

First Human Clinical Experience with Adherus Dural Sealant for Watertight Dural Closure

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SUMMARY: This preliminary short term trial was performed to confirm the safety and effectiveness of Adherus Dural Sealant when used in lieu of or in conjunction with standard methods of dura repair to prevent cerebrospinal fluid (CSF) leaks. The PEG-based hydrogel sealant was used in 25 patients with confirmed CSF leaks in the cranial or spinal dura using either an open or transsphenoidal approach. Adherus Dural Sealant was 100% effective (17/17) at achieving intraoperative watertight dural closure when used as an adjunct to suture and 88% effective (7/8) in creating watertight closures when used as a method of primary dural closure. In this fourteen (14) day follow up study, no device related events or surgical site infections were observed.

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, hemostatic agents, and surgical sealants or adhesives are commonly used. Adherus Dural Sealant has been intentionally designed as a dural sealant which overcomes the shortcomings of many of these products. Specifically, Adherus Dural Sealant addresses concerns related to degradation rate, sealant swelling, mechanical strength, and the ability to achieve an immediate watertight seal.¹

Adherus Dural Sealant has undergone extensive in vitro biocompatibility, and preclinical safety and effectiveness testing. Of note, during pre-clinical testing using two established canine durotomy repair models^{2,3} in either the cranium or spine, there were no sealant-related adverse events. During these studies, Adherus Dural Sealant was 100% effective in sealing cranial CSF leaks intraoperatively and postoperatively at day 7

at CSF pressures up to 60 cm H₂O. In addition, Adherus Dural Sealant did not appear to impede healing of the dura. Adherus Dural Sealant was also 100% effective in sealing spinal CSF leaks intraoperatively and postoperatively (based on blinded MRI scans on study day 5 or 6) and again did not appear to hinder the rate of dural healing. Furthermore, when compared to controls, Adherus Dural Sealant significantly limited peridural scar formation and dural adhesions when applied to the spinal dura mater.

MATERIALS and METHODS

The Adherus Dural Sealant system (HyperBranch™ Medical Technology, Inc.) is a hydrogel sealant designed for use as an adjunct to standard methods of cranial 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 polyethylene glycol (PEG) based hydrogel. The resultant hydrogel is

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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 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 6% dimensional change in any axis¹. 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.

This prospective non-randomized study enrolled patients between September 2008 and July 2009 at a single center in South Africa (Sandton Medi-Clinic). Patients included in the study were those undergoing a variety of elective neurosurgical procedures including subjects with pre-existing CSF leaks and prior intracranial or spinal procedures within the last 12 months. Following dural closure, Adherus Dural Sealant was applied if a CSF leak was noted either spontaneously or upon Valsalva maneuver. After Adherus Dural Sealant was applied, a subsequent Valsalva maneuver was performed to demonstrate an intraoperative watertight seal. All patients in the study have been followed for at least two weeks postoperatively.

RESULTS

Twenty five patients between the ages of 38 and 71 received treatment with Adherus Dural Sealant following an elective neurosurgical procedure. Fourteen (56%) of the patients were male and eleven (44%) were female. Ten patients (40%) underwent treatment of the spinal dura following procedures such as discectomies and

laminectomies, and fifteen subjects (60%) received treatment of the cranial dura via craniotomy or transsphenoidal surgery.

Four patients exhibited a small defect within the spinal dura, in the range of 1mm X 0.5mm to 1mm X 2mm. In all four cases, a single application of Adherus Dural Sealant successfully closed the dura as a method of primary closure. Four subjects were also treated with Adherus Dural Sealant as a method of primary closure following a transsphenoidal surgical approach to resect a tumor or seal a spontaneous CSF leak. Three of these patients had a watertight closure following one Adherus Dural Sealant application. One patient developed a CSF leak upon Valsalva maneuver. This case was the first use of Adherus Dural Sealant in the sphenoid sinus and the CSF leak was most likely due to a poor application of the sealant. The patient was retreated a few days after surgery with a vascular pedicle graft and had no CSF leak at a 30 day follow-up visit. Since this case, the subsequent three transsphenoidal cases were sealed with Adherus Dural Sealant using another commercially available applicator with a longer applicator shaft. A second patient, originally presenting with a spontaneous CSF leak associated with Sternberg's canal, developed another spontaneous CSF leak after a leak-free two week follow-up visit. This patient was retreated with a fat graft and Adherus Dural Sealant and has not had further CSF leaks. It should be noted that within this group of eight patients, Adherus Dural Sealant was 88% effective in creating watertight closures when used as a method of primary dural closure.

