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A Pivotal Randomized Clinical Trial Evaluating the Safety and Effectiveness of a Novel Hydrogel Dural Sealant as an Adjunct to Dural Repair

BACKGROUND: A watertight dural repair is critical to minimizing the risk of postoperative complications secondary to cerebrospinal fluid (CSF) leaks.

OBJECTIVE: To evaluate the safety and efficacy of a novel hydrogel, Adherus Dural Sealant, when compared with control, DuraSeal Dural Sealant System, as an adjunct to standard methods of dural repair.

METHODS: In this 17-center, prospective, randomized clinical trial designed as a noninferiority, single-blinded study, 124 patients received Adherus Dural Sealant (test sealant) and 126 received DuraSeal (control). The primary composite endpoint was the proportion of patients who were free of any intraoperative CSF leakage during Valsalva maneuver after dural repair, CSF leak/pseudomeningocele, and unplanned retreatment of the surgical site. Each component was then analyzed individually as a secondary endpoint. Patients were followed for 4 mo after surgery.

RESULTS: The primary composite endpoint at the 120-d follow-up was achieved in 91.2% of the test sealant group compared with 90.6% of the control, thus showing that the test sealant was statistically significantly noninferior to DuraSeal ($P = .0049$). Post hoc analysis of the primary composite endpoint at 14 d demonstrated superiority of the test sealant over the control ($P = .030$). Primary endpoint failures in the control group tended to occur early in follow-up period, while a majority of test dural sealant failures were identified through protocol-required radiographic imaging at the 120-d follow-up visit.

CONCLUSION: The test sealant, Adherus Dural Sealant, is a practical, safe, and effective adjunct to achieving a watertight dural closure after primary dural closure in cranial procedures.

KEY WORDS: Cerebrospinal fluid leak, Dural repair, Dural sealant, Hydrogel, Polyethylene glycol

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Of approximately 600 000 cranial neurosurgical procedures performed in the United States each year, more than half involve opening the dura mater.¹ Meticulous dural closure has long been advocated to help prevent complications, such as intracranial hemorrhage, hydrocephalus, focal neurological deficit, meningitis, pseudomeningocele, and cerebrospinal fluid (CSF) fistula. Standard methods of dural repair include use of running or interrupted sutures, occasionally supple-

mented with adhesives, hemostatic agents, and dural substitutes that include autologous, allogenic, or xenogenic collagenic connective tissue grafts, synthetic grafts and films, and newly formulated hydrogels.^{2–4} Despite the use of these techniques, the incidence of postoperative CSF leak commonly ranges from 0.9% to 10.9%.^{5–10} Furthermore, many of the newer materials currently used to augment dural closures are associated with potential drawbacks, such as inadequate seal formation,¹¹ central nervous system toxicity,^{12,13} and expansion in situ that can cause compression of neural structures.^{14,15}

Given the persistence of CSF leaks in clinical practice, an opportunity exists to refine current

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methods of dural closure. In this pivotal Food and Drug Administration (FDA) investigational device exemption clinical trial, 17 centers evaluated the safety and effectiveness of Adherus Dural Sealant when used as an adjunct to primary dural closure after a cranial procedure. This novel hydrogel was specifically formulated to address the most significant disadvantages to present methods of augmented dural closure such as lack of dimensional stability and variable mechanical strength of the sealant in the early postoperative period.¹⁶ Our multicenter trial evaluated primary and secondary endpoints during a 4-mo follow-up period and noted adverse events (AEs) by neurological evaluation, laboratory data, and magnetic resonance imaging (MRI) scans.

METHODS

Study Centers

Patients were enrolled between September 2010 and September 2012 at 17 centers in the United States (Carolina Neurosurgery & Spine Associates, Borgess Research Institute, SUNY Stony Brook, Rush University Medical Center, University of Virginia at Charlottesville, Colorado Brain and Spine Institute, West Virginia University Medical School, Saint Louis University, Oklahoma Spine and Brain Institute, University of Iowa Hospitals and Clinics, University of South Florida, Wayne State University, Florida Hospital, Mayfield Clinic, Penn State University, NorthShore University, and Wake Forest School of Medicine).

Adherus Dural Sealant

The Adherus Dural Sealant (HyperBranch Medical Technology, Durham, NC) is a novel hydrogel sealant designed for use as an adjunct to standard methods of dural repair (eg, sutures) to achieve watertight closure. The FDA approved this sealant system in March 2015 for this indication.¹⁷ It consists of 2 precursor solutions: one contains a modified polyethylene glycol (PEG) polymer with terminal electrophilic ester groups, and the other polyethyleneimine (PEI) solution has a component containing nucleophilic amine groups. To prepare the sealant, the 2 precursor solutions are first mixed within the supplied applicator. The result is crosslinking and the formation of a solid, absorbable, biocompatible PEG-based hydrogel that can be used for up to 2 h.

