A Unique Dual-function Device — A Dural Sealant with Adhesion-prevention Properties

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Introduction

Neurosurgical procedures in the spine often require dural closure. Intentional incisions of the dura mater and arachnoid are usually relatively easily sutured, while incidental tears are often more difficult to close. If the dural incision or tear is not properly repaired, and watertight closure is not achieved, cerebrospinal fluid (CSF) can escape from the subarachnoid space into the extradural compartment, presenting a risk for significant morbidity. Failure of standard techniques to achieve watertight closure may be due, in part, to the fact that the suture pinholes and gaps between the sutures create high-pressure defects allowing for CSF seepage. The integrity of intra-operative closures are often tested with Valsalva’s manoeuvre, which if successful, is predictive of post-operative success. Typically, if a CSF leakage is controlled intra-operatively and tested under pressure with a Valsalva’s manoeuvre, the dural repair is considered to remain watertight after surgery.

Separate from the challenging complication of post-operative CSF leakage, the formation of post-operative peridural scar tissue is part of a natural healing process following spinal operations. Of approximately 800,000 patients undergoing lumbar surgeries per year worldwide, 5–40% experience recurrent back pain and limitation in activities. Approximately 15% of patients will require reoperation within five years following initial surgery. At reoperation, dense scar tissue is frequently encountered at the surgical site, rendering the dissection of intraspinal elements more challenging and time-consuming for the surgeon, and putting surrounding tissue at higher risk of iatrogenic injury.

Various different surgical techniques and treatments have been evaluated to minimise peridural fibrosis, many with inconsistent results. A dual-function device that both reduces post-operative CSF leaks and prevents peridural fibrosis would present a new treatment paradigm to neurological and orthopaedic spinal surgeons.

Materials

DuraSeal™ is a synthetic hydrogel developed to reduce (CSF) leaks and post-operative peridural fibrosis following cranial and spinal surgery. The hydrogel system consists of two aqueous-based precursor solutions. The first solution contains a modified polyethylene glycol (PEG) precursor, and the second contains a low molecular weight amine precursor. When mixed, these two solutions crosslink within seconds to form a strong tissue-adhering, absorbable hydrogel. The formed hydrogel remains impervious to fibroblasts and adherent to dura for four to eight weeks. During this period the hydrogel separates the dura from the extradural tissues, allowing them to heal independently, thus preventing scar formation. The hydrogel then breaks down into water-soluble PEG molecules through hydrolytic degradation and is cleared primarily through the kidneys. Federal Food, Drug and Cosmetic Act (FD&C) blue No.1 dye is added to one of the precursor solutions to aid visualisation of product application. The colorant diffuses out from the hydrogel within hours following application and is excreted by the kidneys from the body.

DuraSeal Sealant was evaluated for neurotoxicity when placed in direct contact with neural tissues. Micro forcesps were used to implant pieces of DuraSeal into brain parenchyma in test animals, and to create sham injuries in controls. Following implantation, animals were regularly examined for clinical signs of disease or abnormality. At days 4 and 42 after implantation, four animals per treatment group were euthanised. The brain and proximal portion of the cervical spinal cord were dissected and removed. No neurological deficits were noted and no adverse reactions were observed for any of the test sites at explant.

In order to allow precise DuraSeal application, a new plug-resistant applicator is now available. The air-assisted MicroMyst™ Applicator allows for precise sealant application in confined or minimally invasive surgery (MIS) procedures, where the greater control of sealant volume and thickness is needed. The
malleable shaft and flexible polymer tip simplify access in many procedures.

The DuraSeal Sealant was recently approved for cranial dural sealing in the US, and has CE Mark approval (European clearance) as a cranial, spinal, thoracic and vascular sealant. The MicroMyst Applicator has both US and CE Mark approvals.

