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

择期开颅术后脑脊液漏的风险因素评估明胶海绵填塞与单独的硬脑膜缝合的对比研究：RCT

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摘要： *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.

目的：脑脊液漏是一个脑外科手术开放硬脑膜后常见的危险，识别脑脊液漏的危险因素、提高硬脑膜缝合技术可能会降低开放硬脑膜关联的并发症及手术风险。本研究评估了缝合硬脑膜时添加明胶海绵与单独的硬脑膜缝合相比是否可以降低术后脑脊液漏及开颅术后其他并发症的发生率。

摘要：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.

作者在择期行开硬脑膜的开颅手术的患者中进行了一项前瞻性、随机、双盲、单中心试验他们对比了只进行硬脑膜缝合（必要时使用硬脑膜补丁）的患者与同样方法行硬脑膜缝合但在缝合的顶部添加了明胶海绵的患者。主要观察指标是脑脊液漏的发生率，定义为30天内的脑脊液引流和任何的开放的脑脊液漏。

摘要：Methods

- 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.

主要观察指标是脑脊液漏的发生率，定义为30天内的脑脊液引流和任何的开放的脑脊液漏。次要观察指标：感染、在此手术<手术修正>的发生率及ICU住院时间和中期照护<即国内普通病房住院时间>。手术部位、糖尿病史、脑膜瘤的诊断、需要缝合硬脑膜、血液指标等作脑脊液漏发生的危险因素进行评估。

摘要：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).

实验共招募241名患者，纳入研究的有229人，26人发生脑脊液漏、占纳入研究总患者的13.5%且大多是自限性（局限性）帽状腱膜引流（8位患者为侵入性治疗占3.5%（6人帽状腱膜下穿刺、1人腰大池引流、1人手术修正）。

摘要：Results

- 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% CI0.23–1.15], 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.

糖尿病、术前高水平的CRP、术中需要补硬脑膜、与主要观察指标呈正相关(p分别=0.014,0.01,和0.049,)。脑脊液漏（9.7%VS17.2%，OR0.53，[95% CI 0.23–1.15], p = 0.108）和感染(OR 0.18 [95% CI 0.01–1.18], p = 0.077)的发生率实验组均低于对照组.

摘要：Results

- 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.

明胶海绵可以显著降低中期照护时间1天或者更长(OR 0.53 [95% CI 0.27–0.99], p = 0.048)。术后硬膜外血肿和积脓症仅在对照组发生发生。

摘要：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.

糖尿病、术前高CRP及术中需要补硬脑膜常常和择期开颅术后脑脊液漏的发生相关。

摘要：Conclusions

- 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.

本随机对照试验统计结果没有显示缝合硬脑膜时添加明胶海绵可以降低术后脑脊液漏和感染的发生率，但是中期照护时间明显减少。明胶海绵作为硬脑膜下填塞物是安全的无不良反应。

关键词Key Words

cerebrospinal fluid leakage •	脑脊液漏
dural sealant •	硬脑膜的密封剂
surgical quality •	手术质量
surgical site infection •	手术部位感染
surgical technique	手术技术

背景Backgrounds

- 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]

进行颅手术,硬脑膜的紧密、牢靠关闭是及其重要的。脑脊液漏导致并发症发病率增加、住院时间延长、二次手术发生及住院费用和手术费用的增加[15.19]脑脊液漏的发生率被报道与手术部位有关（例如：多发生在后窝）[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] 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.

也跟手术和硬脑膜切口大小、患者自身因素（如：免疫状态等）、病情进展等相关。硬脑膜的关闭通常采用密缝合完成，同时还会填塞止血的药剂，比如：纤维蛋白胶或者集合纤维素[2.4.12]。几项研究表明填塞可以有效避免幕上、[4.20.28.33]幕下[15]、经蝶骨的[5.10.21]、颅底[23]和椎管[18.20]脑脊液漏。

- According to the literature, CSF complications vary from 4% in transsphenoidal procedures to 32% in posterior fossa 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]

根据文献，脑脊液漏的发生随手术方式不同而不同，从蝶窦手术的4%到后颅窝手术的32%，[20]用填塞剂后脑脊液漏的发生率波动在0.9%[20]-10.7%[15]。有描述称硬脑膜下填塞物与自身硬脑膜代替材料联合使用是安全的[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 etal.[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.

然而，硬脑膜关闭没有一个一致的标准，只有少数的临床研究以随机对照的方式评估了不同种类的关闭方法。Kim和Wright[19]及Osbun等[25]，前瞻性评价了根据外科医生的选择在标准方式下聚氧乙烯水凝胶填塞与其他硬膜下填塞物效果。

- 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]

然而只有少数对照组为单独的硬膜缝合。膜密封法硬膜下填塞物的准备在实验组中更快，实验组和对照组临床明显术后脑脊液漏保持同样低的发生率。在脊髓的研究中，术中硬膜下水密封出奇的好。[19]近几年，明胶海绵作为一种随时可用的一层有生物活性的人凝血纤维、酶作为膜覆盖的胶原海绵放入市场主要用于内脏、胸腔、妇科及泌尿外科手术。[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 Tacho-Sil and a higher postanastomotic complication rate, resulting in an unfavorable recommendation for this agent.[7]

在肝脏手术中，明胶海绵止血要优于对照组中的氩激光止血。[13]一些动物实验证实明胶海绵止血的效果优于其他的止血方法。[11.16]另外一些研究表明明胶海绵在内脏器官吻合术（如：肠、食道等的吻合）中的止血能力优于常规标准手术方法，被证明是安全的医药填塞物。[24.26.34]然而，一项最近的动物研究显示在明胶海绵覆盖的缝合区域附近有显著的炎症反应和较高的吻合术后并发症发生率，因此不推荐使用此药剂。[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.