Study Objectives

In this prospective, randomized, controlled, multicenter pivotal trial, our objective was to demonstrate the noninferiority of the Adherus Dural Sealant (test sealant, test dural sealant) compared with a commercially available control (DuraSeal® Dural Sealant System, Integra LifeSciences, Plainsboro, NJ) when used as an adjunct to standard methods of dural repair in cranial procedures. The study is registered with clinicaltrials.gov, titled “Safety and Effectiveness of the Adherus Dural Sealant System When Used as a Dural Sealant in Cranial Procedures,” and the ID is NCT01158378. Each study site obtained approval from their respective institutional review board (IRB) for this investigation prior to enrolling patients.

Preoperative Inclusion and Exclusion Criteria

Candidates met preoperative inclusion criteria as adult patients undergoing elective cranial procedures involving a dural incision and a Class I/Clean wound. Preoperative exclusion criteria included planned penetration of air sinus or mastoid air cells, pre-existing external ventricular shunts or drains, clinical evidence of altered CSF dynamics or hydrocephalus, a prior intracranial procedure in the same anatomic location, radiation treatment to the surgical site or standard fractionated radio-beam therapy planned within 10 d postindex procedure, trauma resulting in basilar skull fracture or fractures involving the paranasal sinuses within 30 d prior to the planned index procedure, chemotherapy treatment within 3 wk before the planned index procedure, planned use of intracavitary chemotherapy wafer (bis-chlorethyl nitrosourea (BCNU-carmustine)), or planned systemic chemotherapy treatment within 2 wk after the index procedure, compromised immune system or autoimmune disease, systemic infection near planned operative site, uncontrolled diabetes, renal or hepatic dysfunction, or pregnancy, breast feeding, or intent to become pregnant during the study. Patients signed an informed consent form approved by each center's IRB and met all preoperative inclusion/exclusion criteria.

Intraoperative Inclusion and Exclusion Criteria

During the procedure, additional inclusion and exclusion criteria were used. Intraoperative inclusion criteria were a ≥ 2 cm durotomy, a ≥ 3 mm dural margin from edges of bony defect, and the presence of a CSF leak after completion of primary dural closure (either spontaneously or during Valsalva maneuver at up to 20 cm H₂O for up to 5 s). Exclusion criteria included the requirement for the intraoperative placement of a CSF diversion device and gaps in the dura or between the edge of dura and duraplasty material exceeding 2 mm. Those who did not meet intraoperative inclusion/exclusion criteria were excluded and were not randomized, treated, or counted as treated patients.

Randomization and Study Blinding

To ensure baseline homogeneity, equal numbers of patients who would undergo a supratentorial (ST) or infratentorial (IT) surgical approach were randomized using a computer-generated randomization scheme to receive either the new sealant or control using a 1:1 randomization ratio. Patients scheduled for surgeries using an IT approach were randomized independently from subjects scheduled for surgeries using a ST approach. Patients were enrolled by trained, on-site study coordinators in cooperation with the treating physician. Treatment assignments had been prepared and delivered to each center in sequentially numbered, sealed, opaque envelopes. Patients, core laboratory evaluators, and the Clinical Events Committee (CEC) were masked to the study treatment assignments throughout the study. The investigators/surgeons remained masked to the treatment assignment until dural closure but would recognize the distinctive applicator of either treatment. Therefore, this clinical trial was not considered to be a masked trial.

Treatment

The sealant (test or control) was applied to the dural defect and tested, approximately 30 s after application, by Valsalva maneuver (up to 20 cm H₂O for 5 s) to confirm an intraoperative watertight seal. If a leak was identified using the Valsalva maneuver, the sealant was reapplied and set, and the Valsalva maneuver was repeated. A maximum of 2 sealant applications, followed by Valsalva maneuver, were allowed. If watertight closure was not achieved after the second application, conventional management of the CSF leakage was performed at the discretion of the

investigator. The wounds were closed according to each center's standard practices (including the potential use of subgaleal or subfascial drains).

Follow-up Visits and Assessments

After the index procedure, patients were followed at either 24 to 96 h or at hospital discharge (whichever occurred first), and thereafter at 14, 45, and 120 d. Follow-up included a physical examination, complete neurological assessment, laboratory testing (including a comprehensive metabolic panel, prothrombin time/international normalized ratio, and partial thromboplastin time), and assessments for CSF leak and pseudomeningocele, surgical site infection, and wound healing. The extent of the patient's disability or dependence was determined using the modified Rankin Scale. Any reported AEs were documented for each assessment interval. An MRI or CT image of the head was obtained before the planned index procedure and at 120-d follow-up examination. An MRI was also performed if a CSF leak or pseudomeningocele was suspected at any time before the 120-d follow-up or if CT results indicated a suspected leak. Any MRI and CT image interpreted as positive or potentially positive for CSF leak or pseudomeningocele by the participating institution was sent to an imaging core laboratory for independent radiological evaluation, regardless of the clinical significance of the findings as determined by the involved investigator.

