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Safety and efficacy of the porcine small intestinal submucosa dural substitute: results of a prospective multicenter study and literature review

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Object. Dural substitutes are often needed after neurosurgical procedures to expand or replace dura mater resected during surgery. A new dural repair material derived from porcine small intestinal submucosa (SIS) was evaluated in a prospective multicenter clinical study.

Methods. Between 2000 and 2003, 59 patients at five different institutions underwent dural reconstruction with the SIS dural substitute, with a minimum follow up of 6 months. The primary goals of the study were to assess the efficacy and safety of the SIS dural substitute according to the rate of cerebrospinal fluid (CSF) leakage, infection, and meningitis.

Chiari malformation Type I decompression (32 patients) and tumor resection (18 patients) were the most common procedures performed, with 81% of SIS grafts implanted in the posterior fossa or spine. There was one case of a CSF leak (1.7%), two cases of wound infection (3.4%), and no cases of bacterial meningitis (0%) in the 58 patients available for follow up. In both cases of wound infection, the SIS graft acted as a barrier to infection and was not removed. Intraoperatively, a watertight seal was achieved in all 59 cases. On follow-up imaging available in 27 patients there was no evidence of any adverse reaction to the graft or of cerebral inflammation.

Conclusions. The SIS dural substitute demonstrated substantial efficacy in these patients after a mean follow up of 7.3 $\pm$ 2.2 months. Rates of infection, CSF leakage, and meningitis were comparable to those reported for other dural substitute materials. A lack of adverse reactions to the graft, favorable safety profile, and clinical efficacy all point to the utility of this material as an alternative for dural repair.

KEY WORDS • Chiari malformation Type I • tumor resection • dural substitute • extracellular matrix • small intestinal submucosa • cerebrospinal fluid leak

DURAL substitutes are often needed after neurosurgical procedures to expand or replace dura that was resected during the procedures. Synthetic materials or biomaterials derived from allogenic or xenogenic sources have been used, but these implanted materials may be associated with adverse reactions as a consequence of their placement, ranging from graft dissolution, encapsulation, and foreign body reaction, to excessive scarring and adhesion formation. The ideal goal of implant grafting is for the implant to be remodeled and rapidly integrated into the patient's surrounding tissues to form a new and completely natural tissue. Small intestinal submucosa, a biomaterial derived from porcine intestine, has demonstrated these ideal properties in animal models and in clinical use where tissue repair was required.[4,22]

The submucosa of the small intestine provides strength to the intestine and is located between its mucosal and muscular layers. The SIS is harvested from the intestine, and the cells are removed, leaving the ECM intact.[10] The resulting biomaterial is a naturally derived, complex ECM containing structural collagens, other bioactive proteins, and cytokines that guide host-tissue remodeling.[11,12,15,16]

In neurosurgery, SIS has been investigated for its utility as a dural substitute in rats and in dogs, with favorable results evident for as long as 120 days.[6,7] Based on these successes in animal models, a prospective multicenter clinical study to evaluate the safety and efficacy of the SIS dural substitute Durasis (Cook Biotech Incorporated) was conducted according to a US Food and Drug Administration-approved investigational device exemption regulation. The safety of the graft was assessed in comparison with a primary study hypothesis that the rates of CSF leakage, infection, and meningitis would be equivalent to the same measures from studies of dural substitutes reported in the literature.[2,3,5,13,14,17–21] Data regarding the incidence of other complications and the performance of the device were also collected.

Clinical Material and Methods

Study Design and Population

This prospective multicenter clinical study was conducted at five separate institutions across the US and was de-

Abbreviations used in this paper: CSF = cerebrospinal fluid; ECM = extracellular matrix; SIS = small intestinal submucosa.

signed to enroll approximately 60 patients who required implantation of a dural substitute. The study protocol and informed consent statements were reviewed and approved by the respective governing independent institutional review boards. Written informed consent was obtained from each patient or patient representative prior to enrollment. Eligible patients were 18 years of age or older, suffered from a cranial or spinal dural defect requiring placement of a dural substitute for repair, and had a life expectancy longer than 6 months.

