Application of a hydrogel sealant improves watertight closures of duraplasty onlay grafts in a canine craniotomy model

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Object. The authors evaluated whether a polyethylene glycol–based hydrogel sealant system improved dural closures with collagen-based duraplasty onlay grafts.

Methods. Dural defects 1.5 cm in diameter were created in 12 canines and repaired with one of two commercially available duraplasty onlay products. In six animals, hydrogel was applied onto the dural onlays, and the other six animals underwent duraplasty only. Before bone flap replacement, watertight closure was assessed. After the animals were killed, the craniotomy was reopened, adhesions were rated by a neurosurgeon blinded to the treatment groups, and dural integrity was assessed using pressure testing.

Results. The animals that received the hydrogel sealant in addition to the duraplasty withstood intraoperative Valsalva maneuvers up to 20 cm H₂O without cerebrospinal fluid (CSF) leakage. The duraplasty-only animals leaked CSF at spontaneous pressures (p = 0.0022). Postoperatively, all six duraplasty-only dogs developed CSF subcutaneous accumulations, compared with only one (16.7%) dog who underwent hydrogel application (p = 0.0152). At the time of harvesting (8 weeks after implantation), duraplasty-only dogs had extensive scarring between the bone flap and the dura mater (median adhesion score 4, range 3–4). The animals receiving hydrogel showed minimal scarring (median adhesion score 0.5, range 0–2). In hydrogel-treated dogs, the mean adhesion score was 82.6% lower than the scores in duraplasty-only animals (p = 0.0043). In animals receiving hydrogel, the mean dural leak pressure was 56.8 ± 2.5 cm H₂O compared with 9.8 ± 3.8 cm H₂O in duraplasty-only dogs (p = 0.0392). Application of the hydrogel was not associated with neurotoxicity, delayed healing, degenerative changes, or increased dura–cortex adhesions.

Conclusions. The hydrogel sealant applied to collagen-based dural grafts significantly reduced CSF leakage and functioned as an adhesion barrier. Such technology could be an important tool for cranial surgery.

Abbreviations used in this paper: ANOVA = analysis of variance; CSF = cerebrospinal fluid; ICP = intracranial pressure; PEG = polyethylene glycol.

Grafts suitable for replacing missing dura mater are often needed during cranial and spinal procedures. Available materials include autologous, cadaveric, synthetic, and xenograft dural substitutes. Historically, these implants have been sutured in place to prevent migration, create a watertight closure, and provide a surface along which new dura could be generated. The use of xenograft duraplasty “onlay” grafts that require no suturing is along which new dura could be generated. The use of xenograft duraplasty “onlay” grafts that require no suturing is unknown. We postulated that such a hydrogel system could significantly augment the effectiveness of the seal formed by nonautologous dural onlay grafts.

This study did not compare the efficacy of the dural graft materials themselves nor is it an endorsement of the hydrogel system used in this study. The hydrogel used in this study is the only US Food and Drug Administration–approved hydrogel system for augmentation of sutured dural closures in cranial procedures, however. Several hydrogel-based products have been approved for use as vascular or lung air-leak sealants and as adhesion inhibitors in abdominal or pelvic surgery, such as SprayGel (Confluent Surgical, Inc.), FocalSeal-L (Genzyme Biosurgery), and CoSeal (Angiotech Pharmaceuticals, Inc.). Although a new generation of biomaterials that inhibit scars, fibrosis, and adhesions has been introduced in various other surgical
disciplines, such advantageous materials have only recently been introduced in neurosurgery.

**Materials and Methods**

**Duraplasty Grafts and Sealant**

This study was conducted at the Neurosurgery Research Laboratories in the Division of Neurological Surgery of the Barrow Neurological Institute and St. Joseph’s Hospital and Medical Center, in compliance with experimental approval from the St. Joseph’s Hospital and Medical Center’s Institutional Animal Care and Use Committee.

Two different commercially available collagen duraplasty onlay grafts were evaluated in conjunction with application of a spray-on hydrogel system: DuraGen Dural Graft Matrix (Integra Lifesciences), derived from bovine Achilles tendon, and Durepair Dura Re-Generation Matrix (Medtronic Neurosurgery), derived from fetal bovine skin. Both products were prepared as directed in their respective “Instructions For Use” and were used as onlay grafts without suturing.