Primary Endpoint

The primary endpoint was a composite evaluation of the safety and effectiveness of the test sealant as a sealant for dural repair. Failure on the primary endpoint was defined by the appearance of any one or a combination of elements that defined the composite. The composite endpoint included the following elements: proportion of treated patients free of (1) intraoperative CSF leak during Valsalva maneuver, (2) CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay, or imaging study within 120 d of the surgical procedure, and (3) unplanned retreatment of the surgical site (adjudicated by the CEC to be device related) for complications other than a CSF leak or pseudomeningocele, or those related to the patient's pre-existing condition, within 120 d of the surgical procedure.

Secondary Endpoints

Secondary endpoints, including the individual components of the primary composite endpoint, were then quantified. Secondary endpoints included the proportion of treated patients free of intraoperative CSF leaks after up to 2 dural sealant applications during Valsalva maneuver; free of CSF leak diagnosed by physical examination, biochemical assay, or imaging study within 120 d of the surgical procedure; free of unplanned retreatment of the surgical site (adjudicated by the CEC to be device related) for complications other than a CSF leak or pseudomeningocele, or those related to the patient's pre-existing condition, within 120 d of the surgical procedure; and free of postoperative surgical wound infections or meningitis through 120 d. Neurological function decline and wound healing were also assessed at the 120-d follow-up period, and all AEs were collected. AEs were classified as mild, moderate, or severe, and a CEC of 3 board-certified neurosurgeons independently reviewed all events that could have been device related and all serious AEs.

Statistical Analysis

A final analysis was performed to determine study success or failure using statistical tests performed with SAS statistical software (Version 9.0; SAS Institute, Cary, NC). Study outcomes were considered successful if the proportion of test article-treated patients with positive outcomes were

statistically significantly noninferior to the proportion of control-treated patients. Statistical significance was defined as a P -value $< .05$.

Sample size estimation was performed using a Monte Carlo simulation. The optimal effective sample size with 80% power to rule out (with less than 5% type I error rate) that Adherus Dural Sealant was unacceptably worse ($>10\%$ worse) than the control in treatment success was determined to be a total of 220 patients when randomized in a 1:1 ratio. The trial was approved to treat up to 274 patients, randomizing patients to the test dural sealant or control in a 1:1 ratio. This sample size incorporated up to 20% attrition because of expected deaths and other unexpected losses to follow-up.

All study data were pooled across study centers to facilitate hypothesis testing in accordance with the sample size estimation and power analysis. Comparability between study sites was examined using summary statistics calculated by site.

The primary analysis was conducted on the per-protocol (PP) analysis set, whereby patients were analyzed according to the randomized treatment they received. The PP analysis set was defined as all patients who received treatment with evaluable 120-d follow-up data. This definition is also synonymous with the notion of a standard complete case population, as no additional requirements were placed on the definition of PP other than having evaluable 120-d data.