的确临床文献中很少有有关对氧化纤维素、可吸收明胶海绵和明胶海绵便宜反应的报道。[1]另外一个动物实验证实明胶海绵填塞区域成纤维细胞活跃但是没有发现炎症反应。[34]12例病人的大动脉[22]、肠[27]吻合的临床可行性研究没有叙述关于明胶海绵应用的一个不利事件。

- In convexity and posterior fossa neurosurgery, Tacho-Sil 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]

在神经外科中、后颅凹术中，明胶海绵的使用具有个人特色未标准化，基于外科医生的个人偏爱。一个最近发表的实验室研究发现包括明胶海绵在内的多种硬膜下填塞物有很好的水密封性，间断缝合效果亦是如此。[6]作者发现明胶海绵优于纤维蛋白胶（Baxter）和生物胶（CryoLife）。一项经蝶骨手术的回顾性研究发现明胶海绵有同样的效果，与单纯的脂肪填塞硬脑膜缺陷相比可以同样消除术后的脑脊液漏。[32]

- The occurrence of CSF leaks is especially critical in posterior fossa surgewhen 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.ry. Arlt et al.2 found no difference

脑脊液漏在后颅凹术后更易发生。Arlt等[2]回顾性分析发现使用“三明治法”（硬膜上下使用明胶海绵）比单独在硬脑膜上使用没有区别。然而尽管使用了明胶海绵两组中脑脊液漏的发生率均保持较高水平（7.3%和10%）

我们假定在硬脑膜缝合顶部添加明胶海绵可以减少术后脑脊液漏的发生。为了验证假设，我们进行了一项单中心、前瞻性、双盲随机对照实验来对比缝合硬脑膜时使用明胶海绵和不使用的效果。

方法 Methods：纳入、排除标准

- The protocol of this clinical trial 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.

本临床实验的协议根据Harmonisation-Good国际临床实验标准，由巴塞尔大学公共伦理委员会认可，在瑞士国家药品管理局、瑞士医药协会注册为第四阶段实验。巴塞尔大学附属医院（700张床位）的所有择期开颅手术患者均收到此实验邀请，均为择期手术且有必要切开硬脑膜，年龄18岁及以上。

- 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.

排除标准为实验前存在感染、外伤、相同手术区域手术史、怀孕、参与另一研究、对实验用品过敏者。除了这些术前排除标准，手术医生可以在术中剔除那些用或没用硬脑膜替代品缝合硬脑膜的患者。

方法 Methods：研究过程和随机化

- 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.

颅骨切开后，用5-0号连续的可吸收的人造酯聚合线结扎硬脊膜达到水密封效果。在硬脑膜有缺陷且伴有脑脊液漏阻碍主要缝合的例子中，一种硬脑膜替代品（字体的[例如：突出的硬脑膜或肌肉]或者牛心包移植物[TutoPatch，RTI Biologics or Neuropatch，B.Braun]将缝合到硬脑膜上，以达到密封效果。在硬脑膜缝合顶部不添加任何其他的添加剂/填塞物。

- 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).

登记后，用电脑软件随机分配病人到对照组或者实验组。只有手术室人员指导该手术室病人的治疗方案在水密硬脑膜关闭后直接告诉手术医生。实验组，明胶海绵条用在整个硬脑膜缝合的顶部，如果可以的话，硬脑膜补丁周围也用上，在缝合区的周围及两边均覆盖明胶海绵至少1cm。硬脑膜关闭后，放回骨瓣用CranioFix(B.Braun AG))钛铆钉夹或者MatrixNeuro(Synthes AG)钛螺丝和金属板固定。

- 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.

分两层缝合皮肤（皮下腱膜层和皮层缝合）。可根据医生的考虑使用头部引流管来避免出血（参考流程图Fig.1.）。硬脑膜缝合长度，颅骨切开的尺寸、位置，病变的类型和手术发生的并发症在手术后直接记录在一个在线数据库。术后病人常规在ICU一天，第二天在IMC。

