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Comparative analysis of a fully-synthetic nanofabricated dura substitute and bovine collagen dura substitute in a large animal model of dural repair

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A R T I C L E   I N F O

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- Dural repair procedures
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A B S T R A C T

Objective: Dura substitutes are commonly required to repair the dura mater during routine neurological procedures. Biologic materials composed of xenogenic collagen represent the most prevalent dura substitute, yet often incite undesirable tissue responses that impair wound healing. Synthetic materials that overcome the shortcomings of existing products and facilitate effective and reliable repair of native dura are needed. The aim of the present study was to compare the performance of a novel synthetic non-biologic nanofabricated dura substitute to a crosslinked bovine collagen dura substitute as a means of facilitating successful dural repair.

Patients and methods: The biocompatibility and efficacy of fully-synthetic nanofabricated dura substitute (Cerafix\textsuperscript{TM} Dura Substitute, Acera Surgical, Inc., St. Louis, MO) and bovine dural substitute (DuraMatrix\textsuperscript{TM} Collagen Dura Substitute Membrane, Stryker, Inc., Kalamazoo, MI) was compared in a rabbit duraplasty model. Bilateral dural defects were repaired with either material and secured with non-tension sutures. Animals were monitored post-operatively for neurological sequelae and cerebrospinal fluid leak. Repair sites were explanted 4 weeks after implantation and evaluated by histopathology to assess neoduralization, cortical adhesion, implant resorption, local inflammation, and tissue response.

Results: Both the fully-synthetic and bovine collagen dura substitutes were effective in repairing dural defects and preventing cerebrospinal fluid leakage post-operatively. Histopathology revealed increased neoduralization and reduced cortical adhesion in defects repaired with the nanofabricated synthetic dural substitute versus defects repaired with the bovine collagen membrane. Histological analysis further demonstrated that the bovine collagen dural substitute induced a greater inflammatory response than the fully-synthetic nanofabricated material, with greater infiltration of inflammatory cells in bovine collagen implants at the terminal time-point.

Conclusions: Synthetic nanofabricated dural substitute and bovine collagen dural substitute demonstrated effective repair of induced dural defects and successfully prevented CSF leakage without infection or damage to underlying brain tissue. Nanofabricated dura substitute exhibited increased neoduralization, reduced cortical adhesions, and progressive resorption compared to the bovine collagen membrane. Fully-synthetic nanofabricated dura substitute further demonstrated less inflammation, irritation, and fibrosis than the bovine collagen material. Nanofabricated dura substitute thereby provides a unique non-biologic option in dural repair procedures, and offer reduced risk of inflammation and adhesions commonly associated with traditional xenogenic collagen products.

1. Introduction

Neurosurgical procedures commonly result in the perforation or removal dura mater. In most of these cases, the dura is repaired in a watertight manner in order to prevent damage to cortical tissues and leakage of cerebrospinal fluid. Numerous materials are currently in use as dural substitutes, including autograft, allograft, xenograft, and non-biologic synthetic materials. An ideal dura substitute should adequately restore the continuity of the dura mater and prevent CSF leak while minimizing infection. The mechanical properties of the material should facilitate suturing and/or tacking, yet also mimic the compliance of natural dura to allow ease of draping over cortical tissues. Furthermore, an ideal dura substitute will minimize local tissue inflammation and preferably encourage the infiltration of cells and vasculature to expedite the reconstruction of native dura without inducing undesired outcomes of fibrosis or cortical adhesions.
Autograft materials utilized in dural repair commonly include tissues harvested from the patient’s own pericranium or fascia latae. These tissues can be desirable because of minimal inflammatory response and similarity to native dura, but their use may be limited by poor availability in the particular patient and harvest site morbidity. Similarly, xenograft materials can be used as dural substitutes and may be derived from bovine or porcine sources in the form of decellularized pericardium, small intestine submucosa, and dermis, or in the form of collagen rich matrices such as bovine Achilles tendon. While these materials are readily available and do not require harvest from a separate donor site, they may incite inflammatory reactions and be prone to resorption and graft degradation.

