Results of the Prospective, Randomized, Multicenter Clinical Trial Evaluating a Biosynthesized Cellulose Graft for Repair of Dural Defects

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BACKGROUND: After intradural cranial surgery, a dural substitute is often required for dural closure. Although preferred, limitations of autograft include local availability and additional surgical site morbidity. Thus, allografts, xenografts, and synthetics are frequently used.

OBJECTIVE: To report 6-month results of a randomized, controlled trial of a biosynthesized cellulose (BSC) composed duraplasty device compared with commercially available dural replacements.

METHODS: A total of 99 patients (62 BSC; 37 control) were treated on protocol, using a 2:1 (BSC:control) blocked randomization schedule. Physical examinations were performed pre- and postoperatively within 10 days and at 1, 3, and 6 months. Magnetic resonance imaging was performed preoperatively and at 6 months. The primary study endpoint was the absence of pseudomeningocele and extracerebral fluid collection confirmed radiographically and the absence of cerebrospinal fluid fistula at 6 months.

RESULTS: At 6 months, the primary hypothesis, noninferiority of the BSC implant compared with the control group, was confirmed ($P = .0206$). Overall success was achieved by 96.6% of BSC and 97.1% of control patients. No significant difference was revealed between treatment groups for surgical site infection ($P = 1.0000$) or wound healing assessment ($P \geq .3685$) outcomes, or radiologic endpoints ($P \geq .4061$). Device strength and seal quality favored BSC.

CONCLUSION: This randomized, controlled trial establishes BSC as noninferior to commercially available dural replacement devices. BSC offers a hypothetical advantage concerning prion and other infectious agent exposure; superior handling qualities are evident. Longer term data are necessary to identify limitations of BSC and its potential equivalence to the gold standard of pericranium.

KEY WORDS: Allograft, Biosynthesized cellulose, Dural substitute, Dura mater, Duraplasty, Pericranium

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A graft is often required to replace, repair, or reinforce closure of the dura after intradural cranial surgery. Autograft, including pericranium, temporalis fascia, and fascia lata, is the most widely accepted substitute but is available in very limited supply.[1-3] Autogenous grafts are preferred; however, allograft, xenografts, and synthetic materials are frequently used when either autograft is unavailable locally and/or the surgeon wants to avoid the morbidity of a second surgical site.[4] The goal of duraplasty is to attain a watertight closure to reduce the risk of infection, the formation of a pseudomeningocele, cerebrospinal fluid (CSF) fistula, herniation of neural contents, and inflow of blood and contaminants and provide a surface for "neodura" to generate.[1,5-7] A variety of materials have been used as dural substitutes, dating back to the first report on the clinical implantation of rubber tissue used as a dural substitute, by Abbe in 1895.[7] Autografts, harvested from collagenous membranes, like the pericranium, temporalis fascia,

ABBREVIATION: BSC, biosynthesized cellulose

TABLE 1. Control Group

Control	Graft Material	Company	No. (%)
Duraform Dural Graft Implant	Bovine tendon collagen	Codman & Shurtleff, Inc.	15 (40.5)
DuraGen II Dural Regeneration Matrix	Bovine tendon collagen	Integra LifeSciences Corp.	8 (21.6)
DuraGen Dural Graft Matrix	Bovine tendon collagen	Integra LifeSciences Corp.	10 (27.0)
Durepair Dura Regeneration Matrix	Fetal bovine skin collagen	Medtronic Neurosurgery	2 (5.4)
Other			2 (5.4)
Preclude Dura Substitute	Synthetic material	W. L. Gore & Associates, Inc.	
DuraGen Plus Dural Regeneration Matrix	Bovine tendon collagen	Integra LifeSciences Corp.	
Total			37 (100)

TABLE 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Patient is between 18 and 75 years of age.	Patient has a cranial metallic implant(s) that would interfere with evaluation of the device or recovery.
Patient is scheduled for an elective cranial procedure requiring a dural incision.	Patient is somnolent or comatose (Glasgow Coma Scale score <8).
Patient has undergone magnetic resonance imaging no earlier than 2 months before the date of enrollment.	Patient has had a previous intracranial neurosurgical procedure in the same anatomic location.
Surgical wound is expected to be class I/clean.	Patient will require use of a dural adhesive or sealant.
Patient is available and willing to participate in the investigation for the duration of the study.	Patient has known hydrocephalus.
Patient has signed a written informed consent to participate in the study before any study-mandated determinations or procedures. This does not include magnetic resonance imaging that may be performed before obtaining informed consent.	Patient's life expectancy is <6 months.
	Patient has a systemic infection (eg, urinary tract infection, active pneumonia) or evidence of any surgical site infection, fever $>101^{\circ}$F, positive blood culture, and/or a chest x-ray positive for an acute infectious process.
	Patient has known allergy to device component (cellulose).
	Patient is an acute cranial trauma surgical case.
	Patient has a local cranial infection.
	Patient has had chemotherapy and/or radiation treatment within 12 weeks before surgery or has chemotherapy and/or radiation treatment planned 10 weeks post-surgery.
	Patient has been clinically diagnosed with malignancy (other than basal cell carcinoma or low-grade glioma), uncontrolled diabetes, sepsis, systemic collagen disease.
	Patient has creatinine levels >2.0 mg/dL.
	Patient has total bilirubin level >2.5 mg/dL.
	Patent has clinically significant coagulopathy with a partial thromboplastin time ≥ 35 or international normalized ratio. ≥ 1.2 or is taking Coumadin (warfarin).
	Patient has a compromised immune system or autoimmune disease (white blood cell count <4000/UL or $>20\,000$/UL).
	Patient is participating in another clinical trial using investigational devices/drugs.
	Patient is pregnant or breastfeeding or wishes to become pregnant during the course of the study.
	Patient is unable or unwilling to sign a consent form.