**DuraSeal Evaluations**

**Evaluation of DuraSeal Sealing Strength**

Burst pressure testing was performed to determine the pressure-holding strength of DuraSeal when applied to collagenous materials (ASTM 2392-04). Collagen casing (#320, Nippi, Inc., Tokyo, Japan) with six uniform needle holes (CV-301 needle on a 6-0 Surgilene suture, Tyco Healthcare) was clamped into a pressure vessel. DuraSeal was applied to the needle-punched collagen surface (1–2mm sealant thickness). One minute following DuraSeal application, the vessel was pressurised, and the pressure at which DuraSeal leaked water through the needle holes was determined.

A total of 30 samples were evaluated. The average DuraSeal thickness tested was 1.6 ± 0.3mm, which resulted in an average burst pressure of 317 ± 56 mmHg (+ SD). All failures were cohesive, in that the failures occurred through the gel, rather than at the gel-collagen interface. This data supports observations of excellent tissue adherence with this material.

**Sealing Strength in the Canine Model**

A study was performed to evaluate both the safety and effectiveness of the DuraSeal Sealant in a canine cranial durotomy model. In 26 adult dogs a 2cm incision of cranial dura and arachnoid was created and loosely repaired. Hydrogel was applied over the 2mm dural gap in 13 dogs, while 13 control dogs received no hydrogel application. Terminal procedures were performed at 1, 4, 7 and 56 days. At that time, animals were anaesthetised, bone flaps were raised and the dural closure was leak-tested with Valsalva’s manoeuvre up to 55 cmH2O.

All dogs remained neurologically intact throughout the study. After bone flap was removal, the dural pressure integrity was tested. At every time point, dura in control animals leaked CSF at pressures much lower than the dura in DuraSeal-treated animals (p< 0.05). Although not a specific aim of this study, marked peridural adhesions to the bone flap were encountered in most of the control dogs at the 7-and 56-day time points. These adhesions were the putative cause for dural tearing during bone flap elevation in one control animal. No dural adhesions were observed in the hydrogel-treated group.

Pathologist evaluation of tissues found that the DuraSeal-treated animals exhibited normal progression of dural healing, no dural adhesions and no underlying effects on the brain. While dural healing progressed normally, the control animals displayed marked peridural adhesions.

**Evaluation of Adhesion Prevention**

**Laminectomy Model**

A study was performed in a canine lumbar laminectomy model to evaluate the ability of DuraSeal to prevent post-laminectomy epidural scar formation. Laminctomies were performed at two levels (L3 and L5) and were separated by an un-operated level in 12 canines. The two surgical sites were randomised to either treatment or control in each animal. The site randomised to treatment had DuraSeal applied to the laminectomy site, followed by a sterile saline rinse. Control sites received no additional treatment. All animals were terminated at 12–14 weeks post-operatively. At that time, six animals were selected for gross pathological examination and surgical re-exploration by a blinded neurosurgeon, and the remaining six animals for histopathological examination by a blinded pathologist.

The general health of the animals remained excellent throughout the study. During gross re-exploration of the surgical sites in six animals, the blinded neurosurgeon measured the extent and severity of peridural scar attachment to the dura. Five of the control sites (87%) had peridural scar observed on the dura, compared with three of the treated sites (50%). One of the treated sites had a small 4mm2 scar. If a threshold of peridural scar formation of 10mm2 is selected, then only 33% of the treated sites had scar, while the incidence of the control sites remains unchanged.

The blinded pathologist evaluated healing, gel compatibility, and peridural adhesion formation at each surgical site for the six non-treated vertebral sites, DuraSeal decreased the severity and incidences of periosteal-dural adhesions, i.e. complete adhesions were observed in four of six non-treated sites, whereas partial adhesions were observed in two of six treated sites.
The strength of DuraSeal.  
The precision of Xact.

During critical spine procedures, a watertight dural seal is essential to prevent post-op CSF complications. 

**The DuraSeal Xact™ Sealant System**

enhances the delivery of the DuraSeal hydrogel technology that has revolutionized the way a surgeon achieves a precise, TRUE watertight dural seal. The DuraSeal Xact Sealant System is exactly what you need to seal the spinal dura.

Please refer to DuraSeal Xact Instructions for Use for indications, contraindications, warnings and precautions. 