Despite the range of existing dura substitute materials available in contemporary neurosurgical operating rooms, there remains a need for a dura substitute that offers improved handling characteristics, mechanical properties, and safety compared to biologically derived grafts. Non-biologic synthetic materials have been explored to overcome the limitations of biologic grafts, whereby material strength, resorption, and safety can be controlled with much greater precision. For example, expanded polytetrafluoroethylene film (Preclude™ Dura Substitute) is a non-degradable graft that can provide a long-term barrier to CSF leakage, but its permanent presence in the body often leads to fibrosis that may interfere with the proximal cortex and surrounding tissues. [6] Polyglactin 910/polydioxanone fleece and polydioxanone film (Ethi-sorb™ Dura Substitute) is an alternative synthetic graft formed from a composite of a synthetic polymer that is fully resorbable following neo-duralization. [6] Despite these offerings, tissue response to synthetic grafts has yet to be optimized. Synthetic grafts also fall short in their approximation of the mechanical properties of the dura mater, such that these materials often have poor handling that complicates their clinical use. Based on the shortcomings of the current clinically available materials, there remains a need for an improved resorbable non-biologic dura substitute that provides better handling and ease of use and improves the local tissue response during reconstruction of the native dura.

Electrospun nanofiber materials present a new class of fully-synthetic, biomimetic materials capable of providing an optimal combination of both intraoperative handling and biocompatibility and improving upon existing non-biologic material platform. A novel non-biologic dura substitute (Cerafix® Dura Substitute) produced utilizing electrospun nanofiber material present a unique approach to dura repair and offers an opportunity to provide optimal strength, handling, and sutureability, while reducing local inflammation to provide improved wound healing and dura regeneration (Fig. 1). The non-woven material synthesized by electrospinning of biodegradable polylactic-co-glycolic acid/polydioxanone, creates an architecture that is reminiscent of native extracellular matrix. [7] This method of synthesis creates a material that is mechanically strong, while providing the look and feel of native dura. The architecture of this non-biologic graft furthermore supports tissue ingrowth and neo-duralization with minimal inflammation. The nanofabricated dura substitute may thereby provide a novel solution to dura repair, improving upon the performance of existing graft materials. The present study was designed to evaluate the performance of the fully-synthetic nanofabricated dura substitute against a commercially available xenogenic dura substitute product in a clinically-relevant animal model.

2. Materials and methods

2.1. Study design

Ten female New Zealand White rabbits (5.0–5.5 months, Western Oregon Rabbit Company) were randomized into two groups (I, II) of five animals each (n = 5). Group I served as the positive control as all animals underwent bilateral craniotomy and dural resection followed by bilateral surgical repair of the induced dural defects utilizing a commercially-available bovine collagen dura substitute (DuraMatrix™ Collagen Dura Substitute Membrane, Stryker, Inc. Kalamazoo, MI). Group II served as an experimental group as all animals underwent bilateral craniotomy and dural resection followed by bilateral surgical repair of the induced dural defects utilizing a novel non-biologic nanofabricated dura substitute (Cerafix® Dura Substitute, Acera Surgical, Inc. Saint Louis, MO). All animals underwent daily/weekly behavioral assessment and examination for signs of neurotoxicity, neurological sequelae, CSF leakage, and infection. Four weeks post-operatively all animals were euthanized and repair sites, including proximal skull and underlying cortical tissue, were explanted for histological and histopathological analysis. All animal procedures were performed in strict accordance with guidelines set by the Animal Welfare Act (AWA), the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), and Institutional Animal Care and Use Committee (IACUC) of the University of Utah.

2.2. Surgical procedure: Bilateral craniotomy

Prior to surgery, all animals were administered butorphanol, acepromazine, cefazolin, and dexamethasone, as well as a transdermal fentanyl patch for prophylactic analgesia. All animals were anesthetized via ketamine and diazepam, administered intravenously via catheterization of the marginal ear vein, and maintained through the duration of the surgery via isoflurane. The cranium was then aseptically prepared and sterilized from the frontal ridge to the occiput. All hair was removed and the surgical site was prepared with povidone iodine and isopropyl alcohol. A 6 cm midline sagittal incision was then made extending through the scalp and the underlying periosteum. The periosteum was then elevated and retracted. Bilateral bone flaps were then created on either side of the skull utilizing a high-speed neurosurgical drill fitted with a matchstick bit. Resulting bone flaps measuring approximately 10 mm x 12 mm were then elevated and removed exposing the underlying dura mater. The dura mater was incised bilaterally utilizing a micro-dissection blade and two circular dural defects each approximately 8 mm x 10 mm were created under microdissection.