Seventeen patients received treatment with the Adherus Dural Sealant device as an adjunct following primary dural closure with suture. Of these patients, cranial dura was closed in eleven patients with vicryl sutures, primarily following tumor resection or aneurysm clipping, and spinal

dura was closed in six patients with 5.0 prolene sutures, typically following incidental durotomy. The mean length of the durotomy was 4.2 cm (range 0.1 – 12.0 cm). Duraplasty materials were used in 10 patients, most commonly DuraGen Dural Graft Matrix (n=5) (Integra LifeSciences Co.), Spongostan Standard (n=3) (Ferrosan A/S) and then Gore Preclude PDX Dura Substitute (n=2) (W. L. Gore & Associates, Inc.). Following primary closure with suture, a CSF leak occurred in all seventeen patients, either spontaneously or following Valsalva maneuver. A single Adherus Dural Sealant application was 100% effective in obtaining a watertight closure where none existed previously in all seventeen patients when used as an adjunct to suture.

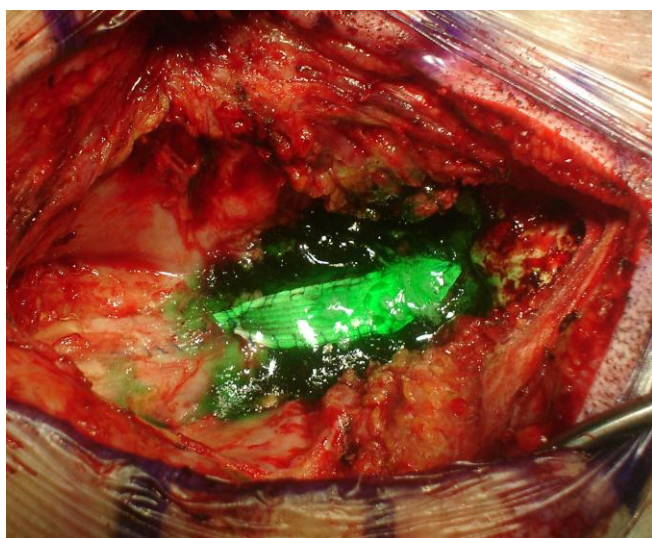


Figure 1 Adherus Dural Sealant applied over Preclude PDX Dura Substitute following procedure to correct Arnold Chiari malformation.

In all twenty five cases, the Adherus Dural Sealant formulation set immediately and provided a water tight seal during all cases on visual inspection. An average volume of 3.9 mL of Adherus Dural Sealant was used during each case. The hydrogel surgical sealant continued to provide a water tight seal in twenty-two of the twenty-three cases (96%) following Valsalva maneuver. A water tight seal was confirmed by a Valsalva maneuver in all ten patients with a spinal

dural defect and in twelve of thirteen patients with a cranial dural defect. A Valsalva maneuver was not performed in two patients who received treatment of the cranial dura.

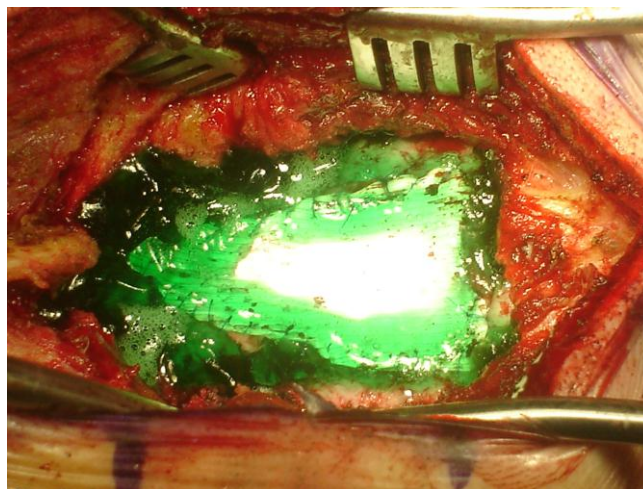


Figure 2 Adherus Dural Sealant as an adjunct to dural closure following removal of a posterior fossa tumor.

