However, despite application of TachoSil, the occurrence of CSF leaks remained high in both groups (7.3% and 10%).

We hypothesize that addition of TachoSil on top of the dural suture reduces postoperative CSF leakage in elective craniotomies. To ascertain this hypothesis, we conducted a single-center, prospective, double-blinded randomized trial to compare dural closure with or without application of TachoSil.

Methods

Patients and Inclusion/Exclusion Criteria

The protocol of this clinical trial (clinical trial no. NCT00999999 http://www.ClinicalTrials.gov) was designed according to International Conference of Harmonisation-Good Clinical Practice standards, approved by the institutional ethical committee (University Hospital Basel) and was registered as a Phase IV trial at Swissmedic, the Swiss national drug association. All patients scheduled for elective craniotomy with dural opening at the University Hospital Basel (an urban 700-bed tertiary care teaching center) were asked to participate. Preoperative inclusion criteria were scheduling for elective cranial surgery involving a dural incision and age 18 years or older. Exclusion criteria were the presence of infection, trauma, previous surgery at the same site, pregnancy, concomitant participation in another study, and hypersensitivity to the study product. In addition to these preoperative exclusion criteria, the surgeon was allowed to exclude patients intraoperatively if he or she could not perform a dural suture with or without a suturable dural substitute.

Study Procedures and Randomization

After craniotomy, the dura mater was closed with a continuous, resorbable synthetic monofilament copolymer of glycolid and caprolactone 5-0 suture to obtain a watertight closure. In case of an obvious dural defect with CSF leakage impeding primary suturing, a dural substitute (autologous [for example, galea or muscle] or a xenograft of bovine pericardium [TutoPatch, RTI Biologics or Neuropatch, B. Braun]) was sutured to the dura mater, aiming at a watertight closure. No other additives were allowed on top of the dural suture.

After study enrollment, a computerized tool (www.sakk.ch/sinatras) randomized the patient to either control or study treatment. Importantly, the allocation of treatment was only visible to dedicated operating room staff and was communicated to the surgeon directly after watertight dural closure. In the study treatment group, strips of TachoSil were applied on top of the entire dural suture and, if applicable, on top of the suture or borders of the dural substitute. TachoSil covered at least 1 cm of the dura or dural substitute on both sides of the suture. After closure of the dura, the bone flap was replaced and fixed in place using CranioFix titanium clamps (B. Braun AG) or MatrixNeuro titanium screws/plates (Synthes AG). The skin was closed in 2 layers (galeal/subcutaneous and cutaneous stitches). The use of epicranial drainage (Jackson

Pratt) to avoid hemorrhagic complications was allowed according to the surgeon's preference and recorded (refer to the study flowchart in Fig. 1). Length of dural suture, size of craniotomy, location, the type of pathological process, and intraoperative complications were recorded using an online database directly after surgery.

Postoperatively, patients were routinely placed overnight in the intensive care unit (ICU) and over the 2nd night in the intermediate care (IMC) unit.

Follow-Up Procedures and Blinding

Each patient was clinically assessed on postoperative Days 5–7 and Days 28–32 for occurrence of any CSF collection and possible interventions due to CSF collections or active CSF leakage. Patients and outcome assessors (study nurse and trial physician) were blinded to treatment allocation, and the written operation report did not reveal the means of dural closure. We developed a grading scheme to assess CSF collection (Table 1). Each CSF collection was measured clinically and with ultrasonography or other imaging modalities, and stepwise interventions were undertaken to relieve major CSF collection according to the grading scheme. Briefly, subgaleal collections were classified clinically and by ultrasound as minor, moderate, or major according to their size (diameter ≤ or > 5 cm), volume (≤ or > 20 ml), and tension, whereby major collections were typically treated invasively, by puncture, and/or lumbar drainage, or revision. Surgical site infection or meningitis and respective treatment, any surgical complication requiring revision, wound healing quality, and length of stay in the ICU or IMC were recorded.

