Safety and Efficacy of a Novel, Self-Adhering Dural Substitute in a Canine Supratentorial Durotomy Model

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BACKGROUND: Cerebrospinal fluid (CSF) leaks increase postoperative risk for complication, likelihood of reoperation, and costs.
OBJECTIVE: To investigate a novel, self-adhering polyethylene glycol-coated collagen pad (PCC) as a dural substitute relative to Duragen XS (DGX; Integra LifeSciences Corporation, Plainsboro, New Jersey) and as a dural sealant relative to Tachosil (Takeda Austria GmbH, Linz, Austria), a fibrinogen and thrombin-coated collagen pad (FTC).
METHODS: A canine supratentorial durotomy surgical model was used to investigate the safety and efficacy of PCC. For safety, 4 animals were bilaterally treated with DGX or PCC and recovered for 1, 8, or 16 wk; total 24 animals. Each animal underwent physical and neurological examinations weekly and 16-wk animals underwent a magnetic resonance imaging (MRI) examination at each time point. For efficacy, 9 animals were unilaterally treated with FTC or PCC and underwent a burst pressure test intraoperatively or 14 d postoperatively; total 36 animals.
RESULTS: In the safety study, no abnormal clinical signs or changes were noted on physical and neurological examinations, or in clinical pathology, CSF analysis or histopathology of DGX or PCC-treated animals. No consistent signs of cerebral compression, CSF leak, hemorrhage, or hydrocephalus were noted on MRI. In the efficacy study, no significant difference was found between FTC and PCC at each time point or overall (13.9 vs 12.3 mm Hg, n = 18 per group, $P = .46$).
CONCLUSION: PCC is safe for use as a dural substitute and effective as a dural sealant. The novel, self-adhering combination of a polyethylene glycol-based sealant and a collagen pad may offer unique benefits to the advancement of duraplasty.

KEY WORDS: Cerebrospinal fluid leak, Dura mater, Collagen, Polyethylene glycol, Hemopatch, Tachosil, Duragen

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Cerebrospinal fluid (CSF) leaks occur within up to 10.7% of patients undergoing a cranial durotomy.[1] Patients with a CSF leak have increased postoperative risk for complications, likelihood of reoperations, and costs.[1-3] In preventing CSF leaks, neurosurgeons have widely used synthetic and biological sealants to reinforce suture lines.[1,4,5] However, new investigations explore the use of dural patches that both seal suture lines and bridge dural gaps to act as a dural sealant and substitute.[6]

A novel, reactive polyethylene glycol (PEG)-coated collagen pad (PCC) has been demonstrated to be an effective sealing hemostat in animal models and clinical investigations,[7] and demonstrated to provide clinically relevant adherence for use as a dural sealant in an in vitro model.[8] Reactive PEGs are monomers that rapidly form hydrogels and crosslink with proteins on tissue within seconds without being exothermic. The formed hydrogel is highly biocompatible and has adequate strength to prevent postoperative CSF leaks.[9] In addition, collagen is known to have a biodegradable profile suitable for use as a dural substitute.[10-14]

ABBREVIATIONS: ANOVA, analysis of variance; **CSF,** cerebrospinal fluid; **DGX,** DuraGen XS; **FTC,** fibrinogen and thrombin-coated collagen pad; **IV,** intravenous; **MRI,** magnetic resonance imaging; **PCC,** PEG-coated collagen pad; **PEG,** polyethylene glycol; **SC,** subcutaneous; **SEM,** scanning electron microscopy

Therefore, the objective of this study is to investigate the safety and efficacy of a novel, sealing dural substitute PCC.

METHODS

Dural Substitutes and Sealants

PEG-Coated Collagen Pad

Hemopatch (Sealing Hemostat; Baxter AG, Vienna, Austria) is a sealing hemostat being investigated as a dural substitute and sealant. It is an absorbable collagen pad derived from bovine epidermis, types I and III collagen, and coated with N-hydroxysuccinimide functionalized PEG. The uncoated, nonactive surface is marked with blue squares. The blue squares are a low concentration of Brilliant Blue (FD&C Blue No 1), a clinically established and well-tolerated dye used as a colorant in drug formulations and dural sealants.[7] PCC is applied dry with digital pressure for 2 min using dry gauze. Currently, PCC is not cleared by FDA.

DuraGen XS Dural Substitute

DuraGen XS (DGX; Dural Regeneration Matrix; Integra LifeSciences Corporation, Plainsboro, New Jersey) is an absorbable collagen pad derived from bovine Achille's tendon and composed of type I collagen. DGX is cleared by FDA as a dural substitute for the repair of dura mater for which clinical acceptability and biocompatibility characteristics have been established.[14,15] DGX was applied dry then moistened with saline followed by digital pressure for 2 min with dry gauze.

TachoSil (Fibrinogen and Thrombin-Coated Collagen Pad) Dural Sealant

TachoSil (Absorbable Fibrin Sealant Patch; Takeda Austria GmbH, Linz, Austria) is a fibrinogen and thrombin-coated collagen pad (FTC). Tachosil is not FDA approved for dural sealing; however, its use as a dural sealant is well accepted in the scientific and clinical literature.[16-21] It is an appropriate comparator due to the similar self-adhering properties. A liquid-based dural sealant is not an appropriate comparator to seal a dural gap. FTC was applied dry with digital pressure for 3 min using moistened gauze.