The hydrogel system evaluated (DuraSeal Dural Sealant System, Confluent Surgical, Inc.) was developed specifically as a dural sealant. It consists of two dilute aqueous precursor liquids that crosslink (solidify) within 1 to 2 seconds of spraying (Fig. 1). One precursor liquid contains a small molecular weight amine; the other contains a dilute concentration of PEG with ester end groups. When sprayed, the amine and PEG ester end groups rapidly react by way of an electrophilic–nucleophilic reaction to form a hydrogel network primarily composed of water and PEG. The resulting hydrogel network adheres to tissue and is strong enough to withstand elevated CSF pressures while the dura heals. The hydrogel network then breaks down by way of hydrolyzable linkages in the PEG matrix and is absorbed within 4 to 8 weeks. One precursor liquid also contains Food, Drugs, & Cosmetics Blue No. 1 dye, which allows the thickness and coverage of the hydrogel to be visualized. The chemistry of the PEG makes the hydrogel highly tissue compatible, whereas its synthetic origin eliminates the potential for viral transmission.

**Study Design and Procedure**

Twelve female coonhounds dogs between 2 and 3 years old (range 13–20 kg) were used. Surgical procedures were performed using routine sterile techniques. After anesthesia was induced using a general inhalant, an oval bone flap was raised (5 × 4 cm), and a circular running 3-0 polyglactin 910 Vicryl suture in layers (Ethicon). The temporal muscle, fascia, and galea were repaired with 6-0 Prolene polypropylene sutures (Ethicon). A craniotomy site. Although all canines demonstrated good CSF flow after the dural excision, three dogs were randomized to each of the following four treatment groups: Group 1, DuraGen only; Group 2, DuraGen with hydrogel; Group 3, Durepair only; and Group 4, Durepair with hydrogel. Duraplasty materials were prepared and cut into a circular shape, with diameters 5 to 10 mm larger than the hole in the dura. Grafts were centered over the holes in the dura with no anchoring sutures. Dogs randomized to Groups 2 or 4 had 1 to 2 mm of hydrogel applied over their graft and dura (Fig. 2). The blue color provided sufficient contrast to determine sealant thickness and coverage, whereas the rapid sealant polymerization allowed complete duraplasty patching and surrounding dura coverage without runoff. In each dog, application of the hydrogel lasted only seconds (average, 2.0 seconds; range over eight dogs 1.0–2.9 seconds).

Surgical procedures continued without complications, although two dogs required larger dural openings because their dura tore when the bone flap was removed. Dogs randomized to receive the hydrogel sealant treatment received the application of the sealant within 20 seconds. The bone flap was then cannulated percutaneously and ICP was slowly increased using injected saline. During the injection, the dural surface was observed using an operating microscope. The pressure at which CSF leaked onto the dural surface was recorded as the leak pressure. To avoid brain herniation, pressure testing ceased at 55 to 60 cm H2O if no CSF leak was noted.

After this evaluation, the dogs were heparinized and killed. The animal heads were pressure-perfused with formalin after a saline rinse. Tissues were embedded in paraffin, cut, and stained with H & E for evaluation by a veterinarian pathologist blinded to the animal’s treatment group. The neurosurgeon then rated the extent of the adhesion formed between the dura and bone flap using a five-point scoring system (Table 1). The cisterna magna was then cannulated percutaneously and ICP was slowly increased using injected saline. During the injection, the dural surface was observed using an operating microscope. The pressure at which CSF leaked onto the dural surface was recorded as the leak pressure. To avoid brain herniation, pressure testing ceased at 55 to 60 cm H2O if no CSF leak was noted.

After this evaluation, the dogs were harpinized and killed. The animal heads were pressure-perfused with formalin after a saline rinse. Tissues were embedded in paraffin, cut, and stained with H & E for evaluation by a veterinarian pathologist blinded to the study groups. The focus of the microscopic examination of the tissue samples was tissue healing, with special attention to neurocompatibility, dural thickness, implant absorption, and dural–cerebral cortex scar (adhesion) formation.