Prospective patients were excluded if they had prior implantation of a nonautologous dural substitute, a known allergy to porcine-derived products, or known systemic collagen disease (collagen vascular disease). Patients were also excluded for: chronic usage of corticosteroids or immunosuppressive agents within the 3 weeks before surgery; a known or suspected infection, meningitis, or cerebritis; a religious or cultural objection to the use of blood or porcine products; or enrollment in a clinical investigation for another device or drug. Monitoring of patients was coordinated by a contract research organization (CRO, MED Institute).

Protocol and Evaluations

All study data were collected using standard data forms. For patients consenting to study participation and meeting all entry criteria, information regarding the medical history and preoperative condition of each patient was recorded. The SIS dural substitute was cut to the appropriate size and used to repair the dural defect with standard sterile surgical techniques. After repair of the dural defect, the site was visually inspected for evidence of CSF leakage during a Valsalva maneuver to evaluate the quality of the dural repair. The target pressure for the Valsalva maneuver was 25 cm H_2O for 10 seconds. The surgical site was then closed using appropriate standard methods. Data for evaluating the efficacy of the device was recorded using the scoring system listed in Table 1. Device handling characteristics were also recorded and scored on a scale from 0 to 4 for ease of use, strength, suture capability, and quality of the seal at the suture line.

Patients were evaluated postoperatively for complications after approximately 10 days, and at 1, 3, and 6 months after implantation. A subset of these patients was also followed up for as long as 12 months. Complication rates were compared with the rates given in 10 different peer-reviewed publications from 1971 to the present.[2,3,5,13,14,17–21] The published rates were pooled for statistical purposes, and compared with the incidence rate observed in the current study using the two-tailed Fisher exact test.

Cranial images were acquired postoperatively and were obtained according to the standard of care at each site. These images were evaluated using the criteria presented in Table 2. Observations related to the condition of the implanted SIS dural substitute were reported. Furthermore, any notable abnormalities were evaluated for a possible relationship to the SIS dural substitute, the surgical procedure, or the underlying disease. Graft integrity, if visible, was also assessed.

TABLE 1

Scoring system used to define device success

Observation	Score
watertight seal	5
leakage due to defect in native dura	4
leakage from SIS dural substitute suture-hole elongation	3
leakage through SIS dural substitute material (porosity)	2
leakage from SIS dural substitute tear	1

Results

Patients and Procedures

A total of 59 patients were enrolled in the study at five different investigative sites between November 1, 2000, and September 10, 2003. The mean age of the patients was 46 ± 16 years, and 43 patients (73%) were female. A variety of neurosurgical procedures were required, including surgery for treatment of Chiari Type I malformations (32 patients), tumors or meningiomas (18 patients), aneurysms (3 patients), spinal cord tethering (3 patients), pseudomeningocele (1 patient), seizure disorder (1 patient), and benign cyst (1 patient). Patient characteristics are summarized in Table 3.

Operative results for all patients are summarized in Table 4. The mean size of the SIS dural substitute implanted was 16.0 cm^2 (range 1–140 cm^2). Other devices were used in some procedures as noted in Table 4. The Valsalva maneuver conducted in the majority of patients to assess CSF leakage used a mean pressure of 30.1 ± 6.2 cm H_2O with mean duration of 9.8 ± 1.5 seconds. The average time until patient discharge was 3.8 ± 2.6 days.

Mean patient follow up was 7.3 ± 2.2 months. Fifty-eight patients completed at least 6 months of follow up. One patient died during the study at 96 days after implantation due to metastatic melanoma, the disease for which the initial treatment was given. Eighteen of the 59 patients were followed 7 to 12 months postoperatively, and follow up of four patients was greater than 12 months postoperatively.

