A multicenter, prospective, randomized clinical study to evaluate the efficacy and safety of fibrin sealant as an adjunct to sutured dural repair

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To the Editor: Cerebrospinal fluid (CSF) leakage increases the risk of post-operative complications following cranial surgery, and its progression is not always predictable. Currently, surgeons use various methods to achieve watertight closure of CSF, including synthetic sealants, collagen or gelatin based sponges,[1] and fibrin sealants (FS).[2,3] Bioseal (Porcine Fibrin Sealant Kit, Guangzhou Bioseal Biotech Co., Ltd., Guangzhou, China) is a virus-inactivated porcine plasma-derived FS that has been approved as a supportive treatment to control surgical bleeding.[4] Two phase 4 trials (ClinicalTrials.gov, Nos. NCT02094885 and NCT02034799) in two different clinical settings (neurosurgery and vascular surgery) demonstrated that Bioseal is safe and effective as an adjunctive hemostatic agent. This multicenter, prospective, randomized, controlled, single-blinded clinical trial was designed to evaluate the safety and effectiveness of Bioseal as an adjunct to sutured dural closure for achieving intra-operative watertight closure in subjects undergoing cranial neurosurgical procedures.

From September 2017 to September 2019, subjects with CSF leakage who underwent elective posterior fossa or supratentorial craniotomy with primary dural suture in the nine study centers in China (see Supplementary Table 1, http://links.lww.com/CM9/B360) were randomized by 2:1 to receive adjunctive Bioseal sealant (Bioseal group) or sutures alone (sutures alone group). After adjusting for dropout rate, the sample size for Bioseal and sutures alone groups was 133 and 67, respectively. The main inclusion criteria were ≥18 years of age and underwent elective craniotomy or craniectomy for underlying conditions including benign and malignant tumors, vascular malformation, *etc.*, with CSF leaks after suture closure of the dural incision evaluated by Valsalva maneuver of 10 to 20 cm of H_2O pressure for 5 to 10 s. If a spontaneous leak was apparent immediately after dural closure, no Valsalva would be performed. Subjects who had a class I surgical wound, permitted penetration of mastoid air cells during partial mastoidectomy, and had the cuff of native dura along the craniotomy edge >10 mm wide were included. The key exclusion criteria were: (1) a dural repair from a recent surgery that still had the potential for CSF leakage, (2) underwent previous craniotomy/craniectomy within six months or radiation therapy within two years before this surgery, (3) chemotherapy or radiation therapy scheduled within seven days following surgery, (4) with severely altered renal and/or hepatic function, (5) conditions compromising the immune system or existence of autoimmune disease, (6) evidence of potential infection along the planned surgical path as per investigator's discretion, (7) known hypersensitivity to the porcine FS product, (8) native

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002413

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Chinese Medical Journal 2022;135(20)
Received: 25-08-2022; **Online:** 07-11-2022 **Edited by:** Yuanyuan Ji

dura cuff during craniotomy/craniectomy that could not be completely repaired, (9) use of implants made of synthetic materials, (10) persistently increased brain surface tension that may lead to an incomplete repair requiring, and (11) two or more separate dura defects during surgery. Detailed methods are given in Supplementary Materials (http://links.lww.com/CM9/B223). This clinical trial was carried out in accordance with the *Declaration of Helsinki*, approved by the Ethics Committee of Huashan Hospital, Fudan University (Protocol number: 2017-026-4), and all subjects signed a written informed consent form. The trial was registered on the ClinicalTrials.gov (NCT03110783).

The primary efficacy endpoint was the proportion of successes (watertight closure) in the treatment of intra-operative CSF leakage. The safety endpoints included incidence of CSF leakage post-surgery to discharge; incidence of CSF leakage post-surgery to 30 (±7) days post-operatively; incidence of dural sealing related adverse events (AE); and incidence of surgical site infections (SSIs) according to Surgical Site Infection Prevention and Control Guideline criteria up to 30 (±7) days post-operatively.

The primary endpoint analysis was based on the full analysis set (FAS) and the per-protocol (PP) analysis set. All safety endpoints were analyzed using the safety set.

A total of 200 subjects were recruited from nine sites (Bioseal, $n = 137$; sutures alone, $n = 63$), with the mean (± standard deviation) age of 51.7 ± 12.2 years.

In the FAS, the success rate was higher in the Bioseal group (97.8%, 134/137 subjects, 95% confidence intervals [CI]: 93.7–99.5%) compared with the suture alone group (49.2%, 31/63 subjects, 95% CI: 36.4–62.1%). As shown in Figure 1, the difference in success rates of achieving intra-operative watertight closure between groups was 48.6%. The two-sided 95% CI for the difference in success rates using the Normal approximation *Z* (pooled) statistic was 37.3% and 59.9%. Since the lower limit of the CI is >0, it is concluded that the success rate in the Bioseal group is significantly higher than the suture group. The results of the primary endpoint analysis in the PP analysis set were similar to those in the FAS.

