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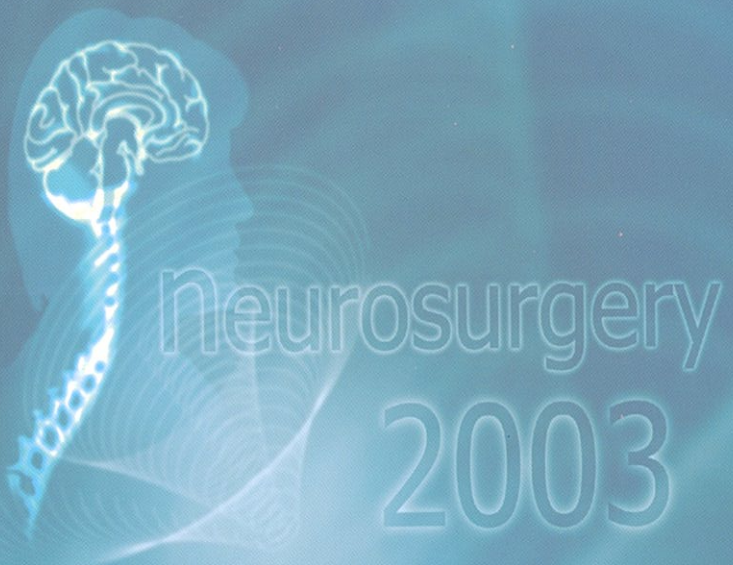

MONDUZZI EDITORE
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DURASIS: A Novel Dural Substitute. Results of a Multi-Center Study

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Abstract

Introduction: Small Intestinal Submucosa (SIS) is a naturally occurring extracellular matrix extracted from porcine small intestine. It has been used as wound dressing (Oasis Wound Matrix), and for hernia and soft tissue repair (Surgisis, Stratasis) in over 150,000 patients. SIS has numerous properties, including promoting new vessel growth and providing a scaffold for remodeling by the host tissue. Durasis is a SIS-based product developed for use as a dural substitute. We report the results of a prospective multicenter study on Durasis.

Methods: The study was carried out in 5 centers: the University of Pittsburgh, the Barrow Neurological Institute, the University of Miami, Wayne State University and Methodist Hospital of Indianapolis. Patients older than 18 years requiring spinal or cranial dural graft substitute were recruited. Clinical information was recorded preoperatively, intraoperatively, 7-10 days, 1 month, 3 month and 6 months postoperatively. Postoperative imaging was analyzed. Endpoints for analysis were incidence of adverse events and assessment of device performance.

Results: The results reported are on 51 patients, with a mean age of 47 years and a 3/1 female/male ratio. Average follow-up was 6.5 months. The pathologies included: Chiari malformation (29), tumors (14), aneurysm (3), tethered cord (2), pseudo-meningocele (1), epilepsy (1), and benign cyst (1). Three patients (6%) had a spinal graft. Seventy two percent of cases were infratentorial. There was one case of CSF leak (2%), and two cases of wound infection (4%); all three cases resolved. In one case of wound infection, the wound was re-explored and the graft found to be intact. When images were obtained, there was no evidence of brain or spinal cord adverse reaction. No device failures were recorded. Various handling characteristics of the device ranged from 3.96/4 to 4/4.

Conclusion: The results obtained in this multicenter study are encouraging. The incidence of CSF leak was 2%, which is low considering the fact that 78% of the grafts were used in the posterior fossa or spine. There was no evidence of rejection or inflammatory reaction. In the wound infections reported, there was no evidence of Durasis being affected. Similar results were seen in use of SIS for herniorraphy where it was shown to be suited for use in contaminated fields. Handling characteristics were also excellent. Durasis seems promising as a dural graft substitute.

Introduction

The Durasis Dural Substitute is comprised of acellular, collagenous material derived from porcine small intestinal submucosa (SIS). Biocompatibility testing and *in vitro* physical performance testing of the product provide evidence that the device has ideal characteristics for use in repairing the dura mater. Animal studies further suggest that the material comprising Durasis allows for complete repair of dural defects.[1,2] We report the early results of a prospective, multi-center clinical study to evaluate the safety of Durasis Dural Substitute conducted under an FDA approved Investigational Device Exemption (IDE).

Study Entry Criteria

Inclusion criteria:

1) cranial or spinal dural defect requiring placement of a dural substitute;
2) 18 years of age or older;
3) life expectancy greater than six months;
4) informed consent.

