A Novel Absorbable Hydrogel for Dural Repair: Results of a Pilot Clinical Study

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SUMMARY: This report details a 47 patient, prospective, non-randomized, single-center clinical study to evaluate the safety and performance of a new synthetic dural sealant as an adjunct to standard surgical dural repair techniques to prevent cerebrospinal fluid (CSF) leakage. A consecutive series of patients scheduled for cranial and spinal intradural surgery each received standard dural closures. After sutured closure, 94% of patients had dural incisions that still exhibited intraoperative CSF leakage. Patients with intraoperative CSF leakage then had sealant applied to suture lines. Following sealant application, no patients exhibited intraoperative leakage during a subsequent Valsalva maneuver to 20 cmH2O (100% efficacy). Following surgery two patients developed overt postoperative CSF leaks, and one patient developed a pseudomeningocele. There were no adverse events other than those related to the disease or to the surgical procedure itself. This synthetic, absorbable dural sealant appears to be a useful adjunct to achieve watertight dural closure of sutured dura.

INTRODUCTION

The need for a tight dural repair has been commonly stated since the early 1900s. Meticulous dural repair reduces complications related to postoperative cerebral spinal fluid (CSF) leakage. CSF leakage is a complication associated with other possible serious complications like meningitis, and often requires re-operation. Prolonged hospitalization and high health care costs are the consequence. Current methods of dural repair consist of the application of either continuous or interrupted sutures and the use of dural replacement materials (duraplasty). Fibrin sealants or absorbable gelatin are often used on the sutured dural closure to render it “watertight.” Despite the widespread use of these adjuncts, it is widely recognized that the optimal device has yet to be developed. Recently, a new synthetic, biocompatible hydrogel, the DuraSeal™ Dural Sealant device (Figure 1), was investigated in a canine durotomy repair model.10 That evaluation demonstrated rapid intraoperative and prolonged postoperative sealing. The present study is the first evaluation of this novel sealant in human durotomy procedures, with special attention to efficacy and adverse events.

MATERIALS AND METHODS

The DuraSeal Dural Sealant System (Confluent Surgical, Inc., Waltham, MA) consists of two aqueous solutions that when mixed together rapidly polymerize to form a hydrogel. One solution, clear colored, contains a low molecular weight, water-soluble amine. The other solution contains an end-modified polyethylene glycol (PEG) and a blue dye, FD&C Blue #1, to allow sealant visualization. The PEG is functionalized with reactive end groups and a degradable ester linkage. The liquids mix together within the applicator when sprayed onto tissue. This mixing results in a rapid electrophilic-nucleophilic reaction between the ester and amine, resulting in crosslinking within 2 seconds without the generation of detectable heat. The resultant hydrogel is tissue adherent and strong. After several weeks, hydrolyzable linkages within the gel begin to break, causing the gel to liquefy back to the constituent PEG molecules, which are absorbed and cleared primarily through the kidneys. DuraSeal is completely synthetic, with no animal or human components. Thus, unlike sealants made from pooled human or animal blood, the potential for viral transmission with DuraSeal is eliminated.

This study was designed as a prospective, non-randomized, single-center clinical trial. A consecutive series of patients, scheduled for elective cranial and spinal intradural surgery, between 18 and 75 years of age were included. Patients had to sign a written informed consent form to participate in the study that was approved by the Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen.

Figure 1: DuraSeal Dural Sealant consists of two fluids that polymerize rapidly when mixed. One fluid contains a dilute blue dye, allowing for improved sealant visualization.
Preoperative exclusion criteria included pre-existing cerebrospinal fluid (CSF) leakage, internal or external CSF shunt, hydrocephalus or elevated intracranial pressure and a prior intracranial or spinal neurosurgical procedure within the last 12 months, as well as radiotherapy within 12 months or chemotherapy within 6 months prior to the procedure. A systemic or local infection was also an exclusion criterion. Intraoperative inclusion criteria were a linear extent of durotomy of at least 2 cm and the dural margin from edges of bony defect of at least 3 mm throughout to allow effective application of the sealant. Intraoperative exclusion criteria were no spontaneous CSF leakage after dural closure or after Valsalva maneuver up to 20 cmH₂O for 5 to 10 seconds. Autologous duraplasty materials to aid in the sutured closure (i.e., fascia, fat, pericranium, or muscle) were used as necessary, but patients where the dura could not surgically be closed were excluded.