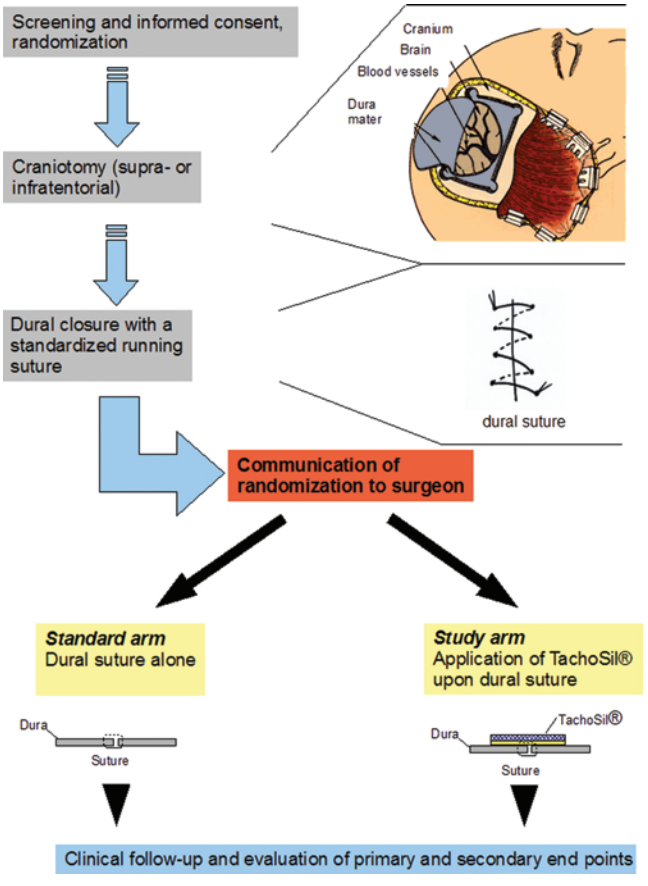

Fig. 1. Trial flowchart.

Statistical Analysis

Study data on enrollment, eligibility, procedures in the operating room, and follow-up visits as well as adverse event and termination data were stored in an online database using electronic case report forms. The original power analysis is described in detail in the trial protocol. The primary stratification parameter was the presence of a supra- or infratentorial process; in the per-protocol data set, 80.6% (n = 184) of patients had surgery for supratentorial lesions, and 19.4% (n = 45) of patients had surgery for infratentorial lesions.

After enrollment of 226 patients, a blinded sample size reassessment was performed, which resulted in the additional recruitment of 17 patients. A sample size of 243 patients was estimated to ensure a power of at least 90% (at a significance level of 5%) to detect a difference in CSF leakage rates of 15% (absolute risk difference), assuming an overall CSF leakage rate of 14.3% and a dropout rate of 7%.

Demographics as well as baseline and surgery characteristics were summarized by trial arm. Data are presented as frequencies and percentages for categorical variables and as mean ± SD and median for continuous variables (Table 2). We report outcome analyses performed per protocol, although we had intended an intention-to-treat analysis as primary analysis and a per-protocol analysis as sensitivity analysis. This decision was due to the fact that 2 patients with CSF leakage randomized to control actually received TachoSil (Fig. 2). We analyzed these patients as treated (TachoSil) in the per-protocol analysis, which is more conservative in this case. In contrast, these patients had to be analyzed as control patients in the intention-to-treat analysis, which was overly favorable for the TachoSil treatment. The primary end point was the occurrence of any CSF leakage within 1 month from surgery, that is, at least at 1 follow-up visit. We used a generalized linear model (GLM) with binomial error distribution to test the effect of TachoSil versus control (as the received treatment) on the probability of CSF leakage. The model included the factor TachoSil (TachoSil vs control) together with the factor infratentorial (infratentorial vs supratentorial). The latter was used to stratify in the randomization process.

As a sensitivity analysis, we fitted a model that additionally included all important baseline variables and thereby adjusts the treatment effect for potential bias due to outcomes not missing completely at random.[14] In addition to the overall odds ratio of TachoSil versus control, ORs (and 95% CIs) were calculated for various patient subgroups, that is, infra- versus supratentorial craniotomy, presence or absence of diabetes mellitus, meningioma versus other diagnoses, need versus no need of dural patch used, and use or no use of subgaleal drainage. The interaction between TachoSil and each subgroup factor was tested for potential differences between subgroups.

The following secondary end points were analyzed: incidence of infection (meningitis or subcutaneous infec-

TABLE 1: CSF collection grading scheme

Grade	Clinical Assessment	Ultrasound Assessment	Consequence
minor	palpable collection <5 cm in diameter, no tension	20 ml	watch & wait
moderate	palpable collection >5 cm in diameter, no tension	>20 ml	watch & wait, possibly pressure dressing
major	any collection >5 cm in diameter, tension	>20 ml	local puncture, lumbar drainage, revision

tion) within 1 month; incidence of a complication requiring an intervention (revision) within 1 month; 1 day or longer in the ICU; 1 day or longer in the IMC; and the maximum size of the CSF collection at the first or second follow-up (minor, moderate, or major).