Stereomicrograph and Scanning Electron Micrograph Images

Dry, naïve pieces of DGX, FTC, and PCC were characterized using stereomicrography and scanning electron microscopy (SEM). Each was removed from their packaging, cut into smaller specimens, coated with metal to enhance conductance, and examined in a JSM 7600F Thermal Field Emission SEM (JEOL, Peabody, Massachusetts).

Animal Welfare Statement

Animal activities were performed according to the Guide for the Care and Use of Laboratory Animals and the United States Animal Welfare Act in an institution accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International following Institutional Animal Care and Use Committee Approval. The canine durotomy model is the accepted animal model to investigate dural sealants and substitutes.[9,22-25] When compared to clinical data, the model is predictive of clinical performance.[4]

Canine Supratentorial Durotomy Model

Animals received acepromazine (0.1 mg/kg, subcutaneous [SC]) and atropine (0.05 mg/kg, SC) for sedation and Propofol (6 mg/kg, intravenous [IV]) for induction then intubated and maintained on isoflurane. The skin overlying the cranium was then prepared with aseptic solutions and infiltrated with bupivacaine (up to 2 mg/kg, SC). Buprenorphine (0.02 mg/kg, IV) and buprenorphine SR (0.06 mg/kg, SC) were administered for perioperative analgesia. Cefazolin (25 mg/kg, IV) and cefovecin (8 mg/kg, SC) were administered prophylactically as antibiotics. Lactated Ringer's solution (10-11 mL/kg/h, IV) was administered with anesthesia.

A craniotomy, measuring 1.5 × 1.5 cm for the safety study and 2 × 2 cm for the efficacy study, was created using a 3-mm diameter Carbide round cutting bur (MicroAire, Charlottesville, Virginia) on a MiniMag Micro drill (DePuy Synthes Power Tools, Palm Beach Gardens, Florida). The bone flap was then removed and a 5-mm diameter supratentorial durotomy was performed and treated (Figure 1).

The bone flaps of animals being recovered were reattached using 2-0 polypropylene suture. The overlying muscle was sutured together and the SC tissues were closed with absorbable suture. The skin was approximated with subcuticular suture and skin glue. Animals were then recovered and received meloxicam (0.2 mg/kg, SC q 24 h) for 3 d.

Safety Study

Twelve male and 12 female (7.8±1.1 kg) naïve beagle dogs underwent a bilateral craniotomy and durotomy, and were bilaterally treated with either DGX or PCC (1.5 × 1.5 cm), so that 2 animals per sex and per group were maintained for a 1, 8, or 16-wk recovery period. Each dura substitute was placed in direct contact with the parenchymal surface of the brain in an onlay fashion without suturing.

Physical and neurological examinations (Table 1) were performed by a veterinarian prior to and weekly following surgery. Prior to surgery and at euthanasia, blood was collected to evaluate hematology, coagulation parameters, and blood chemistry. Concurrently, CSF was collected from the cisterna magna.

Animals were euthanized with sodium pentobarbital solution and exsanguinated via perfusion fixation with 10% neutral buffered formalin. The implant sites were collected en bloc with the underlying brain tissue intact and stored in 10% neutral buffered formalin. Tissue samples were trimmed, processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin and Masson's trichrome. Histological slides were evaluated using a semiquantitative scale by a board-certified veterinary pathologist (SDR) for implant degradation and cellular response.

Sixteen-week animals had MRI scans performed prior to and following surgery, and at 1, 8, and 16 wk to detect signs of cerebral compression, CSF leakage, hydrocephalus, infection, or hemorrhage. T1- and T2-weighted images without contrast were generated using a Philips 1.5 T Intera MRI System (Philips Healthcare, Amsterdam, the Netherlands).

Efficacy Study

Thirty-six (7.5±1.2 kg) naïve beagle dogs underwent a unilateral craniotomy and durotomy, and were treated with either FTC or PCC (1.5 × 1.5 cm); 9 animals (5 males and 4 females) per group underwent a dural burst pressure test at the time of surgery and following a 14-d recovery.

A 3F Millar catheter was placed in the subarachnoid space of the contralateral hemisphere to obtain pressure measurements. After a baseline pressure was obtained (P_0, mm Hg), saline containing

