Adherus Dural Sealant as an Adjunct to Sutured Dural Repair in a Canine Cranial Durotomy Repair Model

Anthony L. Asher, MD, FACS¹, Michael A Carnahan, PhD², Eric L. Adams³, Robert B. Boyd, DVM³, Mark T. Butt, DVM., DACVP⁴


SUMMARY: The objective of this study was to evaluate the safety and effectiveness of Adherus Dural Sealant when used as an adjunct to sutures in dural closure in a canine durotomy repair model. The effectiveness was evaluated at time of surgery, Day 8 and again at approximately 6 months by pressure testing. The safety and endurance of the test article was evaluated over approximately six months using magnetic resonance imaging, clinical evaluations, clinical pathology, and histopathology. During pressure testing at all specified time points, Adherus Dural Sealant provided 100% water-tight closure. None of the Adherus Dural Sealant-treated incisions leaked at intracranial pressures up to 50 mmHg. MRI scans at 2 to 4 days post surgery and monthly thereafter showed the test material clearly visible in all images (T2, FLAIR, T1, and T1 with contrast) two to three days following surgery. The test article continued to be visible, although degrading, through the 3 month scan, barely discernible in a portion of the scans at 4 months, and not present in the 5 and 6 month scans (T2 images). Adherus Dural Sealant was well-tolerated and none of the treated animals experienced test article related clinical signs after surgery. There were no test article related changes in body weight, food consumption, neurological/physical examination parameters, and clinical pathology parameters. Histopathologic evaluations indicate that there were no morphologic changes associated with a single topical administration of Adherus Dural Sealant to a durotomy site in beagle dogs at seven days post surgery or at six months post surgery.

INTRODUCTION

Despite meticulous sutured closure of the dura following neurosurgical procedures, cerebrospinal fluid (CSF) leaks are frequently observed. To augment this closure, a variety of onlay grafts, haemostatic agents, and surgical sealants or adhesives are commonly used. Most of these products either do not provide watertight closure or are hemostats that actively participate in the clotting cascade and are not indicated for use in neurosurgery.

While many of these products work well when used within their indicated fields, neurosurgical devices such as dural sealants require tenacious tissue adherence to provide a mechanical CSF barrier, minimal swelling to prevent mass effects and neurological complications and an extended rate of degradation since the dura is relatively slow to heal.

Adherus Dural Sealant was specifically designed to provide a strong, watertight barrier to compromised dura and maintain its strength over the entire course of dural healing while remaining dimensionally stable. The architecture and ratio
of the unique crosslinking components within Adherus Dural Sealant impose the formation of a densely crosslinked network. This constricted network and the selection of relatively robust degradable linkages make the sealant strong over the course of multiple weeks and dimensionally stable in the presence of bodily fluids.\(^1\)

Following the completion of a battery of biocompatibility testing which demonstrated that the synthetic hydrogel was non-toxic, non-hemolytic, non-irritant,\(^2\) and not neurotoxic,\(^3\) the safety and efficacy of Adherus Dural Sealant was confirmed using an established canine durotomy repair model.\(^4,5\)

**MATERIALS and METHODS**

**Adherus Dural Sealant**

The Adherus Dural Sealant system (HyperBranch Medical Technology, Inc.) is a hydrogel sealant designed for use as an adjunct to standard methods of dural repair, such as sutures, during neurosurgical intervention to provide watertight closure. The hydrogel sealant requires the preparation of two precursor solutions that, once mixed within the supplied applicator, rapidly cross-link in situ to form a solid, absorbable, biocompatible PEG-based hydrogel. The resultant hydrogel is primarily composed of water (approximately 85% by weight) and the remaining components are fully synthetic, containing no human or animal derived products. The first precursor contains a modified polyethylene glycol (PEG) polymer with terminal electrophilic ester groups, while a second precursor solution possesses a component containing nucleophilic amine groups. The complementary end groups undergo an electrophilic-nucleophilic reaction, resulting in crosslinking and the formation of a hydrogel. Once implanted, Adherus Dural Sealant minimally swells, exhibiting only a 8% dimensional change in any axis.\(^1\) It slowly degrades over approximately 90 days through the hydrolysis of ester linkages. The hydrolyzed polymer constituents are primarily cleared through the renal and hepatic pathways.