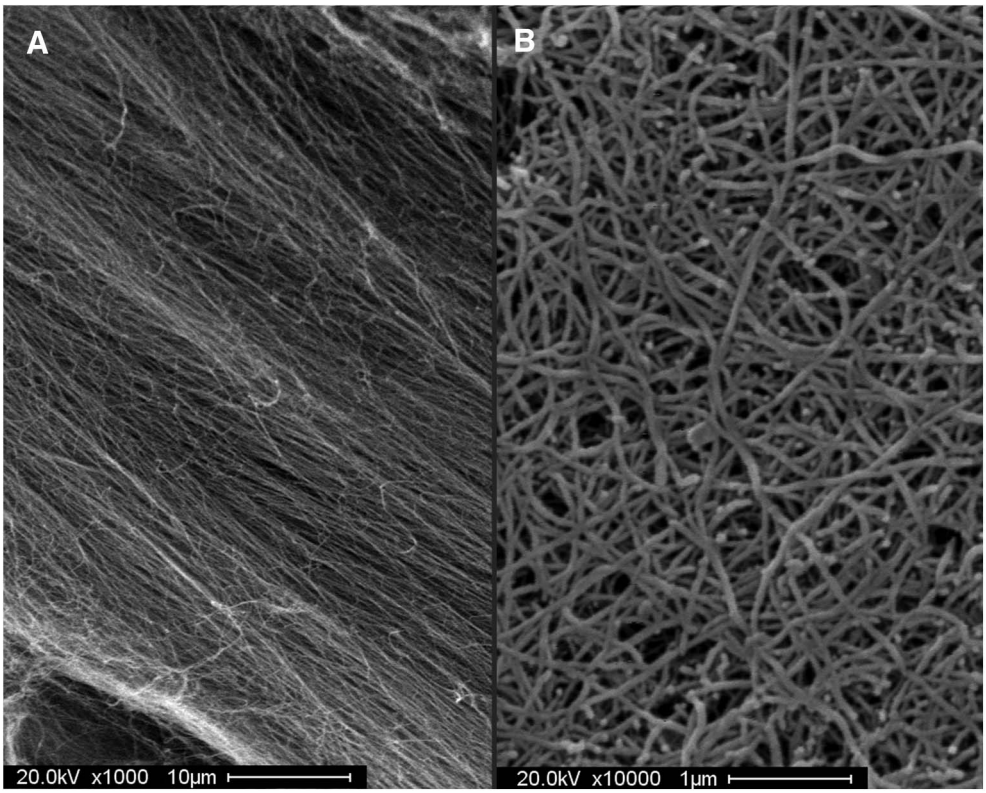

FIGURE 1. **A**, *scanning electron microscope image of side view (left) of biosynthesized cellulose showing a multilayered structure (magnification, ×1000; scale bar, 10 µm).* **B**, *scanning electron microscope image of top view (right) of biosynthesized cellulose. Each layer has a nonwoven porous structure (magnification, ×10,000; scale bar, 1 µm).*

and fascia lata, are commonly used as dural substitutes because they do not induce an immunologic or severe inflammatory response; however, a secondary surgical site may be necessary and there are limitations regarding the amount of accessible tissue that can be harvested to close large dural defects.[1,6,8] Campbell et al first used freeze-dried, vacuum-stored human dural tissue in 1958.[7] More recently, commonly used human cadaveric dural tissue has been associated with the transmission of viral infections, including Creutzfeldt-Jakob disease.[1,9,10] Synthetic materials, eg, expanded polytetrafluoroethylene, Vicryl mesh, polyurethane, polyglactin 910-polydioxane, and polysiloxone-carbonate film have been used as dural substitutes.[1,9] If a wound infection occurs after implantation of a nonautologous, nonresorbable graft, the graft often becomes chronically colonized, promotes continued growth of microorganisms, and must be removed to eradicate the infection.[2] Xenografts, typically composed of animal collagens, namely, bovine and porcine tissues, processed to remove cellular and other immunogenic components, have proven successful.[9,11] After the epidemic of bovine spongiform encephalopathy in cattle, the emergence of a new variant of Creutzfeldt-Jakob disease, first described in 1996,[12] suggests that collagen grafts derived from animal tissues must be carefully monitored. Nonautogenous grafts have been associated with complications

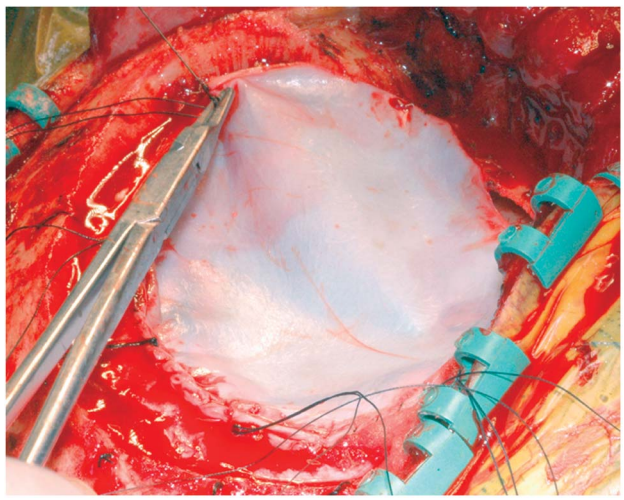

FIGURE 2. *Intraoperative photograph showing a dural repair using SyntheCel Dura Replacement Substitute. (Used with permission of Barrow Neurosurgical Associates, Ltd.)*

TABLE 3. Patient Demographics and Intraoperative Data[a]