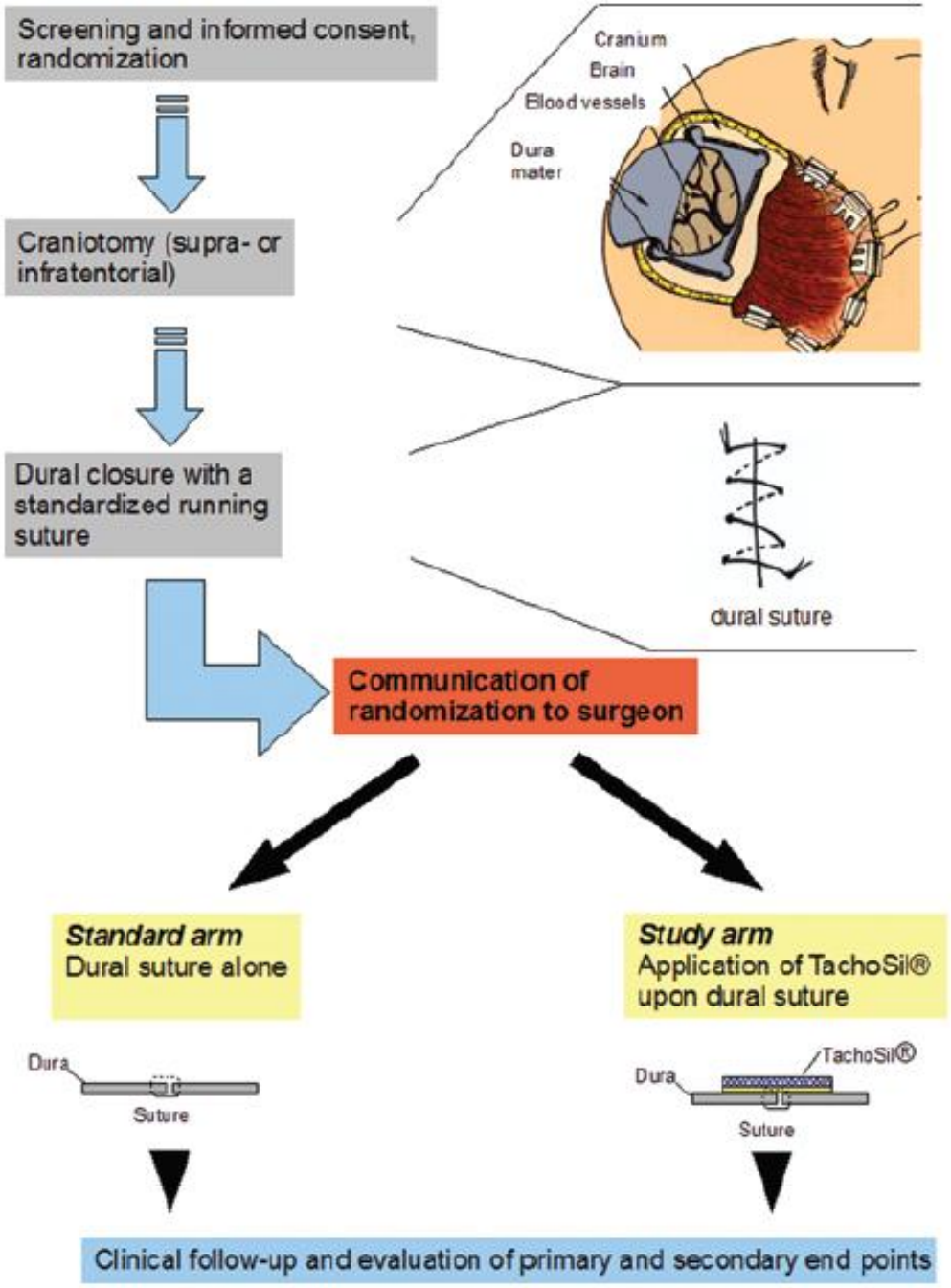


FIG. 1. Trial flowchart.

方法Methods：后续程序和盲法

- 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.

每位病人均通过临床诊断评估术后5-7d和28-32d的任何脑脊液采集/引流和因为脑脊液采集/引流的介入和活跃的脑脊液漏。病人和评价结果人员（研究护士或实验医生）均不知道病人手术是实验组还是对照组并且书写报告上不透露硬脑膜关闭的方法。我们制定了评估脑脊液采集量的分阶标准（Table1）。每个脑脊液采集在临床使用超声或其他成像形式手段测量，根据分级标准逐步干预释放较多的脑脊液。

TABLE 1：CSF聚集分等表

等级	临床标准	超声评定	结果
少量	明显聚集直径<5cm，无张力	20mL	观察和等待
中等	明显聚集直径>5cm，无张力	>20mL	观察和等待、可能减压
大量	聚集直径>5cm，有张力	>20mL	局部穿刺、腰大池引流、二次修复

- 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. Surgicalsite 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.

短暂的帽状腱膜下聚集根据临床方法借助超声分为少量、中等和大量根据大小（直径≤or＞5cm）、体积（≤or＞20mL）和张力，大量聚集时具有代表性的处理方法为有创治疗，如：穿刺、腰大池引流或再次手术。手术区域感染、脑膜炎、相应治疗、任何需要修正的手术并发症、伤口愈合情况、ICU住院时间和IMC住院时间均被记录。

方法Methods：统计分析

- 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.

研究数据注册、资格、程序以及随访均在操作室内以电子病历的形式储存在一个网上数据库中。实验方案中详细描述原始资料的分析，每个数据资料按幕上和幕下做初级分组，幕上手术病人占80.6%（n=184），幕下手术病人占19.4%（n=45）。

- 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).

226名病人登记后，额外招募了17名患者，进行一个盲样本量评估。估计一个243位病人的样本90%（在5%的显著水平）确保可以检测分辨出脑脊液漏的发生率在15%（绝对危险因素）以内的差异，假设总的脑脊液漏发生率为14.3%和7%的数据/样本丢失。实验助手总结人口统计学基线资料和外科手术特征。分类变量以频率和百分比呈现，连续变量以平均数加减标准差和中位数的形式呈现（Table 2）尽管我们计划做一个意向治疗分析作为初步分析和一个个案分析做灵敏性分析，但是我们还是讲每个案例的结果都做了分析。这是因为我们随机到对照组的两个病人使用了明胶海绵发生了脑脊液漏。（Fig.2）