2.3. Surgical procedure: Dural repair

Induced dural defects were repaired with either xenogenic bovine collagen matrix (DuraMatrix™) or fully resorbable non-biologic dura substitute material (Cerafix®) (Fig. 2). Both dura substitute materials were provided sterile and stored at room temperature prior to use. Prior to implantation, both bovine collagen and fully-synthetic...
nanofabricated graft materials were hydrated in sterile saline according to their respective instructions for use. Hydrated graft materials was then placed on the surgical field and trimmed to fit each dural defect. The size and shape of the graft material was selected to achieve at least a 2 mm overlap with the adjacent dura mater around the circumference of the defect. Hydrated grafts were then draped onto the dura defect to maximize contact between the graft material and the underlying dura and promote watertight closure. Graft materials were then secured to the native dura utilizing four interrupted, non-tension sutures (7-0 PDS) spaced equidistant around the circumference of the defect. Graft materials were implanted such that each animal received either two bovine collagen implants (n = 5 animals) or two fully-synthetic nanofabricated implants (n = 5 animals). Following repair of induced dural defects, each surgical site was irrigated and closed in two layers (periosteum/muscle, skin). Excised bone flaps were not replaced during closure.

Following surgery all animals were recovered prior to reintroduction into the general housing facility. Butorphanol was administered as a post-surgical analgesic in addition to the fentanyl transdermal patch. Post-operatively all animals were observed daily and evaluated weekly for behavioral signs of neurotoxicity (posture, pupillary light reflex, limb placement, proprioception reflex, corneal reflex, gait), indications of CSF leakage, and change in body weight.

2.4. Tissue harvesting/CSF evaluation

All animals were humanely euthanized 4 weeks post-operatively. CSF was collected for physiochemical analysis by inserting a needle into the cisterna magna and aspirating 1-2 ml of fluid which was then placed in cold-storage. Following CSF collection, the skull, brain, and implant sites were excised en bloc and fixed in neutral buffered formalin. Draining lymph nodes were similarly explanted and fixed in neutral buffered formalin. CSF fluid was sent Logan Regional Hospital (Logan, UT) for physiochemical analysis. CSF was analyzed for cellular content (white blood cells, neutrophils, lymphocytes, monocytes/macrophages, eosinophils, basophils, lining cells, red blood cells) as well as glucose and protein levels.

2.5. Histological/Histopathological analysis

Explanted skulls and peripheral lymph nodes were embedded in epoxy resin, blocked, and sectioned. Sections of the implant site (including neodural tissue and adjacent skull/brain) were stained with Luxol Fast Blue and Hematoxylin & Eosin (H&E) to visualize and evaluate the general health of neodural tissue, cortical tissue, and myelin. Sections of the implant site were also immunostained for Glial Fibrillary Acidic Protein (GFAP) to visualize local glial cells/astrocytes and evaluate the inflammatory response at the implant site. Sections of the lymph nodes were stained only with Hematoxylin & Eosin (H&E). Representative photomicrographs were then obtained utilizing light microscopy under a 40× optical objective and a Nanozoomer automated slide scanner provided by the Hope Center, Washington University School of Medicine, St. Louis, MO.

The local tissue response to implanted dura substitute materials was quantified via microscopic scoring of neovascularization, vascularization of the tissue within the implant site, fibrosis, adhesions of the implant to the pia mater, and neoduralization. Fibrous capsule thickness (in μm) was averaged between three measurements in each implant site. If the presence of implant was not well defined, the thickness of fibrous tissue at the implant site was reported. Inflammation at the implant site was quantified by microscopically scoring the degree of infiltration of polymorphonuclear cells, lymphocytes, plasma cells, eosinophils, macrophages, and multinucleated giant cells into the implant field. Necrosis was scored as the severity of nuclear cellular debris from inflammatory cell death.