**Surgical Procedure**

Fifteen male beagle dogs (Covance Research Products, Inc., Kalamazoo, Michigan) were quarantined for at least ten days before the study was initiated. The study was conducted at Northern Biomedical Research, Inc. in accordance with the United States Food and Drug Administration (FDA) Good Laboratory Practice Regulations (GLP) (21CFR Part 58), the Japanese Ministry of Health, Labor, and Welfare (MHLW) Good Laboratory Practice Standards Ordinance 21, and the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C (97) 186/Final]. The dogs were approximately 13-16 months old and weighed 11.1 to 14.2 kilograms. The animals were randomly assigned to the treatment groups as illustrated in Table 1.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1 Week (Histopathology, pressure test)</th>
<th>6 Month (MRI, Histopathology, pressure test)</th>
<th>6 Month Histopathology Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherus Dural Sealant</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 1** Treatment groups and number of animals at each necropsy interval.

The animals were pretreated with atropine sulfate (0.04 mg/kg at 0.54 mg/ml) as a subcutaneous injection. Approximately 15 minutes later, an IV dose of thiobarbiturate (16 mg/kg at 50 mg/ml) was provided to induce sedation. Animals were then intubated and maintained on approximately 1 liter of oxygen and 2.0% isoflurane. The anesthetic gases and mixtures varied as required for each individual animal. Prednisolone sodium
succinate IV (30 mg/kg at 50 mg/ml) and flunixin meglumine IM (2 mg/kg at 50 mg/ml) were administered prior to surgery. Using routine sterile techniques, an approximate 3 cm x 2 cm bone flap was removed from the left front parietal region of the skull using a 1.4 mm burr drill bit and the dura and arachnoid were incised to a length of approximately 2 cm in the parasagittal plane for all animals. The incision was then loosely approximated with 6-0 nylon suture, leaving a gap of approximately 2 mm. All durotomy sites continued to leak CSF following primary closure with suture. The treated animals then had the durotomy site blotted dry and test article applied to a depth necessary to cover the suture knots (Figure 1 and 3). Once the test article had cured, confirmation of closure was evaluated using a Valsalva maneuver up to 20 cm of H₂O for approximately 5 seconds. If leakage occurred, additional test article was applied. The control animals received no treatment upon the observation of a leaking wound (Figure 2 and 4). The bone flap was replaced and secured with 3-0 nylon sutures and dental acrylic (DuraLay, Reliance Dental Manufacturing Company, Worth, Illinois). The skin and musculature were closed in layers with sutures (3-0 nylon and 2-0 nylon respectively), followed by tissue adhesive. Animals were recovered from anesthesia, provided butorphanol tartrate IM (0.05 mg/kg at 2 mg/ml) and placed on a post surgical antibiotic, cefiofur sodium IM (5 mg/kg at 50 mg/ml) b.i.d. (one injection during or prior to surgery followed by three injections post surgery).

Figure 1 Photographs comparing an Adherus Dural Sealant-treated durotomy site at day 1 (intraoperative), on the left, with the same site at day 8, on the right.

Figure 2 Photographs comparing a control durotomy site at day 1 (intraoperative), on the left, with the same site at day 8, on the right.

Following surgery, body weights were monitored weekly, clinical observations were performed daily, clinical pathology was collected one week after surgery, food consumption was monitored daily, and neurological and physical examinations were performed at one month and before necropsy.

One week following surgery, the six animals in the 1 Week group were sedated, evaluated, pressure tested, perfused with saline and 10% neutral buffered formalin, and tissues were harvested for histopathological analysis.

Monthly scans were conducted on the 6 Month (MRI, Histopathology, Pressure Test) animals to determine the presence of the test article. Six months following surgery the remaining seven animals had MRI scans and were sedated, evaluated, pressure tested (except those in the histopathology only group), perfused with saline and 10% neutral buffered formalin, and tissues were harvested for histopathological analysis.
At the end of their treatment periods, all animals were subjected to a full necropsy. Prior to necropsy, animals were provided with an I.V. bolus of heparin Na, 200 IU/kg. The animals were perfused via the left cardiac ventricle with 0.001% sodium nitrite in saline followed by 10% neutral buffered formalin fixative. Tissues from all animals were harvested and saved in 10% neutral buffered formalin.