If a CSF leak was demonstrated following sutured closure and the patient met all of the intraoperative eligibility criteria, the dural sealant was applied (Figure 2). Following the application of the dural sealant, a subsequent Valsalva maneuver was conducted to evaluate post-application CSF leakage. The primary endpoint was defined as no leak with Valsalva maneuver after dural sealant application. The patients were followed for 3 months postoperatively to evaluate health and check for CSF leakage. In addition, concomitant medications, neurological examination and adverse events at preoperative, at 7-days postoperative, 1-month and 3-month follow-up visits were recorded.

**RESULTS**

Between February and September 2002, sixty-one consecutive patients were enrolled in the study. Of the 61 patients enrolled, 50 met all of the eligibility criteria prior to the baseline Valsalva maneuver and were tested for CSF leak. Following primary sutured dural closure, 35 (70%) patients had a spontaneous CSF leak, while 12 (24%) patients leaked at baseline Valsalva maneuver. Only 3 (6%) patients did not exhibit a CSF leak during the Valsalva maneuver.

Of the 47 patients who met the intraoperative eligibility criteria and were treated with the dural sealant, 25 (53%) were male and 22 (47%) were female, with a mean age of 52 years, ranging from 21 to 73 years. Two (2) patients had intradural spinal operations, while 45 had cranial surgery either using a craniotomy (38) or craniectomy (7). Cranial surgical approaches included the convexity (21), lateral suboccipital (13), pterional (3), suboccipital (6) and supraorbital (2). A wide variety of pathologies treated included astrocytomas (11), vestibular Schwannomas (7), and metastatic disease (6). Length of durotomy ranged from 2.5 cm to 26 cm with a mean of 7.25 cm. Fascia, pericranium or muscle autologous duraplasty material was used in 16 (34%) patients.

Hydrogel application took only seconds in all cases, with an average of 2.2 ± 1.1 mL sealant used. There were no training patients in this trial due to device ease of use. Following sealant application, no patients (0%) had intraoperative CSF leaks during the subsequent Valsalva maneuver (Table I). Thus, in sutured dural closures that were shown to leak CSF, the sealant was 100% effective at creating a watertight dural closure.

<table>
<thead>
<tr>
<th></th>
<th>No CSF Leak</th>
<th>Spontaneous CSF Leak</th>
<th>Valsalva CSF Leak</th>
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<tbody>
<tr>
<td>Suture Closure</td>
<td>3/50* (6%)</td>
<td>35/50 (70%)</td>
<td>12/50 (24%)</td>
</tr>
<tr>
<td>Suture Plus DuraSeal</td>
<td>47/47 (100%)</td>
<td>N/A</td>
<td>0/47 (0%)</td>
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*Patients with no CSF leak following suturing did not receive DuraSeal Sealant treatment.

All of the 47 treated patients completed the discharge follow-up. Forty-three patients completed their 1-month follow-up (2 patients refused to return; 1 died due to basilar artery thrombosis; and 1 died due to hematoma). One additional patient was lost to the 3-month end of study visit (patient death due to sepsis after a diverticulitis resulting in a sigmoid resection).

Figure 2: Dura following suture closure (A), and following DuraSeal Dural Sealant application (B). Blue dye allows for sealant visualization (Patient A01).
Of the 47 DuraSeal treated patients, there were two cases of overt postoperative CSF leak (4.3% – one rhinorrhea and one incisional). The patient that developed rhinorrhea was treated for a temporal arachnoid cyst using a right frontobasal / supra-orbital approach. During the procedure, the investigator noted two small gaps remaining in the dura and an open frontal sinus. The patient presented with rhinorrhea at the 1-month follow-up visit and was treated with an external lumbar drain, bedrest and oxygen for 3-5 days. Although initially effective, the patient presented again with rhinorrhea at the 3-month follow-up, and was successfully re-operated. The patient who developed the incisional CSF leak had an enlarged ventricle prior to surgery that was thought to be due to a cyst compressing the ventricle. At the 1-month follow-up, the patient had incisional CSF leak that required percutaneous aspiration, then continuous lumbar CSF drain for 3-5 days followed by lumbar peritoneal CSF shunting. According to the investigator, the CSF leak may have developed due to pre-existing hydrocephalus which was not known prior to the surgery. Pre-existing hydrocephalus was an exclusion criterion and enrollment of this patient was deemed a protocol deviation. No additional leaks were noted at the 3-month follow-up visit.