3. Results

3.1. Intraoperative/Postoperative performance of dura substitute materials

Both biologic and non-biologic dura substitute materials were successfully utilized to repair induced bilateral dural defects created in female New Zealand White rabbits. Intraoperative observations demonstrated that both commercially-available xenogenic collagen-based grafts and fully-synthetic nanofabricated grafts possessed suitable properties for effective dural repair. Upon surgical implantation nanofabricated implants were noted to be less thick and more flexible/compliant than crosslinked bovine collagen implants. Nanofabricated materials were also observed to better conform to underlying native dura and were more easily sutured in place compared to xenogenic grafts.

Post-operatively all animals survived to the terminal time point and all animals exhibited normal behavior, neurological function and general health. Regular examination of the implant site confirmed that 0/10 implant sites containing bovine collagen grafts and 0/10 implant sites containing non-biologic nanofabricated grafts exhibited signs of CSF leakage or focal implant site infection during the course of the study. Post-mortem examination of the repair sites further confirmed the absence of CSF leaks and pseudomeningocele in all animals on study. Post-operative observation demonstrated that both nanofabricated and bovine collagen materials were efficacious in repairing dural defects and preventing CSF leakage.
sections further demonstrated more complete neoduralization across the cortical surface of non-biologic nanofabricated grafts. Noted differences in tissue response to the implanted materials further related to the state of graft resorption at the time of explantation. At 4 weeks post-operatively, bovine collagen implants demonstrated minimal cellular infiltration and resorption, while nanofabricated implants demonstrated marked cellular infiltration and initial resorption (Fig. 3).

Quantitative scoring of histologic sections provided additional comparison of the tissue level reaction to both dura substitute devices. Microscopic scoring of histopathological examinations of the implant site revealed significant differences in the inflammatory and tissue-level responses to nanofabricated grafts, as compared to bovine collagen grafts (Fig. 4). Non-biologic nanofabricated implants were observed to recruit a reduced number of inflammatory cells (e.g. monocytes and lymphocytes) compared to bovine collagen grafts. Nanofabricated materials also exhibited less fibrosis and lower fibrous capsule thicknesses compared to bovine collagen materials. Histopathological scoring of inflammation and tissue response further indicated that nanofabricated implants exhibited a lower inflammatory response, and was therefore classified as non-irritant, compared to bovine collagen materials.

Quantitative histopathological analysis also confirmed qualitative observation of graft performance in vivo. Microscopic scoring demonstrated robust neoduralization and modest neovascularization of nanofabricated implants in all animals (Fig. 4). Histopathological analysis also demonstrated lower levels of fibrosis and low rates of cortical adhesions associated with the non-biologic implants. In contrast, quantitative histopathological analysis demonstrated significantly lower neoduralization and greater incidence of cortical adhesions associated with the bovine collagen graft. Neovascularization was also evident in implant sites receiving bovine collagen, albeit at a reduced occurrence in comparison to those receiving nanofabricated grafts. Quantitative analysis further confirmed observations of modest resorption of synthetic nanofabricated implants at 4 weeks post-operatively, largely as a result of phagocytosis of resorbable materials via infiltrating macrophages. Comparatively, minimal resorption or cellular infiltration of bovine collagen matrices was observed, coinciding with increased levels of fibrosis proximal to the implant.

3.2. Analysis of cerebrospinal fluid/sentinel lymph nodes

Cellular and physiochemical analysis of CSF collected from animals undergoing dural repair utilizing bovine collagen and fully-synthetic nanofabricated grafts was conducted in order to identify potential signs of neurotoxicity, inflammation, and/or infection resulting from implant materials. Complete blood counts and protein analysis conducted on collected CSF appeared normal in all animals implanted with both bovine collagen and nanofabricated grafts. Negative findings in CSF analysis suggest that neither implant material induced neurotoxic or inflammatory responses in regional cortical tissue. Histological analysis of sentinel lymph nodes was conducted in order to further examine the inflammatory and foreign body response to the dural substitute implants. Animals implanted with both bovine collagen and fully-synthetic nanofabricated grafts exhibited normal appearing lymph nodes upon H&E staining suggesting no regional inflammatory or foreign body response to the grafts.