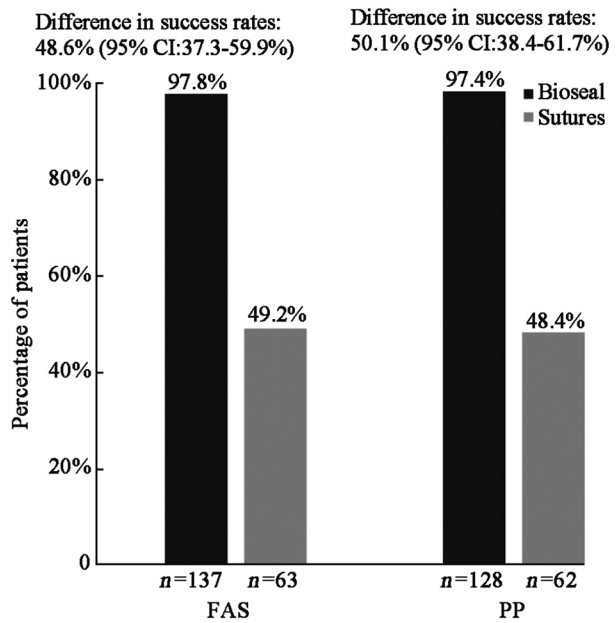

Figure 1: Success rates (watertight closure) by treatment group in FAS and PP analysis set. FAS: Full analysis sets; PP: Per-protocol.

The incidences of CSF leakage post-surgery to discharge were 3.7% (5/136) in the Bioseal group and 1.6% (1/63) in the suture alone group. From post-discharge to 30 ± 7 days, the incidence of CSF leakage was 0.8% (1/132) in the Bioseal group and 1.6% (1/62) in the suture group. Compared with the suture group (50.8%, 32/63), the incidence of dural sealing-related AE was significantly lower in the Bioseal group (5.1%, 7/137; 95% CI for difference sutures-Bioseal: 33.9–57.5%). SSI up to 30 (±7) days post-operatively occurred in one subject (0.7%) who received Bioseal treatment, while no subjects in the suture group experienced SSIs.

The results were comparable to the FS study by Green *et al*,[5] who achieved higher success rate of 92.1% using FS compared with 38.0% in the control group.

The incidence of CSF leakage post discharge to 30 (±7) days observed in this study was 0.8% in the Bioseal group and 1.6% in the control group, while the study by Green *et al*[5] reported CSF leak rates of 2.2% in the FS group *vs.* 2.0% in the control group. Moreover, the incidence of SSIs in this trial was extremely low in both groups (0.7% for Bioseal *vs.* 0 for sutures), whereas the observed incidence of SSIs in the previous study with human FS (EVICEL) was 1.1% in the FS group *vs.* 2.0% in the control group.[5]

The incidence of dural sealing-related AE was significantly lower in the Bioseal group (5.1%, 7/137) compared with the suture group (50.8%, 32/63). The incidence of surgical site AE was lower in the Bioseal group (9.5%, 13/137) than in the suture group (14.3%, 9/63 subjects) at discharge. Regarding the results of rescue therapy, in the Bioseal group, suture as additional treatment was used in one subject, gelatin in one subject, autologous dural patch in one subject, and biologic or other non-autologous dural patch in one subject. In the Sutures group, glues were used in three subjects, suture as additional treatment in one subject, oxidized regenerated cellulose in two subjects, gelatin in six subjects, autologous dural patch in two subjects, and biologic or other non-autologous dural patch in 19 subjects.

This study has some limitations. First, the subjects with higher risk of post-operative CSF leak who were immunocompromised or had dura repaired with synthetic patches were excluded. Second, only the subjects were blinded to the treatment, while investigators were not, which may result in some biases.

In conclusion, the results of this study strongly support the use of Bioseal as an adjunctive sealant to sutured dural repair by showing a markedly increased success rate compared with the control (suture alone). Thus, Bioseal may be considered a superior treatment option to sutures alone for the prevention of CSF leakage, with a favorable

safety profile. Similar death rates were observed in Bioseal and control arms. Two cases of death (one in each treatment group) occurred, and both were assessed as not related to the study treatment. The results of this study demonstrate that Bioseal is effective adjunct to achieve watertight closure after sutured dural repair in cranial surgery, while other applications can be explored in the future.

Conflicts of interest

This study was funded by the Guangzhou Bioseal Biotechnology Co., Ltd.

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How to cite this article: Yu R, Zhu W, Kocharian R, Ilie B, Wang Z, Kang D, Zhao G, Yang H, Shu K, Liu X, Ke Y, Qu S, Mao Y. A multicenter, prospective, randomized clinical study to evaluate the efficacy and safety of fibrin sealant as an adjunct to sutured dural repair. Chin Med J 2022;135:2506–2508. doi: 10.1097/CM9.0000000000002413