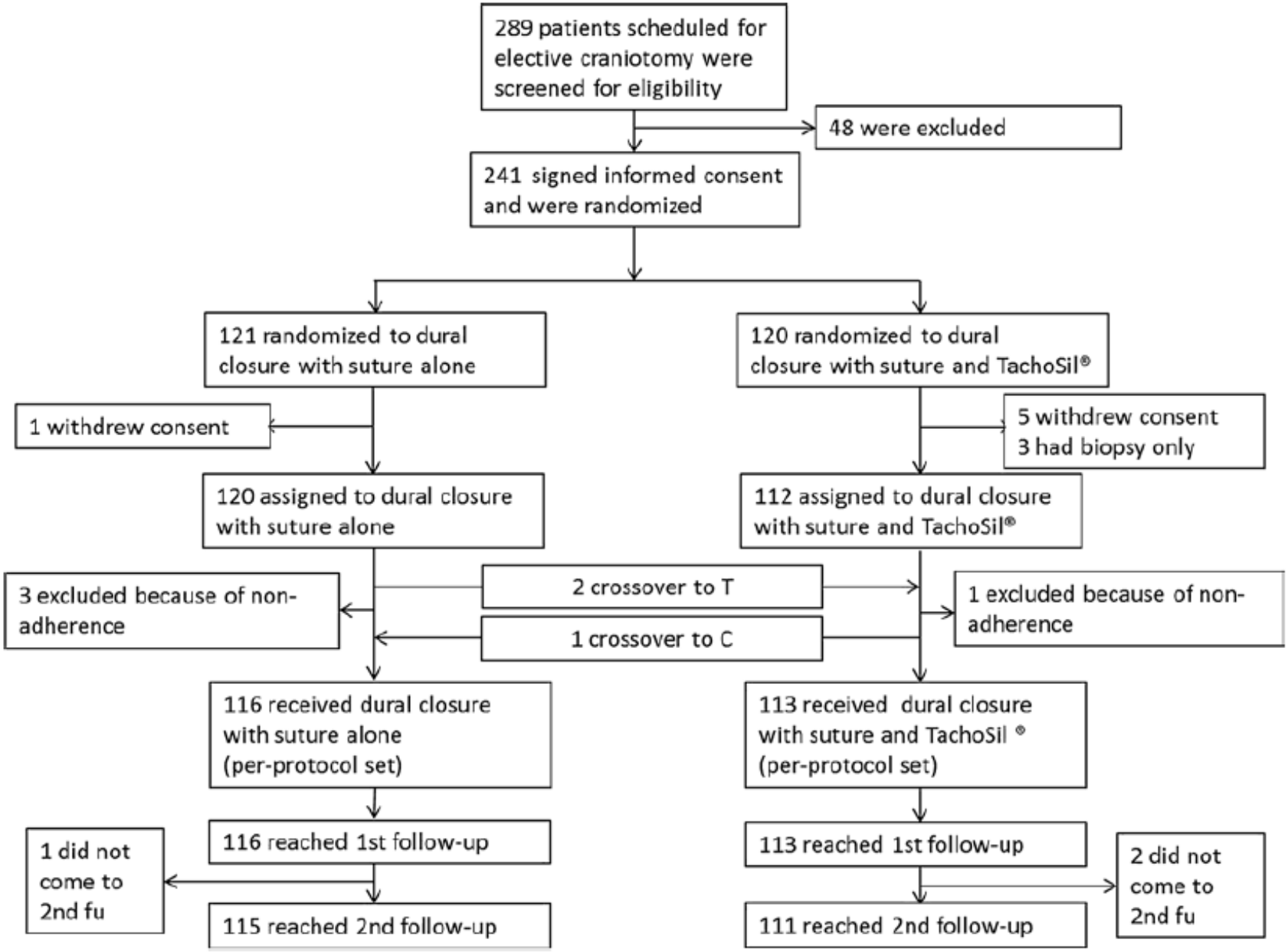


Fig. 2. Trial overview. All patients who had at least 1 follow-up visit (n = 229) were included in the per-protocol analysis. C = control; fu = follow-up; T = TachoSil.

Table2：两个实验组病人特征

变量	值		P值
	对照组（n=116）	明胶海绵组（n=113）	
年龄平均值	56.4±14.6	56.8±15.1	0.61
性别			0.21
男	50（43.1）	59（52.2）	
女	66（56.9）	54（47.8）	
诊断			0.76
颅内肿瘤	68（58.6）	75（66.4）	
转移肿瘤	12（10.3）	9（8）	
血管病变	16（13.8）	15（13.3）	
癫痫	12（10.3）	9（8）	
其他	8（6.9）	5（4.4）	
过敏			1
是	24（20.7）	24（21.2）	
否	92（79.3）	89（78.8）	
糖尿病			1
是	8（6.9）	8（7.1）	
否	108（93.1）	105（92.9）	

脑膜炎			0.77
是	19（15.5）	15（13.3）	
否	98（84.5）	98（86.7）	
病变位置			0.5
额叶	48（41.4）	40（35.4）	
顶叶	17（14.7）	20（17.7）	
颞叶	27（23.3）	19（16.8）	
枕叶	6（5.2）	7（6.2）	
后颅凹	16（13.8）	23（20.4）	
脑干	2（1.7）	4（3.5）	
边（左右）			0.65
左侧	7（6）	4（3.5）	
右侧	57（49.1）	55（48.7）	

主要硬脑膜缝合			0.26
是	80（69）	69（61.1）	
否	36（31）	44（38.9）	
补丁使用			1
是	55（47.4）	53（46.9）	
否	61（52.6）	60（53.1）	
补丁类型			0.03
帽状腱膜	12（21.8）	5（9.3）	
肌肉	14（25.4）	7（13）	
人工硬脑膜	8（14.6）	18（33.3）	
生物膜	21（38.2）	22（40.7）	
其他	0（0）	2（3.7）	
全部	55（100）	54（100）	

手术并发症			0.97
是	3（2.6）	4（3.5）	
否	113（97.4）	109（96.5）	
开颅直径平均值（cm）	7±2.7	6.6±2.5	0.21
主要缝合长度平均值（cm）	9.5±3.5	9.1±3	0.47
地塞米松			0.79
是	27（23.3）	29（25.7）	
否	89（76.7）	84（74.3）	
幕下的			0.35
是	19（16.4）	25（22.1）	
否	97（83.6）	88（77.9）	
伤口引流			0.2
是	43（37.1）	32（28.3）	
否	73（62.9）	81（71.7）	

- 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-totreat analysis, which was overly favorable for the Tacho-Sil 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.

案例分析中这些病人较为保守作为处理组。相比之下，在意向治疗分析中这些病人作为对照组过度有利于明胶海绵的治疗。最终指标是术后一个月内脑脊液漏的发生，也就是至少又一次脑脊液漏发生。我们采用广义线性模型的二项式误差分布来分析实验组和对照组在脑脊液漏发生上的差异。模型包括明胶海绵因素（明胶海绵VS对照组）和幕上手术（幕上手术VS幕下手术），后者用于随机化过程中的亚组分类。

- 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.

我们设计了另外一个模型包括了重要的基线资料作为敏感性分析进而在没有完全缺失的随机结果中调整治疗效果的偏差。[14]、除了明胶海绵组较对照组总比例的增加，还计算了各类病人（亚组）的ORs（和95%CI），比如：幕上/幕下颅脑手术、是否有糖尿病史、脑膜瘤VS其他诊断、使用与不使用硬脑膜补丁、是否有帽状腱膜下引流等。分子明胶海绵和各个亚组的相关因素之间的相互影响是否存在差异。

- The following secondary end points were analyzed: incidence of infection (meningitistion) 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.