The binary secondary end points were analyzed with a GLM as the primary end point. The maximum size of the CSF collection (if present) was analyzed by a 3 × 2 contingency table and a chi-square test of independence.

In an additional exploratory analysis we tested for an association of the craniotomy diameter with the incidence of a CSF leakage in a GLM including the craniotomy diameter and TachoSil (vs control) and the interaction between the two. Likewise, we tested for an association of length of the primary dural suture with the incidence of a CSF leakage. The information on the length of dural suture was missing for 20 patients.

Furthermore, we tested for an association of patch surface (patch length × patch width) with the incidence of a CSF leakage in the patient subgroup receiving a dural patch. The model also included TachoSil and the interaction between patch size and TachoSil.

Results

A total of 241 patients were randomized for this trial, and 229 patients (116 in the control group and 113 in the TachoSil group) were included in the per-protocol analysis (Fig. 2). The study recruitment period was between October 2009 and August 2012, with the last follow-up visit in October 2012. The trial was completed as planned according to the protocol and after an amendment (blinded sample size reassessment), which increased the sample size from 226 to 241. Demographics and baseline and surgery characteristics are listed in Table 2.

Risk Factors for CSF Leakage

As shown in Table 3, the baseline variables diabetes mellitus (OR 5.56 [95% CI 1.57–19.11], p = 0.014) and elevated preoperative C-reactive protein (CRP) values (OR 1.04 [95% CI 1.01–1.08], p = 0.010) and the intraoperative need for a suturable dural patch for dural closure (OR 2.43 [95% CI 0.96–6.35], p = 0.049) were significantly associated with an increased risk of CSF leakage.

Effect of TachoSil on CSF Leakage

Cerebrospinal fluid leakage occurred less often in the TachoSil arm (11 [9.7%] of 113 patients) than in the control arm (20 [17.2%] of 116 patients), corresponding to a 7.6% absolute risk difference. However, the difference was not statistically significant (OR 0.53 [95% CI 0.23–1.15], p = 0.108; Fig. 3A). The sensitivity analysis with baseline adjustment pointed at a slightly stronger but still nonsignificant effect of TachoSil (OR 0.45 [95% CI 0.18–1.06], p = 0.095; Table 3 and Fig. 3A). The site of craniotomy (infratentorial vs supratentorial) had no effect on the occurrence of CSF leakage.

In a subgroup analysis, we investigated whether certain factors might modify the effect of TachoSil on the probability of CSF leakage. No significant difference in the effect of TachoSil between subgroups was found for any of the subgroup factors investigated (Fig. 3B and Table 4). In patients with diabetes mellitus, TachoSil may have a more favorable effect (that is, more strongly reduce the risk of CSF leakage) compared with standard treatment, than in patients without diabetes (TachoSil × diabetes interaction, p = 0.107; Table 4).

Effect of TachoSil on Secondary End Points

Five patients in the control group, compared with only 1 in the study group, suffered from postoperative wound infection or meningitis, suggesting that the application of TachoSil may be beneficial (OR 0.18 [95% CI 0.01–1.18], p = 0.077; Fig. 4 and Table 5). One patient in the control group had a fulminant epidural empyema requiring urgent surgical decompression and debridement on the 14th postoperative day, whereas patients with meningitis could be treated conservatively with intravenous antibiotics.

TachoSil also significantly reduced the probability of a patient to stay 1 day or longer in the IMC unit (OR 0.53 [95% CI 0.27–0.99], p = 0.048; Fig. 3B and Table 5), but no significant reduction for staying 1 day or longer in the ICU.

Nine patients (5 in the control group, 4 in the TachoSil group) needed an intervention due to CSF leakage, which included simple pressure dressing, lumbar puncture/lumbar drainage, or reopening of the wound and pressure dressing, and 12 patients had revision surgery after the first operation not related to CSF leakage (Table 6). However, the frequency of CSF leakage–related interventions and of surgical revisions did not significantly differ between the 2 groups (Fig. 4 and Table 6). Two patients, both in the control group, had postoperative epidural hematomas requiring urgent evacuation.