**Durotomy Site Evaluations by MRI**

Two to three days following the surgical procedure, four Adherus Dural Sealant and three control animals in the 6 month group were sedated and taken to the onsite MRI for evaluation. For the MRI, an IV catheter was inserted and the animals were maintained on inhalant anesthesia. The animals were placed in a nylon stereotaxic head holder prior to imaging so that the positioning could be replicated at subsequent time points. The animals were then scanned on a Picker (Phillips) 1T MRI Scanner. The following sequences were utilized for the evaluation: T2-weighted, FLAIR, T1-weighted, and T1 weighted with contrast. Gadodiamide IV (0.2 ml/kg at 287 mg/ml) was utilized as the contrast agent. The sequence parameters are listed in Table 2. These same animals were reevaluated monthly after the initial surgery until the test article was no longer visible with MRI. The animals were anesthetized in the same manner as previously stated and subsequent MRI evaluations were performed using the same sequences.

<table>
<thead>
<tr>
<th>Sequence Parameters for MRI evaluation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo Time (ms)</td>
</tr>
<tr>
<td>Repeat Time (ms)</td>
</tr>
<tr>
<td>Field of View (cm)</td>
</tr>
<tr>
<td>Slice Thickness (mm)</td>
</tr>
<tr>
<td>Gap (mm)</td>
</tr>
<tr>
<td>Resolution</td>
</tr>
<tr>
<td>Flip Angle</td>
</tr>
<tr>
<td>Signal Averages</td>
</tr>
</tbody>
</table>

**Pressure Testing**

All animals subject to necropsy at one week and seven animals in the 6 month sacrifice group underwent pressure testing prior to perfusion. Animals were sedated as stated previously and intubated. Under inhalant anesthesia, the surgical site was exposed and the bone flap was carefully removed.

Once the durotomy site was examined for spontaneous CSF leaks, the cisterna magna was cannulated with a 20 gauge spinal needle with attached three-way stopcock containing the ICP (intracranial pressure) transducer (Codman Microsensor ICP Transducer) and saline. Once the baseline intracranial pressure was measured using the ICP transducer, saline was slowly injected to a maximum ICP of at least 40 mmHg and the maximum intracranial pressure reached was recorded. During the procedure, the durotomy site was closely monitored for the presence of any CSF leakage. If leakage occurred, the pressure at which it began to leak was noted.
Histopathology

Three full coronal (transverse) sections through the brain (including the pia/arachnoid layers of the meninges) underlying the durotomy site and three sections through the calvarium and dura (also through the durotomy site) were trimmed and embedded from each animal. The tissues from each section were placed into oversized blocks. The other tissues, including the bone flap, were trimmed and embedded in regular sized blocks. All tissue sections were embedded in paraffin, sectioned at approximately 5 μm, and stained with hematoxylin and eosin (H&E). The resulting glass slides were examined by a board certified veterinary pathologist with specific expertise in the examination of the nervous system.

Statistical Analysis

Body weights, body weight changes, clinical pathology data (hematology, serum chemistry and coagulation), heart rate, body temperature, respiration, and food consumption data were analyzed by a one-way analysis of variance and comparison of the control group to the treated group by Dunnett’s test. Analysis was two-tailed for significance levels of 5% and 1%.

RESULTS

Clinical and Neurological Evaluations

All animals recovered quickly from the surgical procedure, the surgical sites healed as expected and the animals remained neurologically intact throughout the course of the study. Furthermore, there were no test article-related clinical observations, changes in food consumption or body weight, nor were there any changes in clinical pathology parameters for the six animals sacrificed on Day 8 or for the nine animals sacrificed after 6 months.

MRI Evaluations

Seven animals, four treated and three controls, in the 6 month group were subject to MRI throughout the study. Animals were scanned 2 to 3 days following surgery and monthly thereafter to assess the degradation profile of the test article as well as any morphologic changes that may have occurred.

Figure 5 Representative T2 MRI images of one treated animal over the course of the first 90 days.

A review of the scans showed the test material clearly visible in all images two to three days following surgery and can be followed for approximately three months. The degradation, indicated by a decrease in size over time, was most clearly monitored in the T2 images which showed a hyperintense becoming isointense signal over time due to the inherently large amount of water in the hydrogel (Figure 5). Partial degradation was noted at the 1 month scan. This degradation continued through the 2 and 3 month scans and the test material was barely discernible in some of the 4 month T2 images. The test material was not discernible in the 5 and 6 month T2 images. The degradation can also be followed in the T1 images (hypo intense signal) but is not as dramatic as what can be seen in the T2 images.

The test material exhibited a hyper intense signal visible in the T1 images suggesting that it was contrast positive. The signal was not visible in the test material at the Day 3/4 scan, suggesting there was no uptake of contrast by the test material. Then, at 1 month it was clearly visible in the test material and followed a similar degradation pattern to what is seen in the T2 images.
The uptake was clearly visible through the 4 month scan on all animals then dissipates in the 5 and 6 month scans.