Exclusion criteria:

1) prior implant of a non autologous dural substitute;
2) known allergy to porcine-derived products;
3) known systemic collagen disease (i.e., collagen vascular disease);
4) chronic usage of corticosteroids or immune suppression agents up to three weeks prior to procedure;
5) known or suspected infection,
6) inability to approximate the graft and dura edge along entire extent of defect;
7) therapeutic radiation to the site, either prior to the procedure or expected during the three week period following the procedure;
8) religious or cultural objections to the use of blood or porcine products; or
9) enrolled in a clinical investigation for another device or drug.

Methods

Patients were evaluated post-operatively, at approximately 10 days, and at 1, 3, and 6 months after implantation of the Durasis Dural Substitute for the occurrence of complications. Cranial images that were acquired post-procedure were conducted according to the site's standard of care, and observations related to the condition of the implanted Durasis Dural Substitute were reported.

Results

A total of 53 patients were enrolled in the study at five investigative sites from November 1, 2000 through June 4, 2003. A listing of patient enrollment by site is presented in Table 1.

As of June 4, 2003, procedural data have been received for 51 patients. Patient characteristics are summarized in Table 2. Operative results are sum-

Table 1. Patient Enrollment

Investigative Site	Patients
University of Pittsburgh Medical Center	32
Barrow Neurological Institute, St. Joseph's Hospital	15
University of Miami School of Medicine	3
Wayne State University, Harper University Hospital	2
Indianapolis Neurosurgical Group, Methodist Hospital	1
Total	**53**

Table 2. Patient Characteristics

Parameter	N = 51
Age (years)	47.1 ± 16.3
Gender	
Females	38 (74.5%)
Males	13 (25.5%)
Neurosurgical Diagnosis	
Chiari Malformation	29 (57%)
Tumor/Meningioma	14 (27%)
Aneurysm	3 (6%)
Cord Tethering	2 (4%)
Other (pseudomeningocele, seizure disorder, benign cyst)	3 (6%)
Surgical site	
Cervical	1 (2%)
Frontal	5 (10%)
Frontal/Temporal or Temporal	3 (6%)
Parietal or Parietal/Occipital	2 (4%)
Thoracic/Lumbar	3 (6%)
Suboccipital	37 (72%)

Table 3. Operative Results

Parameter	N = 51
Mean graft size (cm^2)	18.0
Mean suture spacing (mm)	1.9 ± 0.3
Other devices used	
Shunt	1
Clips	4
Plates	2
Drainage catheters (2 lumbar, 1 parasagittal, 1 ventricular)	4
Fibrin glue	3
Gelfoam	2
Fibrin glue & gelfoam	11
Valsalva maneuver	
Mean duration (seconds) (N=36)	9.8 ± 1.7
Mean pressure ($cm \cdot H_2O$) (N=30)	30.3 ± 6.1
Days to discharge	3.7 ± 2.7

Table 4. Patient Follow-Up (as of June 4, 2003)

Followed to	N
Discharge	8
10 days	3
1 month	4
3-5 months	5
6 months	10
7-12 months	17
> 12 months	4
Total	**51**

marized in Table 3, and the extent of patient follow-up available as of June 4, 2003 is summarized in Table 4 (mean follow-up duration is 6.5 ± 3.7 months).

Patient outcomes with respect to the primary study hypothesis of events are summarized in Table 5. One CSF leak and two cases of wound infection have been observed. The CSF leak was reported in a patient at 9 days, this event was resolved at 1, 3, and 6-month follow-up. Two patients who had not yet reached 6 month follow-up exhibited a draining wound and an epidural collection, respectively. In the latter case, on wound exploration the implanted Durasis Dural Substitute appeared to be intact and in good condition with a watertight seal. Durasis was left in place, with resolution of the infection with antibiotic treatment.

Device performance was evaluated in terms of device success, handling characteristics, and procedural success. Device success of the Durasis Dural Substitute and its suture line was judged based on the degree of water-

tight barrier at the implant site during a Valsalva maneuver following implant. Device success occurred when a score of at least 4 was achieved on the following scale:

Parameter	Score (N=51) (0=poor and 4=excellent)
Ease of use	4.0 ± 0
Device strength	4.0 ± 0
Suturability	4.0 ± 0
Quality of seal at suture line	3.96 ± 0.2

Device success was achieved in all 51 reported patients treated with the Durasis Dural Substitute with a mean score of 4.8 ± 0.4 out of a possible score of 5 (success was defined as a score ≥ 4). Device handling characteristics (including ease of use, device strength, suturability, and quality of seal at suture line using a scale of 1 to 4) were all judged to be excellent and are summarized in Table 5. Procedural success (device success with no complications through the time of discharge) was also achieved in all 51 patients treated with the Durasis Dural Substitute for a procedural success rate of 100%. No device failures were observed.