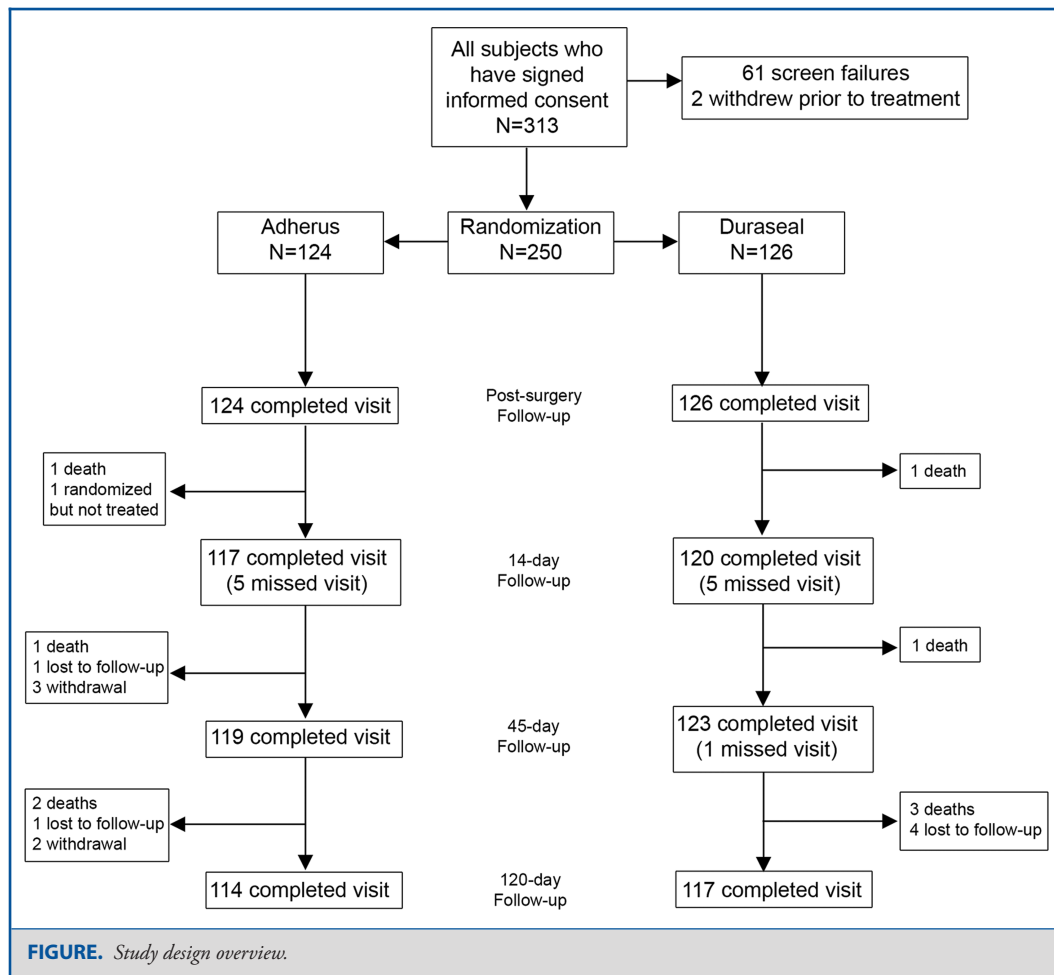
RESULTS

Patient Demographics and Clinical Characteristics

During the study period (September 2010–September 2012) at 17 centers in the United States, of 313 consented patients, 61 did not meet screening criteria and 2 withdrew before randomization/treatment leaving 250 patients. Of these, 124 patients (41 men and 83 women; mean age 51.2 yr, range 19–75) were randomized to the test dural sealant and 126 patients (40 men and 86 women; mean age 49.6 yr, range 19–75 yr) were randomized to the control. A total of 231 patients (92.4%) completed the 120-d follow-up visit, the time point through which the primary endpoint is measured. Excluded from the analysis were 6 patients (2 Adherus and 4 control patients) who did not return for follow-up visits, 9 patients who died (4 Adherus and 5 control patients) before the 120-d examination, 3 Adherus patients who withdrew (1 placed in hospice, 1 incarcerated, and 1 diagnosed with a glioblastoma multiforme enrolled into a different clinical trial), and 1 Adherus patient who was randomized but did not receive treatment (Figure).

There was no statistically significant difference in age ($P = .4$) or sex ($P = .9$) between the 2 groups. Clinical histories and prior neurosurgical history were also similar, with tumors being the most common diagnosis and headache being the most common presenting symptom (Table 1).

Although 3 (2.4%) control patients had a prior history of hydrocephalus, none were determined by the investigator to have clinically significant hydrocephalus at time of enrollment. Two (1.6%) patients treated with the test sealant and 5 (4.0%) control patients had previous history of craniotomy or craniectomy; however, none were reported to be in the same anatomic location. Four (3.2%) test sealant and 1 (0.8%) control patients had previous facial/head trauma. However, all traumas occurred



greater than 30 d before the index procedure and none of the patients were noted to have basilar skull fractures or fractures involving the paranasal sinuses. Of the 3 (2.4%) test sealant and 6 (4.8%) control patients with a history of radiation therapy for various reasons (eg, treatment of breast cancer), no one had previous radiation treatments to the surgical site (Table 1). Finally, there was no difference between treatment groups with respect to baseline general physical examination, neurological examination, or modified Rankin Scale score.

Randomization and Treatment Parameters

No one site enrolled more than 16% of study patients; no interactions were found in post hoc testing between study sites and treatments in the assessment of the primary study endpoint. After randomization based on 2 surgical approaches (ie, IT or ST), treatment parameters at baseline were similar between the 2 sealant groups (Table 2). Similarly, indications for surgery and surgical procedures locations were well matched between the 2 groups. The average length of dural incision was 8.2 cm (range 2.0-21.0 cm) in the test sealant group and 8.0 cm (range 2.0-

30.0 cm) in the control group. The majority of patients in both groups had a linear dural incision.

Of the 250 patients randomized, 1 sealant application was used in 241 patients, whereas 2 applications were used in 2 test sealant patients and 7 controls. Total volume of dural sealant averaged 4.3 mL (range 0.0-11.0 mL) for the test sealant and 3.9 mL (range 0.2-10.0 mL) for the control ($P = .08$). Sutures and autologous duraplasty materials were used for primary dural closure in 29 (23.4%) patients with the test sealant and 34 (27.0%) control patients. Sutures and nonautologous duraplasty materials were used for primary dural closure in 45 (36.3%) test sealant and 39 (31.0%) control patients (Table 2).

