



# Cerafix® Dura Substitute Effectively Repairs Small and Large Dural Defects Independent of Defect Size

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## **ABSTRACT:**

**Background:** Dural substitutes are commonly utilized to repair dural defects incurred during routine neurosurgical procedures. The ideal dura substitute should effectively seal the defect, encourage neoduralization, and regenerate native dura prior to graft resorption. Cerafix® Dura Substitute is a novel non-biologic, fully-resorbable graft that has previously been shown to successfully repair critical dural defects and regenerate native dura in canine and rabbit models. Yet, the resorbable Cerafix® material has not been evaluated in the repair of larger dural defects sizes, where the time course of cellular ingrowth and neoduralization is prolonged. The present study aims to examine whether the resorption rate of the Cerafix® material is suitable for effective repair of large dural defects.

**Methods:** The efficacy of Cerafix® Dura Substitute was evaluated in a canine duraplasty model. Small or large dural defects (equivalent to 1.9 in<sup>2</sup> and 4.4 in<sup>2</sup> dural defects in humans) were created bilaterally and then repaired with Cerafix® secured with non-tension sutures. Animals were monitored post-operatively for signs of CSF leak and neurological abnormalities. Repair sites were explanted 4 or 13 weeks after surgery and evaluated by histopathology to assess neoduralization, implant resorption, and local inflammation [12-14].

**Results:** Cerafix® was observed to effectively repair induced dural defects independent of the induced defect size. Both small and large dural defects were successfully repaired by Cerafix® Dura Substitute, which prevented CSF leakage and infection. Histopathology of the implant site revealed comparable neoduralization and vascularization between small and large defects both 4 and 13 weeks after surgery. Furthermore, histopathology confirmed that the gradual resorption of the graft was balanced by increasing neoduralization over time. By week 13 all defects were healed upon complete neoduralization across the implant site [12-14].

**Conclusions:** Cerafix® demonstrated an optimal time course of resorption suited for repair of both small and large dural defects\*. Cerafix® provided immediate sealing of the dura mater, as well as gradual resorption, after which the graft was completely replaced with neodural tissue 13 weeks after surgery. The present study further demonstrates the ability of Cerafix® Dura Substitute to regenerate pristine dura in variable size defects.

## **1. Introduction**

Neurosurgical procedures frequently compromise the integrity of the dura mater, the fibrous membrane that encases the brain and spinal cord. Damage to the dura must be repaired to protect the underlying cortex and prevent leakage of cerebral spinal fluid (CSF). When primary closure is not

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\***Indications:** Cerafix® Dura Substitute is indicated as a dura substitute for the repair of dura mater. This device is indicated for defects of 4.4 in<sup>2</sup> (28.3 cm<sup>2</sup>) or less in area. For example, 4.0 in x 1.1 in (10.1 cm x 2.8 cm) would be an acceptable defect size.

\***Contraindications:** Cerafix® Dura Substitute is not designed, sold or intended for use except as described in the indications for use and is contraindicated in the following situations: For repair of spinal neural tube defects; anterior spinal surgery with dura resection (e.g., transoral surgery), In infected regions, To cover dura defects involving mastoid air cells, Large defects at the skull base following surgery. Specifically, an area greater than 4.4 in<sup>2</sup> (28.3 cm<sup>2</sup>) is contraindicated. For example, 4.0 in x 1.1 in (10.1 cm x 2.8 cm) would be an acceptable defect size but a greater surface area would be contraindicated.

achievable, a dura substitute is commonly utilized to seal and repair the dural defect. An ideal dural substitute should provide an immediate mechanical barrier to CSF leakage, and encourage gradual remodeling and new tissue ingrowth in order to facilitate defect repair via neoduralization [1-11].

Cerafix® Dura Substitute is a novel synthetic graft material composed of biodegradable poly(lactic-co-glycolic acid) and poly(dioxanone) (Fig. 1). Synthesis of Cerafix® by electrospinning creates a material whose non-woven, fibrillar nanoscale architecture mimics that of the natural extracellular matrix. [1] This architecture encourages the infiltration of cells that can remodel the graft, resulting in resorption of the dura substitute as it is replaced via neoduralization. Furthermore, the unique structure of Cerafix® results in a graft that is both mechanically strong and compliant. The material is therefore suturable and malleable and can be manipulated and draped with a feel similar to native dura.



