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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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ABSTRACT

Objective: Dura substitutes are commonly required to repair the dura mater during routine neurosurgical 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® Dura Substitute, Acera Surgical, Inc., St. Louis, MO) and bovine dural substitute (DuraMatrix™ 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.

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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 matrixes 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 (Ethisorb™ Dura Substitute) is an alternative synthetic graft formed from a composite of a synthetic polymer that is fully resorbable following neoduralization. [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 suturability, while reducing local inflammation to provide improved wound healing and dura regeneration (Fig. 1). The non-woven material synthesized by electrospinning of biodegradable poly(lactic-*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 neoduralization 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.

Fig. 1. Cerafix® Dura Substitute. A non-woven fully-resorbable material optimizing for repair of dural defects.

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 × 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 × 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