**Statistical Analysis**

Histological data from the two brands of collagen patches were pooled because their use and effect were indistinguishable as measured by the four parameters described previously. To determine the effect of the hydrogel treatment, the presence of intraoperative and postoperative CSF leaks and the dura–bone flap adhesion scores were analyzed using a two-sided Fisher exact test. The CSF leak pressure at the time of harvest was analyzed with SAS statistical soft-
Fig. 2. Intraoperative photographs of the experimental procedure. After the craniotomy and creation of the dural defect, the pia-arachnoid was cut to ensure CSF outflow (left). After duraplasty placement (in this case with Durepair), the hydrogel was applied to the dural graft and dural edges to obtain a watertight seal (right).

Results

Clinical and Neurological Evaluations

Eleven dogs tolerated the surgical procedures well. Throughout the postoperative course, these 11 dogs remained in excellent general health and were neurologically intact. Fifteen days after surgery, one dog in Group 4 (Durepair and hydrogel) developed a sudden onset of neurological symptoms (ataxia, nystagmus, and weakness). The animal was killed, and an independent veterinary pathologist found recent (<3–4 days) hemorrhage and thrombosis in vessels in the brain stem. Given the location of the hemorrhage and the timing of its onset, the pathologist concluded that the thromboses were unrelated to the surgical procedure or treatment. This animal was excluded from analysis and replaced by another dog, which was put into the same group as the dog it replaced, and underwent the same experimental procedure as the previous dog.

Intraoperative Sealing Evaluation

As expected, the six duraplasty-only dogs (100%) all had spontaneous CSF leakage that was visible without performing a Valsalva maneuver (Table 2, Fig. 3). The CSF was noted to be slowly dripping from the dependent edge of the duraplasty material. Animals that received hydrogel sprayed over the duraplasty onlay had no spontaneous CSF leaks, and all six withstood the Valsalva maneuver without leaks or postoperative CSF leakage. The intraoperative sealing capabilities of the groups receiving hydrogel in addition to a duraplasty were significantly better (p = 0.0022) than that of the duraplasty alone.

Postoperative CSF Leaks

Wound healing and the appearance of the scalp flap were evaluated daily in the first postoperative week and regularly thereafter. No overt CSF leakage through the incision was noted. In many animals, however, subcutaneous fluid accumulations were obvious within 1 week of surgery. Typically, these accumulations were resorbed within 3 to 4 weeks. These accumulations were sampled, but not evacuated, by 25-gauge needle aspiration after sterile preparation. The withdrawn fluid was confirmed to be CSF using a β2-transferrin test.

These CSF leaks were evident in the six duraplasty-only animals (100%), but in only one of the six animals (16.7%) receiving the hydrogel sealant (p = 0.0152, two-sided ANOVA; Table 2, Fig. 3). Thus, the use of the hydrogel sealant over duraplasty onlays reduced postoperative CSF leaks by 83.3% compared with duraplasty onlays alone.

Dura Mater–Bone Flap Adhesions

Eight weeks after surgery, anesthesia was induced in each dog for exploration of the craniotomy and careful raising of the bone flap by a neurosurgeon blinded to the treatment groups. Typically, the duraplasty-only dogs had extensive scar tissue between the flap and dura (median adhesion score 4, range 3–4). This scar extended under the entire bone flap, including scar to the duraplasty materials (Table 2). In the dogs receiving hydrogel, there was less scarring to the bone flaps (median adhesion score 0.5, 0.8).

Summary of the intraoperative sealing efficacy, postoperative CSF leakage, and adhesion score and CSF leak pressure at termination of study

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Intraop CSF Leak Pressure</th>
<th>Postop CSF Leak</th>
<th>Adhesion Score (range 0–4)</th>
<th>CSF Leak Pressure (cm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>spontaneous</td>
<td>yes</td>
<td>4</td>
<td>11.5</td>
</tr>
<tr>
<td>25</td>
<td>spontaneous</td>
<td>yes</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>31</td>
<td>spontaneous</td>
<td>yes</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>27</td>
<td>spontaneous</td>
<td>yes</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>28</td>
<td>spontaneous</td>
<td>yes</td>
<td>4</td>
<td>7.6</td>
</tr>
<tr>
<td>32</td>
<td>spontaneous</td>
<td>yes</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>no leak at 20 cm H2O</td>
<td>no</td>
<td>2</td>
<td>56‡</td>
</tr>
<tr>
<td>30</td>
<td>no leak at 20 cm H2O</td>
<td>no</td>
<td>0</td>
<td>60‡</td>
</tr>
<tr>
<td>34</td>
<td>no leak at 20 cm H2O</td>
<td>no</td>
<td>1</td>
<td>55‡</td>
</tr>
<tr>
<td>Durepair &amp; DuraSeal‡</td>
<td>no leak at 20 cm H2O</td>
<td>yes</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>26</td>
<td>no leak at 20 cm H2O</td>
<td>yes</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>29</td>
<td>no leak at 20 cm H2O</td>
<td>no</td>
<td>0</td>
<td>60‡</td>
</tr>
<tr>
<td>35</td>
<td>no leak at 20 cm H2O</td>
<td>no</td>
<td>0</td>
<td>55‡</td>
</tr>
</tbody>
</table>

