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Title

A multicentre, prospective, randomized, controlled study to evaluate the use of a fibrin sealant as an adjunct to sutured dural repair

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Abstract

Background

Obtaining intra-operative watertight closure of the dura is considered important in reducing post-operative cerebrospinal fluid (CSF) leak. The purpose of this study was to evaluate a fibrin sealant as an adjunct to sutured dural repair to obtain intra-operative watertight closure in cranial neurosurgery.

Methods

This randomized, controlled multicentre study compared a fibrin sealant (EVICEL® Fibrin Sealant (Human)), to sutured dural closure (Control). Subjects underwent supratentorial or posterior fossa procedures. Following primary dural repair by sutures, the closure was evaluated for intra-operative CSF leak by moderately increasing the intracranial pressure. If present, subjects were randomized to EVICEL® or additional sutures (2:1 ratio); stratified by surgical approach. Following treatment, subjects were successes if no CSF leaks were present during provocative challenge. Safety was assessed to 30 days post-surgery, including incidence of CSF leakage.

Results

139 subjects were randomized: 89 to EVICEL® and 50 to Control. Intra-operative watertight closure was achieved in 92.1% EVICEL®-treated subjects versus 38.0% controls; a treatment difference of 54.1% ($p<0.001$). The treatment differences in the supratentorial and posterior fossa strata were 49.1% and 75.7%, respectively ($p<0.001$).

The incidence of adverse events was similar between treatment groups. No deaths or unexpected serious adverse drug reactions were reported. CSF leakage within 30 days post-operatively was 2.2% and 2.0% in EVICEL® and control groups, respectively.

Conclusions

These results indicate that EVICEL® is safe and effective as an adjunct to dural sutures to provide watertight closure of the dura mater in cranial surgery.

Key words: Cerebrospinal fluid leak, dural repair, fibrin sealant, watertight dural closure

Introduction

Despite advances in neurosurgical techniques and the development of adjunctive methods to repair dura mater defects, cerebrospinal fluid (CSF) leakage remains an important challenge in cranial surgery. Obtaining intra-operative "watertight" closure is considered a key step in minimizing post-operative CSF leakage, which can lead to serious complications such as meningitis and delayed wound healing.[1] Current techniques to obtain an intra-operative watertight closure include a wide variety of options, including supplementary suturing, applying autologous tissue grafts, the use of synthetic or biological sealants[2-8].

Fibrin sealants have been used for various neurosurgical indications, in particular as an adjunct to dura repair, in Europe and Japan for more than 20 years. Whilst there has been no concern about safety, there is surprisingly little scientifically derived evidence of their effectiveness. A limited number of retrospective studies with historical controls are available from the literature with promising results in term of clinical effectiveness[9-14]. Fibrin sealants are typically derived from biological sources consisting of blood coagulation factors (i.e. thrombin and fibrinogen) and may include anti-fibrinolytic agents. They are used as surgical hemostats and wound support products. Their main role is to mimic the final step in the coagulation pathway to form a stable, physiological fibrin clot that assists in healing.

EVICEL® Fibrin Sealant (Human) (ETHICON, Somerville, New Jersey, USA) is a second-generation fibrin sealant that contains two components: a concentrate of human clottable fibrinogen and human thrombin containing calcium. The manufacturing process includes a plasminogen removal step, thus negating the need for aprotinin or tranexamic acid. The safety and effectiveness of EVICEL® has been demonstrated in nonclinical pharmacology and toxicology studies, and investigated in different clinical settings (retroperitoneal or intra-abdominal, liver, orthopedic and vascular surgery)[9, 12, 13, 15.] It is currently indicated as an adjunct for haemostasis in patients undergoing surgery.

Results from a study using a canine model of durotomy repair demonstrated Evicel® to have similar efficacy to an alternative fibrin sealant in obtaining intra-operative watertight closure[16]. The objective of this study was to evaluate the safety and effectiveness of Evicel® when used as an adjunct to dural sutures following elective cranial surgery and confirm its surgical benefit in enabling an intra-operative CSF seal.

Methods

This prospective, randomized controlled, multicentre study was conducted in 14 centers in the UK, France, Germany, Belgium, Finland, Netherlands and Australia. As this was an investigational study, approval to conduct the study was obtained from the relevant regulatory agencies within each country. In accordance with the International Conference for Harmonisation Tripartite Guideline for Good Clinical Practice[17] and the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects as amended in Tokyo, Venice, South Africa and Hong Kong[18], appropriate Ethics Committee approval was obtained for each site prior to commencing the study and all patients provided written informed consent prior to participation.