	Control	BSC	2-Sided *P* Value[b]
No. treated	37	62	
Age at surgery, y			.397
Mean (SD)	48.6 (14.03)	46.4 (12.85)	
Sex, no. (%)			.651
Male	12 (32.4)	17 (27.4)	
Female	25 (67.6)	45 (72.6)	
Race, no. (%)			.913
White	32 (86.5)	51 (82.3)	
African American	3 (8.1)	4 (6.5)	
Asian	1 (2.7)	2 (3.2)	
Hispanic	1 (2.7)	3 (4.8)	
Other	0 (0.0)	2 (3.2)	
Smoking status, no. (%)			.104
Never	24 (64.9)	28 (45.2)	
Current	8 (21.6)	15 (24.2)	
Former	5 (13.5)	19 (30.6)	
Height, in.			.41
No.	37	61	
Mean (SD)	65.4 (4.09)	66.1 (4.16)	
Weight, lb			.463
Mean (SD)	170.6 (41.35)	176.7 (42.62)	
Body mass index, kg/m^2			.605
No.	37	61	
Mean (SD)	27.9 (5.61)	28.3 (5.84)	
Indication for surgery,[c] no.(%)			N/A
Aneurysm	5 (13.5)	6 (9.7)	
AVM	0 (0.0)	1 (1.6)	
Benign or low-grade tumor	16 (43.2)	33 (53.2)	
Chiari malformation	2 (5.4%)	2 (3.2%)	
Decompression	1 (2.7%)	2 (3.2%)	
Epilepsy	1 (2.7%)	0 (0.0%)	
Nonacute trauma	0 (0.0%)	0 (0.0%)	
Other	12 (32.4%)	18 (29.0%)	
Intraoperative time, min			.37
No.	37	62	
Mean (SD)	251.0 (92.79)	273.3 (128.19)	
Estimated blood loss, mL			.126
No.	37	61	
Mean (SD)	325.0 (278.14)	333.1 (703.73)	
Intraoperative complications, no. (%)			1
No	37 (100.0)	62 (100.0)	
Yes	0 (0.0)	0 (0.0)	
Total	37 (100.0)	62 (100.0)	
Length of hospital stay, d			.247
No.	37	62	
Mean (SD)	3.7 (1.38)	4.5 (3.42)	
Location of implant,[d] no. (%)			N/A
Frontal	6 (15.4)	10 (13.3)	
Temporal	2 (5.1)	3 (4.0)	
Frontotemporal	24 (61.5)	30 (40.0)	
Parasagittal	1 (2.6)	4 (5.3)	
Parietal-occipital	0 (0.0)	5 (6.7)	
Posterior fossa	3 (7.7)	9 (12.0)	
Other	3 (7.7)	15 (20.0)	

[a]BSC, biosynthesized cellulose; SD, standard deviation; N/A, not available; AVM, arteriovenous malformation.
[b]Continuous and ordinal variables were analyzed by a Wilcoxon rank sum test, and categorical variables were analyzed using the Fisher exact test to compare control patients with BSC patients.
[c]Patients can have more than 1 indication for surgery. The number of patients treated was used as the denominator to compute all percentages in indication for surgery.
[d]Patients may be included in more than 1 category or have more than 1 implant. The number of patients treated was used as the denominator to compute all percentages.

TABLE 4. Overall Success[a]

	Control (N = 37), No. (%)	BSC (N = 62), No. (%)	Difference (Control-BSC), %	Exact 95% CI (1 Sided) %	Noninferiority *P* Value (10% Margin)	Exact 95% CI (2 Sided, Lower Bound), %	Exact 95% CI (2 Sided, Upper Bound), %
Postop	37/37 (100.0)	61/62 (98.4)	1.6	7.4	0.016	−7.7	8.9
Month 1	36/36 (100.0)	62/62 (100.0)	0.0	4.7	0.005	−9.7	6.1
Month 3	35/35 (100.0)	61/61 (100.0)	0.0	4.8	0.005	−10.0	6.3
Month 6	33/34 (97.1)	57/59 (96.6)	0.5	7.9	0.021	−11.7	9.7

[a]BSC, biosynthesized cellulose; CI, confidence interval; Postop, postoperatively.

ranging from premature graft dissolution, encapsulation, rejection, infection, and bacterium and virus transmission to hemorrhage, excessive scarring, and cerebromeningeal adhesions.[1,3,5,11]

We report the 6-month results of a randomized, controlled trial of a biosynthesized cellulose (BSC) duraplasty device compared with commercially available dural replacement implants. This investigational device has a proposed indication for the repair of dural defects. The primary hypothesis of this study is that, with regard to key clinical outcomes, the BSC device is not inferior to dural replacements cleared for marketing by the U.S. Food and Drug Administration.

MATERIALS AND METHODS

Study Design

A multicenter, prospective, randomized, controlled clinical trial, registered with ClinicalTrials.gov (NCT00859508), was performed under a U.S. Food and Drug Administration–approved investigational device exemption protocol. Before the start of the study, approval was obtained from each site's institutional review board, and patients provided the appropriate written informed consent before surgery. The study population was randomized using a 2:1 ratio of BSC device recipients to control dural replacement recipients and preoperatively blinded. The control group consisted of dural replacement devices that had been previously cleared for marketing by the U.S. Food and Drug Administration via a premarket notification, or 510(k), and thus determined to be substantially equivalent. As a result of their homogeneous nature, these control products were considered the most appropriate choice for the control group. The control group devices used in this trial are listed in Table 1.

Inclusion and exclusion criteria (Table 2) had to be met before enrollment. The key inclusion criteria consisted of a scheduled elective cranial procedure requiring a dural incision and an expectation of a class I/clean wound. Acute cranial trauma and malignant cranial tumor procedures were exclusions from this study. As an uncontrolled variable, dural adhesives and sealants were excluded so as not to introduce a confounding factor that could influence the results.

Statistical Analysis

The primary endpoint for this study was the absence of pseudomeningocele and extracerebral fluid collection confirmed by radiographic evaluation and the absence of CSF fistula (drainage from wound) at the 6-month postoperative visit. A comparison of the overall success rates at 6 months was based on exact *P* values and an exact 95% 1-sided confidence interval for the difference in success probabilities between the BSC and control groups. Additionally, the proportion of patients with component success at each follow-up visit was compared using the Fisher exact test. Comparisons of modified Rankin Scale scores between the 2 treatment groups were performed using the Wilcoxon-Mann-Whitney test. Radiographic evaluations at 6 months postoperatively were tabulated and compared between the 2 study arms using the Fisher exact test. For safety comparisons, intraoperative time (minutes), estimated blood loss (milliliters), and the length of hospital stay (days) were compared between treatment groups using the Wilcoxon rank sum test. The distribution of the incidence of surgical site infections was compared using the Fisher exact test. The incidence of adverse events was also compared between the treatment groups. A Poisson regression model using treatment group as the only covariate was used to compare the event rates.