Postoperative Mortality

Four patients (2 in the control group, 2 in the TachoSil group) died during the follow-up period; 1 patient suffered from therapy-resistant status epilepticus after resection of a cranial metastasis, 1 patient died of systemic oncological disease after metastasis resection, 1 patient had severe liver disease and cerebral vasospasm due to aneurysmal subarachnoid hemorrhage, and 1 patient died

TABLE 2: Patient characteristics for the 2 trial arms*

Variable	Value† Control (n = 116)	Value† TachoSil (n = 113)	p Value
mean age in yrs	56.4 ± 14.6	56.8 ± 15.1	0.61
sex			0.21
M	50 (43.1)	59 (52.2)	
F	66 (56.9)	54 (47.8)	
diagnosis			0.76
intrinsic tumor	68 (58.6)	75 (66.4)	
metastasis	12 (10.3)	9 (8)	
vascular	16 (13.8)	15 (13.3)	
epilepsy	12 (10.3)	9 (8)	
other	8 (6.9)	5 (4.4)	
allergies			1
yes	24 (20.7)	24 (21.2)	
no	92 (79.3)	89 (78.8)	
diabetes			1
yes	8 (6.9)	8 (7.1)	
no	108 (93.1)	105 (92.9)	
meningioma			0.77
yes	19 (15.5)	15 (13.3)	
no	98 (84.5)	98 (86.7)	
localization			0.5
frontal	48 (41.4)	40 (35.4)	
parietal	17 (14.7)	20 (17.7)	
temporal	27 (23.3)	19 (16.8)	
occipital	6 (5.2)	7 (6.2)	
posterior fossa	16 (13.8)	23 (20.4)	
brainstem	2 (1.7)	4 (3.5)	
side			0.65
bilat	7 (6)	4 (3.5)	
lt	57 (49.1)	55 (48.7)	
rt	52 (49.1)	55 (47.8)	
primary dural suture			0.26
yes	80 (69)	69 (61.1)	
no	36 (31)	44 (38.9)	
use of a patch			1
yes	55 (47.4)	53 (46.9)	
no	61 (52.6)	60 (53.1)	
type of patch			0.03
galea	12 (21.8)	5 (9.3)	
muscle	14 (25.4)	7 (13)	
Neuropatch	8 (14.6)	18 (33.3)	
Tutopatch	21 (38.2)	22 (40.7)	
other	0 (0)	2 (3.7)	
all	55 (100)	54 (100)	
intraop complications			0.97
yes	3 (2.6)	4 (3.5)	
no	113 (97.4)	109 (96.5)	
mean craniotomy diameter (cm)	7 ± 2.7	6.6 ± 2.5	0.21
mean length of primary dural suture (cm)	9.5 ± 3.5	9.1 ± 3	0.47
dexamethasone			0.79
yes	27 (23.3)	29 (25.7)	
no	89 (76.7)	84 (74.3)	
infratentorial			0.35
yes	19 (16.4)	25 (22.1)	
no	97 (83.6)	88 (77.9)	
wound drain			0.2
yes	43 (37.1)	32 (28.3)	
no	73 (62.9)	81 (71.7)	

* Baseline hemoglobin, leukocyte count, thrombocyte count, L-aspartate aminotransferase, L-alanine aminotransferase, γ-glutamyltransferase, and international normalized ratio were also assessed and showed no significant differences between the treatment arms.
† Values are number of patients (%) unless noted otherwise.

of acute myocardial infarction on the 8th postoperative day. From these patients, at least 1 follow-up visit was recorded, and the patients were therefore not excluded. The patient who died of therapy-resistant status epilepticus was randomized to and received TachoSil. His status epilepticus was, however, already present before surgery and did not change upon metastasis resection.

Influence of Dural Patch, Length of Dural Suture, or Craniotomy Size (Additional Exploratory Analyses)

In a large number of patients (55 in the control group and 53 in the TachoSil group), the dura could not be closed primarily, but a dural substitute was interposed according to the surgeon's choice. The size of the substitute varied between 1 × 1 cm and 12 × 14 cm. In addition, we recorded the length of the dural running suture and the craniotomy diameter. Overall, the variation of these parameters was not associated with a higher risk of CSF collections, and addition of TachoSil on a longer suture, a larger patch, or craniotomy did not significantly influence the occurrence of CSF collections (Table 7).