3.3. Histological/Histopathological analysis of implant sites

Histological and histopathological analyses of surgical repair sites were conducted in order to qualitatively and quantitatively evaluate the efficacy of various dura substitute materials and the tissue/inflammatory response to the implanted grafts. Qualitative analysis of representative sections of defect sites repaired with either bovine collagen or fully-synthetic nanofabricated grafts demonstrate significant differences in the efficacy of the implanted material (Fig. 3). Coronal sections obtained from defect sites repaired with collagen-based grafts demonstrated poor cellular infiltration and incorporation into the graft material. Sections further demonstrated frequent fibrous adhesions or connective tissue bridging the bovine collagen graft and the underlying cortical tissue. Qualitative observations further demonstrated frequent incomplete neoduralization across the cortical surface of the bovine collagen grafts. In comparison, qualitative analysis of representative histological sections obtained from defect sites repaired with fully-resorbable nanofabricated material demonstrated increased cellular infiltration and lower incidence of fibrous cortical adhesions. Coronal

Fig. 3. Hematoxylin & Eosin-stained sections. Sections obtained from defects repaired with (A, C) fully-synthetic nanofabricated dura substitute and (B, D) bovine collagen dura substitute 4 weeks post-operatively.
Histopathological evaluation of underlying and proximal cortical tissue was further performed to examine the effect of the surgical procedure and the implanted graft material on local neural tissue. Local brain tissue appeared normal in H&E, LFB, and GFAP sections in the majority of animals implanted with nanofabricated and bovine collagen materials. Mild astrocytosis, neuronal necrosis, and microgliosis were observed in four animals across both groups and were attributed to the surgical procedure rather than to either the dura substitute materials.

4. Discussion

The present study offers a comparative analysis of a fully-resorbable non-biologic dural substitute and a xenogenic dural substitute in a bilateral rabbit duraplasty model. Both materials demonstrated effective repair of induced dural defects and prevention of CSF leakage without damaging proximal neural tissue. This functional comparison demonstrates equivalent performance of the fully-synthetic nanofabricated material with gold-standard bovine collagen matrices widely used in contemporary neurosurgical clinics. Histopathological analysis of the implant site 4 weeks post-operatively revealed, however, that the performance of the nanofabricated and bovine collagen grafts were not equivalent when considering local inflammatory and tissue-level responses elicited at the site of implantation. Non-biologic nanofabricated materials exhibited distinct advantages in local tissue response including reduced fibrosis/fibrous capsule formation and decreased cortical adhesions compared to bovine collagen (Fig. 3A–B). Nanofabricated dura substitutes induced greater neoduralization than bovine collagen at the implant site, and in some cases nanofabricated material supported complete neoduralization of the defect by the time of examination (Fig. 3C).

Autograft materials utilized in dural repair are commonly acquired from a patient's own pericranium or facia latae. These tissues are desirable due to their minimal inflammatory response and their similarity to native dura. However, the use of these grafts is limited by the poor availability and host-site morbidity of the autograft material.

Alternatively, human tissue is commonly utilized in the form of allografts, which are obtained from cadaveric dura (e.g. Lyodura™). This tissue can be collected, sterilized, and stored to provide greater availability of graft material to repair large dural defects. However, risk of disease transmission limits the use of allografts in contemporary neurosurgical settings. [1]

Xenograft materials are also commonly utilized as dura substitute products. Xenogenic materials are derived from bovine or porcine sources and are available in the form of decellularized tissues of the pericardium, small intestinal submucosa, and dermis (e.g. Lyoplant™, Tutopatch™, Dura-guard™, Durasis™, and Durepair™) or in the form of processed materials synthesized from collagen-rich sources such as the bovine Achilles tendon (e.g. Duraform™, DuraMatrix™, and DuraGen™). Like allografts, xenografts have an inherent risk of zoonotic disease transmission and furthermore have the potential to incite allergic and inflammatory reactions. [2] Many biologic grafts have the advantage of being fully remodeled, whereby the natural components of the graft (e.g. collagen) recruit cell infiltration and angiogenesis that participate in the restructuring of the graft material. However, the rate at which a biologic graft is remodeled and resorbed is not well controlled, such that graft degradation can occur prematurely. This mismatch between graft resorption and native tissue regeneration can result in thin, weak tissue in the dura defect. [3]