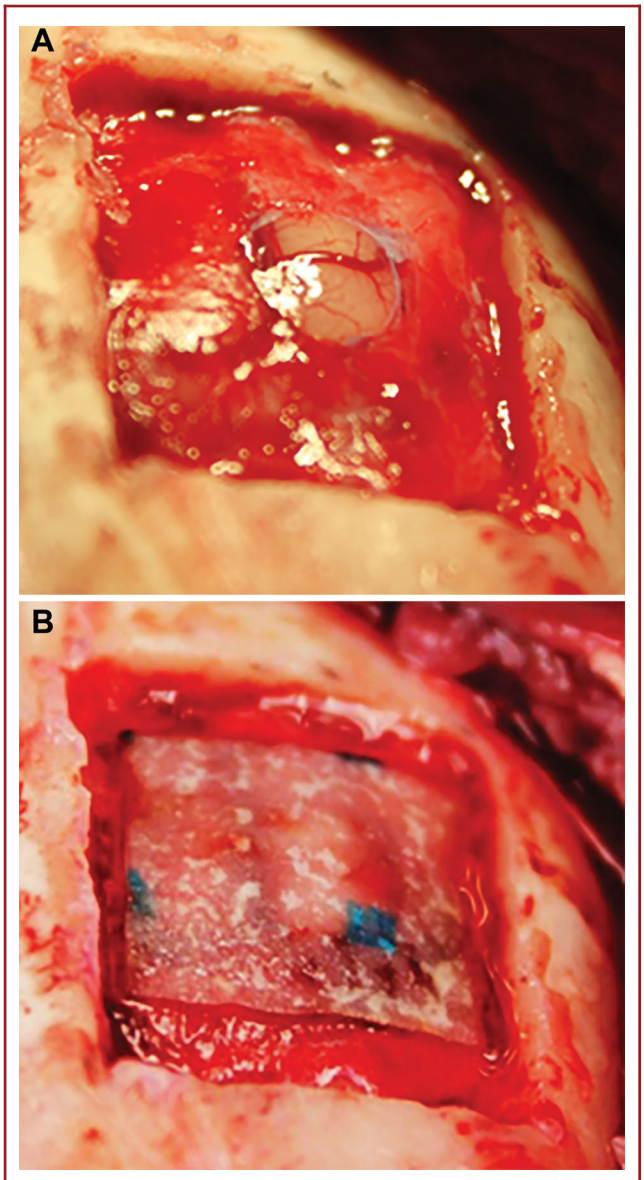

FIGURE 1. *Treatment of a canine supratentorial durotomy with Hemopatch, a polyethylene glycol-coated collagen pad. A 5-mm diameter supratentorial durotomy is performed through a 1.5 × 1.5 cm craniotomy (A), which is then treated with Hemopatch (B). Hemopatch is a 2.0-mm thick collagen pad composed of types I and III collagen that is coated with N-hydroxysuccinimide functionalized polyethylene glycol to be a self-adherent dural sealant and substitute.*

TABLE 1. Physical and Neurological Examination

Physical examination
General appearance: body weight and condition, mentation, posture and gait, and hydration status
Vital signs: temperature, heart rate and rhythm, peripheral pulse strength, respiratory rate, rhythm and effort, and mucous membrane color
Body systems: Eyes, nose and nares, oral cavity, lymph nodes, limbs and joints, feet and nails, skin and hair coat, and abdominal palpation
Neurological examination: cranial nerves
Pupil light reflexes (left and right, direct and consensual)
Palpebral response (left and right)
Eye position (left and right)
Gag reflex
Tongue movement
Neurological examination: central and peripheral nerves
Conscious proprioception (left and right, fore and hind limbs)
Hopping reflex (left and right, fore and hind limbs)
Righting response (left, right)
Withdrawal reflex (left and right, fore and hind limbs)
Panniculus
Patellar reflex (left and right hind limbs)
Anal reflex
Superficial pain

Each dog was evaluated prior to study and weekly while on study for abnormal physical and neurological signs.

0.01 mg/mL methylene blue was administered into the cisterna magna at a rate of 0.45 mL/min to increase subarachnoid pressure. Once a CSF leak was observed visually, the burst strength (P_{max}, mm Hg) and failure mode (cohesive, adhesive, and/or substrate) were recorded.[26]

A rate of 0.45 mL/min is the rate of CSF production in humans.[27] Therefore, pressurization was at 2 times the normal rate of CSF production (ie, 0.9 mL/min, where the animal produced 0.45 mL/min and the syringe delivered 0.45 mL/min). Animals spontaneously breathed during the pressure test to avoid ventilator-induced pressure increases.[28]

Statistical Methods

For continuous endpoints, descriptive statistics consisted of means, standard deviations, and group size. For categorical endpoints, descriptive statistics consisted of incident counts.

In the safety comparison, sexes were pooled and a Levene's test was performed. If not significant, a mean square error was computed for a 1-way analysis of variance (ANOVA) and used by a Dunnett's comparison.

In the efficacy comparison, a 3-way ANOVA was used to compare P_{max} for the effects of treatment, time, and sex. Results of pairwise comparisons are reported at the .05 and .01 significance levels. All tests were 2-tailed tests.