Surgical Complications

Patient outcomes were recorded according to the primary study hypothesis of the incidence of complications (CSF leakage, pseudomeningocele, fistulae, infection, and meningitis). Of the 58 patients who reached the 6-month follow up, one CSF leak (1.7%), two wound infections (3.4%), and no cases of meningitis, pseudomeningocele, or fistulae were observed. The CSF leak was reported in a patient 9 days after T11–L1 repair of the spinal dura after intramedullary tumor removal. The procedure required the placement of a temporary lumbar drain and the CSF leak was noted as resolved at the 1-, 3-, and 6-month follow ups. One of the cases of wound infection was reported 10 days postoperatively, with *Staphylococcus aureus* identified on culture. The wound was debrided and closed, and the drainage resolved. Infection resolved with no evidence of recurrence at the 3- and 6-month follow-up visits. The other case of infection was noted 56 days postoperatively in epidural collection with *Propionibacterium acnes* identified on culture. This wound was debrided and irrigated, and the SIS graft was exposed and found to be intact and not affected. The patient was discharged home 3 days later while taking antibiotics, and the infection resolved with no further intervention. No recurrent infection was observed at the 6-month follow up.

TABLE 2

Summary of criteria used to evaluate postoperative cranial images

Category	Score	Criteria
cerebral reaction		
edema	none	no signal change
	mild	signal change, <10 mm thickness
	moderate	signal change, >10 mm thickness
	severe	
amount of enhancement	none	absent
	mild	patchy (<2 mm)
	moderate	linear continuous (2–5 mm)
	severe	nodular ≥5 mm
soft tissues		
swelling	none	no signal change
	mild	<10 mm thickness
	severe	>10 mm thickness
amount of enhancement	none	absent
	mild	patchy (<2 mm)
	moderate	linear continuous (2–5 mm)
	severe	nodular ≥5 mm
CSF leakage (fluid collection)		
distribution pattern	none	
	layered	
	ovoid	
size	none	absent
	small	<3–5 cm in diameter
	large	>3–5 cm in diameter

No cases of device rupture were observed. Complications other than the defined primary study complications were observed, but were considered typical for patients experiencing the underlying disease and undergoing the surgical procedures included in this study. None of these complications were judged by investigating physicians to be device related.

To compare the incidence of CSF leakage and infection when the SIS dural substitute was used with the incidence reported for other devices in the literature, 10 different published articles were reviewed for complication rates. The incidence rates in the studies were pooled and compared with the results of the current study. Rates of CSF leakage in the reviewed studies are presented in Table 5, and infection rates are summarized in Table 6. In the current study, the CSF leakage rate was 1.7% and the infection rate was 3.4%. These incidences compare favorably ($p < 0.05$) with the published overall leak rate of 5.2% and the overall infection rate of 5.0% observed with other graft materials.

TABLE 3

Summary of patient characteristics

Parameter	No. (%)
mean age (yrs)	46 ± 16
sex	
female	43 (73)
male	16 (27)
neurosurgical diagnosis	
Chiari malformation	32 (54)
tumor/meningioma	18 (31)
aneurysm	3 (5)
spinal cord tethering	3 (5)
other (pseudomeningocele, seizure disorder, benign cyst)	3 (5)
surgical site	
posterior fossa	40 (68)
frontal	6 (10)
spinal: cervical	4 (7)
spinal: thoracic & lumbar	4 (7)
frontal/temporal or temporal	3 (5)
parietal/occipital or parietal	2 (3)

TABLE 4

Summary of operative results

Parameter	Value
mean graft size (cm^2)	16.0
mean suture spacing (mm)	1.9 ± 0.3
other devices used (patients)	
fibrin glue & Gelfoam	16
fibrin glue	6
clips	4
drainage catheters (2 lumbar, 1 parasagittal, 1 ventricular)	4
Gelfoam	3
plates	2
shunt	1
Valsalva maneuver	
mean duration (sec)*	9.8 ± 1.5
mean pressure (cm H_2O)†	30.1 ± 6.2
mean days until discharge	3.8 ± 2.6

* In 42 patients.
† In 36 patients.