Data from available patient imaging was evaluated to characterize the healing response. Images obtained 6 weeks or more after implantation of the Durasis Dural Substitute were reviewed, and any observations were evaluated for possible relationship to the Durasis Dural Substitute, the surgical procedure, or the underlying pathology. Graft integrity was also assessed, if visible.

Assessment of cerebral reaction revealed no occurrence of edema in images of the 26 patients and two instances of moderate enhancement in the 15 cases of imaging with contrast; both instances were judged likely due to the patient's primary pathology. Assessment of soft tissues found two cases of swelling, one mild and one severe. The severe swelling noted at 5 months post-procedure had resolved on imaging at 10 months post-procedure. Of the 15 images with contrast, two presented mild enhancement and three severe; all three were judged to be consistent with the normal post-operative appearance for the procedure. Assessment for CSF leak showed one case of fluid

Table 5. Device Handling Characteristics

Observation	Score
watertight seal	5
leakage due to defect in native dura	4
leakage from Durasis Dural Substitute suture hole elongation	3
leakage through Durasis Dural Substitute material (porosity)	2
leakage from Durasis Dural Substitute tear	1

in a layered distribution, not a true pseudomeningocele. One pseudomeningocele was observed, but was resolving on subsequent imaging and found to be clinically irrelevant. No evidence of scar tissue formation or encapsulation or loss of graft integrity was observed on any imaging.

Illustrative Case

A thirty eight year old female presented with Adult Chiari Malformation (Figure 1 left). After obtaining appropriate informed consent a suboccipital craniectomy, C1 laminectomy, and duraplasty using SIS were performed (Figure 1 middle). Postoperative MRI did not show any evidence of adverse reaction of the adjacent tissue and adequate decompression (Figure 1 right).

Discussion

Implanted biomaterials used for repair and replacement of damaged tissues face various challenges. Their fate can include breakdown leading to dissolved support, a foreign body reaction leading to encapsulation and a rigid fibrotic scar tissue, or incorporation leading to remodeled tissue (Figure 2). The latter is usually the ideal goal for an implanted biomaterial. Small Intestinal Submucosa (SIS) has shown the latter properties in various animal models as well as in numerous clinical applications where tissue repair is the goal (wound dressing, soft tissue repair, hernia repair, etc.)

Small Intestinal Submucosa (SIS) is a naturally derived complex extracellular matrix that can guide host tissue remodeling [3] (Figure 3). The porcine submucosa is located between the mucosal and muscle layers of the small intestine (Figure 4), providing strength to the intestine. It is formed by a complex matrix of collagen (type I, III, V, VI). It is also a reservoir for cytokines. SIS is harvested from the intestine in a manner that all cells are removed leaving the matrix intact (Figure 5). It is primarily a protein with

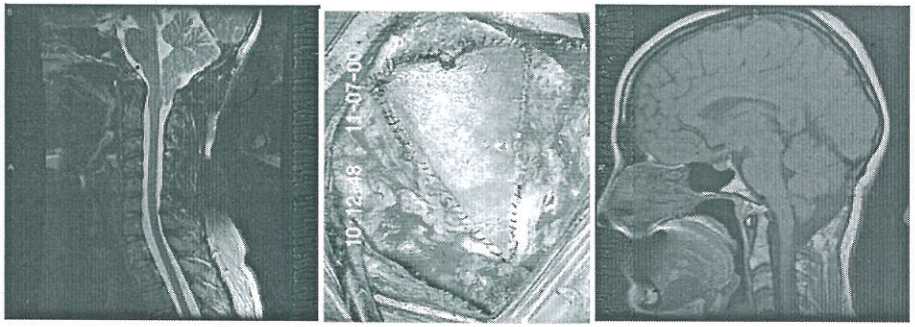

Figure 1: MRI shows the Chiari Malformation preoperatively (left). Watertight closure is achieved after Durasis is implanted (middle). The postoperative MRI does not reveal any evidence of adverse reaction (right).