Between June 2010 and September 2011, patients undergoing elective craniotomy/craniectomy for pathological processes in the posterior fossa or in the supratentorial region, aged 18 years or older, were eligible for the study. Patients were screened within 21 days of surgery to determine their eligibility for study enrolment. The pre-operative and intra-operative inclusion and exclusion criteria are presented in Table 1.

Upon completion of the primary sutured dural repair, the closure was evaluated for intra-operative CSF leakage with a baseline Valsalva maneuver of 20-25 cm H_2O for 5-10 seconds (unless there was already an obvious spontaneous CSF leak). Patients who had an identified CSF leak (spontaneous or as identified with the Valsalva) were randomized to treatment, by the opening of a sealed envelope in the operating room. The timing of the randomization was planned in an attempt to avoid bias in the conduct of the surgical procedure. Due to the differences in appearance of the two treatment groups, it was not possible to blind the surgeon to the allocated treatment.

Patients were randomized to either EVICEL® or to Control, defined as adjunctive dural closure techniques using additional repair sutures only, in a 2:1 allocation ratio and were stratified by surgical procedure, posterior fossa or supratentorial. The reason for stratification was the expected differences in effectiveness on the primary endpoints between these two groups[19].

For patients randomized to receive EVICEL®, a thin layer was applied to the entire length of the suture line and the adjacent area to at least 5mm away, including all suture holes. If necessary, a second layer of EVICEL® was applied. A cure time was allotted between layers to allow for polymerization. If CSF leakage

was still apparent during the Valsalva maneuver, a second treatment application (with allowance for a further two layers) with EVICEL® was applied. CSF leakage was re-evaluated with a new Valsalva maneuver. If watertight closure was not evident after this final Valsalva maneuver, the patient was deemed a treatment failure.

Patients randomized to Control received additional dural repair sutures as deemed necessary by the surgeon. If watertight closure was not evident after further Valsalva maneuver, the patient was deemed a treatment failure.

For treatment failures in either the Evicel® or Control group, the surgeon reverted to his/her standard of care (SOC) for closure, using as many and any combination of techniques and products as deemed required to obtain intra-operative watertight closure.

In the event of treatment success in the Evicel® group, no further adjunct was to be used. However, in the Control group, if watertight closure was achieved but the surgeon felt that an adjunct (excluding the use of fibrin sealants) was required to assure durability of closure then such a treatment was applied. This was to be considered a treatment success. In both groups, closure of the remaining layers of the surgical site was performed according to the surgeon's standard practice.

Patients were followed post-operatively through discharge and for 30 days (±3 days) post-surgery. The incidence of CSF leaks was assessed within 5 days (±2 days) and 30 days (±3 days) post-operatively as detected by clinical observation, according to the hospital's standard care, or the need for surgical intervention to treat a CSF leak or pseudomeningocele. Surgical site assessment was evaluated according to the Centers for Disease Control and Prevention National Healthcare Safety Network criteria for Defining a Surgical Site Infection (SSI).

The primary endpoint (successful watertight closure) in the treatment of intra-operative CSF leakage was to be analyzed based on the Full Analysis Set (FAS) (which was to treat missing data as failures). An analysis of the Per Protocol Set (PP Set) was to be used as a sensitivity analysis. Secondary endpoints were the incidence of CSF leakage within 5 days (± 20) and 30 days (± 3) post-operatively, the incidence of adverse events, and the incidence of SSIs within 30 days (± 3) post-operatively.

Statistical Methods

An adaptive design employing a triangular test[20] for a binary response variable using PEST software (version 4.4) with a two-sided alpha 0.025 and power 0.90 was selected due to the short duration of the effectiveness variable in the trial, and the expected large treatment difference. The assumed success rate in the control arm was 70% and in the EVICEL® arm was 90%. The study was monitored using the group sequential triangular test, the first interim analysis was planned for the first 135 randomized patients, subsequently followed by analyses at completion of every 45 subjects. At each interim the independent biostatistician assessed if pre-defined boundaries were crossed, at which time recruitment was terminated.

In addition the proportion of successes following randomization and incidence of CSF leakage was analyzed using a Logistic model with treatment and baseline covariates (smoking and age).

It was planned to handle any missing data as failures, though the sensitivity analyses were planned, which imputed missing data as: success; failures for Evicel® group and successes for Control; successes for Evicel® group and failures for Control.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA® Version 11.0).