接下来分析次要观察指标：一个月内感染（脑膜炎和皮下感染）的发生率、需要干预（二次修复）的并发症的发生率、1天或更长的ICU住院时间、1天或更长的IMC住院时间、第一或/和第二次观察时脑脊液漏的最大尺寸（少量、中等或者大量）。二元次要结果用一个广义线性模型分析作为结果，脑脊液漏的最大尺寸（如果发生）用3*2的交叉表和卡方检验分析。

- 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.

我们在另外一个包含开颅直径和是否使用明胶海绵以及两者相互做用的多元线性分析中分析了颅骨切开直径和脑脊液漏发生率的相关性。同样的，我们也分析了脑脊液漏的发生率和硬脑膜切开长度的相关性。有20个病人的硬脑膜切开长度的信息丢失了。

此外，我们在使用硬脑膜补丁的亚组中分析了硬脑膜补丁的大小（长*宽）和脑脊液漏发生率的关系。模型也包含了明胶海绵及明胶海绵和补丁大小之间的相互影响。

结果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.

共有241位患者参与实验，229位（对照组116例，明胶海绵组113例）纳入研究（Fig.2）实验从2009年10月持续到2012年8月，最后一次访问在2012年10月份。实验根据实验方案修正（盲样本量评估）后按计划进行，修正是的样本量从226增加到了241.人口统计学资料、基线调查和手术特点在Table2中呈现。

结果Results：脑脊液漏的风险因素

- 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.

如Table 3中所示，基线中，糖尿病（OR 5.56[95% CI 1.57-19.11],P=0.014）和术前高CRP（OR1.04[95%CI 1.01-1.08],P=0.010）以及术中缝合硬脑膜需要的硬脑膜补丁（OR 2.43[95%CI 0.96-6.35],P=0.049）显著增加脑脊液漏的风险。

Table 3：每个协议的基线调整，明胶海绵组VS对照组主要观察指标（一个月内脑脊液漏的发生率）的分析

变量	估计	OR值(95%CI)	P值
每个协议分析			
幕下	-0.48	0.62（0.17-1.71）	0.317
使用明胶海绵	-0.64	0.53（0.23-1.15）	0.108
基线调整后个案分析			
使用明胶海绵	-0.79	0.45（0.18-1.06）	0.095
年龄	-0.01	0.99（0.96-1.02）	0.997
男	0.29	1.33（0.56-3.25）	0.185
糖尿病	1.72	5.56（1.57-19.11）	0.014
脑膜瘤	-0.46	0.63（0.15-inf）	0.916
CRP	0.04	1.04（1.01-1.08）	0.01
使用补丁	0.89	2.43（0.96-6.35）	0.049
开颅直径	-0.04	0.97（0.79-1.15）	0.709
地塞米松	0.15	1.17（0.42-2.98）	0.766
幕下	0.12	1.13（0.04-34.85）	0.96
伤口引流	-0.14	0.87（0.32-2.27）	0.774

结果Results：明胶海绵对脑脊液漏的作用

- 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.

明胶海绵组（113例中11[9.7%]）脑脊液漏的发生率低于对照组（116例中20[17.2%]），对应的绝对风险差异为7.6%。然而这个差异没有统计学意义（OR0.53 [95% CI 0.23-1.15],P=0.108;Fig.3A）。基线调整后分析表明明胶海绵组的敏感性较强但仍无统计学意义（OR 0.45 [95%CI 0.18-1.06],P=0.095;Table 3 和Fig.3A）。手术位置（幕下VS幕上）与脑脊液漏发生没有关系。

- 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 ×iabetes interaction, p = 0.107; Table 4).

亚组分析中，我们分析了某些因素是否和脑脊液漏发生可能有关。在使用明胶海绵亚组中我们发现调查的因素没有明显统计差异（Fig.3B和Table4）。标准治疗下，糖尿病亚组明胶海绵使用比非糖尿病组更有益（这里是只可以明显减少脑脊液漏的发生）（明胶海绵*糖尿病相互作用，P=0.107，Table 4）。