RESULTS

Stereomicrograph and Scanning Electron Micrograph Images

DGX and PCC have similar gross appearances with DGX being approximately 2 times thicker than PCC, whereas FTC has a dissimilar gross appearance and is thicker than DGX (Figures 2A-2C). FTC has the least dense cross-sectional structure and PCC has the most dense (Figures 2D-2F). The uncoated surfaces of DGX and PCC appear more open than that of FTC

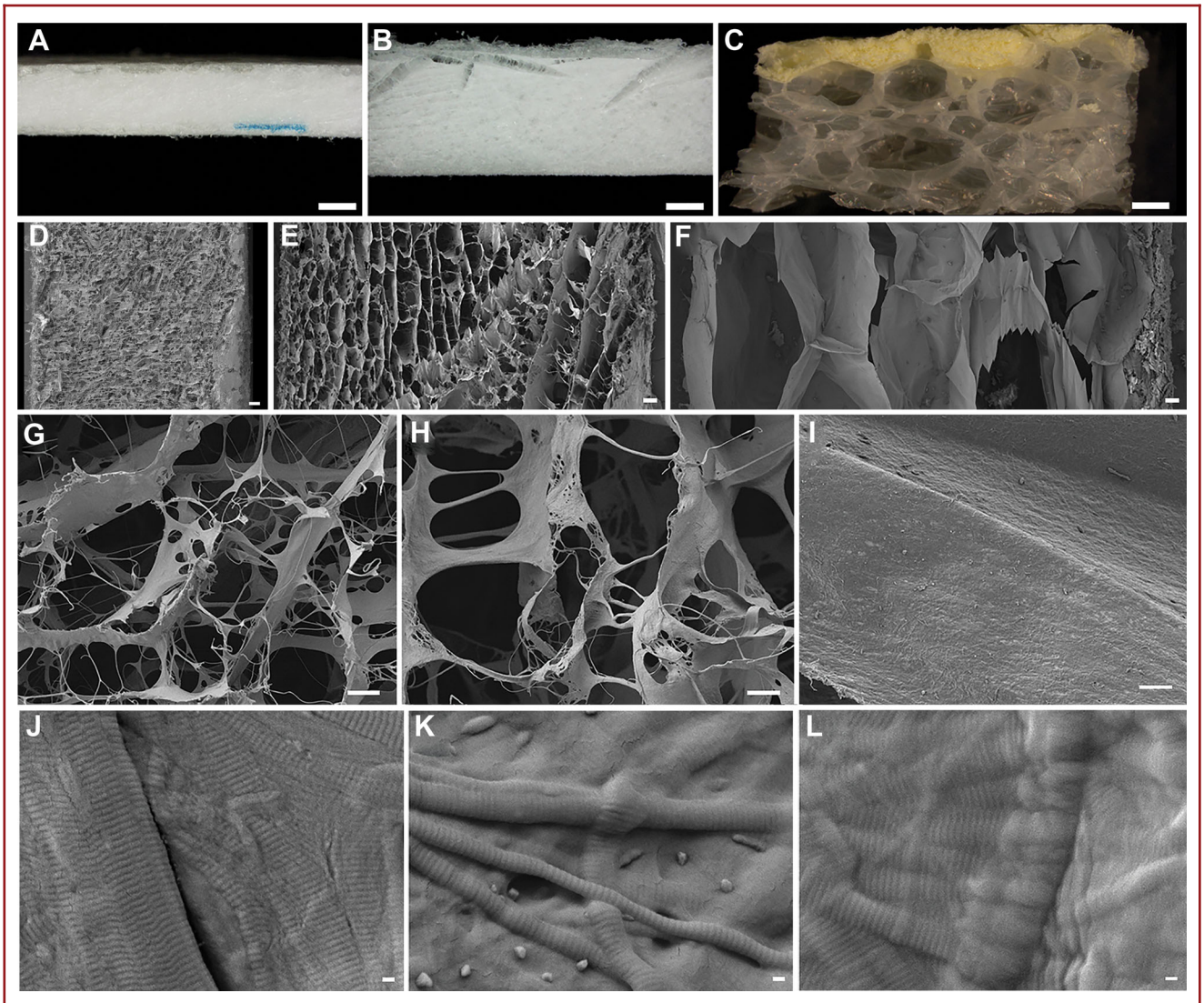

FIGURE 2. *Stereomicrograph and scanning electron micrograph images of Hemopatch, Duragen XS and Tachosil (left to right). Hemopatch is a sealing hemostat being investigated as a self-adherent dural sealant and substitute. Duragen XS is a dural substitute composed of type I collagen. Tachosil is a dural sealant composed of a fibrinogen and thrombin-coated collagen pad. Stereomicrographs (**A-C**) with active surfaces of Hemopatch and Tachosil upward (scale bar is 1 mm). Scanning electron micrographs (**D-F**) of cross-sections with active surface to the right (scale bar, 100 μm), (**G-I**) face of uncoated surfaces (scale bar, 10 μm), and (**J-L**) collagen structure (scale bar, 100 nm).*

(Figures 2G-2I). The collagen fiber morphology is similar among the 3 collagen pads (Figures 2J-2L).

Safety Study

In-life Physical and Neurological Examination Findings

All animals survived the surgical procedure without complication. Localized SC seromas were noted on the rostral aspect of the frontal bones in some animals, which were transient and considered secondary to the surgical procedure. Prior to and weekly following the surgical procedure, no abnormal clinical signs were observed on physical and neurological examinations. No abnormal changes or significant differences were noted in hematology, coagulation, or clinical chemistry between groups. No signs indicative of a generalized inflammatory response or bacterial infection were noted in the CSF analyses (Table 2). All animals gained weight normally.