TABLE 5. Overall Success/Efficacy[a]

			BSC		
		Control, No. (%)	Onlay, No. (%)	Substitute, No. (%)	Total, No. (%)
Postop	Absence of CSF leak	37/37 (100.0)	34/34 (100.0)	27/28 (96.4)	61/62 (98.4)
Month 1	Absence of CSF leak	36/36 (100.0)	34/34 (100.0)	28/28 (100.0)	62/62 (100.0)
Month 3	Absence of CSF leak	35/35 (100.0)	34/34 (100.0)	27/27 (100.0)	61/61 (100.0)
Month 6	Absence of CSF leak	34/34 (100.0)	32/32 (100.0)	27/27 (100.0)	59/59 (100.0)
Month 6	Absence of pseudomeningocele and extracerebral fluid collection	34/35 (97.1)	32/32 (100.0)	25/27 (92.6)	57/59 (96.6)

[a]BSC, biosynthesized cellulose; Postop, postoperatively; CSF, cerebrospinal fluid.

TABLE 6. Distribution of Radiological Endpoints at Month 6[a]

	Control (Treated = 37), No. (%)	BSC (Treated = 62), No. (%)	*P* Value[a]
Pseudomeningocele			1
Absent	35 (100)	58 (98.3)	
Present	0 (0)	1 (1.7)	
Total	35 (100)	59 (100)	
Extracerebral fluid collection			1
Absent	34 (97.1)	57 (96.6)	
Present	1 (2.9)	2 (3.4)	
Total	35 (100)	59 (100)	
Abnormal thickening along graft site			0.406
Absent	34 (97.1)	54 (91.5)	
Present	1 (2.9)	5 (8.5)	
Total	35 (100)	59 (100)	
Brain edema adjacent to graft site			1
Absent	35 (100)	58 (98.3)	
Present	0 (0)	1 (1.7)	
Total	35 (100)	59 (100)	
Adhesion formation			1
Absent	35 (100)	59 (100)	
Present	0 (0)	0 (0)	
Total	35 (100)	59 (100)	
Membrane formation			1
Absent	35 (100)	59 (100)	
Present	0 (0)	0 (0)	
Total	35 (100)	59 (100)	
Other			1
Absent	0 (0)	0 (0)	
Present	1 (100)	1 (100)	
Total	1 (100)	1 (100)	

[a]The only radiographic parameters that are part of the definition of individual patient success are pseudomeningocele and extracerebral fluid collection. If either of these parameters is present, the patient is not considered a success. BSC, biosynthesized cellulose.
[b]Fisher exact test (2-sided) comparing the absence of radiographic characteristics between BSC and control patients.

Baseline characteristics for continuous and categorical type measurements were compared using the Wilcoxon rank sum test and Fisher exact test, respectively. The sample size was based on an exact version, implemented in StatXact-6 for Windows (Cytel Inc., Cambridge, Massachusetts), of the original approximate calculation by Blackwelder.[13] Calculations were performed using a type I error of 5%, power of 80%. As suggested by Donner,[14] calculations were done assuming an equal chance of overall success (ie, absence of CSF leak or pseudomeningocele) at 6 months for both treatment groups and their common value was set at 97%. Using a margin of noninferiority of 0.10, the resulting sample size was 66 for the BSC group and 33 for the control group with correction for 10% attrition. All analyses were performed with SAS, version 9.1.3 (SAS Institute, Cary, North Carolina) and with StatXact-v6 for Windows.

Using a fixed-randomization blocking method of 6 assignments per block, random allocations were generated in a 2:1 ratio. The randomization was held by the sponsor and disclosed to the site only after individual patient enrollment was finalized: the patient had signed the informed consent and the inclusion/exclusion checklist had been completed and received by the sponsor. Because of the nature of the surgery, investigators could not be blinded to the individual treatment assignment. Patients were not informed of their treatment assignment until after surgery unless the information was necessary for insurance purposes.

Device Description

The BSC device, SyntheCel Dura Replacement (Synthes USA Products, LLC, West Chester, PA, USA, West Chester, PA, USA) is composed of nonwoven interconnected BSC fibers and water (Figure 1). There are 2 forms of SyntheCel: Substitute and Onlay. The Substitute differs from the Onlay in that the Substitute contains approximately twice the amount of cellulose; thermal modification of the Substitute results in a conformable dural substitute able to be secured with sutures. The Onlay, containing only approximately half the cellulose of the Substitute, is highly conformable and can be placed without sutures. Both forms are available in various sizes.

Surgical Technique for Duraplasty Using BSC

A duraplasty is performed using BSC cut to the desired shape. The Onlay should be sized to completely cover the dural defect with an overlap of the repaired site of approximately 1.0 cm in all directions. The Substitute should be sized to completely cover the dural defect with an overlap of sufficient size to allow sutures to be placed along the margin of the implant, 0.3 to 0.4 cm in from the edge (Figure 2). To achieve close reapproximation, use the smallest appropriate diameter sutures with a tapered needle, not larger than the diameter of the suture. Hemostasis and a lack of CSF outflow from the graft edge are critical for obtaining a watertight seal.[15]

Clinical Outcome Measurements

Patients were evaluated preoperatively, immediately postoperatively (within 10 days), and at 1, 3, and 6 months. Each visit included a physical examination consisting of the modified Rankin Scale (patient function assessment), wound healing assessment, and CSF leakage assessment. Magnetic resonance imaging was performed preoperatively and at 6 months postoperatively. The 6-month radiographic review included adhesion formation, membrane formation, extracerebral fluid collection, abnormal thickening along graft site, brain edema adjacent to graft site, and pseudomeningocele. The surgeon investigators assessed, by questionnaire, device handling characteristics such as ease of use, strength, seal quality, and sutureability; these data were also summarized and compared between the 2 treatment groups.