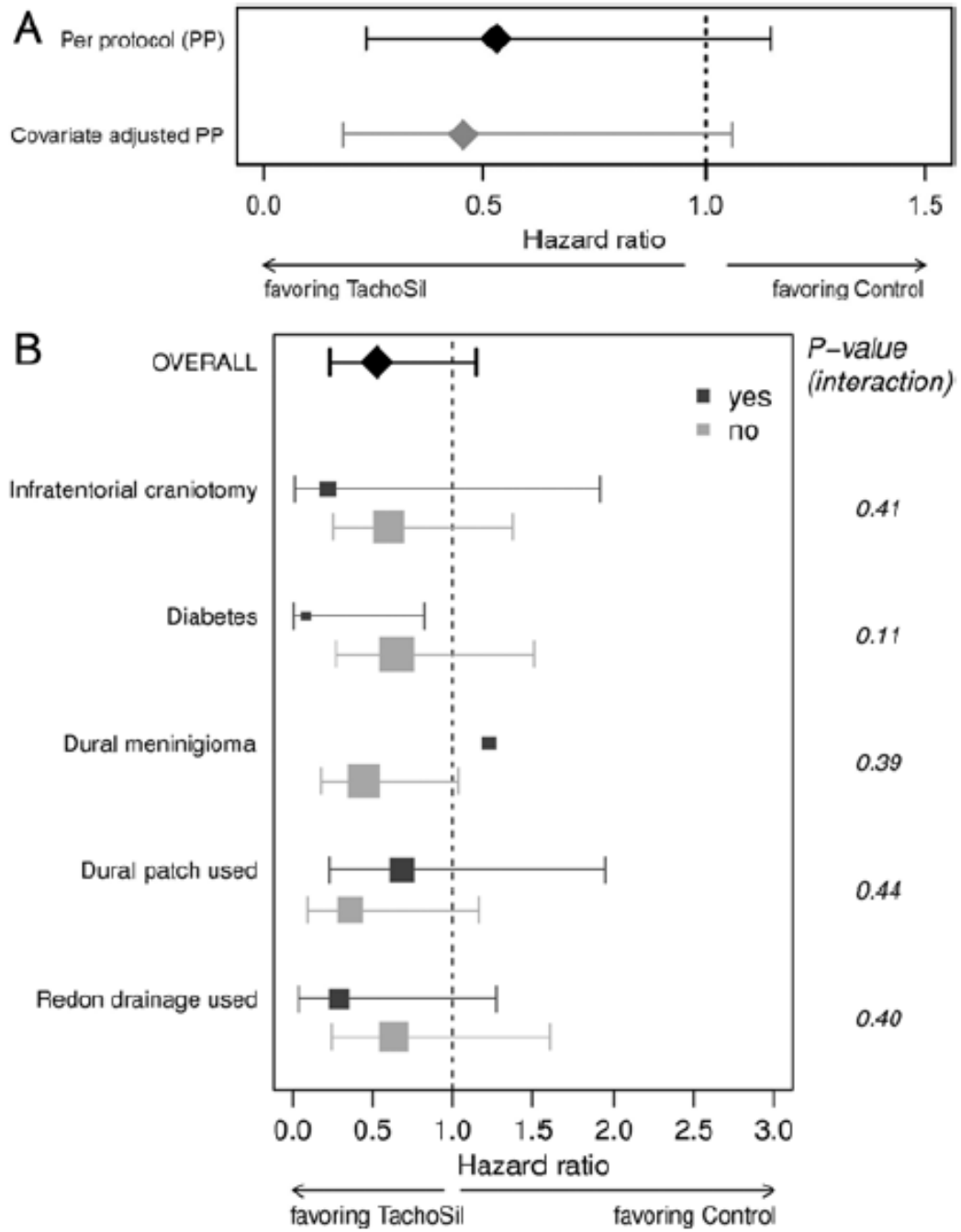

A
Per protocol (PP)
Covariate adjusted PP
0.0
0.5
1.0
1.5
Hazard ratio
favoring TachoSil
favoring Control
B
OVERALL
yes
no
P–value
(interaction)
Infratentorial craniotomy
0.41
Diabetes
0.11
Dural meninigioma
0.39
Dural patch used
0.44
Redon drainage used
0.40
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Hazard ratio
favoring TachoSil
favoring Control

Table4：明胶海绵组和对照组和亚组脑脊液漏发生的各个因素数目

变量	不出现的变量			出现的变量			
	明胶海绵组	对照组	OR（95%CI）	明胶海绵组	对照组	OR（95%CI）	P值
伤口引流	9	12	0.64（0.24-1.60）	2	8	0.29（0.04-1.27）	0.4
使用补丁	4	10	0.36（0.10-1.16）	7	10	0.68（0.23-1.94）	0.439
脑膜炎	9	18	0.45（0.18-1.03）	2	2	1.23（NA）	0.386
糖尿病	10	15	0.65（0.27-1.51）	1	5	0.09（0.00-0.83）	0.107
幕下颅脑手术	10	17	0.60（0.25-1.38）	1	3	0.22（0.01-1.91）	0.411

结果Results：明胶海绵对次要指标的影响

- 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.

对照组中的5个病人，实验组中1个病人术后发生感染或者脑膜炎，提示使用明胶海绵是有益的（OR 0.18[95%CI 0.01-1.18],P=0.077;Fig.4he Table 5）。对照组有一人在术后第14天因爆发性硬膜上积脓症进行外科减压和清创，而脑膜炎病人仅需适当进行抗生素静脉注射即可。

- 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 Tacho-Sil 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.

明胶海绵可以明显降低IMC1天或更长的住院时间（OR 0.53[95CI 0.27-0.99],P=0.048;Fig.3B he Table 5）,但是ICU住院时间1天或更长的减少无统计学意义。9个病人（对照组5个，明胶海绵组4个）因为脑脊液漏需要介入治疗，包括单纯的减压、腰椎引流/腰大池引流或者重新打开切口减压。12位病人进行了和脑脊液漏无关的二次手术（Table 6）。两组之间脑脊液漏相关的介入治疗和外科修复的频率没有统计学差异（Fig.4和Table6）。对照组中两个病人有需要紧急清除的术后硬膜外血肿。