MRI Images

All 16-wk group animals had no persistent signs of cerebral compression, CSF leakage, hydrocephalus, infection, or

TABLE 2. CSF Analysis of Animals Treated With DuraGen XS, a Collagen Dural Substitute, or Hemopatch, a Polyethylene Glycol-Coated Collagen Dural Sealant and Substitute, Prior to Surgery and 1, 8, and 16 wk Following Surgery

		DuraGen XS		Hemopatch	
Parameter	**Study interval**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Total red blood cell count (cells/μL)	Presurgery	12	2508 (6492)	12	2264 (6937)
	1 wk	4	3.0 (3.5)	4	6.5 (7.6)
	8 wk	4	14.5 (28.3)	4	0.8 (1.0)
	16 wk	4	37.8 (74.8)	4	32.0 (37.2)
Total white blood cell count (cells/μL)	Presurgery	12	2.5 (6.0)	12	1.7 (3.0)
	1 wk	4	1.3 (2.5)	4	1.5 (1.7)
	8 wk	4	1.3 (1.5)	4	0.0 (0.0)
	16 wk	4	0.0 (0.0)	4	1.0 (2.0)
Protein (mg/dL)	Presurgery	12	17.5 (4.4)	12	18.8 (5.9)
	1 wk	4	19.0 (2.2)	4	17.5 (2.4)
	8 wk	4	19.3 (2.6)	4	18.8 (1.5)
	16 wk	4	17.0 (1.4)	4	19.5 (3.0)

Samples were taken percutaneously from the cisterna magna. There are no remarkable differences between groups over time or indication of infection. The high red blood cell counts are due to sample contamination during collection. Data presented as mean (standard deviation).

hemorrhage (Figure 3). Following surgery, signs suggestive of slight cerebral compression were present at the surgical site in most animals of both groups, which resolved by week 1 and considered a result of the surgical procedure. One animal in the DGX group had signs suggestive of CSF leak or hemorrhage, which were not present on subsequent MRI examinations. One animal in the PCC group had signs suggestive of a cerebral compression and CSF leak or hemorrhage, which were also not present on subsequent MRI examinations.

Macroscopic Tissue Evaluation

There were no abnormal macroscopic findings associated with either dural substitute at any time point. Week 1 animals did not have full fusion of the craniotomy site, so one bone flap was removed while the contralateral bone flap was left in place to allow for undisturbed tissue analysis. Neither dural substitute showed signs of migration, stretch/shrinkage, or thickening/thinning nor were signs suggestive of CSF leakage, hydrocephalus, or hemorrhage observed.

Microscopic Tissue Evaluation

Both dural substitutes had excellent local biocompatibility as evidence by low-severity subacute inflammation that resolved by week 8 (Table 3). DGX was not detectable at week 16, while PCC was variably present at week 16. Vacuolated macrophages were present in only the PCC-treated animals, which indicate phagocytic bioresorption. The underlying brain was normal in both groups, except for very minimal, occasional, and model-related cortical hemorrhage beneath the durotomy. Neither dural substitute appeared to impede healing at the surgical site in any significant way.

Week 1

The healing response was similar all in groups and showed slight inflammatory response along the periphery, mainly macrophages with a few neutrophils and rare giant cells. There was an increase in low-severity subacute inflammation in the pia beneath PCC compared to DGX. The subjacent cerebral cortex showed no significant changes. There was no evidence of neurodegeneration or gliosis in the cortex of any of the animals.

Week 8

The inflammatory response in both groups was completely resolved and replaced by dense and mature fibrous connective tissue. Low-severity adhesions were present between the pia and healed dura in the PCC-treated group, while not seen in the DGX-treated group. Both dural substitutes underwent intermediate to advanced resorption.

Week 16

The dense and mature fibrous connective tissue did not progress, while vacuolated macrophages slightly decreased. The presence of pia-to-dura adhesions was reduced in the PCC-treated group.

Efficacy Study

There was no significant difference between FTC and PCC-treated durotomy sites when pressurized intraoperatively, on day 14 or overall (Table 4). The common failure mode for FTC was adhesive, while for PCC was cohesive (Table 5).