* Mean CSF leak pressure at termination = 9.8 ± 3.8 cm H2O; mean adhesion score at termination = 3.8 ± 0.4.
† Mean CSF leak pressure at termination = 56.8 ± 2.5 cm H2O; mean adhesion score at termination = 0.7 ± 0.8.
‡ No leak detected at maximum ICP tested.
range 0–2). The scarring tended to occur around the edges of the bone flap, where the sealant would have been thin or not applied. The central areas of the bone flap, where the hydrogel-coated duraplasty materials were located, had few or no adhesions. The adhesion score of the hydrogel-treated dogs was significantly lower than that of the duraplasty-only dogs \( p = 0.0043 \), two-sided ANOVA). The average adhesion score in the hydrogel-treated dogs was 82.6% lower than the scores in the duraplasty-only dogs (Fig. 4).

**Dural Integrity at Harvest**

All six of the duraplasty-only treated animals (100%) exhibited CSF leakage at spontaneous pressures (mean 9.8 ± 3.8 cm H\(_2\)O), without the introduction of saline into the ventricle (Table 2). In contrast, all hydrogel-treated animals withstood pressures up to 55 cm H\(_2\)O without CSF leakage. Five of the hydrogel-treated animals never leaked CSF despite being subjected to pressure as high as 60 cm H\(_2\)O. The mean hydrogel-treated leak pressure was 56.8 ± 2.5 cm H\(_2\)O; in the hydrogel-treated dogs, the leak pressure was 5.8 times higher \( p = 0.0392 \), two-sided ANOVA) than the leak pressure in the duraplasty-only dogs (Fig. 5).

**Histopathological Findings**

The neodura, which was complete in all specimens, was composed primarily of a dense extracellular matrix consistent with mature collagen that spanned the durotomy site. Typically, the neodura was two to four times as thick as the native dura. The hydrogel treatment did not affect the neodura cell types, thickness, or shape compared with neodura that was untreated with hydrogel.

Adhesions between the new dura and the underlying pia-arachnoid were present in 11 of the 12 specimens. Adhesions were common and tended to be diffuse across the durotomy sites. There was no difference between groups regarding neodura pia-arachnoid adhesions.

The dura of animals that leaked CSF (duraplasty-only animals) showed localized tufts or tags of connective tissue on the outer surface of the neodura (Fig. 6). The connective tissue composing this tuft was dense but had a frayed appearance on the outermost surface. This focus of connective tissue likely represents a point along the neodura where there was an adhesion to the overlying calvaria. Locally extensive extravasation of erythrocytes was noted within the host pia-arachnoid in this region. This finding could be related to the removal of the overlying bone flap in an area of neodural adhesion to calvarial bone at the time of tissue procurement.

Chronic inflammation was noted in the neodura, mainly in response to residual collagen from the duraplasty materials (Fig. 7). In all hydrogel-treated specimens, mild to moderate infiltrates of macrophages with cytoplasmic vacuolation were present. The cytoplasmic vacuolation of these macrophages was consistent with phagocytosis of hydrogel components. The presence of these vacuolated macrophages was not associated with degenerative tissue changes within the neodura or adjacent tissues. There was no evidence of neurotoxicity associated with either duraplasty onlay material, with or without hydrogel.

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**Fig. 3.** Bar graph comparing the intraoperative \( p = 0.0022 \) and postoperative \( p = 0.0152 \) sealing efficacy of duraplasty onlay only (0% in both cases) compared with duraplasty and hydrogel sealant (100% and 83.3%, respectively).