At least two weeks of follow up have been completed for all patients. During this visit, one patient presented with a postoperative CSF leak. One patient, initially presenting with a spontaneous CSF leak developed another spontaneous CSF leak 2.5 weeks after surgery. Wound healing progressed as expected in all patients and no patients (0%) developed surgical site or deep surgical site infections. There were also no reported device-related adverse events (0%).

DISCUSSION

During this initial clinical study, Adherus Dural Sealant was 100% effective in sealing intraoperative CSF leaks and 100% effective in preventing postoperative CSF leaks when used as an adjunct to standard methods of dural repair. When combined with cases in which Adherus Dural Sealant was used as a method of primary dural repair, the sealant was 96% effective in sealing intraoperative CSF leaks and 92% effective in preventing postoperative CSF leaks. The only reported CSF leaks were due to trouble

applying the formulation with the supplied applicator during the first transphenoidal case and a spontaneous CSF leak associated with Sternberg's canal in another case. During the follow up for the second case, it could not be determined whether the latest spontaneous CSF leak was coming from the site of the Adherus Dural Sealant application and there is a distinct possibility that the leak was coming from another location on the skull base. There were no hydrogel sealant related adverse events and no surgical site infections of any type.

As expected, Adherus Dural Sealant, like other commercially available hydrogels, is biocompatible, absorbable, flexible, and adherent to tissue. However, Adherus Dural Sealant is specifically designed to degrade at a slower rate than other commercially available sealants. The slower rate of degradation provides a watertight seal for at least one month while the dura heals, preventing complications such as late forming pseudomeningoceles. While healing, the presence of the hydrogel also separates the dura from other tissues, limiting dural adhesions.^{1,2,3}

Due to its enhanced mechanical strength, Adherus Dural Sealant may be applied in a thin profile while providing more than enough mechanical strength to seal CSF leaks. As a neurosurgical sealant, Adherus Dural Sealant is also specifically engineered to swell minimally to further limit mass effects and reduce the potential for adverse clinical events related to compression of neurological tissue. After placement in situ, Adherus Dural Sealant has a gravimetric equilibrium swelling of approximately 20%, or undergoes an approximate 6% dimensional change in any axis, and remains essentially in its initial form for over 1 month.¹

As an additional benefit, Adherus Dural Sealant, when challenged with approximately 10^{-5} to 10^{-6} CFU/0.1 mL of microorganisms such as *S.*

aureus, *B. atrophaeus*, *S. epidermidis*, *C. sporogenes*, *K. pneumoniae*, and *K. rhizophila*, either does not promote any growth or acts as an antimicrobial agent.⁴ The antimicrobial properties of Adherus Dural Sealant are related to the inherent properties of the hydrogel network and not an antimicrobial additive.

CONCLUSIONS

Upon completion of intradural neurosurgical procedures, obtaining a watertight dural closure is an important goal. In this study, Adherus Dural Sealant was 100% effective, both intraoperatively and postoperatively, when used as an adjunctive technique for watertight dural closure. Other than an immediate watertight seal, Adherus Dural Sealant also provided persistent tissue adherence, an adhesion barrier, antimicrobial properties, and a high degree of biocompatibility, with no potential for disease transmission or neurotoxicity. Adherus Dural Sealant treated patients experienced no device related adverse effects and there were no reported surgical site infections. This clinical experience endorses the use of Adherus Dural Sealant to provide safe and effective watertight dural closure when used as an adjunct to sutured dural repair.

DISCLOSURE

Dr. Vizirgianakis is a partner in a South African company that distributes the Adherus line of products. He has also received stock options from HyperBranch™ Medical Technology, Inc for his contribution in developing an ophthalmic bandage for HyperBranch™.

REFERENCES

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

² Data on file at HyperBranch Medical Technology, Inc. and summarized in 2010-CS-04875-04875 R1

³ Data on file at HyperBranch Medical Technology, Inc. and summarized in 2010-CS-04876-04876 R1

⁴ Data on file at HyperBranch™ Medical Technology, Inc.