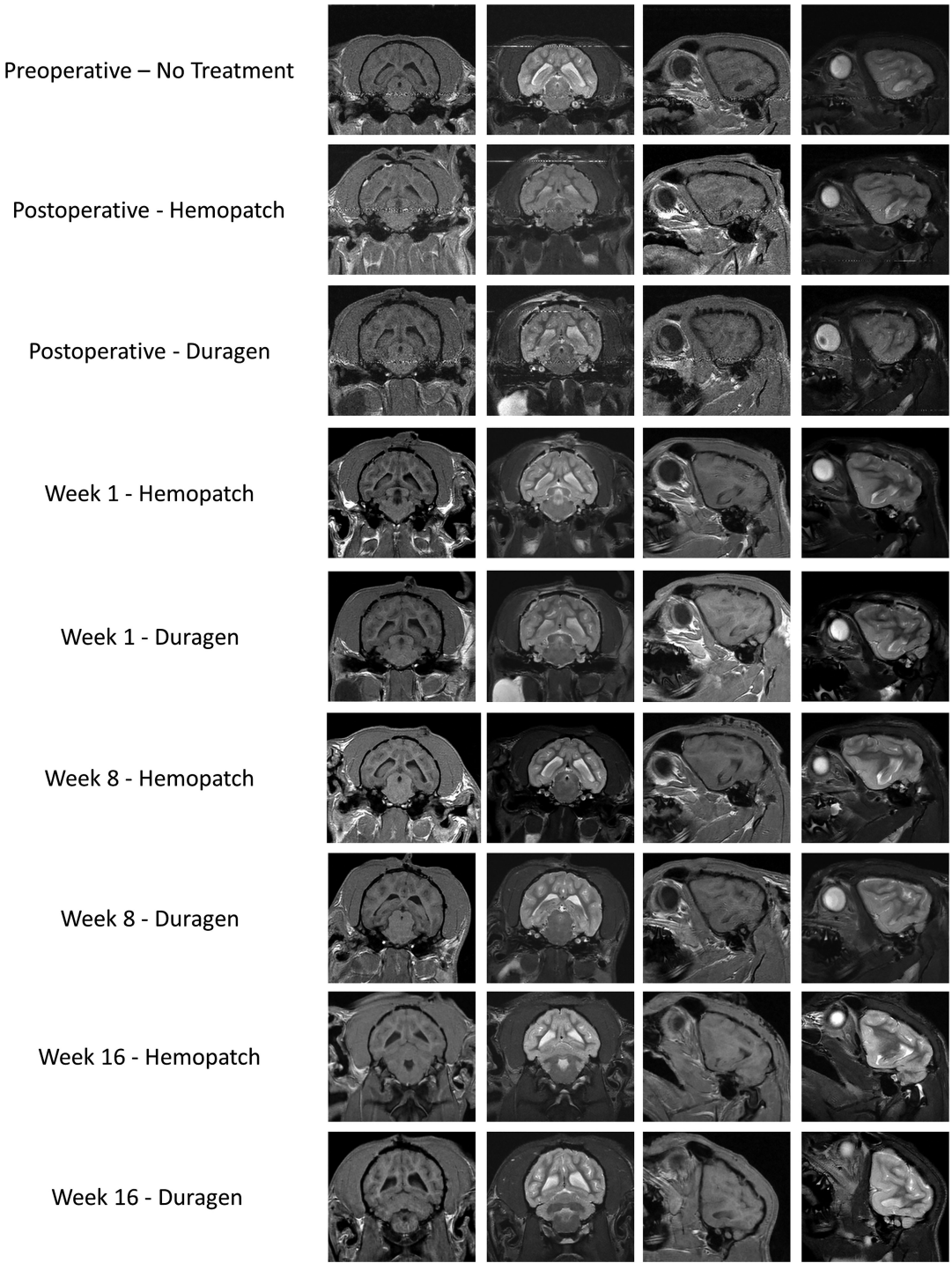

FIGURE 3. *MRI of dogs treated with DuraGen XS, a collagen dural substitute, or Hemopatch, a polyethylene glycol-coated collagen dural sealant and substitute. Serial coronal and sagittal T1- and T2-weighted images were obtained to investigate adverse effects on the brain. Images were obtained preoperatively and postoperatively, and at weeks 1, 8, and 16. Neither collagen duraplasty material is present on MRI. Cerebral compression secondary to the surgical procedure is seen on postoperative images in both groups, which resolves in subsequent MRI. Neither duraplasty material was associated with persistent signs of CSF leak, hydrocephalus, infection, or hemorrhage up to 16 wk after application to the durotomy.*

TABLE 3. Histological Evaluation of Brain and Dura Treated With DuraGen XS, a Collagen Dural Substitute, or Hemopatch, a Polyethylene Glycol-Coated Collagen Dural Sealant and Substitute, 1, 8, and 16 wk After Implantation to Treat a 0.5-mm Diameter Durotomy (n = 8 per Time Point per Group)

	DuraGen XS			Hemopatch		
Histopathology evaluation	**1 wk**	**8 wk**	**16 wk**	**1 wk**	**8 wk**	**16 wk**
Implant						
Implant resorption[a]	0.0 (0.0)	3.1 (0.4)	4.0 (0.0)	0.0 (0.0)	3.0 (0.8)	2.9 (0.8)
Response to implant[b,c]						
Overall inflammation	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Polymorphonuclear cells	0.3 (0.5)	0.0 (0.0)	0.0 (0.0)	0.8 (0.5)	0.0 (0.0)	0.0 (0.0)
Macrophages	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Lymphocytes	0.1 (0.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Plasma cells	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Giant cells	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Vacuolated macrophages	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.4 (0.5)	1.6 (0.5)	1.3 (0.5)
Fibrosis	1.0 (0.0)	1.6 (0.7)	1.6 (0.5)	0.3 (0.5)	1.8 (0.5)	1.9 (0.6)
Granulation tissue	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.4 (0.5)	0.0 (0.0)	0.0 (0.0)
Necrosis	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Vascularization	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Foreign body response	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Edema/hemorrhage	1.5 (0.5)	0.0 (0.0)	0.0 (0.0)	1.4 (0.5)	0.0 (0.0)	0.0 (0.0)
Bacteria presence	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Brain response[c]						
Gliosis	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	0.0 (0.0)
Neurodegeneration	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Adhesion: dura to pia/arachnoid	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	0.6 (0.5)	0.3 (0.5)
Inflammation: pia (durotomy), subacute	0.3 (0.5)	0.0 (0.0)	0.0 (0.0)	0.9 (0.4)	0.1 (0.4)	0.0 (0.0)
Hemorrhage	0.3 (0.5)	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	0.0 (0.0)	0.0 (0.0)
Necrosis	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