Primary Endpoint Analysis

Of patients who completed the 120-d follow-up visit (92.4%), overall success rates for the primary endpoint analysis at completion of the 120-d follow-up period were 91.2% (104/114) in the test sealant group compared with 90.6% (106/117) in the control group (Table 3), proving the test sealant to be statistically significantly noninferior to the control with a noninferiority margin of 10% ($P = .0049$).

TABLE 1. Summary of Demographics and Clinical History

Demographics	Adherus n = 124	DuraSeal n = 126	P-value
Age (mean years (SD))	51.2 (14.0)	49.6 (15.0)	.38
Gender (n (%))			.89
Male	41 (33.1%)	40 (31.7%)	
Female	83 (66.9%)	86 (68.3%)	
Ethnicity (n (%))			.46
Hispanic or Latino	7 (5.6%)	11 (8.7%)	
Not Hispanic or Latino	117 (94.4%)	115 (91.3%)	
Race (n (%))			
White	114 (91.9%)	114 (90.5%)	
Black or African American	10 (8.1%)	10 (7.9%)	
American Indian or Alaska Native		1 (0.8%)	
Other		1 (0.8%)	
Clinical History			
Subject American Society of Anesthesiologists (ASA) score (n (%))			.26
I	2 (1.6%)	8 (6.3%)	
II	47 (37.9%)	50 (39.7%)	
III	69 (55.6%)	62 (49.2%)	
IV	6 (4.8%)	6 (4.8%)	
V	0 (0.0%)	0 (0.0%)	
Prior neurological history (n (%))			
Aneurysms	28 (22.6%)	29 (23.0%)	
Burrhole	1 (0.8%)	1 (0.8%)	
Craniectomy/Craniotomy	2 (1.6%)	5 (4.0%)	
Stereotactic procedure	4 (3.2%)	4 (3.2%)	
CSF leakage	0 (0.0%)	0 (0.0%)	
Hydrocephalus	1 (0.8%)	3 (2.4%)	
CSF shunt	0 (0.0%)	0 (0.0%)	
Facial/head trauma hospitalization	4 (3.2%)	1 (0.8%)	
Headaches	74 (59.7%)	88 (69.8%)	
Intracranial hematomas	3 (2.4%)	6 (4.8%)	
Cerebrovascular Accident (CVA)/Transient Ischemic Attacks (TIAs)	7 (5.6%)	6 (4.8%)	
Meningitis	1 (0.8%)	1 (0.8%)	
Tumors	49 (39.5%)	47 (37.3%)	
Radiation therapy	3 (2.4%)	6 (4.8%)	
Recurrent otitis media	2 (1.6%)	3 (2.4%)	
Seizure disorder	19 (15.3%)	15 (11.9%)	
Spinal surgery involving the dura	1 (0.8%)	2 (1.6%)	
Trigeminal nerve impingement	15 (12.1%)	19 (15.1%)	
Other	54 (44.3%)	63 (50.8%)	

In a follow-up analysis paralleling the dural healing process, the overall success rates, using the composite endpoint analysis (ie, combined percentage intraoperative CSF leak, postoperative CSF leak, and unplanned retreatment of the surgical site), were 99.1% for the test sealant and 95.0% for control at 14-d visit, and 96.6% for the test sealant group and 91.9% for the control group at the 45-d visit (**Tables, Supplemental Digital Content 1 and 2**). Post hoc testing of these outcomes found that the test sealant was noninferior to control with respect to overall success at the 14- and 45-d follow-ups. Furthermore, the test sealant was found to be superior to the control group at 14 d in the test for superiority ($P = .030$) and trended toward significance at the 45-d visit ($P = .056$).

Other supplementary parameters of the primary endpoint analyzed, surgical approach (IT vs ST), showed no statistical difference in overall success rates between the 2 test groups. Multivariate analysis of the primary composite endpoint parameters revealed the utilization of nonautologous duraplasty materials as the only statistically significant ($P = .027$) predictor of primary endpoint failure. However, these findings do not modify the inference drawn from the above testing of the primary endpoint.