**Fig. 4.** Bar graph showing the average dura–bone flap adhesion score and standard deviations (SDs) for duraplasty alone compared with hydrogel-treated duraplasty. Hydrogel-treated animals averaged an 82.6% reduction in adhesions \( p = 0.0043 \).

**Fig. 5.** Bar graph comparing the CSF leak pressures and SDs between duraplasty-only animals and hydrogel-treated animals. After bone flap removal, hydrogel-treated animals had CSF leak pressures 5.8 times higher than duraplasty-only animals \( p = 0.0392 \).
It is widely accepted that achieving a watertight dural closure after most neurosurgical procedures is critical to optimizing postoperative recovery for patients. In a recent study, however, only 6% of conventional sutured closures in cranial and spinal procedures were watertight when tested using a Valsalva maneuver. Unquestionably, this rate is even higher with popular onlay duraplasty grafts.

We have previously reviewed adjuncts to dural closure, such as the introduction of such materials as hydrogel sealants in neurosurgery, and shown that hydrogels can be engineered that are nontoxic and completely biocompatible, even when exposed to the cortical surface. This study extends the description of situations in which many of these new biomaterials, such as PEG-based hydrogels designed as sealants, may be introduced into common neurosurgical use. Two separate clinical trials have demonstrated the capability of a hydrogel sealant system to obtain 100% watertight closures with conventional sutured closures.

Patients in both of those studies received autologous duraplasty materials when needed.

This study augments these prior reports by demonstrating the compatibility of hydrogel sealant systems with the commonly used collagen duraplasty onlay grafts, which are not sutured. We have previously shown, using an in vivo gaping dural incision, that an engineered hydrogel can be used as an adjunct to prevent CSF leakage, and therefore such a control was not included in the present study.

The postoperative reduction in the rate of CSF leaks in the hydrogel-treated animals in this study demonstrates the benefit of intraoperative watertight closures. All of our duraplasty-only dogs had subcutaneous accumulations of CSF, compared with only one animal receiving hydrogel in addition to a duraplasty (an 83.3% leakage reduction). Arguably, this 100% postoperative leakage rate in the duraplasty-only animals is much higher than would be seen clinically; however, an 83.3% reduction in duraplasty onlay postoperative CSF leaks would have clear clinical benefits.

At the time of harvest there was an 82.6% reduction in peridural adhesion formation in the group receiving hydrogel compared with the duraplasty-only group. Peridural adhesions can result in prolonged or arduous reoperations. The PEG structure of the sealant may allow it to act as an inert adhesion barrier, protecting the dura while the surrounding tissues heal. After healing, the tissue layers regain proximity as the hydrogel absorbs. Thus, potentially, the planes created at surgery are preserved.

### Necessity of Sealing the Dura

For this study we chose to produce a relatively large dural defect (at least 1.5 cm in diameter) covered by a dural onlay substitute, thereby creating a situation in which the performance of all materials was tested. We believe the model used in this study represents a worst-case CSF leakage scenario, because canines produce a copious amount of CSF, which is found immediately beneath the dura (unlike in humans). Additionally, the incisions on the pia-arachnoid ensured additional CSF leakage. Moreover, in humans, most dural substitute materials would likely be used in an onlay fashion over slits in the dura or where there are edge-to-edge gaps of dura of only a few millimeters. Thus, in humans CSF leakage may not be as obvious because reliable dural substitute materials need only cover dural breaks of a few millimeters at most. Nevertheless, we believe this study describes the capabilities, benefits, and limits of the materials used. There are often situations in which relatively large areas of gaping dura, or where dura has been damaged or resected, that require wide coverage by a dural patch. In addition, after a craniectomy, the scalp may adhere firmly to the dural surface, creating a difficult situation during reoperation. Adding a hydrogel sealant in these instances may allow the closure and healing to progress more smoothly and potentially with fewer complications and may also allow a separation between tissue layers.

Cerebrospinal fluid leakage after intradural surgery is common (Table 3); the CSF may leak at the dural suture line and pose a risk of significant morbidity and the potential of developing meningitis. Meningitis, the most frequent and severe complication of persistent CSF leakage, is associated with a mortality rate as high as 20%. Prevent-
tion of CSF leakage by means of a watertight dural closure significantly decreases postoperative occurrences of positional headaches, hydrocephalus, and pseudomeningoceles. 5,13,24,31

Postoperative CSF leaks are usually diagnosed using a conservative definition as follows: 1) CSF leakage or pseudomeningocele-related surgical intervention (breaking the skin, such as wound revision, lumbar drain placement, or aspiration); 2) CSF leakage confirmation by diagnostic testing (β2-transferrin); or 3) CSF leakage confirmation by clinical evaluation, including physical examination of the surgical site. It is important to consider the postoperative definition of CSF leakage when comparing our results with those of other reports. Dogs with leaks had large collections of subgaleal CSF, which was confirmed by β2-transferrin testing.