A hyper intense signal can be seen near the bone flap and in the surrounding musculature in the T2 and T1 with contrast images (somewhat in the T1 images) on all seven animals, two to three days following surgery and was suggestive of edema due to retraction at the surgical site. This edema was attributed to the large amount of musculature that had to be reflected to expose a large enough area to accommodate removal and subsequent replacement of an approximate 2 cm x 3 cm bone flap. This hyperintensity, however, had substantially subsided by the 1 month scan in both the control and treated animals.

Minor displacement of the cerebral cortex was noted in the MRI images adjacent to the site of the craniotomy in all animals. The displacement was typically more pronounced when the bone flap was placed over the test material, displacing the brain within a closed vault. The flattening can be seen in the treated animals at one month, but resolved as the test material degraded and was no longer present at 6 months, an observation confirmed at necropsy and during histopathological examination.

**Pressure Testing**

Prior to sacrifice, the six Day 8 necropsy animals had pressure testing conducted to challenge the durotomy repair methods. The results are presented in Table 4 and the average maximum ICP reached at the day 8 time interval is presented in Figure 6. All three of the animals in the control group were leaking at baseline pressures, but there were no leaks at baseline pressures in the test group. Furthermore, all of the Adherus Dural Sealant-treated repair sites remained leak free at maximum ICP pressures between 40 and 50 mmHg (Figure 7).

<table>
<thead>
<tr>
<th></th>
<th>Initial ICP (mm Hg)</th>
<th>Maximum ICP (mm Hg)</th>
<th>CSF Leakagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherus Dural Sealant Group</td>
<td>12</td>
<td>50</td>
<td>No leaks</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>40</td>
<td>No leaks</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>45</td>
<td>No leaks</td>
</tr>
<tr>
<td>Control Group</td>
<td>10</td>
<td>NA</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>NA</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>NA</td>
<td>Baseline</td>
</tr>
</tbody>
</table>

Table 2 Results of pressure testing prior to necropsy on day 8. aBaseline indicates that CSF was leaking when the bone flap was removed. NA=Not applicable.

![Figure 6](image)

**Figure 6** Average terminal CSF leakage pressure for control and Adherus Dural Sealant-treated groups at day 8. Note: None of the Adherus Dural Sealant treated sites leaked at a terminal pressure between 40 and 50 mmHg.

![Figure 7](image)

**Figure 7** Adherus Dural Sealant-treated durotomy site with CSF Pressure at 45 mmHg. Adherus Dural Sealant remained elastic and tissue compliant under high pressures which caused dura to bulge and gape.

Results of the pressure testing procedures conducted prior to the six month necropsy are
presented in Table 5. Two of the three animals in the control group were leaking at baseline pressures, although one of the leaks was most likely caused by a tear in the dura during bone flap removal. No leaks were observed at baseline pressures in the test group. Furthermore, all of the Adherus Dural Sealant-treated repair sites remained leak free at maximum ICP pressures between 46 and 49 mmHg. Only one of the control animals was leak free at maximum ICP pressure of 47 mmHg.

<table>
<thead>
<tr>
<th>Initial ICP (mm Hg)</th>
<th>Maximum ICP (mm Hg)</th>
<th>CSF Leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherus Dural Sealant Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>No leaks</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>No leaks</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>No leaks</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>No leaks</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NA\textsuperscript{a}</td>
<td>NA\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>No leaks</td>
</tr>
<tr>
<td></td>
<td>NA\textsuperscript{b}</td>
<td>NA\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Table 3 Results of pressure testing prior to necropsy at six months. \textsuperscript{a}Dura was leaking when bone flap was removed. \textsuperscript{b}Unable to obtain data due to tear in dura. NA=Not applicable.

**Histopathology**

**Day 8 Necropsy**

During trimming, there were no adhesions noted between the dura and the pia mater. The cerebral cortex underlying the durotomy site was flattened in most of the test and control animals at the day 8 timepoint. Since this observation was made for animals with and without the sealant, the process of replacing the bone plate was identified as a likely contributing factor. Because the flattening of the cerebral cortex did not correlate to any microscopic changes and was resolved by the six month necropsy interval, this change was not interpreted to be an adverse effect.

During microscopic examination, there were no adverse morphologic changes in the brain or the overlying pia/arachnoid meninges. The cerebral hemisphere underlying the site of the durotomy was flattened, but this displacement of cerebral cortical tissue did not cause any microscopic changes.