Secondary Endpoint Analyses

Intraoperative CSF Leakage

The 3 criteria that were combined to evaluate the primary composite endpoint were evaluated individually as secondary

TABLE 2. Summary of Treatment Parameters

Treatment parameters	Adherus n = 124	DuraSeal n = 126	P-value
Primary indication for surgery (n (%))			.96
Tumor	56 (45.2%)	53 (42.1%)	
Epilepsy	1 (0.8%)	1 (0.8%)	
Nerve decompression	17 (13.7%)	21 (16.7%)	
Arteriovenous malformation (AVM)	3 (2.4%)	5 (4.0%)	
Aneurysm	28 (22.6%)	26 (20.6%)	
Chiari malformation	17 (13.7%)	18 (14.3%)	
Cyst	2 (1.6%)	1 (0.8%)	
Other	0 (0.0%)	1 (0.8%)	
Type of procedure (n (%))			.86
Craniotomy	105 (84.7%)	105 (83.3%)	
Craniectomy	19 (15.3%)	21 (16.7%)	
Approach (n (%))			.89
Infratentorial	53 (42.7%)	52 (41.3%)	
Supratentorial	71 (57.3%)	74 (58.7%)	
Location (n (%))			
Frontal	50 (40.3%)	39 (31.0%)	
Occipital	5 (4.0%)	11 (8.7)	
Parietal	10 (8.1%)	10 (7.9%)	
Temporal	35 (28.2%)	33 (26.2%)	
Lateral suboccipital	25 (20.2%)	24 (19.0%)	
Midline suboccipital	21 (16.9%)	21 (16.7%)	
Other	10 (8.1%)	16 (12.7%)	
Length of dural incision (mean cm (SD))	8.2 (4.4)	8.0 (4.5)	.72
Type of incision (n (%))			.87
Linear	101 (82.1%)	102 (81.0%)	
Cruciate	22 (17.9%)	24 (19.0%)	
Primary technique for dural closure (n (%))			.56
Suture	48 (38.7%)	48 (38.1%)	
Suture + autologous dural material	29 (23.4%)	34 (27.0%)	
Suture + nonautologous dural material	45 (36.3%)	39 (31.0%)	
Other	2 (1.6%)	5 (4.0%)	
Dural Sealant second application (n (%))	2 (1.6%)	7 (5.6%)	
Total volume of dural sealant used for application (mean mL (SD))	4.3 (2.0)	3.9 (2.0)	.08

endpoints. First, freedom of intraoperative CSF leakage after up to 2 dural sealant applications to the dural repair was seen in all 114 (100%) test sealant patients and 121 (99.2%) of 122 control patients during Valsalva maneuver, up to 20 cm H₂O for 5 s (Table 3). In 1 leak, the surgeon noted a minimal leak after the first application of dural sealant and opted not to use a second application; the control patient experienced no CSF-leak-related symptoms postindex procedure.

Detection of CSF Leak and Pseudomeningocele Postprocedure

At the 120-d follow-up, 105 (92%) of 114 test patients and 109 (93%) of 117 controls were free of CSF leak and pseudomeningocele as diagnosed by physical examination, biochemical assay, or imaging study (Table 3) ($P = .7$). Postoperatively, 9 test patients had a pseudomeningocele, and 6 control

patients had a pseudomeningocele. In the test sealant patients, 3 pseudomeningoceles were deemed serious and required re-intervention (ie, 1 open surgery, 2 percutaneous interventions); these 3 cases resolved within 12 to 66 d after onset. The remaining 6 pseudomeningoceles of the test sealant group were detected by radiographic imaging at the 120-d visit and had not resolved as they were detected at this study visit.

In the control group, 2 patients had a postoperative CSF leak during the 120-d follow-up. Both patients required percutaneous and open surgical interventions. The CSF leaks resolved within 26 and 33 d after treatment. There were 6 patients in the control group who had a postoperative pseudomeningocele through the 120-d visit. Pseudomeningocele was determined to be serious in 1 patient, who was treated with percutaneous and open surgical interventions. Three out of the 6 pseudomeningocele cases resolved by the 120-d follow-up visit. The remaining 3

TABLE 3. Summary of Primary Composite Endpoint During 120-D Follow-up

Primary endpoint component	Adherus n = 114	Control n = 117	P-value*	P-value (superior)
Subjects free of intraoperative CSF leakage after up to two dural sealant applications (n (%))	114 (100%)	116 (99.1%)		
Subjects free of CSF leak or pseudomeningocele diagnosed by physical examination/biochemical assay/imaging study within 120 d (n (%))	105 (92.1%)	109 (93.2%)		
Subjects free of unplanned treatment of the original surgical site adjudicated by the CEC to be device related (n (%))	113 (99.1%)	115 (98.3%)		
Overall success (n (%))	104 (91.2%)	106 (90.6%)	.0049	.4339

*P-value (difference between groups; delta = 10%).

pseudomeningoceles had not resolved by the 120-d visit, 1 of which was detected by radiographic imaging at the 120-d visit.

The median time to CSF leak or pseudomeningocele was 111 d postindex procedure (range 27-128 d) in the test sealant group. In contrast, in the control group, the median time to CSF leak or pseudomeningocele was 8 d postindex procedure (range 1-111 d).