Discussion

The results of our randomized controlled trial indicate that the addition of TachoSil on top of the dural suture after elective cranial surgery did not significantly reduce the occurrence of CSF leakage within 30 days after surgery. Although the reduction of CSF leakage upon TachoSil application was not statistically significant, we simultaneously observed a lower frequency of serious complications, such as postoperative epidural hematoma and epidural empyema, in the TachoSil group, and a lower rate of postoperative infections. Altogether, these obser-

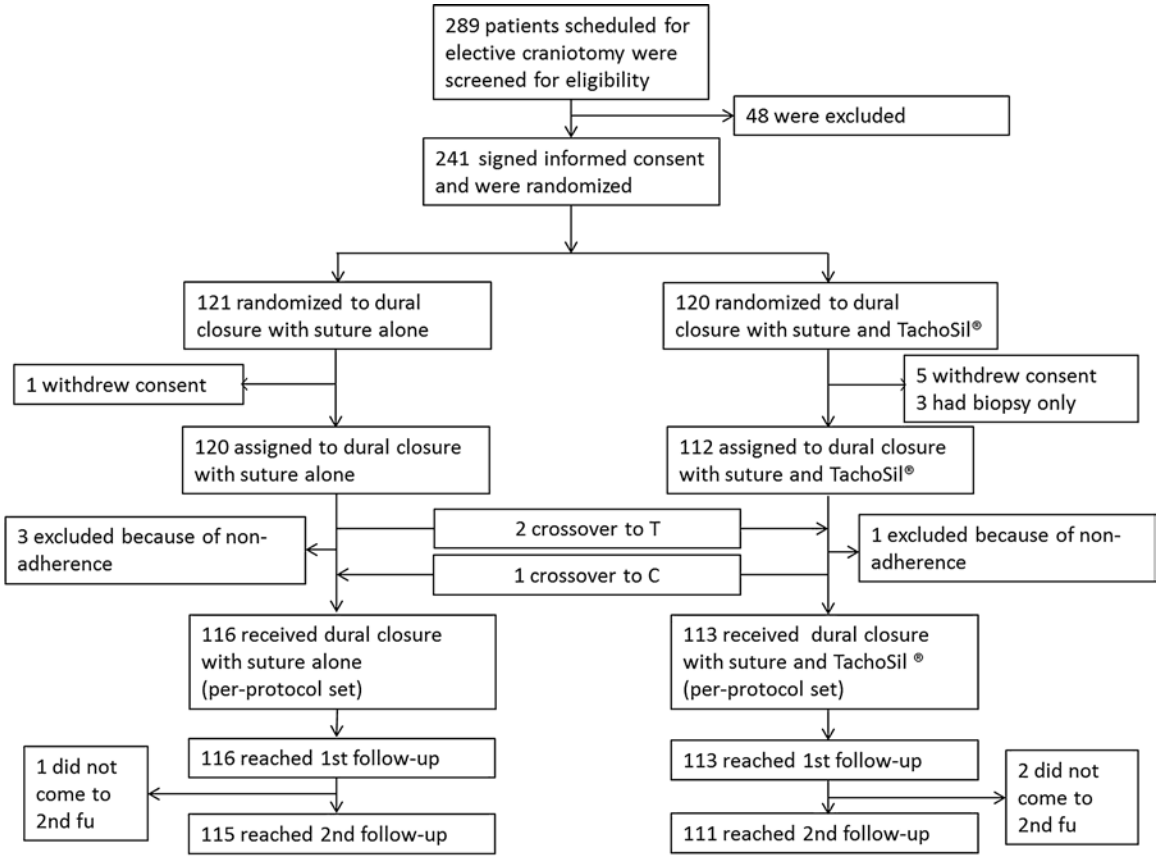

Fig. 2. Trial overview. All patients who had at least 1 follow-up visit (n = 229) were included in the per-protocol analysis. C = control; fu = follow-up; T = TachoSil.

TABLE 3: Per protocol and baseline-adjusted per-protocol analysis of the effect of TachoSil versus control on the primary end point "CSF leakage within 1 month" (i.e., ≥ 1 follow-up visit)*