Results

The first interim analysis for the primary endpoint was carried out when 139 patients had been enrolled, and recruitment was subsequently stopped. Overall, a total of 139 subjects were enrolled and randomized to EVICEL® (n=89) or Control (n=50). There were 9 major effectiveness protocol deviations that may have affected the primary endpoint: 6 were from the EVICEL® treatment group and 3 from the Control group (Figure 1).

Baseline demographic and clinical characteristics for the individual treatment groups are presented in Table 2. Overall, the two treatment groups appeared to be well matched in terms of baseline and surgical characteristics. Median operating time was 155.5 minutes [range 50, 579] in the Evicel® group and 165 minutes [64, 448] in the Control group.

As required by the study protocol, all patients who were randomized had CSF leakage prior to randomization: either spontaneously (75.3% in the EVICEL® group and 68.0% in the Control group) or following the pre-randomization Valsalva maneuver (24.7% in the Evicel group and 32.0% in Control).

The proportion of patients who were deemed a study success is shown in Figure 2. Intra-operative watertight closure (success) was achieved in 92.1% of EVICEL®-treated subjects (82/89 subjects) versus 38.0% of Control (19/50 subjects); a treatment difference of 54.1% ($p<0.001$ from the stratified Cochran Mantel-Haenszel (CMH), which includes surgical procedure in the model), and logistic analysis CMH (controlling for strata) adjusted odds ratio (OR) of 24.87 (95%CI: 8.53 to 72.50; $p<0.001$).

Primary effectiveness analysis was further supported by sensitivity analyses imputing missing data in different ways (Table 3). Furthermore, a statistically significant treatment effect in favor of EVICEL® was observed for both the supratentorial (treatment difference 49.1%, $P<0.001$ (Fishers exact test) and posterior fossa strata (treatment difference 75.7%, $P<0.001$), using missing as failures, as used for the primary endpoint ($p<0.001$), as presented in Figure 3. A stratum effect was demonstrated in favor of the supratentorial strata: CMH adjusted OR was 0.25 (95% CI: 0.08-0.82) ($p<0.022$).

Seven patients from the EVICEL® treatment group were considered failures for the primary endpoint; 5 of whom did not receive EVICEL® due to study related procedural errors, and 2 were failures due to CSF leak. In the Control group, 31 patients were deemed as failures for the primary endpoint; 3 of whom were not assessed due to study related procedural errors.

As shown in Table 4, 4 patients in the EVICEL® treatment group and 28 patients in the Control group had some form of rescue therapy once classified as a study failure. These included the use of glue, hemostatic matrix, autologous dural patch and/or biological dural patch. Ten subjects of the 22 subjects deemed study successes in the Control group (45.5%) did receive further adjunctive techniques or products, either alone or in combination, to provide assurance of the durability of the closure.

In the Evicel® treatment group, 64% of patients (57/89) experienced at least one adverse event compared to 62% of patients (31/50) in the Control treatment group. The most frequent adverse events were headache,

hypertension, hypotension, nausea, vomiting, respiratory failure and swelling, all commonly associated with this type and complexity of surgery.

Ten EVICEL® subjects (11.2%) experienced 12 serious adverse events (SAE) and 4 suture subjects (8.0%) experienced 5 SAEs. There were no deaths and no suspected unexpected serious adverse drug reactions. Adverse events considered possibly related to dural sealing are presented in Table 5.

By 5 days after surgery, one patient in the EVICEL® treatment arm had CSF leakage, which resolved following placement of a single additional suture. By 30 days post-procedure, CSF leakage was reported in a further two subjects; one from each treatment arm. In the patient from the Evicel group, the leak was identified on post-operative day 7, and resolved following wound puncture. One patient in the Control group had impaired wound healing with CSF leakage 13 days post-surgery; the leak resolved following further surgery. Overall, the incidence of CSF leakage within 30 days post-operatively was similar between both groups: 2.2% and 2.0% in the EVICEL® and suture groups, respectively. In addition, there were two cases of CSF rhinorrhoea in the EVICEL® group which both occurred after posterior fossa surgery. Although these occurred at a location separate from the suture line where EVICEL® was applied, when combined with the other CSF leaks, the overall rate in the EVICEL® group was 4.5% (4/89)**.** There were no pseudomeningocoeles reported in either treatment group. The incidence of SSIs was also similar between treatments: 1.1% in the EVICEL® group and 2.0% in the suture group; in each case, the SSI was meningitis.