Unplanned Retreatment

The last component of the primary composite secondary endpoint was unplanned retreatment of the surgical site adjudicated by the CEC to be device related. Unplanned postoperative treatment for infection, meningitis, or complications other than CSF leak or pseudomeningocele that required a return to the operating room was considered. Of 114 test sealant cases, 1 patient underwent unplanned retreatment for an extradural hematoma on CT 2 d after the index procedure. During the craniotomy, the hematoma was evacuated. The dura was reopened, the sealant was removed to ensure no residual hematoma was beneath the dura, and the hematoma resolved 2 d after onset. Of 117 control cases, 2 patients had unplanned reoperations for surgical site infections adjudicated by the CEC to be device related. For an incision-site infection 32 d after the index procedure, a gelatinous mass of control sealant, on lay dural substitute (DuraGen™; Integra LifeSciences, Plainsboro, NJ), and purulent material was identified in the epidural space during reoperation and was collected for culture; infection resolved 46 d after onset. In a postoperative wound infection 45 d after index procedure, the patient underwent surgical debridement and removal of the bone flap, and the event resolved 68 d after onset. The difference between treatment groups was deemed not statistically significant ($P = .51$).

Adverse Events

At no time during the study did any unanticipated AEs occur due to either of the hydrogel sealants. AEs in each treatment group typically were mild or moderate in severity, and over half had resolved by the 120-d follow-up visit. The incidence of serious AEs between the 2 groups was comparable as well: 41 serious AEs in 33 (26.6%) test sealant patients and 40 serious AEs in 33 (26.2%) control patients. Seven (5.6%) test sealant patients had 8 serious AEs adjudicated by the CEC as device related, defined as convulsion ($n = 1$), dysphagia ($n = 1$), extradural hematoma ($n = 1$), headache ($n = 1$), pseudomeningocele ($n = 3$), and respiratory failure ($n = 1$). Five (4.0%) control patients had 5 serious device-related AEs defined as incision-site infection ($n = 2$), infection ($n = 1$), intracranial venous sinus thrombosis ($n = 1$), and pseudomeningocele ($n = 1$).

Nine deaths occurred over the course of the study (4 test sealant patients vs 5 control patients). All deaths were adjudicated by the CEC as not related to the device. Deaths among the 4 test sealant patients were attributed to complications from colitis, disease progression, metastatic lung cancer, and stroke. Deaths among the 5 control patients were attributed to disease progression, multi-organ failure and pneumonia, posterior herniation with severe brain injury, and respiratory failure. One death in each group was determined to be procedure related, and the remaining 7 deaths were not related to the procedure.

Wound Healing

At the 120-d follow-up visit, there was 1 test dural sealant patient whose wound was not healed. The AE was reported as not related to the device or procedure. A small superficial abscess along the incision site (83 d after the index procedure) was drained and the patient was started on Keflex. Antibiotics were discontinued when culture findings of the abscess fluid were negative.

The patient was later advised to restart Keflex and use a topical antibiotic ointment to prevent infection; the abscess resolved 10 d after onset. The craniotomy site wound was healed without complication in all other patients at the 120-d visit.

DISCUSSION

Generalizability

Achieving a watertight dural closure after neurosurgical procedures decreases the risk of postoperative complications and thus reduces overall healthcare costs.⁵ However, various factors can complicate a surgeon's ability to achieve adequate dural closure. These include fragile dura, dural involvement with pathological processes (eg, neoplasms), and tendency for dural contraction during surgical procedures. Various physiological factors can further increase the risk of CSF leaks, including altered CSF dynamics (a condition that may result after ventricular entry during the primary procedure, subarachnoid hemorrhage, or resection of larger tumors) and conditions that compromise wound healing (eg, radiation, systemic chemotherapy, intradural chemotherapy, poor nutrition, prior surgery, and concurrent systemic disease, such as diabetes). Additionally, various surgical approaches, such as skull base procedures, can greatly increase the risk of developing a postoperative CSF fistula.¹⁸

Interpretation

In this prospective, randomized, controlled, multicenter pivotal trial, we demonstrated noninferiority of the test dural sealant vs a control sealant when used as an adjunct to standard methods of dural repair in cranial procedures. No significant differences in patient demographics or characteristics were noted between the 2 treatment groups. Failures in the primary endpoint in the control group tended to occur earlier during follow-up, whereas most test dural sealant failures were identified through the protocol-required radiographic imaging at the 120-d follow-up visit. This is further supported by the fact that the Adherus Dural Sealant was found to be superior to the control group at 14 d in the test for superiority.