In patients, postoperative CSF leaks can manifest overtly as otorrhea, rhinorrhea, and incisional leakage, or with less obvious symptomatology such as minor pseudomeningoceles or subgaleal collections. Without a prospective evaluation, minor fluid collections may go undetected, and depending upon their severity, these fluid collections may even go untreated. Therefore, these types of events would not be reported as CSF leaks. Furthermore, most reviews are retrospective, or patient follow-up is limited. Consequently, the rate of reported CSF leaks likely underestimates the actual incidence of this postoperative complication. The reported literature probably represents a conservative estimate of the true benefit that the hydrogel could provide in terms of preventing postoperative CSF leaks. 4,9–11, 16,17,25–27,32

Use of Dural Sealant Material or Patches in Prospective CSF Leakage Studies

It is difficult to compare the use of other, older liquid “sealant” materials to the newly developed hydrogels that act as true tissue sealants, used with or without dural patches. Few studies based on neurological models have been conducted using tissue sealants to augment dural closures. Alleyene and colleagues’ reported on an intriguing hydrogel (FocalSeal, Focal, Inc.) that was modified from a lung sealant and evaluated as a dural sealant. In a canine model, cranial dural gaps of 1 to 2 mm were treated with a hydrogel application. To stabilize the hydrogel, it was necessary to apply it in two separate phases using a small brush of the liquid primer and sealant solution and a xenon arc lamp for photopolymerization. Despite its resultant effective sealing and decreased adhesion formation, it was never approved or commercialized in the US.

Other comparable prospective studies have examined the prevention of CSF leaks in humans with nonhydrogel seal-
Kumar and associates evaluated the use of a bioadhesive (BioGlue Surgical Adhesive, CryoLife, Inc.) as a dural sealant to prevent CSF leaks. This material is approved in the US for the repair of large vessels to achieve hemostasis. Craniotomies were performed for a variety of indications, including tumor resection, cyst fenestration, microvascular decompression, and aneurysm. A subset of the patient population (11%) underwent craniotomies for resection of acoustic neuromas. Of the 167 craniotomies in this cohort, 70% were supratentorial procedures. The authors provided no criteria for the diagnosis of CSF leakage, and the report appears to exclude pseudomeningoceles. Furthermore, patients were required to return for only one follow-up visit at 6 weeks. Postoperative CSF leaks, described as fistulas, occurred in two craniotomy patients (1.2%). No BioGlue was used in combination with a dural patch.

Histological Considerations of Dural Patch or Sealant Materials

Based on our histological evaluation, the dura and neodura thickness, integrity, and composition were similar in the hydrogel-treated and duraplasty-only animals. Therefore, the reason for the CSF leaks remains unknown. Based on gross inspection at exploration, the surrounding dura and duraplasty portion of the hydrogel-treated animals appeared stronger than in the animals without the hydrogel. We postulate that the robust initial surface seal provided by the hydrogel allowed the dura to withstand the high ICP during testing for CSF leaks. Perhaps adhesions between the duraplasty onlay and bone flap contained minute channels through which CSF traveled through the graft. Histological examination of tissue samples from the duraplasty-only animals did reveal tufts or tags of tissue on the outer surface of the neodura that were related to adhesions sites on the underside of the calvaria. Removal of the overlying bone flap in this region of neodura adhesions may have damaged the neodura, accounting for (at least in part) leakage of the CSF during pressure testing. Identification of continuous channels through the thickness of the neodura was not possible to locate histologically (explaining the lack of histological evidence), and presumably these would have lysed or collapsed when the bone flap was removed or would not be apparent unless there was fluid traveling at pressure through the channels.