Discussion

All neurosurgical procedures require that the surgeon passes through the dura mater to gain access to neural elements, whether brain or spinal cord. Among the envelopes which contain and protect the neural structures, the dura mater is the most important as it is the only one that can be surgically repaired. At the completion of surgery, the dural repair must be as watertight as possible so as to prevent post-surgical CSF leakage and complications. Post-operative CSF leak occurs in approximately 10% of patients and is associated with considerable financial costs, although the risk in posterior fossa procedures is much higher than that for supratentorial procedures[21]. Moreover, CSF leak is associated with a greater risk of meningitis with potential further morbidity and mortality. In one study of skull base surgery, the risk of meningitis without CSF leak

was 4.5%, compared to a risk of 66% with CSF leak[1]. Therefore, the prevention of post-operative CSF leak is of paramount importance in any cranial surgery.

The results of this study demonstrated that EVICEL® was highly effective as an adjunct to primary dural sutures to provide watertight closure of the dura following elective neurosurgical procedures. The robustness of the data was supported by additional sensitivity analyses using different imputation methods for the missing data. Our decision to stratify was confirmed by the results, with a statistically significant treatment effect in favor of EVICEL® observed for both strata, with a significant difference evident between the strata in favour of supratentorial. Our reported success rate following the use of EVICEL® as an adjunct to dural suturing was comparable to other studies investigating the polyethylene glycol hydrogel sealant, Duraseal, in spinal and cranial surgical procedures[5, 6, 22]. The observed success rate for EVICEL® (92.1%) was slightly better than the expected rate (90%). However for the control group, the observed success rate was far less (38.0%) than expected (70%) accounting for the highly significant treatment difference reported.

Overall, the incidence of CSF leakage and surgical site infections were comparable between the two treatment groups. BioGlue®, a bovine serum albumin-glutaraldehyde surgical adhesive licensed for use in dural-sealing, has been associated with an increased incidence of SSI after cranial surgery[4]. In this current study, the frequency of SSI was low in both groups.

It is important to highlight that the study could not be designed to demonstrate a treatment difference in post-operative CSF leak. For ethical reasons, we considered that no patients should be left with a patent CSF leak and thus allowed the investigators to use any means they deemed necessary to get a watertight closure of the dura. As a consequence of this rescue therapy, no significant difference in term of postoperative CSF leaks was expected as watertight closure was obtained for all patients in the study. A key assumption is that intra-operative watertight dural closure is associated with a reduced post-operative complication rate. Whilst some studies have suggested that this may not be the case[23], these types of studies are inherently biased because, being retrospective, patients more likely to develop a post-operative CSF leak are the ones most likely to receive adjunctive dural sealants and other products. The fact that surgeons did opt to use further adjunctive therapies for durability of the closure in the Control group in almost half of the study successes suggests the importance of the surgeon's desire to have assurance of intra-operative watertight dural closure.

The overall low incidence of post-operative CSF leak observed in this study does create a challenge to demonstrating a clinical benefit to the use of fibrin sealants as adjunct therapy. However, it is not possible to answer the question of relationship between intra-operative dural closure and post-operative CSF leak because the majority of patients randomized to further sutures ended up having rescue therapy. Potential ways to answer this question would be to exclude this rescue therapy or have a third treatment arm to address spontaneous sealing, but both options were considered unethical by the study investigators. However, it stands to reason that preventing post-operative CSF leak is much more likely following watertight dural closure than when this is not the case.

Whilst this study benefitted from a randomized control design with multiple participating centers, there were some limitations to the design. One limitation was the exclusion of patients who could potentially considered higher risk of post-operative CSF leak, such as those on long-term steroid use or requiring chemotherapy or radiation within a week following surgery. However, in the absence of prior data, it was deemed inappropriate to expose those higher-risk patients to the investigational use of this fibrin sealant. The inability to blind the surgeon to the treatment was a further limitation, but was minimized by the timing of the randomization after completion of the primary dural repair and confirmation of CSF leak. Another limitation was the lack of an objective measure to confirm the incidence of post-operative pseudomeningocoele.

Conclusion

As demonstrated in this study by the use of rescue therapies in the subjects who failed the primary endpoint, surgeons will use all methods at their disposal to ensure intra-operative watertight closure is obtained. Therefore, the need for an effective adjunct to sutures to achieve a watertight seal to sutured dural closure still exists. This study demonstrates that EVICEL® is safe, that it is highly effective as an adjunct to primary dural sutures to provide watertight closure of the dura mater.

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Declarations of Interest

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