RESULTS

A total of 105 patients were randomized from February 2006 to January 2009 at 8 sites across the United States. Six patients did not participate after being enrolled and were not treated. Reasons for not participating included change in diagnosis, postenrollment ineligibility per exclusion criterion, voluntary withdrawal, and intraoperative surgeon decisions. Overall, 99 patients were treated, 62 in the BSC group (Onlay, 34 patients; Substitute, 28 patients) and 37 in the control group. The decision to use Onlay versus Substitute was made intraoperatively by the surgeon, based on the size of the defect and type of repair needed

TABLE 7. Device Handling Characteristics[a]

Characteristic[b]	Control (Treated = 37), No. (%)	BSC (Treated = 62)			*P* Value[c]
		Onlay, No. (%)	Substitute, No. (%)	Total, No. (%)	
Ease of use					.342
No	1 (2.6)	0 (0)	0 (0)	0 (0)	
Yes	38 (97.4)	45 (100)	30 (100)	75 (100)	
Total	39 (100)	45 (100)	30 (100)	75 (100)	
Device strength					<.0001
Poor	1 (2.6)	0 (0)	2 (6.7)	2 (3.3)	
Fair	12 (30.8)	0 (0)	0 (0)	0 (0)	
Good	19 (48.7)	24 (53.3)	15 (50)	39 (51.7)	
Excellent	7 (17.9)	21 (46.7)	13 (43.3)	34 (45)	
Total	39 (100)	45 (100)	30 (100)	75 (100)	
Device sutureability					N/A
Poor	5 (12.8)	0 (0)	0 (0)	0 (0)	
Fair	2 (5.1)	0 (0)	3 (10)	3 (5)	
Good	4 (0.3)	1 (2.2)	7 (23.3)	8 (12.8)	
Excellent	2 (5.1)	0 (0)	18 (60)	18 (30)	
N/A	26 (66.7)	44 (7.8)	2 (6.7)	46 (52.2)	
Total	39 (100)	45 (100)	30 (100)	75 (100)	
Device seal quality					.032
Poor	2 (5.1)	1 (2.2)	0 (0)	1 (1.1)	
Fair	10 (25.6)	7 (15.6)	2 (6.7)	9 (11.1)	
Good	22 (56.4)	27 (60)	14 (46.7)	41 (53.3)	
Excellent	5 (12.8)	10 (22.2)	14 (46.7)	24 (34.4)	
Total	39 (100)	45 (100)	30 (100)	75 (100)	
Device completely sutured in?					N/A
No	7 (17.9)	9 (20)	5 (16.7)	14 (18.3)	
Yes	8 (20.5)	0 (0)	23 (76.7)	23 (38.3)	
N/A	24 (61.5)	36 (80)	2 (6.7)	38 (43.3)	
Total	39 (100)	45 (100)	30 (100)	75 (100)	

[a]BSC, biosynthesized cellulose; N/A, not available.
[b]Patients may have more than 1 implant. The number of implants was used as the denominator to compute all percentages.
[c]Two-sided Fisher exact test comparing the distribution of response in device handling characteristics between control and combined BSC patients.

to achieve a watertight seal. Patient accountability revealed that at 6 months postoperatively, there was a follow-up rate of 94.9% (BSC, 95.2%; control, 97.2%; $P = 1.0000$).

Overall patient demographics of the 2 treatment groups were not statistically different with respect to age, sex, race, body mass index, height, weight, or smoking status ($P \geq .1036$). Neurosurgical indications included benign or low-grade tumors (BSC, 33 patients; control, 16 patients), aneurysms (BSC, 6 patients; control, 5 patients), Chiari type I malformations (BSC, 2 patients; control, 2 patients); decompressions (BSC, 2 patients; control, 1 patient), arteriovenous malformation (BSC, 1 patient; control, none), epilepsy (BSC, none; control, 1 patient), and other (BSC, 18 patients; control, 12 patients).

Intraoperative data showed no significant differences between patients implanted with BSC and control patients with regard to operative time, estimated blood loss, intraoperative complications, or length of hospital stay ($P \geq .1260$). Patient aspects are summarized in Table 3.

One control patient died during the study, approximately 6 months after implantation, of their past medical condition of thrombic thrombocytopenic purpura; initial treatment was for an aneurysm.

Absence of CSF Leak

The results confirm the primary hypothesis of this study: with regard to key clinical outcomes, the BSC implant is noninferior to the control group ($P = .0206$; 7.9% 1-sided upper 95% confidence interval). At 6 months, 96.6% (57/59) of patients implanted with BSC and 97.1% (33/34) of control patients showed an absence of CSF fistula (drainage from wound or sinus) and the absence of pseudomeningocele and extracerebral fluid collection (Table 4). Furthermore, as seen in Table 5, the overall success outcome was not different between patients implanted with the BSC Onlay (95.3%) and Substitute (93.1%) at 6 months ($P = 1.0000$).

Of the 59 patients implanted with BSC who reached the 6-month follow-up, 2 patients presented with pseudomeningocele (with extracerebral fluid collection) that occurred after supratentorial benign/low-grade tumor removal; neither patient required further intervention. Of the 35 control patients who reached the 6-month

TABLE 8. Distribution of Wound Healing Assessment[a]

	Control (Treated = 37), No. (%)	BSC (Treated = 62), No. (%)	*P* Value[b]
Postoperatively			.409
Fully healed	16 (43.2)	23 (37.1)	
Mild	18 (48.7)	37 (59.7)	
Moderate	3 (8.1)	2 (3.2)	
Severe	0 (0)	0 (0)	
Month 1			.369
Fully healed	26 (72.2)	47 (75.8)	
Mild	10 (27.8)	12 (19.4)	
Moderate	0 (0)	3 (4.8)	
Severe	0 (0)	0 (0)	
Month 3			1
Fully healed	34 (97.1)	58 (95.1)	
Mild	1 (2.9)	3 (4.9)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	
Month 6			1
Fully healed	34 (100)	59 (100)	
Mild	0 (0)	0 (0)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	

[a]The percentages were calculated using the number of respondents at the visit as the denominator. BSC, biosynthesized cellulose.
[b]Fisher exact test (2-sided) comparing distribution of response in wound healing assessment between BSC and control patients.

follow-up, 1 case of extracerebral fluid collection was reported after posterior fossa benign/low-grade tumor removal. No further treatment was required.