**Figure 8** Representative photomicrographs of histology slides from Adherus Dural Sealant (A) and Control (B) at day 8 necropsy showing incised dura. In Figure 8A, Adherus Dural Sealant is present on the periosteal surface of the medial dural flap (indicated with arrow). Figure 8B shows the medial dural flap of a control animal in which granulation tissue is evident. Minimal infiltrates of mononuclear cells (macrophages and plasma cells/lymphocytes) and neutrophils into the pia mater layer of the meninges were present in control and treated animals, an expected observation in any procedure that opens the dura. Minimal focal vacuolation, noted in a single treated and control animal, was only superficial and immediately adjacent to an area of thickened meninges (thickened by an
influx of inflammatory cells and possibly hypertrophy or slight hyperplasia of meningeal cells). Focal necrosis in the brain of a single control animal was due to trauma related to the initial creation of the bone flap. This iatrogenic lesion was of no biologic significance. All changes in the brain and meninges were due to the surgery and would be expected at a durotomy/craniotomy site.

Overall, there was no indication that the presence of the sealant was having any adverse effect on the dura, the surrounding tissues (including the brain) or the rate of dural closure.

**Six Month Necrospy**

During trimming, the brain, arachnoid, and dura for each animal sacrificed at six months was also normal. Dural attachments to the pia mater were limited in both groups. One pin-point adhesion between a suture and the underlying pia was noted in one of the Adherus Dural Sealant-treated animals and pinpoint adhesions were noted in one control animal. The flattening of the cerebral cortex, noted in the animals at the Day 7 sacrifice was not present.

There were no test article related changes in the animals sacrificed six months after surgery and there were no microscopic changes in the brain of any animal. Cellular infiltrates noted in the animals sacrificed at day 8 were completely resolved.

Dura bridged the previous durotomy site in all control and test article treated animals so there were no dura flaps. The dura was thickened in all animals, but the thickening was consistent with normal dura tissue which is essentially a specialized fibrous connective tissue. Adherus Dural Sealant was no longer visible on the dura of any of the treated animals.

---

**Figure 9** Representative photomicrographs of histology slides from Adherus Dural Sealant (A) and Control (B) at day 8 necropsy showing the pia (meninges). In Figure 9A and 9B, minimal infiltrates are evident (original magnification x 10).

The dural incision was identified in all animals. Adherus Dural Sealant was present on the periosteal surface of the dura in all three treated animals, indicating resorption of the sealant was not complete seven days post surgery (Figure 8A). As would be expected at 7 days post surgery, the 2 mm gap in the dura was not fully healed in either the test or control animals. Although there consistently was a gap between the medial and lateral dura flaps, it is likely that the process of trimming, processing, paraffin embedding and microtomy caused some interruption to the surgical site, making differences in the determination of early healing impractical.
In all animals, the bone flap was partially vascularized and partially populated by osteoblasts.

The calvarium was normal in all but one control and one treated animal. In one control animal, foreign body giant cells were present around remaining suture material in soft tissue adjacent to the bone of the calvarium. In one Adherus Dural Sealant-treated animal, a portion of bone at the medial side of the previous craniotomy site was necrotic and associated with granulation tissue, mononuclear cell infiltrates, osteoblast proliferation and focal necrosis at the periosteal surface of the dural side. These changes, were consistent with the resorption of a necrotic piece of bone. The most likely cause of these changes was trauma to the bone at the time of craniotomy, resulting in death of the resident osteoblasts and the subsequent resorption reactions. There was no evidence that these changes were in any way related to the test article, especially given the lack of changes in the other animals.

DISCUSSION

Once applied to the target tissue, Adherus Dural Sealant set in approximately one second, limiting the potential for run-off. The sealant seemed strong, tenaciously adherent to the dura and compliant with the pulsations caused by the dynamic changes in intracranial pressure.

Following application of Adherus Dural Sealant to a canine durotomy repair, there were no adverse clinical effects related to the application of the test article. There were no test article related clinical observations made in the 6 month period following application. Body weights and food consumption data remained consistent with that of the control animals over the same period. Physical and neurological evaluations performed over the six month period revealed no significant findings such as epidural mass effect, epidural or subdural hematomas, infection, or unusual inflammatory reaction that could be attributed to the test article. Clinical pathology parameters taken prestudy, one week, two months and 6 months following application showed no significant differences between treated and control groups that could be attributed to the test article. At necropsy, there were no significant differences in organ weights between control and treated animals.