As it heals, collagen-based duraplasty material is likely not as integrally strong as normal dura, and under pressure could allow CSF egresses through small channels. As observed under the operating microscope, most of the leaking CSF came directly through the collagen duraplasty material and appeared as “weeping” or small microdroplets collecting on the duraplasty surface. During postoperative healing, the hydrogel sealant may seal or prevent the formation of a continuous channel.

### TABLE 3

Summary of the incidence of CSF leakage in retrospective reviews of posterior fossa surgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Pathology Treated</th>
<th>CSF Leakage Criteria</th>
<th>Rate of CSF Leaks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patir &amp; Banerji, 1990</td>
<td>179 (no preop shunt)</td>
<td>various posterior fossa tumors (34% acoustic neuromas) Chiari malformation Type I via suboccipital craniotomy</td>
<td>incisional CSF leaks &amp; pseudomeningoceles (undefined) epidural fluid collections requiring aspiration &amp; compression bandage</td>
<td>17.2 (9.2% CSF leaks &amp; 8.0% pseudomeningocele)</td>
</tr>
<tr>
<td>Cristante et al., 1994</td>
<td>26</td>
<td></td>
<td></td>
<td>11.5</td>
</tr>
<tr>
<td>Narotam et al., 1995</td>
<td>67 (posterior fossa w/ DuraGen duraplasty)</td>
<td>not specifically described</td>
<td>CSF leaks requiring repair or lumbar drainage (undefined), apparently no pseudomeningoceles</td>
<td>4.5</td>
</tr>
<tr>
<td>Anson &amp; Marchand, 1996</td>
<td>13 (suboccipital)</td>
<td>various lesions (meningioma, Chiari malformation, trigeminal neuralgia, no acoustics), duraplasty w/ DuraGuard</td>
<td>CSF leaks/pseudomeningoceles (undefined)</td>
<td>7.7</td>
</tr>
<tr>
<td>Matthis et al., 1996</td>
<td>134</td>
<td>posterior fossa meningiomas related to the cerebellopontine angle</td>
<td>CSF fistulas requiring drainage or surgical intervention &amp; subcutaneous CSF collections requiring diversion (apparently no pseudomeningoceles treated w/ aspiration/compression bandage)</td>
<td>6.2</td>
</tr>
<tr>
<td>Vanaclocha &amp; Saiz-Sapena, 1997</td>
<td>26 (13 per group)</td>
<td>Chiari malformation Type I via suboccipital craniotomy comparison of cadaveric dura vs. occipital pericranium with fibrin sealant</td>
<td>CSF leaks requiring surgical intervention (additional stitches or aspiration)</td>
<td>15.4 in cadaver dura group; 0 w/ occipital cranium &amp; fibrin sealant</td>
</tr>
<tr>
<td>Manley &amp; Dillon, 2000</td>
<td>339</td>
<td>posterior fossa craniotomies</td>
<td>pseudomeningoceles requiring treatment</td>
<td>5.6</td>
</tr>
<tr>
<td>Munshi et al., 2000</td>
<td>23 (w/ duraplasty)</td>
<td>Chiari malformation Type I, follow-up performed through 6 mos</td>
<td>CSF leaks requiring intervention</td>
<td>8.7 (4 subgaleal CSF or seroma collections resolved w/ conservative treatment, not included in leak rate)</td>
</tr>
<tr>
<td>Alzate et al., 2001</td>
<td>66</td>
<td>Chiari malformation, duraplasty w/ DuraGuard</td>
<td>CSF leaks requiring wound revision or drainage clinically apparent postop pseudomeningoceles requiring treatment</td>
<td>6.2</td>
</tr>
<tr>
<td>Gnanalingham et al., 2003</td>
<td>84</td>
<td>posterior fossa tumors including astrocytomas, medulloblastomas, &amp; others</td>
<td></td>
<td>16.0</td>
</tr>
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</table>
of such channels, increasing CSF leak pressure at the time of harvest. Regardless of origin, increasing the integrity of the dura mater would be beneficial if further surgical procedures become necessary.

Based on the histological examination results, the healing of the durotomy site was comparable between both groups. Healing was characterized by the formation of a neodura composed of dense connective tissue with areas of adhesions to the underlying cerebral cortex. These dura-cortex adhesions appear to result from the overlying collagen grafts, because no difference was seen in animals in which hydrogel was applied. The application of the hydrogel did not affect formation of the neodura because there was no difference in collagen absorption and replacement with endogenous tissues between the groups. Application of the hydrogel sealant was not associated with neurotoxicity, delayed healing, degenerative changes, or increased dura–cortex adhesions.