Radiographic Evaluation

At 6 months, magnetic resonance imaging of all patients were radiographically evaluated for pseudomeningocele and extracerebral fluid collection, abnormal thickening along graft site, brain edema adjacent to graft site, adhesion formation, membrane formation, and other. Radiographic assessment at the 6-month follow-up of the 59 patients implanted with BSC demonstrated 2 cases of pseudomeningocele and extracerebral fluid collection (3.4%), 5 cases of abnormal thickening along the graft site (8.1%), 1 case of brain edema adjacent to graft site (1.7%), and 1 case (1.7%) of enhancement of left internal auditory canal. One case of pseudomeningocele and extracerebral fluid collection (2.9%), and 1 case (2.9%) of persistent pachymeningeal enhancement in the region of previous resection were observed in the 35 control patients. There were no statistically significant differences between the BSC group and control group for any of the radiologic endpoints ($P \geq .4061$). The incidence of device implant reactions based on radiographic evaluations is presented in Table 6.

The incidence of abnormal thickening along the graft site reported in 5 patients implanted with BSC (8.1%) and 1 control patient (2.7%) was not statistically significant ($P = .4061$). One of the 5 patients in the BSC group had the only abnormal thickening event considered device related by the surgeon investigator. The incidental findings of thickening were characterized as within the range of the normal healing process, and no additional treatments were deemed necessary.

Modified Rankin Scale: Patient Function Assessment

Response propagation in the modified Rankin Scale revealed no statistical differences between the BSC and control groups at any postoperative follow-up time points ($P \geq .3280$).

Device Handling Characteristics

Device handling attributes (ease of use, strength, sutureability, and seal quality) were evaluated by the surgeon and showed a statistically significant difference in favor of patients implanted with BSC over control devices for both device strength ($P < .0001$) and device seal quality ($P = .0317$). Complete device handling characteristics are shown in Table 7.

Infections and Wound Healing

The incident of surgical site infections served as the primary safety endpoint. Three BSC patients (4.8%) and 2 control patients (5.4%) exhibited a superficial site infection. A deep site infection developed in 1 patient (1.6%) implanted with BSC during the short-term follow-up (>10-30 days). However, no significant difference was revealed between BSC and control patients for surgical site infection outcomes ($P = 1.0000$). Wound healing, the examination of the surgical site, was assessed as clean and/or fully healed, mild (wound erythema), moderate (superficial inflammation of the whole wound, serous discharge, or localized infection), or severe (wound breakdown, sinuses, fistulae, cellulitis, or infection of more than one third of the wound). As shown in Table 8, outcomes of the wound healing assessment presented no statistically significant difference between treatment groups at any follow-up time points ($P \geq .3685$).

In the 59 BSC patients who reached the 6-month follow-up, 2 cases of a superficial surgical site wound infection involved a suture abscess that required antibiotic treatment. The third superficial surgical site infection was not confirmed; the incision was tender, but was treated with a course of antibiotics. The deep surgical site infection presented with slight dehiscence in the superficial part of the scalp incision with some questionable purulent drainage. No redness appeared around the incision; no fever was present. It was consistent with a Vicryl stitch abscess. The wound was cultured (cultures were negative for bacteria), the patient was brought into the operating room for irrigation and washout of wound infection and revision of wound, and placed on empirical antibiotics. The graft was not removed. All 4 infections were resolved before the 6-month follow-up visit. Of the 35 control patients who reached the 6-month follow-up, 1 superficial surgical site wound infection was reported as *Staphylococcus*, requiring hospitalization for intravenous antibiotics and a second course of oral antibiotics. The other infection involved a suture abscess that required antibiotic

TABLE 9. Adverse Events[a]