**Figure 1:** Cerafix® Dura Substitute, a non-woven fully-resorbable material optimizing for repair of dural defects.

The performance of Cerafix® Dura Substitute was previously evaluated in the repair of dura defects in a rabbit duraplasty model and compared to the performance of DuraMatrix™ Collagen Matrix, a clinical gold standard of biologic dura substitutes. Cerafix® was as effective as DuraMatrix™ at repairing dura defects and preventing CSF leakage. Cerafix®, however, exhibited increased neoduralization and reduced prevalence of cortical adhesion compared to DuraMatrix™. Cerafix® was further shown to induce less local inflammation compared to the collagen-based xenograft. Yet, prior studies did not examine whether the fully-resorbable Cerafix® material was suitable in repairing larger sized dural defects wherein a longer period of time may be required for adequate neoduralization and healing. Herein we demonstrate that Cerafix® Dura Substitute is effective at repairing dura defects independent of defect size by comparing its performance in repairing small and large dura defects in a canine duraplasty model. This study illustrates the suitable time course of resorption of the Cerafix® Dura Substitute and further support the use of the material in the repair of dura defects with dimensions relevant to human neurosurgical applications.

## 2. Materials and Methods

### 2.1. Study Design

Twelve female hounds (51-71 wks, Covance Research Products, Inc.) were randomized into four groups (I-IV) of three animals each (n=3). Groups I and III served as positive controls as all animals underwent bilateral craniotomy and induction of a small dural defect followed by bilateral surgical repair of the induced dural defects utilizing fully resorbable non-biologic Cerafix® Dura Substitute (Acera Surgical, Inc. Saint Louis, MO). Groups II and IV served as experimental groups as all animals underwent bilateral craniotomy and dural resection followed by bilateral surgical repair and induction of a large dural defect followed by bilateral surgical repair of the induced dural defects utilizing Cerafix® Dura Substitute. All animals underwent daily / weekly behavioral assessment and examination for signs of neurotoxicity, neurological sequelae, CSF leakage, and infection. Four and thirteen weeks post-operatively all animals in Groups I/II and III/IV, respectively, 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

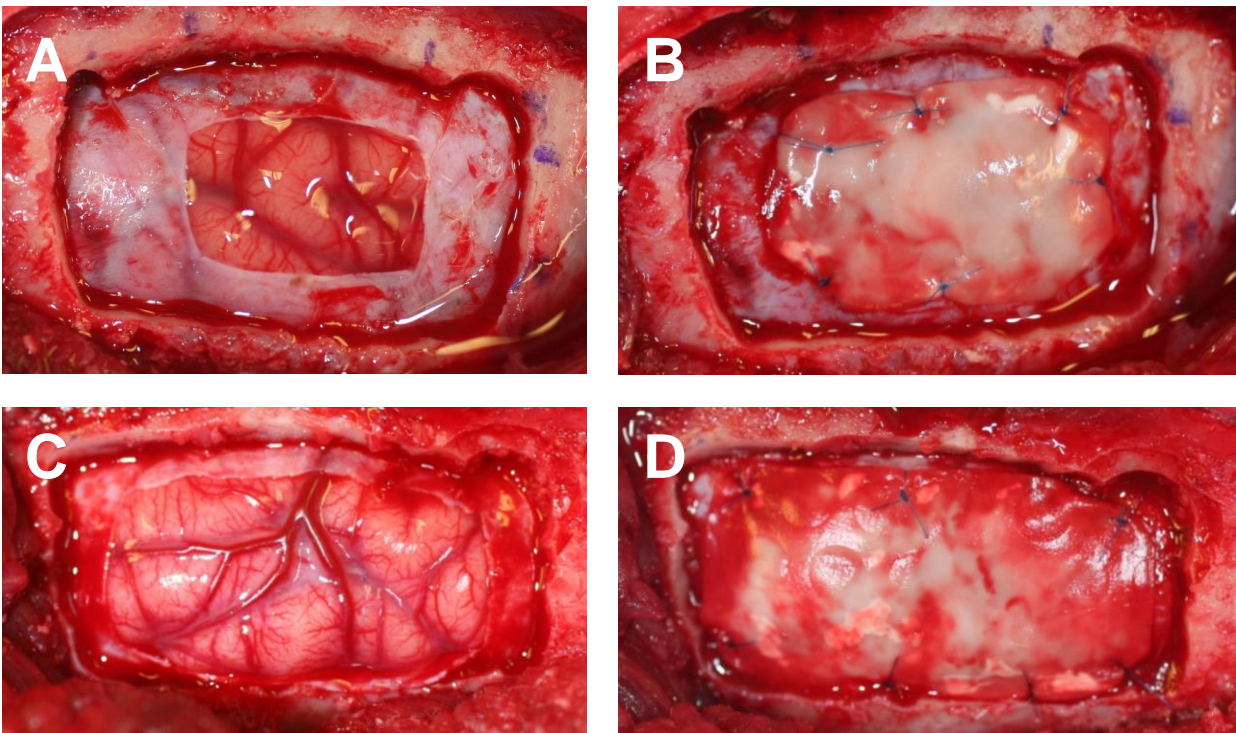
Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), and Institutional Animal Care and Use Committee (IACUC) of the University of Utah.