[a]Implant resorption scale grade 0: no implant resorption; grade 1: minimal resorption (<25%); grade 2: <50% resorption; grade 3: >50% resorption; grade 4: fully resorbed.
[b]Inflammatory cell scale grade 0: not present, none; grade 1: rare, estimated 1 to 5 cells per high-power field (phf), grade 2: mild, estimated 5 to 10 cells phf; grade 3: moderate, heavy infiltrate; grade 4: severe, packed cells.
[c]All other parameters. Grade 0: absent/none; grade 1: minimal, present but minimal feature; grade 2: mild, notable feature; grade 3: moderate; prominent feature that does not disrupt tissue architecture and is not overwhelming; grade 4: severe, overwhelming feature or feature that effaces or disrupts tissue architecture.
DuraGen XS degraded faster than Hemopatch. Tissues treated with Hemopatch had a greater number of vacuolated macrophage than DuraGen XS. Data presented as mean (standard deviation).

TABLE 4. Subarachnoid Pressure Test

Time point	n	Baseline (mm Hg)		P_{max} (mm Hg)		
		Tachosil	Hemopatch	Tachosil	Hemopatch	*P* Value
Overall	18	3.23 (1.50)	4.21 (3.06)	13.9 (6.74)	12.3 (3.47)	.46
Day 0	9	2.73 (1.23)	3.75 (2.19)	13.8 (8.52)	12.9 (4.41)	.85
Day 14	9	3.74 (1.64)	4.67 (3.81)	14.0 (4.89)	11.7 (2.32)	.39

TachoSil, a fibrinogen and thrombin-coated collagen pad, and Hemopatch, a polyethylene glycol-coated collagen dural sealant and substitute, withstood similar subarachnoid pressure prior to failure. Data presented as mean (standard deviation).

TABLE 5. Subarachnoid Pressure Test Failure Mode

	Tachosil			Hemopatch		
Failure mode	**Overall**	**Day 0**	**Day 14**	**Overall**	**Day 0**	**Day 14**
Cohesive	2	0	2	14	8	6[a]
Adhesive	16	9	7	5	1	4[a]
Substrate	0	0	0	0	0	0

[a]Both failure modes were noted simultaneously in one animal.
Tachosil failed adhesively, while Hemopatch failed cohesively when the subarachnoid pressure was increased. Data presented in frequencies.

DISCUSSION

This is the first investigation of the safety and efficacy of PCC as a dural substitute and sealant. When used as a dural substitute and sealant in a canine durotomy model, PCC was not associated with signs of neurological deficits, central nervous system inflammation, delayed wound healing, or CSF leakage. PCC was biocompatible as compared to DGX for use as a dural substitute and was effective as FTC as a dural sealant.

Safety of PCC

Consistent with clinical use, DGX and PCC were well tolerated and had an acceptable biodegradation profile when used in dogs. Both collagen pads primarily contain type I collagen, which is the same collagen composing human dura.[29] In contrast to DGX, PCC was associated with an increase presence of vacuolated macrophage and a slower degradation. The increased presence of vacuolated macrophage is consistent with the breakdown of PEG-based hydrogels.[9,22] The low-severity adhesions in PCC-treated animals are also consistent with other PEG-based dural sealants in this model.[24] The formation of such adhesions should be considered if a reoperation is anticipated. The slower degradation is likely due to the collagen pad density. Consistent with other investigations, PCC has a lower porosity and greater density of collagen fibers than DGX as seen on SEM.[7,25] The lower porosity and greater density may reduce the rate of cellular ingress leading to a slower degradation. In contrast, DGX is reported to degrade quickly leaving the brain exposed to the calvarium.[30] Though both materials are thicker than normal human dura, 0.4 to 0.6 mm[25], neither was associated with consistent signs suggestive of cerebral compression on MRI.

PEG hydrogels are hydrophilic and are known to swell 50% to 300% in volume.[31,32] As seen in stereomicrograph images, the dry, nonactivated thickness of PCC is less than DGX. In addition, PCC has a noncompressed thickness of 2.0 mm and a maximum thickness when submerged in citrated human plasma for 24 h of 2.8 mm.[8] The extensive swelling of other PEG-based dural sealants is associated with postoperative complications due to "mass effect."[32-37] By coating a collagen pad with only one type of reactive PEG, the amount of swelling is limited thereby reducing the risk of "mass effect."

Based on a cellular analysis of the CSF, no animals treated with PCC or DGX suggested an inflammatory response or infection. This study could have been strengthened by including CSF ELISAs to assess interleukin-6 for inflammation, neuron-specific enolase for neuronal injury, and S-100B protein for brain injury.[38] Similarly, a test for β2-transferrin could rule out postoperative seromas from being a postoperative pseudomeningocele. These sensitive assays, however, were not available for this study. Additionally, the study could have been strengthened by including a no treatment control to confirm and characterize the clinical presence of postoperative CSF leaks on MRI in this model.