A third patient with a midline-suboccipital craniotomy for a high-grade cerebellar glioma developed a pseudomeningocele that was treated with percutaneous aspiration.

Wound healing was excellent in most patients. One patient developed a deep wound infection that required bone flap removal (2.2% deep wound infection rate). Postoperative laboratory values were mostly within normal ranges, and were as expected given the surgical procedures performed. The primary safety endpoint was defined as no device-related procedure-related complications and adverse events. There were a total of 51 adverse events: cardiovascular 4, pulmonary 2, urogenital 2, abdominal 7, general 6 and neurological 30. The neurological adverse events were related to the disease or the operation; none were related to the dural sealant.

DISCUSSION

Standard dural repair methods consist of direct application of interrupted sutures, with or without the use of dural replacement materials (duraplasty). CSF leakage can be associated with significant morbidity and costs. Postoperative CSF leak rates range from 4% in transsphenoidal procedures to 32% in posterior fossa surgery. Incremental costs due to CSF leaks range from 5.7% to 22.9% of total costs depending on the procedure (mean 10.3%). Prevention CSF leakage by means of a “watertight” closure remains an elusive target. Adjunct dural repair techniques consist of biological adhesives, gelatin or collagen sponges, and the application of various autologous and non-autologous materials. The disadvantages of these techniques include rejection of foreign tissue by the host, immune and inflammatory reactions, neurotoxicity, space-occupying effect, poor elastic compliance, formation of adhesions, failure to remain in situ, and lack of effectiveness. Also, products of biological origin have the potential for transmitting blood-borne diseases through viral agents and for inducing anaphylaxis.

Hydrogels, especially PEG hydrogels, offer promise as a new biomaterial for this use. Recent animal studies showed their potential as vascular sealants, hemostatic agents, lung sealants, and adhesion inhibitors. DuraSeal Dural Sealant was recently tested in a canine durotomy repair model. This sealant provided immediate intraoperative and prolonged postoperative dural sealing, a normal progression of dural healing, no dural adhesions, and no underlying effects on the brain. The attributes of this sealant are outlined in Table II.

Table II: DuraSeal Dural Sealant Attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>DuraSeal Sealant</th>
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<tbody>
<tr>
<td>Biocompatible</td>
<td>PEG-based; does not interfere with healing</td>
</tr>
<tr>
<td>Synthetic</td>
<td>No potential for viral transmission</td>
</tr>
<tr>
<td>Absorbable</td>
<td>Absorbable within 8 weeks</td>
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<tr>
<td>Tissue Adherent</td>
<td>Flexible and tissue adherent</td>
</tr>
<tr>
<td>Strong</td>
<td>Seals against pressure throughout healing</td>
</tr>
<tr>
<td>Easy to Apply</td>
<td>Sprayable, with rapid polymerization</td>
</tr>
<tr>
<td>Visible</td>
<td>Blue dye assists visualization</td>
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</table>

The primary study endpoint was intraoperative sealing efficacy. As can be seen in Figure 3, DuraSeal Dural Sealant was effective at sealing 100% of suture lines known to be leaking CSF.
CONCLUSIONS

DuraSeal Dural Sealant, a synthetic hydrogel, is a useful adjunct for dural closure. After the application, there were no intraoperative CSF leaks despite Valsalva maneuver in all treated patients. There are no evident adverse effects. The 4.3% postoperative overt CSF leak rate is exceptionally low, relative to the challenging series of patients.

ACKNOWLEDGMENTS

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REFERENCES