Device Performance

Device performance was evaluated in terms of device success, handling characteristics, and procedural success. Device success (defined as a score ≥ 4 using the criteria presented in Table 1) was achieved in all 59 patients treated with the SIS dural substitute (mean score 4.8 ± 0.4). Device handling characteristics (including ease of use, device strength, suture capability, and quality of seal at suture line) were all judged to be excellent using a scale of 0 to 4. Procedural success (device success with no complications associated with the dural graft through the time of discharge) was achieved in all 59 patients treated, for a procedural success rate of 100%. No device failures (rupture of SIS or patient death due to placement) were observed.

Postoperative Imaging

Postoperative magnetic resonance images were available for 26 patients, and computed tomography scans for one patient. Assessment of cerebral reaction to the device revealed no occurrence of edema in any of the 27 patients, but two instances of moderate enhancement were reported; both instances were judged likely due to the patient's primary disease. Assessment of soft tissues revealed two cases of swelling; one case was rated as mild and the other was rated as severe. In the patient with severe swelling, the swelling was noted 5 months postoperatively and had resolved 10 months postoperatively. Two patients presented with mild enhancement and three with severe enhancement; all enhancements were judged to be consistent with the normal postoperative appearance for the procedure. Assessment for CSF leakage showed one case of fluid in a layered distribution, not a true pseudomeningocele. One pseudomeningocele was observed, but was resolving on

TABLE 5

Incidence of CSF leakage in published studies of dural substitutes

Authors & Year	Implants	No. of Patients	Leaks	Incidence (%)
Abbott & Dupree, 1971	lyophilized human dura	170	3	1.8
Macfarlane & Symon, 1979	lyophilized human dura	100	8	8.0
Laun et al., 1990	bovine pericardium or lyophilized human dura	102	0	0.0
Narotam et al., 1995	collagen sponge	172	7	4.1
Anson & Marchand, 1996	bovine pericardium	35	2	5.7
von Wild, 1999	Ethisorb Dura-Patch	101	13	12.9
	total	680	33	4.9
patients w/ Chiari malformations				
Vanaclocha & Saiz-Sapena, 1997	lyophilized human dura	13	2	15.4
Munshi et al., 2000	various materials	23	2	8.7
	total	36	4	11.1
	overall total	716	37	5.2

subsequent imaging and found to be clinically irrelevant. No evidence of scar tissue formation or encapsulation or loss of graft integrity was observed.

Histopathological Findings

One patient underwent surgery for recurrent metastatic disease 14 months after graft implantation. There were no adhesions between the brain and the graft upon reexploration except for minimal adhesions under the suture line itself (Fig. 1). A sample from the graft underwent histopathological analysis. On examination, the tissue was found to be composed of two well-demarcated layers of dense mature fibrous connective tissue roughly equal in thickness. The first layer was composed of longitudinally arranged thick, coarse collagen fibers as thick as 15 μm (Fig. 2A and B). Very few fibrocytes and capillaries were dispersed throughout the layer. Remnant vascular structures suggested this layer was persistent SIS with a few host cells infiltrating and separating the SIS layers. The second layer was more cellular and was interpreted as the host fibrous response to the SIS (Fig. 2A and B). In this section, low numbers of long, spindle-shaped fibrocytes were widely separated by very fine collagen fibers (usually < 2 μm thick). The tissue was evenly vascularized with arterioles, venules, and capillaries. Very minimal inflammation consisted of low numbers of mononuclear cells (hemosiderin-laden macrophages) (Fig. 2C) and rare granulocytes. These results revealed the patch to be integrated with host cells to form dense, strong, connective tissue with a minimal and expected inflammatory response. The layer with more coarse collagen fibers and remnant vascular structures was interpreted to be persistent SIS.