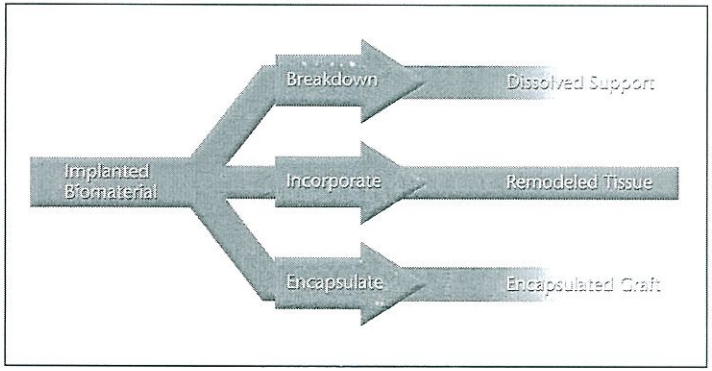

Figure 2: Possible results of implanted biomaterials

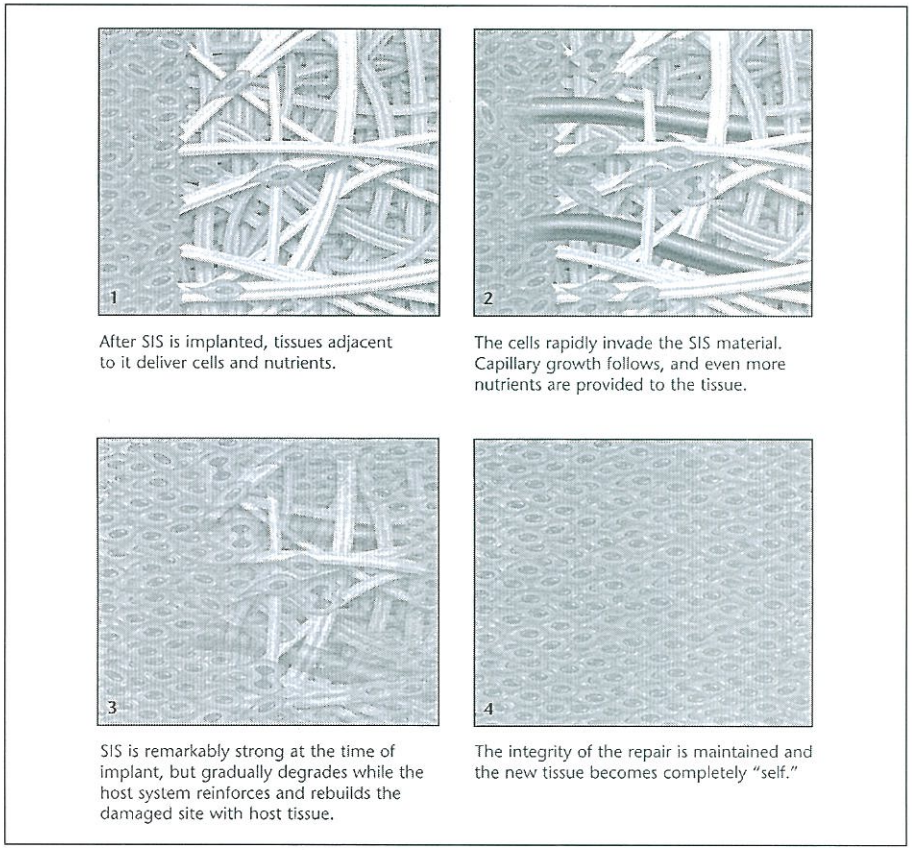

Figure 3: Mechanism of action of SIS: 1- adjacent tissues deliver cells and nutrients, 2-capillary growth follows, 3-SIS is gradually degraded as the host rebuilds the damaged site, 4- until the new tissue becomes completely self with complete resorption of the SIS.

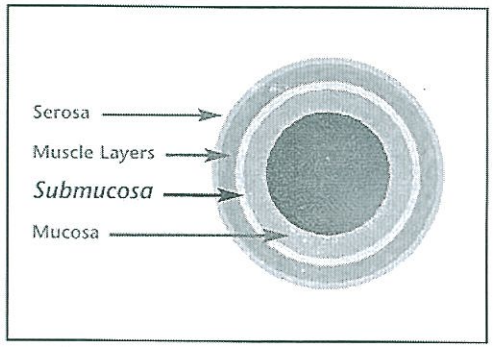

Figure 4: Cross section of porcine small intestine.

some lipids and carbohydrates. The harvesting process leaves the matrix molecules intact such as the collagen, the glycosaminoglycans, the proteoglycans, the glycoproteins, and various growth factors (TGF-beta, FGF-2, VEGF) that signal host cells to repopulate the SIS scaffold with host tissues [4,5,6,7].