An important consideration is the histological structure imposed by the dural graft material on the healing process. Lyodura, Duragen, Durepair, and DuraSeal are replaced by granulations of collagenous tissue. In animal experiments, Gore-Tex has been incorporated with fibroblastic and osteoblastic penetration.28 This migration of the tissue elements that prevents CSF egress takes time. In animals with spinal dural leaks, primary fibroblastic bridging of a 2-mm durotomy was not seen until postoperative Day 6; not until postoperative Day 10 was ablation of this defect seen uniformly.7

Biocompatible hydrogels such as PEG hydrogel appear to function as a bridge or scaffold, which may be conducive to cell migration and the development of the cytoarchitecture undergoing the healing process; however, cells cannot migrate through such a PEG-based hydrogel barrier. It is believed that after application, the PEG hydrogel persists as an inert space-filler, which separates tissues while they heal independently. This separation is maintained while the tissues heal, and then the hydrogel absorbs without creating significant inflammation, resulting in the preservation of the surgical plane between the dura and surrounding tissues.

The characteristics of PEG hydrogels uniquely suit them as next-generation sealants that could be tailored for many neurosurgical situations. In comparison, fibrin glue lacks the sealant properties of engineered PEG-based hydrogels.35 The core strength of these materials is the PEG composition. Polyethylene glycol is one of the most widely used polymers in the pharmaceutical industry, in both solid and liquid forms. The PEG structure makes the sealant highly compatible with tissue, whereas its synthetic origin eliminates the potential for viral transmission.35 After implantation these hydrogels consist of more than 90% water, while the remaining solids consist of more than 96% PEG. Once in the bloodstream, PEG is rapidly cleared,44 and is highly compatible with tissue.40 The crosslinking chemistry occurs in seconds without being exothermic and has adequate strength to prevent postoperative CSF leaks. The prevention of postoperative adhesions observed in this study may reflect the presence of the inert, adherent hydrogel layer on the dura. This physical separation allows the dura and extradural tissues to heal in the surgical plane so that subsequent hydrogel absorption in the natural extradural planes is maintained.

We did not observe evidence of complications, clinical or histological, produced by swelling of the hydrogel used in this study. Hydrogels, including those based on PEG and other compounds, are well known to swell when exposed to water or other fluids, and thus care must be taken to apply them in a fashion consistent with their design and where space may allow for potential increase in their volume. The hydrogel in this study was effective at thin layer applications (average of 2 mm). Hydrogels in development will offer minimal degrees of swelling while preserving effect.

Clinical comparisons of these new biomaterials will be needed. Nonetheless, advantages such as biocompatibility, decreased neurotoxicity, elimination of viral transmission, and important adhesion capabilities should improve neurosurgical technique, especially as these materials continue to be refined.

Conclusions

In an experimental canine model of cranial dural resection in which a marked CSF leak was created, and after undergoing onlay of a collagen-based xenograft duraplasty alone, 100% of the animals demonstrated CSF leakage. In contrast, application of a hydrogel sealant to the duraplasty prevented CSF leakage in 83.3% of animals exposed to ICP well beyond typical physiological levels. The inert nature of the synthetic PEG chemistry of the hydrogel used in this study maintains a separation between the dura and overlying tissues during healing, reducing the formation of epidural adhesions (reduced by 82.6% in this study). This improvement in dural integrity was demonstrated by the 5.8-fold increase in the pressure needed to induce a CSF leak after bone flap removal for hydrogel-treated animals.

This hydrogel technology possesses the dual attributes of a sealant and an adhesion barrier and could be an important tool for cranial surgery. The potential to reduce postoperative morbidity related to CSF leakage, coupled with the reduced formation of peridural scar tissue and enhanced dural integrity, suggests that such hydrogel sealants may offer advantages for neurosurgical techniques resulting in significant patient benefits.

Disclosure

Confluent Surgical, Inc., Waltham, Massachusetts, provided the hydrogel for this study and a grant to offset costs of the study. Robert F. Spetzler, M.D., did not take part in surgery, blinded analysis, or assessment of the data because of his position as a stockholder in Confluent Surgical, Inc., but did participate in the conception of the study.

Disclaimer

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