As expected, based on in vitro data\(^1\), MRI evaluations showed a consistent degradation profile over approximately 3 months with accompanying tissue ingrowth (thickening of the periosteum) at the durotomy site continuing for the next 3 months. The hydrogel was best visualized with T2-weighted images. When compared to control animals, the hydrogel was consistently visualized as a uniform, high signal band immediately adjacent to the dura. CSF collections and/or edema were typically visualized as irregular, hyperdense signal abnormalities.

During the first month, there were minimal changes in the size of the hydrogel. These findings were also noted with more frequent MRI images obtained at post-op days one, 14, and 21 during a pilot cranial durotomy repair study of the same design\(^6\). Furthermore, necropsy at the 14 and 21 day time intervals during this pilot animal study visually confirmed that the Adherus hydrogel did not undergo any appreciable dimensional changes. Volumetric expansion was likely constrained by the dense crosslinked network and the hindered degradation rate of the Adherus Dural Sealant. In comparison, other hydrogel sealants may undergo at least five times more volumetric expansion, especially during the first few weeks after implantation and have been observed to create neurological signs and symptoms secondary to volumetric expansion in both spine and cranial surgeries\(^7,8,9\).
The test article continued to be visible, although degrading, through the 3 month MRI scans (indicated by a decrease in volume of the hydrogel), barely discernible in a portion of the scans at 4 months, and not present in the 5 and 6 month scans (T2 images). Bone growth was not impeded by the sealant and can be seen between the bone flap and skull in the T1 images at the 4, 5, and 6 month scans and was confirmed macroscopically at necropsy.

Edema was noted near the bone flap and in the surrounding musculature in the T2-weighted and T1 with contrast MRI images for all animals. In the Adherus-treated animals, this imaging feature was not contiguous with the subdural space, presented above the hydrogel and lacked homogenous signal characteristics. These observations provided no radiographic evidence of a CSF leak in any of the six month animals receiving Adherus Dural Sealant.

Pressure testing at up to three weeks highlights the strength and durability of Adherus Dural Sealant, especially when comparing the 1 week necropsy interval to other dural sealants. Under similar test conditions with the same dural defect, DuraSeal Sealant System (Confluent Surgical, Waltham, MA) was leak free at pressures greater than approximately 40 mmHg in only 38% of the adequately sealed animals within the first week of testing. Furthermore all three animals tested at the 1 week time point reportedly experienced a leak at intracranial pressures between approximately 27 and 40 mmHg. These tests indicate DuraSeal begins to lose a significant amount of its functionality before the dura has had time to heal.

Over the course of the study, the dura and surrounding tissues healed as expected. Adherus Dural Sealant did not seem to cause adhesions between the dura and underlying pia mater even though it was directly applied over the gaping hole in the dura, crosslinking on and directly contacting the cerebral cortex. Finally, there were no histopathological changes in the brain, calvarium, meninges, or non-nervous system whereas only 1/6 of the control animals reached this level and 5/6 were leaking at baseline. Although the ICP pressures were limited in this study to prevent inadvertent trauma to neurological tissues such as brain stem herniation, higher pressures were reached during the pilot cranial durotomy repair study. In this study, pressures of 81 and 77 mmHg were reached at 14 and 21 days respectively without any leaks. The ability to sustain elevated ICP pressures for several weeks is unique to Adherus Dural Sealant (most other adhesives and sealants have significantly or completely degraded within two to three weeks) and corroborates previous in vitro testing.
organs associated with the test article in any of the animals.

CONCLUSIONS

Following surgical procedures involving compromised dura, Adheorus Dural Sealant provides a safe fluid barrier with exceptional strength and durability, minimizing postoperative complications associated with CSF leaks and pseudomeningoceles. Once applied, the sealant practically maintains its implantable dimensions, acting as a part of the native dura while it is gradually replaced by new tissue over approximately 3 months.

DISCLOSURE

Dr. Asher is a compensated consultant to HyperBranch Medical Technology, Inc. and has received compensation in the form of consultant fees, stock and stock options.

REFERENCES

1 Data on file at HyperBranch Medical Technology, Inc. and summarized in 2010-TR-04867-04867 R1

2 Data on file at HyperBranch Medical Technology, Inc.

3 Data on file at HyperBranch Medical Technology, Inc. and summarized in 2011-TR-05583-05583 R1


6 Data on file at HyperBranch Medical Technology, Inc.