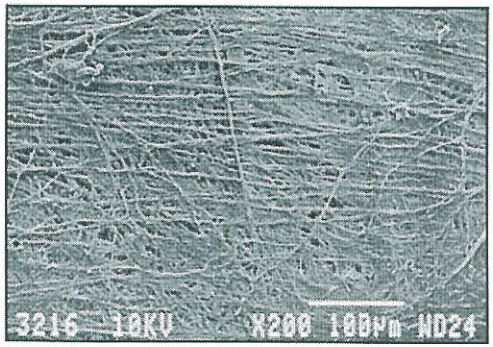

Figure 5: Microstructure of the SIS matrix.

Figure 6: SIS is strong and easy to handle. This photo shows Durasis after rehydration and ready to size.

Animal studies using SIS as a dural substitute were performed on a rodent model (Sprague-Dawley rats) [1], and a large animal model (mongrel dog) [2]. These studies looked at the histology at the graft site for up to 120 days after surgery as well as the histology at repeat SIS placement in the same animal for up to 60 days follow-up. These studies revealed that SIS is completely absent by day 60 at the implantation site. No involvement of the underlying cortex was observed at any time. No meningo-cerebral adhesions were seen. Although we do not have a delayed histological analysis, we have not encountered any radiological or clinical evidence of any adverse reaction to Durasis.

In this clinical application of Durasis, there was no evidence of device failure. To evaluate the overall efficacy of Durasis in preventing CSF leak, and the incidence rate of infection, we performed a metanalysis of 10 series of patients undergoing placement of dural grafts [8-17], including two series of patients undergoing decompressive surgery for Chiari Malformation [16,17]. The overall CSF leak rate in our series was 2% and the over-

Table 6. Incidence of CSF Leak in Published Dural Substitute Studies

Ref	Implants	Leaks	Incidence
[8]	Lyophilized human dura (n=170)	3	1.8%
[9]	Bovine pericardium (n=35)	2	5.7%
[11]	Bovine pericardium or lyophilized human dura (n=102)	0	0.0%
[12]	Lyophilized human dura (n=100)	8	8.0%
[13]	Collagen sponge (n=172)	7	4.1%
[15]	Ethisorb Dura-Patch (n=101)	13	12.9%
Total	**n=680**	**33**	**4.9%**
Series of Chiari patients			
[16]	Various materials (n=23)	2	8.7%
[17]	Lyophilized human dura (n=13)	2	15.4%
Total	**n=36**	**4**	**11.1%**
Grand Total n=716		**37**	**5.2%**

Table 7. Incidence of Infection in Published Dural Substitute Studies

Ref	Implants	Infection	Incidence
[8]	162	10	6.2%
[9]	35	2	5.7%
[10]	804	48	6.0%
[11]	102	2	2.0%
[12]	100	1	1.0%
[13]	459	28	6.1%
[14]	160	1	0.6%
Total	**1822**	**92**	**5.0%**

all infection rate was 4%. These incidences compare favorably with the 5.2 % leak rate and the 5% infection rate observed with other grafts (Table 6, 7). These results are even more striking if we take into consideration the fact that 72% of the patients in our series were infratentorial cases, more prone to leak than supratentorial cases. Also, if we compare our results using Durasis for patients with the Chiari Malformation, our leak rate is non existent (0/29 or 0%) compared with the 11.1% CSF leak rate encountered in the literature (Table 6) [16-17]. In the infected case that was re-explored, Durasis acted as barrier to the infection, and was left in place. Similar results were seen in use of SIS for herniorraphy where it was shown to be suited for use in contaminated fields [18].

When it came to handling characteristics, the device had perfect scores (4.0/4.0) in device ease of use, strength, and suturability and an almost perfect score (3.96/4.0) on the quality of suture line. Refer to Figure 6 for a picture of the rehydrated device ready for implantation.

Conclusions

In conclusion, clinical evaluation of the Durasis Dural Substitute demonstrates safety equivalent to predicate devices reported in the literature, a very high rate of device and procedural success, and excellent device handling characteristics. There was no evidence of scar tissue formation or encapsulation of the Durasis Dural Substitute. No new issues of safety or effectiveness have been raised.

Acknowledgement

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