Variable	Estimate	OR (95% CI)	p Value
per-protocol analysis			
infratentorial	−0.48	0.62 (0.17–1.71)	0.317
TachoSil received	−0.64	0.53 (0.23–1.15)	0.108
baseline-adjusted per-protocol analysis			
TachoSil received	−0.79	0.45 (0.18–1.06)	0.095
age	−0.01	0.99 (0.96–1.02)	0.997
male	0.29	1.33 (0.56–3.25)	0.185
diabetes mellitus	1.72	5.56 (1.57–19.11)	0.014
meningioma	−0.46	0.63 (0.15–inf)	0.916
CRP	0.04	1.04 (1.01–1.08)	0.01
use of a patch	0.89	2.43 (0.96–6.35)	0.049
craniotomy diameter	−0.04	0.97 (0.79–1.15)	0.709
dexamethasone	0.15	1.17 (0.42–2.98)	0.766
infratentorial	0.12	1.13 (0.04–34.85)	0.96
wound drain	−0.14	0.87 (0.32–2.27)	0.774

* The table shows the model estimates from the generalized linear model on the logit scale and as ORs with 95% CIs (as shown in Fig. 3A), as well as p values from likelihood-ratio chi-square tests. n = 229 patients. inf = infinity.

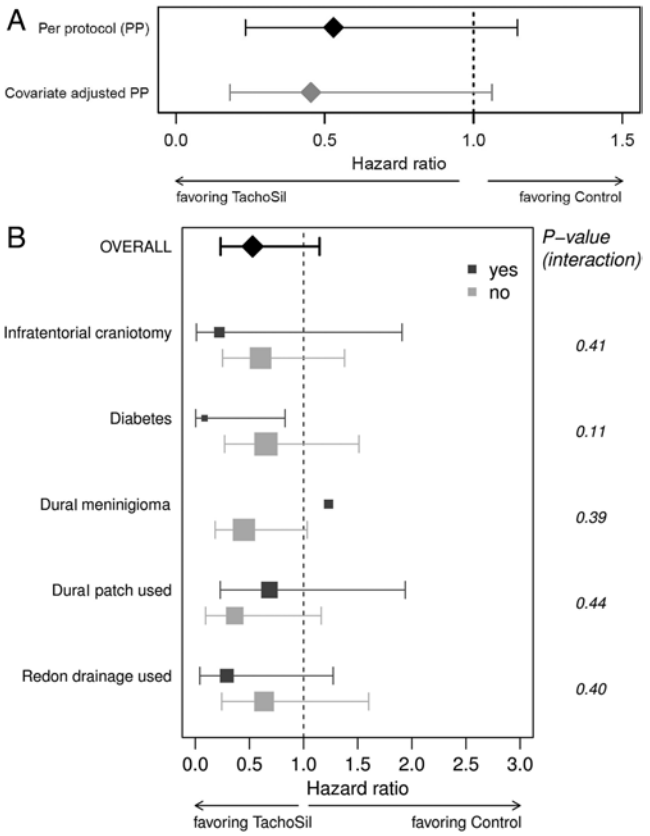

Fig. 3. **A:** Odds ratio estimates for TachoSil versus control for the primary end point occurrence of CSF leakage within 1 month after craniotomy, in the main analysis (OR 0.53 [95% CI 0.23–1.15], p = 0.108) and the covariate-adjusted sensitivity analysis (OR 0.45 [95% CI 0.18–1.06], p = 0.095). **B:** Odds ratio estimates (with 95% CIs) for TachoSil versus control for the primary end point occurrence of CSF leakage within 1 month after craniotomy, overall *(diamond)*, and in various subgroups *(squares)*. The size of the square represents the size of the subgroups. The p values are derived from likelihood-ratio chi-square tests for the interaction between treatment and subgroup. Overall, 16 patients had diabetes mellitus: 1 of 8 in the TachoSil group and 5 of 8 in the control group had CSF leakage. Thirty-three patients had a meningioma, of whom 2 with TachoSil and 2 with control had CSF leakage. These low numbers resulted in undefined CIs (not shown).

vations could be due to the application of TachoSil and to its sealing and hemostatic effect, but could as well be related to other circumstances. However, the addition of TachoSil might be indirectly responsible for the reduction

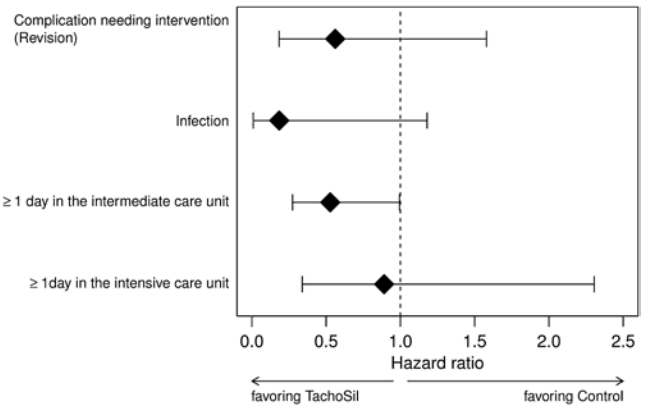

Fig. 4. Odds ratio estimates (with 95% CIs) for TachoSil versus control for the analysis of binary secondary end points.

of the length of stay in the neuro-IMC unit (p = 0.048) in patients in the study group. Interestingly, diabetic patients and patients with a preoperative elevated CRP value had higher CSF leakage rates.