Product not available in all geographies. DuraSeal is a registered trademark and Xact is a trademark of Confluent Surgical, Inc.
Discetomy Model

A separate study was performed in a canine cauda equina discetomy model to assess the acute and subchronic dural sealing, along with adhesion prevention of the dural sealant when applied to the lumbar region following spinal decompressive surgery. Wound healing, tissue response, scar formation and nerve root mobility were evaluated using gross dissection and histopathology. Animals were observed daily for general health with emphasis on neurological deficits and pain. In addition, neurological examinations were conducted on days 3, 7, 10, and 14 post-treatment, and weekly thereafter up to eight weeks. A total of 18 canines underwent discetomies through the L7-S1 intervertebral space. After dorsal midline incision, the interarcuate ligament was excised, exposing the cauda equina. Fat around the cauda equina and nerve roots was aspirated, and a partial discetomy was performed. Following removal of a section of disc, the dorsal aspect of the cauda equina and nerve roots were abraded. Following injury, animals were randomised to either have the dural sealant applied to the discetomy and abrasion sites, or to receive no further treatment (control). All animals were terminated at eight weeks post-operatively. In 16 animals (eight test and eight control), the sites were grossly evaluated for nerve root mobility prior to histopathology. In two animals (one test and one control), the sites were removed en bloc and microscopically evaluated only.

Animals were healthy over the course of the study, no significant neurological deficits were noted and no adverse reactions were macroscopically observed for any of the dural sealant treated or control sites. All animals had normal healing of the skin, fascia and paraspinal muscles. No wound healing tissue response difference was noted between the test and control groups. Eight weeks following implantation, the animals were euthanised, the spines recovered, and fixed in 70% ethanol. Following fixation, transverse sections of spine were cut through the discetomy site, and a blinded surgeon evaluated nerved root mobility microscopically using a qualitative scoring system. The median nerve root mobility score for the DuraSeal-treated and control sites was 1.0 and 2.5, respectively. This represents a 60% improvement in median nerve root mobility score in the DuraSeal-treated animals.

Histological examination revealed more foamy macrophages in the DuraSeal sites than in the controls. The magnitude of this macrophage response was limited and expected due to the degradable nature of the test article. There was no sign of neurotoxicity, neurological damage or mass effect in any of the animals evaluated. Also observed was a reduced amount of scar protrusion into the dural sac in the DuraSeal-treated animals. There was a 30% reduction of ventral scar protrusion, and a 21% reduction of dorsal scar protrusion in the DuraSeal group, relative to control. These results suggest that the sealant or space,filling properties of DuraSeal may have helped maintain the dural sac morphology.

This study demonstrated an improvement in nerve root mobility, and preservation of the dural sac morphology in DuraSeal-treated animals. It is believed that following application, DuraSeal persists as an inert space-filler, which separates tissues while they heal independently. This separation is maintained while the tissues heal, and then the gel absorbs without creating significant inflammation, resulting in the preservation of the surgical plane between the dura and surrounding tissues.

Post-operative Sealant Swelling

DuraSeal Dural Sealant, like many absorbable hemostatic agents, has the potential to absorb fluid and increase dimensionally following implantation. The basic spray applicator provided with the DuraSeal kit may not provide adequate control to limit applied thickness, and hence, could potentially result in a large amount and thickness of hydrogel deposition and neural compression. Thus, the MicroMyst Applicator has been developed to provide increased control of applied volume and thickness. The fine tip and the air-assisted spray assists in achieving a controlled coating of tissues. With this applicator, it is recommended that maximum sealant thickness be limited to 1–2mm. This increased control allows for safe and effective sealant application, as demonstrated in the animal studies described herein.

Conclusions

The DuraSeal Dural Sealant has been evaluated in several preclinical studies to demonstrate lack of neurotoxicity, ability to seal against egress of CSF, and reduce the formation of peridural scarring. It appears to promote healing of dural incisions while reducing the formation of scar between the dura and adjacent tissues. It also possesses dual attributes of a sealant and an adhesion barrier and could be an important tool for spinal surgery. The MicroMyst spray applicator has been specifically designed to allow the controlled delivery of DuraSeal in spinal surgery.