## 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 10cm 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 were then elevated and removed exposing the underlying dura mater. The dura mater was incised bilaterally utilizing a micro-dissection blade. In Groups I and III, two small rectangular dural defects, each approximately 11mm x 15mm, were created under microdissection. In Groups II and IV, two large rectangular dural defects, each approximately 16mm x 25mm, were created under microdissection. Small and large dural defects created in the canine model were the equivalent to 1.9 in<sup>2</sup> and 4.4 in<sup>2</sup> dural defects in humans. [14]

## 2.3. Surgical Procedure: Dural Repair

Induced dural defects were repaired with fully resorbable non-biologic dura substitute material (Cerafix®) (Fig. 2). Cerafix® was provided sterile and stored at room temperature prior to use. Prior to implantation, Cerafix® graft materials were hydrated in sterile saline according to the instructions for use.



**Figure 2:** Bilateral dural defects induced in canine animal model repaired with Cerafix® Dura Substitute. Representative view of small dural defect (11mm x 15mm) created via microdissection (A) and repaired with Cerafix® graft material (B). Representative view of large dural defect (16mm x 25mm) created via microdissection (C) and repaired with Cerafix® graft material (D).

Hydrated graft material 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 2mm overlap with the adjacent dura mater around the circumference of the defect. Hydrated grafts were then draped onto the dural defect to maximize contact between the graft material and the underlying dura and to promote watertight closure. Graft materials were then secured to the native dura utilizing interrupted, non-tension sutures (7-0 PDS) spaced equidistant around the circumference of the defect. Graft materials were implanted such that each animal received two Cerafix® implants. 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. Flunixin and enrofloxacin were also administered 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*

Animals were humanely euthanized at either 4 weeks or 13 weeks post-operatively. CSF was collected for physiochemical analysis by inserting a needle into the cisterna magna and aspirating 1-2ml 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 40X optical objective and a Nanozoomer automated slide scanner provided by the Hope Center, Washington University School of Medicine.

The local tissue response to the implanted dura substitute material was quantified via microscopic scoring of neoduralization, tissue ingrowth, neovascularization, fibrosis, and adhesions of the implant to the pia mater. Fibrous capsule thickness (in  $\mu\text{m}$ ) 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.

### **3. Results**

#### *3.1. Intraoperative / Postoperative Performance of Dura Substitute Materials*

Cerafix® Dura Substitute material was successful in repairing induced bilateral dural defects created in female hounds independent of defect size. Intraoperative observations demonstrated that fully-resorbable synthetic Cerafix® grafts possessed suitable properties for effective dural repair. Upon surgical



implantation Cerafix® implants were noted to be flexible and compliant and easily conformed to underlying cortex and native dura.

Post-operatively all animals survived to the terminal time point without evidence of CSF leakage. Regular examination of implant sites confirmed that 0 out of 12 implant sites involving a small dural defect, and 0 out of 12 implant sites involving a large dural defect, 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.