A possible adverse event of the application of TachoSil might be an accompanying inflammatory reaction combined with overreactive scar tissue.[7] One patient in the TachoSil group suffered from therapy-resistant status epilepticus because of a cerebral metastasis. His status did not resolve after resection of the metastasis. We do not infer a causal relation between the application of TachoSil and the status epilepticus, although the occurrence of this complication cannot be ruled out in a longer follow-up period.

The number of reinterventions due to CSF leakage was equally low in both groups, with 1 major intervention (surgical wound revision) in the control group. Interestingly, we could not detect differences in CSF leakage rates in supratentorial versus infratentorial craniotomies with a similar, low leakage rate in both patient cohorts. This opposes current literature findings that stated a higher risk for CSF leakage in infratentorial craniotomies.[15] The reason for the low rate of CSF leakage after infratentorial craniotomies in our series is unclear. It may be due to the standard closure technique, aiming at a watertight closure with continuous microsuture with/without a patch in every case. Not all centers and authors, in fact, do advocate such a meticulous effort.[3]

An interesting finding of our study was the overall identification of factors associated with the risk of CSF

TABLE 4: Numbers of patients with the primary end point event (CSF leakage) in the TachoSil or control arm in various subgroups*

Variable	Variable Absent			Variable Present			
	TachoSil	Control	OR (95% CI)	TachoSil	Control	OR (95% CI)	p Value†
wound drainage	9	12	0.64 (0.24–1.60)	2	8	0.29 (0.04–1.27)	0.4
use of dural patch	4	10	0.36 (0.10–1.16)	7	10	0.68 (0.23–1.94)	0.439
meningioma	9	18	0.45 (0.18–1.03)	2	2	1.23 (NA)	0.386
diabetes mellitus	10	15	0.65 (0.27–1.51)	1	5	0.09 (0.00–0.83)	0.107
infratentorial craniotomy	10	17	0.60 (0.25–1.38)	1	3	0.22 (0.01–1.91)	0.411

* Values are number of patients unless stated otherwise. See Fig. 3B for the corresponding graphical display. NA = not applicable.
† Chi-square test.

TABLE 5: Primary and secondary end points (categorical variables)*

Variable	Control		TachoSil		Total	
	No. of Patients (%)	%∑	No. of Patients (%)	%∑	No. of Patients (%)	%∑
CSF leakage						
no	96 (82.8)	82.8	102 (90.3)	90.3	198 (86.5)	86.5
yes	20 (17.2)	100	11 (9.7)	100	31 (13.5)	100
total	116 (100)		113 (100)		229 (100)	
revision						
no	106 (91.4)	91.4	107 (94.7)	94.7	213 (93)	93
yes	10 (8.6)	100	6 (5.3)	100	16 (7)	100
total	116 (100)		113 (100)		229 (100)	
infection						
no	111 (95.7)	95.7	112 (99.1)	99.1	223 (97.4)	97.4
yes	5 (4.3)	100	1 (0.9)	100	6 (2.6)	100
total	116 (100)		113 (100)		229 (100)	
>1 day in IMC unit						
no	84 (72.4)	72.4	94 (83.2)	83.2	178 (77.7)	77.7
yes	32 (27.6)	100	19 (16.8)	100	51 (22.3)	100
total	116 (100)		113 (100)		229 (100)	
>1 day in ICU						
no	106 (91.4)	91.4	104 (92)	92	210 (91.7)	91.7
yes	10 (8.6)	100	9 (8)	100	19 (8.3)	100
total	116 (100)		113 (100)		229 (100)	
CSF collection size						
minor	14 (70)	75	5 (45.5)	45.5	19 (61.3)	64.5
moderate	5 (25)	100	6 (54.5)	100	11 (35.5)	100
major	1 (5)	5	0 (0)	0	1 (3.2)	3.2
total	20 (100)		11 (100)		31 (100)	

* %∑ = cumulative percentage.

leakage. The need for a dural patch to achieve dural closure was one of these factors. This finding is intuitive, since primary dural suture, whenever possible, is more likely to be watertight than a closure with a dural substitute. The strong association between CSF leakage and diabetes mellitus as well as high preoperative levels of CRP was more surprising and has so far not been identified in the current literature.