The mechanical properties of xenograft materials also vary greatly due to differences in material processing such as crosslinking and protein denaturation. [3] Select products have limited mechanical strength as to only be suitable for use as onlay grafts without the option of suturing (e.g. DuraGen™). Other xenograft materials provide the tear resistance and tensile strength required for suturing (e.g. Dura-Guard™, Durepair™, and DuraMatrix™). Bovine-derived collagen materials (e.g. DuraMatrix™) are commonly crosslinked to provide the mechanical strength necessary for suture repair of a dural defect. This manipulation of the mechanical properties causes undesirable effects in the handling of the material, leading to a dura substitute with decreased compliance. Furthermore, the crosslinking of bovine collagen matrices has been
shown to interfere with the degradation expected of its biologic collagen composition, leading to prolonged presence at the implant site with poorly defined material resorption. [4] The effect of crosslinking to retard the resorption of xenograft collagen materials is likely twofold: first, by preventing the migration of host cells into the material and second, by interfering with the mechanism of degradation for native collagen. [5] For biologically derived dura substitutes, desirable mechanical properties for suturability and desirable resorption properties for tissue remodeling are often mutually exclusive. [3]

The difference in tissue response to nanofabricated and xenogenic grafts is likely influenced by differences in the composition of the implants and, specifically, differences in the resorbable nature of the material. Bovine collagen materials did not appear to undergo significant resorption 4 weeks after implantation, but rather was associated with minimal cellular/tissue infiltration and significant fibrous capsule around the acellular, crosslinked collagen material. Thus, although xenogenic graft material is composed of biologically-derived animal-based collagen, the biological response to the implanted material is unlike what may be expected of native tissue. Xenogenic grafts, despite the biologic composition, exhibit an in vivo response significantly divergent to that of native or fresh tissue.

Alternatively, the synthetic nanofabricated implants demonstrated modest resorption in parallel with increased cellular infiltration of the material. Particularly, resorbing elements of the synthetic implant were observed to be localized within macrophages that had infiltrated the implant site. This observation confirms the resorbable and transient nature of the non-biologic nanofabricated material. The synthetic electrospun material utilized in the construction of the nanofabricated graft provided an environment in which cells could migrate and which could be broken down to allow subsequent remodeling of the tissue. Fully-resorbable synthetic implants may possess multiple advantages over long-term or permanent implants in that the material serves as an acute barrier and scaffold for new tissue formation yet resorbs following tissue regeneration precluding undue chronic reactions to the implanted material. Furthermore, the lack of animal-derived, xenogenic, or allogenic constituents may effectively reduce the incidence of allogenic or inflammatory responses to the implanted dura substitute material commonly associated with existing biologic graft materials.

The lack of resorption of the implanted xenogenic graft is likely an effect of the post-processing utilized in the construction of the biologic material. The crosslinking of bovine collagen required to provide the mechanical strength necessary for intraoperative use and suturability simultaneously affects the biologic and structural elements of the material. As demonstrated in this study, fully-resorbable synthetic dura substitutes can provide adequate mechanical strength for suturability, optimal handling and compliance, as well as reliable resorption that encourages tissue remodeling in the form of neoduralization. The nanofabricated material is unique, however, in that the non-biologic dura substitute also exhibits reduced inflammation, decreased fibrosis, and fewer adhesions to the pia mater than gold-standard biologic dura substitutes presently in use in neurosurgical clinics. The non-woven architecture, created by electrospinning, may be attributed with an improved tissue response, as compared to alternative synthetic dura substitutes. Furthermore, this mechanism of synthesis provides a material with superior handling and drapability as compared to alternatives with reduced compliance. The fully-synthetic nanofabricated dura substitute thereby offers a unique and attractive option in dural repair procedures that provides ease of handling, efficacy, and biocompatibility, ultimately leading to improved dural repair.

5. Conclusions

Synthetic nanofabricated dura substitute material offers a combination of mechanical strength for suturability and compliance for ease of handling. The non-woven architecture of the electrospun nanofiber graft permits cellular infiltration and supports full resorption of the implant material while encouraging regeneration of native dura. Nonbiologic nanofabricated dura substitute material effectively closed dura defects equivalent to a gold-standard xenogenic dura substitute and induced a superior local tissue response characterized by decreased inflammation and increased neoduralization. Non-biologic nanofabricated dura substitutes thereby offers significant advantages over existing dura substitutes that may lead to improved clinical outcomes in multiple neurosurgical settings.

Declarations of conflicts of interest

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