	Control (Treated = 37), No. (%)		BSC (Treated = 62), No. (%)		
	Patients	Events (E/Pt)	Patients	Events (E/Pt)	*P* Value[b]
Any adverse event[c]	30 (81.1)	144 (3.89)	57 (91.9)	324 (5.23)	0.1239
Neurosurgical procedure related[d]					
Brain edema	1 (2.7)	1 (0.03)	2 (3.2)	2 (0.03)	
CSF leak	0 (0)	0 (0)	3 (4.8)	3 (0.05)	
Diplopia	2 (5.4)	2 (0.05)	1 (1.6)	1 (0.02)	
Dizziness	2 (5.4)	2 (0.05)	10 (16.1)	10 (0.16)	
Headache	11 (29.7)	13 (0.35)	27 (43.5)	30 (0.48)	
Hydrocephalus	1 (2.7)	1 (0.03)	2 (3.2)	2 (0.03)	
Infection: surgical site deep	0 (0)	0 (0)	1 (1.6)	1 (0.02)	
Infection: surgical site superficial	2 (5.4)	2 (0.05)	3 (4.8)	3 (0.05)	
Neurologic	15 (40.5)	19 (0.51)	34 (54.8)	63 (1.02)	
Pain at incision	5 (13.5)	5 (0.14)	7 (11.3)	7 (0.11)	
Paresthesia	4 (10.8)	7 (0.19)	5 (8.1)	6 (0.1)	
Seizure	2 (5.4)	2 (0.05)	1 (1.6)	1 (0.02)	
Seroma	1 (2.7)	1 (0.03)	3 (4.8)	3 (0.05)	
Stroke	1 (2.7)	1 (0.03)	2 (3.2)	2 (0.03)	
Subdural hematoma	1 (2.7)	1 (0.03)	1 (1.6)	1 (0.02)	
Surgery: reoperation (index site)	0 (0)	0 (0)	2 (3.2)	3 (0.05)	
Other					
Anemia	1 (2.7)	1 (0.03)	3 (4.8)	3 (0.05)	
Cardiovascular	8 (21.6)	9 (0.24)	5 (8.1)	6 (0.1)	
Death	1 (2.7)	1 (0.03)	0 (0)	0 (0)	
Dermatologic	1 (2.7)	1 (0.03)	7 (11.3)	8 (0.13)	
Drug reaction	6 (16.2)	6 (0.16)	10 (16.1)	14 (0.23)	
Edema	3 (8.1)	3 (0.08)	13 (21)	15 (0.24)	
Fatigue	2 (5.4)	2 (0.05)	9 (14.5)	9 (0.15)	
Fever	1 (2.7)	1 (0.03)	4 (6.5)	5 (0.08)	
Gastrointestinal	11 (29.7)	13 (0.35)	20 (32.3)	27 (0.44)	
Genitourinary	0 (0)	0 (0)	1 (1.6)	1 (0.02)	
Hematoma	1 (2.7)	1 (0.03)	1 (1.6)	2 (0.03)	
Hemorrhage	0 (0)	0 (0)	1 (1.6)	1 (0.02)	
Hoarseness	0 (0)	0 (0)	2 (3.2)	2 (0.03)	
Infection: other	3 (8.1)	3 (0.08)	4 (6.5)	4 (0.06)	
Insomnia	2 (5.4)	2 (0.05)	4 (6.5)	5 (0.08)	
Musculoskeletal	4 (10.8)	5 (0.14)	9 (14.5)	11 (0.18)	
Other	5 (13.5)	5 (0.14)	16 (25.8)	23 (0.37)	
Pain	13 (35.1)	16 (0.43)	13 (21)	16 (0.26)	
Pruritus	1 (2.7)	1 (0.03)	3 (4.8)	3 (0.05)	
Psychological	5 (13.5)	5 (0.14)	6 (9.7)	6 (0.1)	
Respiratory	4 (10.8)	4 (0.11)	4 (6.5)	6 (0.1)	
Sore throat	0 (0)	0 (0)	1 (1.6)	1 (0.02)	
Surgery: other	2 (5.4)	2 (0.05)	2 (3.2)	2 (0.03)	
Thrombosis	0 (0)	0 (0)	1 (1.6)	1 (0.02)	
Urinary tract infection	0 (0)	0 (0)	2 (3.2)	2 (0.03)	
Wound issues: other	4 (10.8)	6 (0.16)	6 (9.7)	8 (0.13)	

[a]Potential risks and adverse events that could occur from the implantation of material to or adjacent to cerebrospinal fluid space include, but are not limited to, inflammatory reaction, neurologic compromise, allergic reaction, and/or delayed healing. BSC, biosynthesized cellulose; E/Pt, events per patient.
[b]Two-sided Fisher exact test comparing the incidence of adverse events between treatment groups.
[c]Patients with adverse events in more than 1 category are counted only once.
[d]The incidence and nature of the adverse events observed in this patient population are consistent with the type and complexity of the surgery performed and the comorbidity of the treated patients.

treatment. Both infections were resolved before the 6-month follow-up visit.

Secondary Complications

Primary complications (CSF fistula, pseudomeningocele and extracerebral fluid collection, wound infection) defined the premise of this study. The occurrence of secondary complications was regarded as standard for patients with neurosurgical indications of those included in this study. There was only 1 complication determined by the investigating surgeon to be probably related to the implant. The diagnosis for this patient in the BSC group was a benign/low-grade tumor, and a parasagittal surgical approach was used. At the 1-month follow-up visit, magnetic resonance imaging showed a right parietal fluid collection. A course of steroid therapy was administered, and the hematoma/seroma resolved 3 weeks later.

Two patients implanted with BSC required further surgery, after partial tumor resections. The first patient underwent a complete resection of a grade II astrocytoma that had increased in size. The second patient required a complete resection of a grade II pleomorphic xanthoastrocytoma. All study adverse events are summarized in Table 9.

DISCUSSION

The ideal dural substitute should prevent CSF leaks, have similar mechanical properties, especially strength and flexibility, to human dura, be nonimmunogenic, not cause potential risk of infections, and be abundantly available and easy to store.[2,16] BSC has previously been shown to be a suitable substitute for dura mater in animal studies. It was found to exhibit low foreign body reactions, the absence of cortical adhesion, as well as the property of malleability.[17]

At the 6-month endpoint of this study, the efficaciousness of BSC, the absence of CSF leakage, pseudomeningocele, and extracerebral fluid collection, was not statistically different from the control group of commercially available dural replacements. Device handling qualities of strength and seal quality were shown to significantly favor the BSC device.

The safety of BSC was comparable to that of the control group of dural replacements. Substantial postoperative complications are frequent, given the complexities of open cranial surgery and the comorbidity of the patients treated. Although the number of adverse events appeared higher in the BSC group, when comparing the incidence of all adverse events between the 2 treatment groups, statistical significance was not shown (P = .1239). Of severe adverse events identified as specifically cranial (brain edema, CSF leak, headache, hydrocephalus, neurologic, paresthesia, seizure, stroke, and surgery—reoperation index level), statistical significance was not seen in event rate (P = .0566) or comparison of patient incidence (P = .1368). The infection rate at the surgical site was 6.5% in the BSC group and 5.4% in the control group (P = 1.0000). All wound infections were localized at the site, resolved, and did not recur. The overall wound infection rates were comparable to those cited in other reported series on dural grafts.[9,18,19] Moreover, this study provides further substantiation of the opinion formed in previous studies that dural grafts by themselves do not accordingly influence the risk of wound infections.[9]

CONCLUSION

This study is the first prospective, randomized, controlled dural substitute trial performed to date. This clinical trial was conducted to demonstrate that the BSC dural replacement is noninferior to other commercially available dural replacement devices; the safety and efficacy of this cellulose-based dural replacement are equivalent to those of dural replacement devices currently on the market. The theoretical advantage with respect to prion exposure or other infectious agents is attractive. More experience and further studies will be necessary to identify the limitations of this material in patients with previous surgery, a history of radiation, or malignant lesions. Whether BSC is equivalent to the gold standard of pericranium remains to be seen.