In retrospect, the main limitation of our study is probably the overestimation of the proportion of CSF leakage in our first power analysis. Our initial assumption was a reduction of the leakage rate by 15% (20% without TachoSil, 5% with TachoSil). In reality, we detected leakage rates of 17.2% versus 9.7%, resulting in a difference of only 7.6%. This led to a blinded reassessment and enlargement of the sample size to 241 patients (instead of 226 patients as recorded in the protocol). However, the study was probably underpowered to demonstrate a statistically significant difference for the primary outcome measure. Due to the single-center design and the limited financial resources, the study was not prolonged further.

Previous laboratory studies could show that supplementing dural suture with active hemostatic agents might be beneficial,[6] but these findings have not been translated into clinical practice yet. On a mechanistic level, it might be obvious that additional gluing of a never totally watertight suture would certainly reduce the occurrence of CSF leakage and related complications. On the other hand, one might argue that infections should occur more often when additional foreign material is introduced into a surgical site. An explanation for our observation of the opposite, that is, less frequent infections, might be that optimal sealing of the intradural compartment after surgery avoided bacterial migration through microlesions caused even by the dural suture itself. Thus, it remains speculative whether dural augmentation and protection of CSF outflow by dural sealing may prevent life-threatening postsurgical sequelae. In this context and to statistically confirm the observed risk reduction of 7.6% in the primary outcome measure when applying TachoSil, inclusion of more patients would be necessary.

Previous work by Grotenhuis[15] stated a vast cost implication of CSF leakage and proposed a standardized dural augmentation by DuraSeal, albeit in a retrospective single-center study. We can confirm in a prospective manner that application of a dural sealant in general is safe and not related to major adverse events and led to a nonsignificant reduction of postsurgical CSF leakage of 7.6%.

TABLE 6: Type of surgical complications, infections, and interventions in the 2 study groups

Variable	No. of Patients		
	Total	Control	TachoSil
complication			
epidural hematoma	2	2	0
subdural hematoma	1	0	1
parenchymal bleeding	1	1	0
epidural empyema	1	1	0
residual tumor	5	2	3
other	2		
infection			
epidural empyema	1	1	0
meningitis	4	4	1
type of intervention due to CSF collection			
pressure dressing	1	0	1
puncture & dressing	6	3	3
lumbar puncture	1	1	0
lumbar drainage	0		
wound revision	1	1	0

Conclusions

Our trial is the first prospective randomized study comparing dural closure in elective craniotomies with or without a sealing augmentation. The primary end point analysis showed a statistically nonsignificant reduction of postoperative CSF leakage within 1 month by a dural sealant. Its clinical use for dural augmentation was safe and not related to major adverse events. Furthermore, we could identify clinical risk factors predisposing for post-craniotomy CSF leakage: elevated CRP levels, diabetes mellitus, and usage of a dural patch.

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Disclosure

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TABLE 7: Additional analysis testing the association of the diameter of craniotomy, the length of the dural suture, or the surface of the dural patch with the primary end point (occurrence of incisional CSF leakage within 1 month), together with the effect of TachoSil versus control and the interaction between them*

Variable	Estimate	OR (95 % CI)	p Value†
per-protocol set (n = 229)			
TachoSil received	−0.61	0.54 (0.06–4.93)	0.095
craniotomy diameter	0	1.00 (0.82–1.19)	0.991
TachoSil received:craniotomy diameter	−0.01	0.99 (0.72–1.35)	0.965
part of per-protocol set (n = 209)			
TachoSil received	−0.3	0.74 (0.06–9.60)	0.082
suture length	0.1	1.11 (0.97–1.27)	0.119
TachoSil received:suture length	−0.04	0.96 (0.7–1.23)	0.764
part of per-protocol set (n = 110)			
TachoSil received	−0.1	0.91 (0.26–3.14)	0.606
dura patch area	0	1.00 (0.98–1.03)	0.968
TachoSil received:patch area	−0.01	0.99 (0.94–1.03)	0.623

* The colons indicate the interaction between the 2 variables.

† The p values are from likelihood-ratio chi-square tests.

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