A potential explanation for this observed difference in time of primary endpoint failure is the ability of the test sealant to maintain its architectural integrity over several months. In our previous *in Vitro* studies, Adherus Dural Sealant maintained supraphysiological burst strengths for approximately 50 d, while the DuraSeal Sealant was found to degrade rapidly and maintain supraphysiological strength for approximately 7 d.¹⁶ Furthermore, when visualized radiographically, there was no evidence of CSF leakage for up to 90 d after Adherus application in animals, thus maintaining a watertight barrier while the dura has time to heal (unpublished data).

It is of paramount importance to minimize the number of cases that require unanticipated postsurgical intervention. In this analysis, the number of cases that required open postsurgical intervention due to either CSF leaks or infections was 1/114

patient (0.87%) in the test sealant group and 5/117 (4.3%) in the control group.

Unlike other hydrogel dural sealants that are known to expand *in Vivo* leading to nerve compression,^{14,15,19} Adherus Dural Sealant appears to be volumetrically stable with minimal swelling potential.¹⁶ We did not observe any AEs related to product expansion leading to neurological symptoms. This is consistent with our preclinical observations of an 8% to 9% maximal dimensional change in any one axis.¹⁶ The specially designed architecture of the hydrogel matrix has been postulated to help explain the limited volumetric expansion observed.

We found no statistically significant difference between treatment groups in the secondary endpoints evaluated in this study, specifically the incidence of CSF leakage or pseudomeningocele, unplanned retreatment, deaths, device-related AEs, neurological decline, and serious AEs. In addition, no unanticipated adverse device effects were noted in either treatment group. From these results, we conclude that the novel PEG hydrogel, Adherus Dural Sealant, has equivalent safety to existing methods (eg, DuraSeal) for augmentation of primary dural closure in cranial procedures.

Limitations

A potential limitation of the trial is that the clinicians were not blinded with respect to treatment assignment. This represents a potential source of treatment bias. Additionally, although the trial involved a comparative assessment of 2 dural sealants in multiple treatment settings, use of either agent was not necessarily restricted to patients at highest risk of CSF leak (eg, skull base procedures). In this regard, the trial design may not have been optimized to assess the full therapeutic value and/or limitation(s) of these agents.

CONCLUSION

Based on preclinical and clinical evaluations of the experimental agent, we conclude that Adherus Dural Sealant has equivalent efficacy and safety to other PEG hydrogel sealant products (eg, DuraSeal) for augmentation of primary dural closure in cranial procedures. Furthermore, in the early postsurgical period, Adherus Dural Sealant possibly has an advantage related to limited volumetric expansion, increased structural integrity and strength, and a slower rate of degradation, as evidenced by the analysis at the 14-d follow-up period.

Disclosures

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COMMENT

This well-designed multicenter prospective randomized controlled trial adequately demonstrates the noninferiority of a test dural sealant, Adherus Dural Sealant, when compared with a control dural sealant, DuraSeal Dural Sealant. This dataset was used to obtain FDA approval for this product. The occurrence of CSF leaks in patients postoperatively after elective craniotomies is particularly targeted and specific inclusion/exclusion criteria are outlined well to limit confounders.

The paper asserts that though Adherus Dural Sealant has minimal dimensional swelling properties, it is relatively volumetrically stable compared to DuraSeal Dural Sealant owing to its specially designed architecture of the hydrogel matrix. It is also important to note, however, that the study does acknowledge that dural sealant (test or control) swelling did not lead to any notable AEs. These distinctive architectural differences and swelling properties may be more effectively illustrated in studies investigating dural sealant use, the spinal canal, and neural foraminae where room for swelling is markedly reduced.¹

The study does show significantly noninferior to the control with a noninferiority margin of 10% and then also demonstrates superiority of the test sealant over the control at 14 d. This, however, was elucidated through post hoc analysis of the primary composite endpoint with results unanticipated a priori, which may suggest its own biases.

To the credit of the authors, with the noted indications for use of the dural sealants intraoperatively, it is stated that study design was not optimized to evaluate the full therapeutic value of the dural sealants. Patients who received either the test or control sealant were not necessarily at high risk for CSF leaks. This may lend to the fact that success rates for both sealants were over 95% and is a key point to note when interpreting these data. Especially in the ST space, the need for closure has been found to be perhaps less of an absolute need than in the IT space,² which nevertheless may actually reduce the ability of this trial to let this new product show its value.

When introducing alternatives to already established methods of treatment, a critical step is defining noninferiority, which this paper aptly explicates. An important reminder exists that other dural sealants, ie, fibrin sealants, are also being investigated for safety and effectiveness and may prove to be worthy comparisons for future studies. The results do encourage interesting applications, and further studies demonstrating therapeutic value and superiority are greatly anticipated. It should be noted that the use of the word "pivotal" in the title of this study is used in reference to standard FDA guidelines and not necessarily in the usual meaning (see also <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm373750.htm>).

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