TABLE 6

Incidence of infection in published studies of dural substitutes

Authors & Year	No. of Implants	No. of Infections	Incidence Rate (%)
Abbott & Dupree, 1971	162	10	6.2
Macfarlane & Symon, 1979	100	1	1.0
Cantore et al., 1987	804	48	6.0
Parizek et al., 1989	160	1	0.6
Laun et al., 1990	102	2	2.0
Narotam et al., 1995	459	28	6.1
Anson & Marchand, 1996	35	2	5.7
total	1822	92	5.0

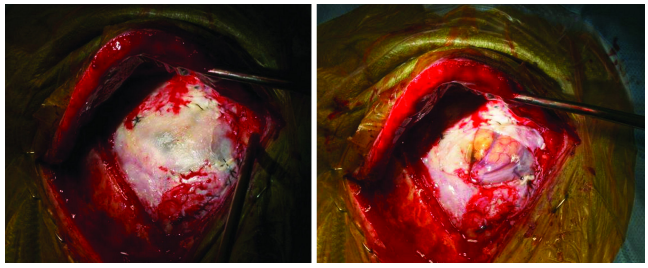

FIG. 1. Photographs of the biopsy procedure in a patient who underwent a second surgical procedure for recurrent metastatic disease 14 months after implantation of the SIS dural substitute. The SIS graft is exposed *(left)*. There were no adhesions between the brain and the graft on reexploration, except for minimal adhesions under the suture line *(right)*. The *yellow area* is scar tissue from the prior corticectomy.

Discussion

In neurosurgery, biomaterials are used as dural substitutes in procedures where the dura has to be expanded or replaced (for example in Chiari malformation decompression and decompressive craniectomies for trauma). The ideal dural substitute should have various technical short- and long-term characteristics, such as strength, elasticity, and impermeability to liquid. Furthermore, it should be easy to handle and suture without suture-hole elongation, and should have a thickness similar to the native dura for ease of manipulation. In the short term it should be able to provide a watertight seal to prevent egress of CSF and ingress of blood, it should be nontoxic, and should not cause inflammation of the underlying nervous tissue or increase the risk of infection. In the long term, the ideal dural substitute should not cause scar or adhesion formation, carry no risk of infectious disease transmission, retain its flexibility, and gradually integrate with the surrounding dura to form a permanent repair. Since Abbe[1] described the first dural graft using rubber laminate in 1895, many potential dural graft materials have been evaluated, only to be discarded for one or more reasons.

In the current case series, a dura mater substitute fabricated from porcine SIS was evaluated for ease of use, safety, and efficacy. Specifically, the safety of the SIS dural substitute in preventing CSF leakage, and limiting the incidence of infection and meningitis after implantation, was evaluated and compared with available published data. The CSF leakage rate associated with the use of SIS was 1.7% and the infection rate was 3.4%. These incidences compare favorably with the 5.2% leakage rate and 5.0% infection rate observed with other grafts in other published studies. These results are even more significant given that the SIS