Table5：主要和次要观察指标（分类变量）

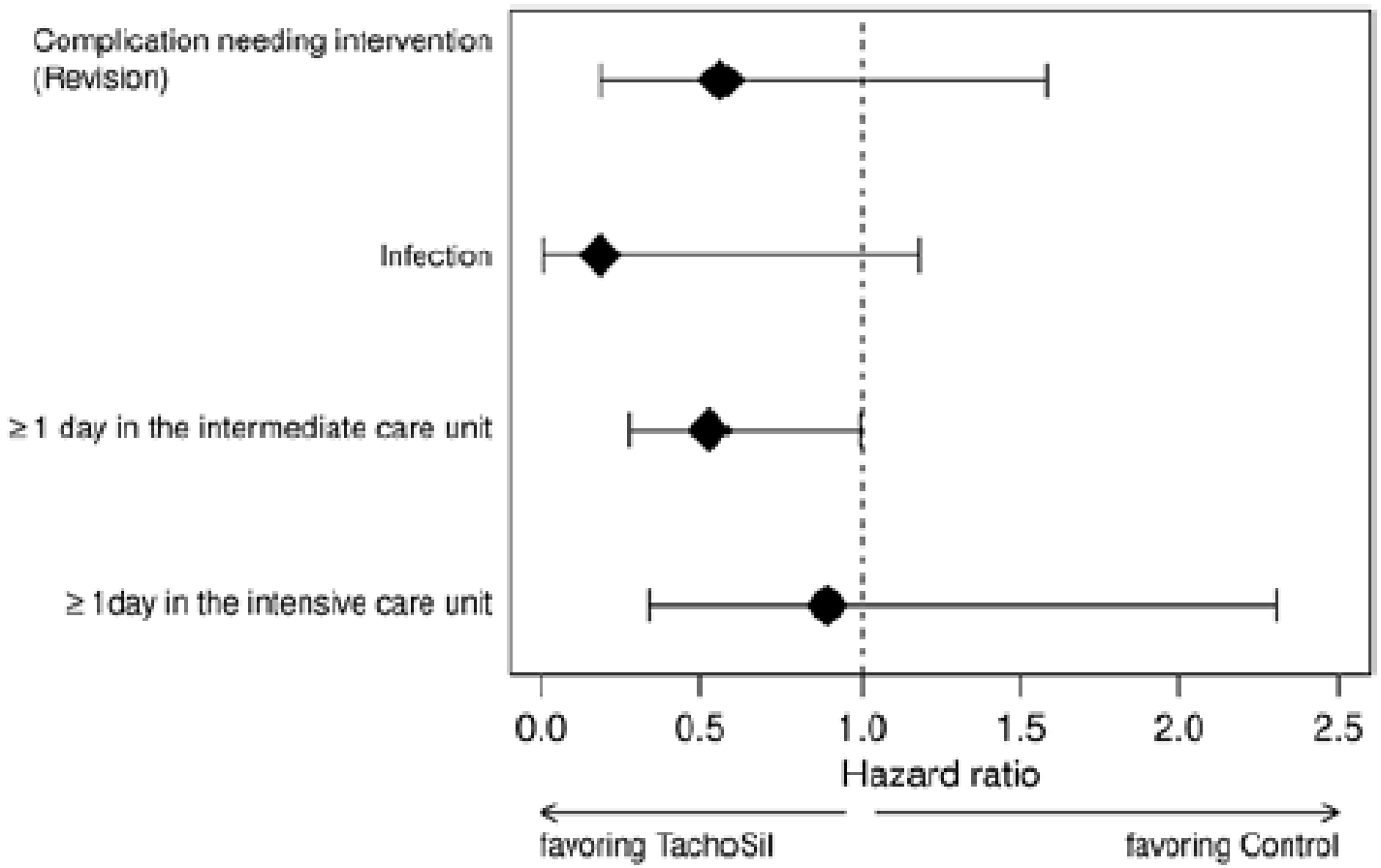
变量	对照组		明胶海绵组		总体	
	病人数量（%）	%∑	病人数量（%）	%∑	病人数量（%）	%∑
脑脊液漏						
否	96（82.8）	8.28	102（90.3）	90.3	198(86.5)	86.5
是	20（17.2）	100	11（9.7）	100	31(13.5)	100
总数	116（100）		113（100）		229(100)	
修复						
否	106（91.4）	91.4	107（94.7）	94.7	213(93)	93
是	10（8..6）	100	6（5.3）	100	16(7)	100
总数	116（100）		113（100）		229(100)	

感染						
否	111（95.7）	95.7	112（99.1）	99.1	223(97.4)	97.4
是	5（4.3）	100	1（0.9）	100	6(2.6)	100
总数	116（100）		113(100)		229(100)	
>1天IMC住院						
否	84（72.4）	72.4	94(83.2)	83.2	178(77.7)	77.7
是	32（27.6）	100	19(16.8)	100	51(22.3)	100
总数	116（100）		113(100)		229(100)	
ICU住院时间>1天						
否	106（91.4）	91.4	104(92)	92	210(91.7)	91.7
是	10（8.6）	100	9(8)	100	19(8.3)	100
总数	116（100）		113(100)		229(100)	
脑脊液聚集尺寸						
少量	41（70）	75	5(45.5)	45.5	19(61.3)	64.5
中等	5（25）	100	6(54.5)	100	11(35.5)	100
大量	1（5）	5	0(0)	0	1(3.2)	3.2
总数	20（100）		11(100)		31(100)	

Table6：在第2小组汇总手术并发症、感染、介入治疗的方式

变量	病人数量		
	总数	对照组	明胶海绵组
并发症			
硬膜要血肿	2	2	0
硬膜下血肿	1	0	1
实质出血	1	1	0
硬膜外积脓症	1	1	0
残余瘤	5	2	3
其他	2		
感染			
硬膜外积脓症	1	1	0
脑膜炎	4	4	1
因脑脊液聚集介入治疗类型			
减压	1	0	1
穿刺 减压	6	3	3
腰穿	1	1	0
腰大池引流	0		
有创修复	1	1	0

Fig4.


Complication needing intervention
(Revision)
Infection
≥ 1 day in the intermediate care unit
≥ 1day in the intensive care unit
0.0
0.5
1.0
1.5
2.0
2.5
Hazard ratio
favoring TachoSil
favoring Control

结果Results：术后死亡率

- 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 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.

4位病人（对照组和明胶海绵组各2位）在随访期死亡；1位病人在脑转移瘤切除术后遭受难治性癫痫持续状态，1位病人死于肿瘤转移切除术后的全身系统肿瘤疾病，1位病人有严重的肝脏疾病和因为动脉瘤导致的蛛网膜下腔出血的脑血管痉挛，1位病人在术后第8天死于急性心肌梗死。这些患者，至少又一次随访记录，因此不排除这些病人。死于癫痫持续状态的病人是随机分派到明教海绵组的。他的癫痫持续状态在手术前就存在且在转移切除术后没有改变。

结果Results：硬脑膜补丁、缝合长度、颅骨切开尺寸的影响（额外的探索分析）

- 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).