Efficacy of PCC

PCC was as effective as FTC, which is a clinically effective dural sealant.[16-21] Furthermore, both sealants were effective over the range of normal human subarachnoid pressure, 7 to 15 mm Hg.[39-41] In contrast, a collagen dural substitute applied in an onlay fashion to a 1.5-cm diameter durotomy provided a burst pressure of 7.2 $\pm$ 2.8 mmHg.[9] Comparing data from different studies is, however, difficult, because test systems and methods vary (eg, durotomy size, anesthetics, pressure transducer placement, head position, etc.). In this study, the subarachnoid space was pressurized by increasing the CSF volume instead of reducing the subarachnoid space through a Valsalva maneuver. This method was selected to standardize the pressurization of the dura for impartial comparisons and to be consistent with previous studies.[9,24]

FTC failed adhesively with CSF separating the collagen pad from the dura. In contrast, PCC failed cohesively with CSF weeping through the collagen, which is the typical failure mode for collagen-based dural substitutes.[9] The difference in failure mode is likely due to the different collagen architecture. As seen on SEM, FTC has a closed-cell structure while PCC has a porous structure. The porous structure of PCC is known to allow migration of fluid through the collagen pad, which reduces the fluid–tissue interface stress level and improves adherence.[42,43] An adhesive failure leads to a continual CSF leak regardless of pressure, whereas a cohesive failure retains function following transient increases in CSF pressure (eg, coughing, sneezing). Recent studies investigating the complication rate of nonwater tight closures suggest that the complication rate is clinically acceptable and comparable to water tight closures,[44-46] whereas true CSF leaks lead to worse surgical outcomes.[1-3]

Use of PCC as a Self-Adhering Duraplasty Material

PCC provides a novel combination of a PEG-based dural sealant and a collagen dural substitute, which is a self-adherent dural substitute that seals dural gaps. The active surface of the collagen pad is coated with PEG that effectively forms a hydrogel between the collagen pad and dura.[7] In contrast, forming a hydrogel on top of a collagen pad and dura is reported with mixed results. In a preclinical investigation by Preul et al,[9] this combination provided a CSF burst pressure of greater than 36 mmHg and prevented CSF leaks in 5 of 6 animals (83.3%) up to 8 wk after surgery.[9] In a clinical investigation by Litvack et al,[47] however, the combination was associated with a significantly increased risk of CSF leak compared to a collagen matrix alone. In other clinical investigations, the combination provided acceptable procedure-related complication rates for CSF leak[48,49] and meningitis.[49] Notably, synthetic dural sealants are not to be used with nonautologous duraplasty materials other than collagen.[49,50]

Use of a hydrogel sealant applied on top of a duraplasty material may introduce a thick layer between the brain and skull. The use of a collagen pad coated with a reactive PEG reduces the thickness

and amount of material reducing the likelihood of causing a mass effect. The PCC may provide tensile strength when bridging dura across a cavity following removal of meningioma, metastatic brain tumor, or glioma, relative to nonself-adhering collagen pads.[51]

While collagen is a natural choice as the dural substitute, either a PEG based or fibrin sealant can be used to fix the collagen pad. PEG-based sealants are reported to have better clinical performance than fibrin-based sealants to seal dura,[4,52] which favors the use of PCC. FTC is demonstrated to provide clinical benefit as a dural sealant.[29] Some investigators have, however, identified complications related to application of thrombin into or on to the brain.[37,53-56] In addition, the self-adherence of PCC removes the need for suturing which reduces surgical time.[29]

CONCLUSION

Based on this study, PCC is safe and effective in treating a supratentorial durotomy in dogs. In addition to clinical data, application to other cranial approaches and procedures is of future research interest (eg, posterior fossa, transsphenoidal, Chiari malformation corrections, etc.). The combination of a PEG-based sealant and a collagen pad may offer unique benefits for the advancement of duraplasty.

Disclosures

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COMMENT

The authors present a well-designed canine model for supratentorial durotomy to test the relative efficacy of a new combined collagen patch/polyethylene glycol sealant compared to DuraGen® (Integra LifeSciences Corporation, Plainsboro, New Jersey) and TachoSil® (Takeda Austria GmbH, Linz, Austria). The authors used a 1.5 × 1.5 cm craniotomy (2 cm for efficacy) but only a 5 mm durotomy. The study is well designed with thorough outcome measures including MIR, neurologic examinations, CSF sampling, and histological analyses. With such a small opening (5 mm), I question whether the sensitivity of the model is sufficient to detect any differences between the alternatives. Certainly, one may consider that a single piece of oxidized cellulose sponge (Gelfoam®; Pfizer, New York, New York) may be sufficient to cover this defect and prevent CSF leak. Overall, the authors found equivalence between the new substitute and the alternatives. However, the authors did find an increased rate of adhesions between the pia and the graft when compared to Duragen®. This might certainly be an important consideration in reoperation. While the current study demonstrates similar safety and efficacy to existing materials, it does not demonstrate a clear advantage. Further testing is necessary with more sensitive models (eg posterior fossa) to determine if there is an advantage to the new substitute and to determine its cost effectiveness.

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