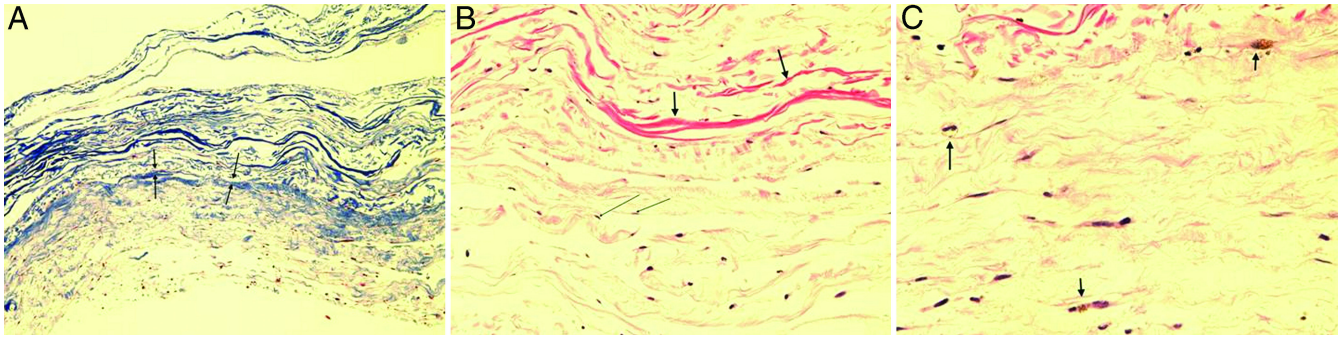

FIG. 2. Photomicrographs of a biopsy specimen from the SIS dural substitute obtained 14 months after implantation. A: *Arrows* indicate the line of demarcation between coarse *(upper)* and fine *(lower)* collagen layers. Trichrome stain, original magnification × 100. B: Higher magnification of panel A. *Thin arrows* point to fibrocytes surrounded by fine collagen fibers. *Thick arrows* point to coarse (thicker) collagen fibers. H & E, original magnification × 200. C: *Arrows* indicate pigmented (hemosiderin-laden) macrophages in the fine collagen layer. Inflammation is nearly absent. H & E, original magnification × 400.

in 81% of the cases in the current series were implanted in the posterior fossa or spine, which are more prone to CSF leakage than cases involving the supratentorial area. In the subset of patients treated for Chiari Type I malformations, the leakage rate of 0% is very favorable when compared with the historical incidence rate of 11.1% in these cases. These data demonstrate equivalence of efficacy and safety data for SIS dural implants with that reported for other dural substitutes.

In the cases of infection that were reexplored, the SIS dural substitute acted as a barrier to the infection and was left in place. Similar results were seen in the use of SIS for herniorrhaphy, in which it was shown to be suitable for use in contaminated fields.[8,9]

The imaging and clinical follow-up data revealed no radiological or clinical evidence of adverse reaction to the SIS dural substitute, and there have been no incidences of patients requiring graft removal or having disease transmission. In the case that was explored because of tumor recurrence, no adhesions were encountered between the graft and the cortex. On histopathological analysis, the graft was incorporated with host cells to form dense connective tissue with a minimal and expected inflammatory response. Investigators in previous preclinical reports on the use of the SIS dural substitute in rats and dogs indicated that histologically the graft becomes initially infiltrated by mononuclear round cells and spindle-shaped cells within an eosinophilic-staining ECM, and neovascularization also occurs. In rats, the cerebral cortex did not respond adversely to the SIS, and in dogs, CSF cytology and routine serum chemistry at the time of killing were normal. Response to repeat grafting was identical to that of initial exposure, indicating no clinical or histological evidence of sensitization or graft rejection. As in the rats, evaluation of the underlying canine cerebral cortex revealed no evidence of any adverse reaction.[6,7] Although the availability of human biopsy specimens is limited, the histological images that are available from this study support the preclinical literature indicating that chronic inflammation and membrane formation are absent when the SIS dural substitute is used in this location.

Unlike the risk of disease transmission that has become apparent when human allografts or bovine xenografts are used as dural substitutes, disease transmission from porcine products to humans has not been reported, nor has the presence of prions in porcine tissue.

Conclusions

This clinical evaluation of the SIS dural substitute demonstrated that rates of common complications associated with the use of dural substitutes compare favorably to experience reported in the literature with other dural substitute products. There was no evidence of scar tissue formation or encapsulation of the SIS dural substitute. The SIS dural substitute was judged to have excellent handling characteristics, and was associated with a very high rate of device and procedural success. Lack of adverse reactions to the graft, a favorable safety profile, and clinical efficacy all indicate the utility of this material as an alternative for the repair of dural defects.

Appendix

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