大量病人中（对照组55例，明胶海绵组53例）硬脑膜不能被基本缝合，进而按照外科医生的选择使用硬脑膜替代品，硬脑膜替代品的大小在1*1cm和12*14cm之间。另外，我们记录的硬脑膜缝合的长度以及切开颅骨的直径。总的来说，这些变化的参数不是脑脊液漏的高危因素。较长的缝合添加明胶海绵、大的补丁和颅骨起开没有明显影响脑脊液漏的发生（Table 7）。

Table7：额外分析检测明胶海绵组和对照组颅骨切开大小、硬脑膜缝合长度、补丁的面积和主要观察指标的相关性（术后一个月内脑脊液发生率）以及各因素之间的相互影响

变量	估计	OR（95%CI）	P值
协议设定			
明胶海绵组	-0.61	0.54（0.06-4.93）	0.095
颅骨切开直径	0	1.00（0.82-1.19）	0.991
明胶海绵组：颅骨切开直径	-0.01	0.99（0.72-1.35）	0.965
协议设定部分			
明胶海绵组	-0.3	0.74（0.06-9.60）	0.082
缝合长度	0.1	1.11（0.97-1.27）	0.119
明胶海绵组：缝合长度	-0.04	0.96（0.7-1.23）	0.764
协议设定部分			
明胶海绵组	-0.1	0.91（0.26-3.14）	0.606
补丁区域	0	1.00（0.98-1.03）	0.968
明胶海绵组：补丁区	-0.01	0.99（0.94-1.03）	0.623

讨论Discussions

- 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 observations 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 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.

我们的随机对照实验结果显示在硬脑膜缝合顶部添加明胶海绵没有明显减少术后30天捏脑脊液漏的发生率。虽然使用明教号面不能显著降低脑脊液漏，但是我们却在明胶海绵组观察到了一些并发症较低的现象，比如：术后硬膜外血肿、术后硬膜外脓肿及感染。总而言之，这些观察结果是由于应用明胶海绵来填塞和止血作用有关，也可能与其他因素有关。然而试验中明胶海绵组病人在神经IMC住院时间明显减少（P=0.048）。有趣的是糖尿病患者和术前高CRP患者有相对较高的脑脊液漏发生率。

- 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.

使用明胶海绵的一个可能的副反应是导致一个伴随验证反应的疤痕。[7]一个病人由于肿瘤脑转移遭受癫痫持续状态，转移切除后他的癫痫没有缓解，尽管这种并发症的发生在后期随访中没有排除，但是我们不能推断使用明胶海绵和癫痫之间有没有因果关系。

- 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]

因为脑脊液漏而再行介入治疗的患者在两组中都很少，对照组中有一例主要介入者（外科有创修复）。此外，我们发现幕上和幕下两组手术患者中脑脊液漏发生率很相近没有差异。相反有文献报道，幕下应该有较高的脑脊液漏发生率[15] 。我们实验中幕下手术患者脑脊液漏发生率低的原因仍不清楚。这可能是由于水密封连续缝合的标准技术有一定关系。事实上，并非所有的中心和作者都倡导这么一丝不苟的努力。[3]

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

我们实验的一个有趣发现是是整体识别与脑脊液漏的风险相关的因素。需要硬脑膜补丁来达到密闭硬脑膜的效果就是其中之一。这个发现是凭直觉的，因为无论何时只要有可能主要硬脑膜缝合的水密封效果都好于使用硬脑膜替代品的关闭。脑脊液漏和糖尿病及术前高水平的CRP的强相关性是惊人的发现而且在现有文献中还尚未发现。

- 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.

回顾发现，我们实验的主要缺陷可能是在先前的趋势分析中过高估计了脑脊液漏的发生率。我们最初的设想是脑脊液漏的发生率会减少15%（不用明胶海绵为20%，使用明胶海绵为5%）。实际上两者脑脊液漏的发生率分别为17.2%和9.7%，相差近7.6%。这导致盲法评估扩大样本量为241（而不是原来协议中的226位患者）。然而研究不足以证实主要结果有统计学意义。由于单中心设计和有限的财政资源，研究没有进一步延长。

- Previous laboratory studies could show that supplementing dural suture with active hemostatic agents might be beneficial,6 but these findings have not been translated 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.

先前的研究显示用有活性的止血剂不充缝合硬脑膜是有益的[6]。但是这些发现都还没有在临床上证实。在机械水平，一个不完全水密封的粘合是可以减少脑脊液漏和相关并发症的发生率的。另一方面，人们可能会认为引入异物到外科手术中更可能发生感染。我们相反的观察的较少的感染，可能是术后最佳的密闭环境组织了细菌穿过微创损伤和缝合本身带来的细小间隙。仍然保持这样的推测，硬膜下增加物和通过硬膜下填塞保护脑脊液外漏是否可以预防术后威胁到生命的后遗症。这篇研究中使用明胶海绵时观察到主要观察指标的风险降低了7.6%，更多病人需要使用填塞物。

- Previous work by Grotenhuis15 stated a vast cost implication of CSF leakage and proposed a standardized dural augmentation by DuraSeal, albeit in a retrospective singlecenter 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%.

Grotenhuis[15]究表明脑脊液漏的大花费意义，并且DuraSeal在一个回顾性单中心研究中建议了标准的硬膜下填塞物。我们可以前瞻性的确认常规使用硬脑膜下填塞物是安全的、无不良反应的并且可以使术后的脑脊液漏发生率降低7.6%，虽然没有统计学意义。

结论**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 postcraniotomy CSF leakage: elevated CRP levels, diabetes mellitus, and usage of a dural patch.

我们的试验择期开颅手术中是最新的关于是否使用密闭填塞物的前瞻性随机对照研究对比。主要指标分析结果显示使用硬脑膜填塞物可以导致一个没有统计学意义术后一个月内的脑脊液漏发生率的降低。临床意义是硬脑膜填塞物是安全的的没有严重副作用的。而且，我们可以确认针对开颅术后脑脊液漏预处理的因素：高CRP水平、糖尿病、硬脑膜补丁的使用。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