Disclosures

Dr Lewis has received an honorarium, Dr Hantel is an employee of, Dr Marciano has received royalties (unrelated to this product) and is a consultant for, and the Department of Neurosurgery at West Virginia University receives fellowship support from Synthes USA Products, LLC. All other authors have no relevant disclosure.

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COMMENTS

This is an industry-sponsored multi-institution prospective clinical trial of a new cellulose dural substitute compared with mostly collagen-based substitutes from other companies used in the absence of fibrin or other sealant. It provides objective and useful data at a very strong evidence level. The follow-up rate of 94.9% is excellent. There are, however, several issues that need to be pointed out, and must be kept in mind.

First, the results cannot be extrapolated to comparison with autologous tissue, xenograft tissue, or other artificial substances because these were not significantly represented in the control arm.

Second, the results likely only have validity only for elective benign tumor and aneurysm craniotomy (two thirds of all cases). The results have no external validity for trauma cases or malignant tumor cases (those with chemotherapy or radiotherapy within 12 months before surgery or planned within 10 months after surgery) as they were specifically excluded from this study.

Third, methodologically, dural grafts fall into 3 categories: intact primary suture line onlay reinforcement, primary suture line with one or more 1-mm or larger gap(s) onlay reinforcement, and sutured dural patch grafting with or without onlay reinforcement. Unfortunately, this study was not designed to track which of the 3 were used in a given case. It is difficult to interpret the study results without this information and knowing that the breakdown was similar in both study and control groups.

Fourth, it is interesting that fibrin glue was not allowed in this study as most consider it standard when dealing with grafts of any type. How the use of fibrin glue might have affected study results is unknown.

Fifth, the average length of stay difference between the 2 groups, although not statistically different, did show a trend at P .2473 in favor of an average of an extra day of hospitalization for the BSC patients. Because the surgeons were not blinded, one wonders whether there was there any difference in postoperative wound care (eg, pressure wrap, postoperative suture reinforcement, postoperative collodian reinforcement, use of lumbar drains) or threshold for discharge versus continued observation between the 2 groups? Unfortunately, the study was not designed to standardize postoperative wound care nor track the potential techniques outlined above.

Finally, as an industry-sponsored trial, there are potential conflict of interest issues for the authors involved that could not be assessed in this commentary because the article reviewers are not provided with the Neurosurgery Author Disclosure Forms for each author. How these conflicts might affect such subjective endpoints as assessment of intraoperative device handling characteristics or choice of postoperative wound care each reader must decide.

Overall, I congratulate the authors on an interesting article that contributes objective new evidence to the neurosurgery wound closure literature.

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The World Health Organization, in their guidelines for prevention of Creutzfeldt-Jackob disease (CJD),[1] recommended avoidance of the use of human dural grafts based on the growing concern of transmissible CJD reports after these procedures.[2,3] They further recommended the use of autologous tissue or synthetic materials even when these may appear suboptimal for dural closure. Various synthetic materials have previously been used for duraplasty; however, search for an ''ideal'' synthetic material continues. In this study, the authors studied biosynthesized cellulose (BSC), SyntheCel Dura Replacement (Synthes USA Products, LLC) in a multicenter, prospective, randomized, controlled fashion. Using a noninferiority design, the authors conclude that the safety and efficacy, measured by absence of CSF fistula and pseudomeningocele formation, are not inferior to other commercially available products on the market including Duraform, DuraGen, and Preclude.

Some concerns remain. SyntheCel Dura Replacement device is available in 2 forms: Substitute, which has to be sutured to the native dura, and Onlay, which is placed on the dural defect without sutures. The study is not powered to allow any conclusion regarding differences between these forms of the material.

More problematic is the authors' decision to lump all other duraplasty devices available in market in the control group based on assumption that all these devices are substantially equivalent with regard to their biochemical characteristics and clinical outcomes. This suggests that the authors began the study with a bias that there are no important differences among dura replacement materials, an assumption that is relevant to the study design and results. Dura-Guard, Durepair, and DuraGen, when compared in a canine model, showed inherent differences in DuraGen's mechanical properties.[4] Such studies in a human model are lacking, to our knowledge. Therefore, the lumping of all other devices into a control group comparison may pose serious questions.

The use of blinded observers to make the outcome assessments would have been a useful addition to the quality of the study.

Noninferiority studies are becoming a common method of bringing drugs, devices, and procedures that are similar to previously validated ones into practice when major differences from existing products or procedures are not expected. Such studies are different from typical controlled trials designed to assess an important difference among treatments. Because these studies intend to show little difference between treatments, they require more attention to the risk of failing to identify a difference (α or type I error) than the usual study where most attention is paid to the risk of inappropriately identifying a difference (β or type II error). The size of difference that is thought to represent a clinically important difference is a critical parameter and must be clearly identified and justified. The power, or likelihood of identifying a difference of that size, is the real measure of the rigor of the study and must also be clearly

stated. The article by Fueglistaler et al[5] is a reasonable explanation of the statistical issues.

Short-term noninferiority studies cannot identify late complications, and the results are highly dependent on the definition of which outcome measures are examined for noninferiority. Careful attention to the definitions of outcome, the magnitude of difference sought, and the power of such studies is critical to their proper interpretation.

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This is a rather elaborate randomized clinical trial to evaluate a new dural substitute. It is basically a cellulose product, which has the advantage over biological materials in that it would not be a source of previous infection, and does not require harvesting. It can be used as an onlay graft or sutured. Because precious infections using modern products are essentially unheard of, it is unclear that there is any real benefit.

The finding of the study is that it appears no worse than a basket of other products in preventing CSF leaks and pseudomeningoceles. It proved no better either, which is not surprising in view of the small number of adverse events. The authors chose relatively low-risk procedures for the study, presumably to amass greater numbers. High risk procedures for leak (cranial base procedures, craniofacial surgery, hemicraniectomy) were not included, and there were only a small number of Chiari malformations and epilepsy cases.

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