Several abnormalities were observed in recovering animals as a consequence of the surgical procedure, rather than the graft material or defect size. One animal receiving a small dural defect in the 4-week time point group exhibited mal-aligned edges of the incision site 10 days after surgery, which were corrected with additional sutures and 5 days of antibiotics. Two animals in the 4-week time point groups receiving small and large dural defects, respectively, developed a seroma at the occipital crest. Two animals in the 13-week time point groups receiving small and large dural defects, respectively, exhibited mild subcutaneous edema at 17-23 days after surgery that resolved without intervention. One animal in the 13-week time point group receiving a large dural defect exhibited impaired rear limb placement and proprioceptive reflex that resolved 4 days after the surgical procedure.

### *3.2. Analysis of Cerebrospinal Fluid / Sentinel Lymph Nodes*

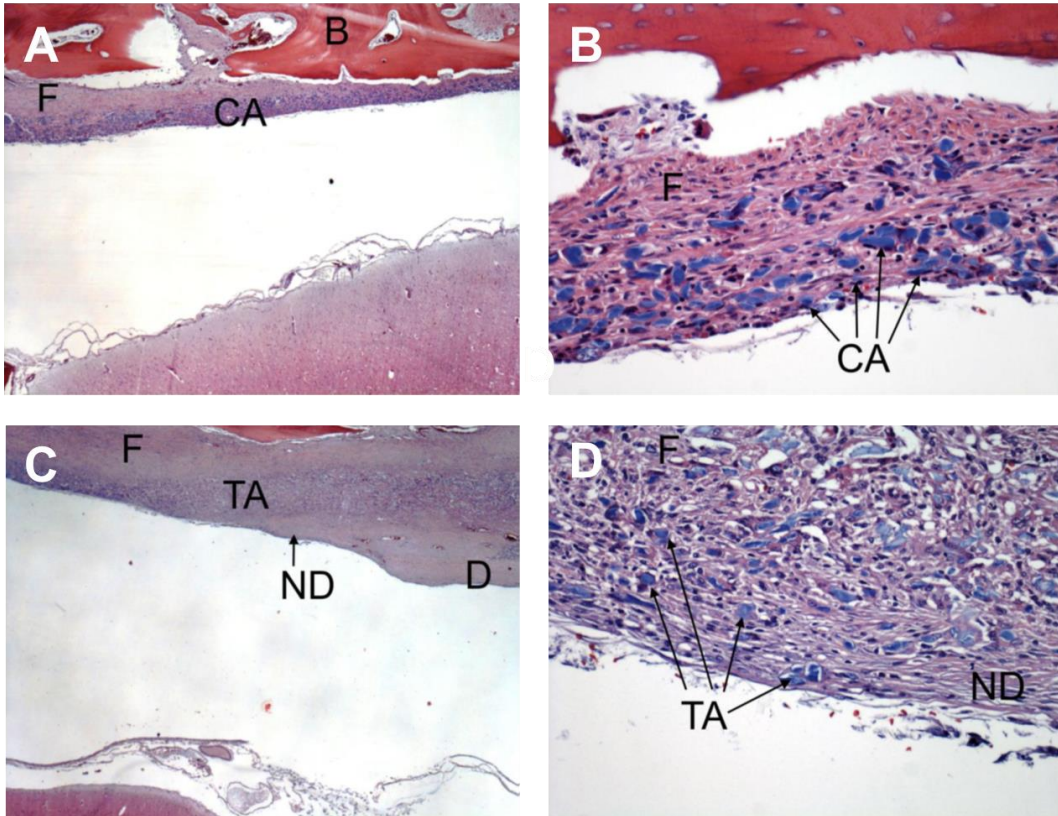
Cellular, protein, and glucose analysis of CSF collected from animals undergoing dural repair was conducted in order to identify potential signs of neurotoxicity, inflammation, and/or infection. Complete blood counts and protein analysis appeared normal and comparable between groups, confirming that Cerafix® prevented local infection and minimized local inflammation when repairing both small and large dural defects 4 and 13 weeks post-operatively. Negative findings in CSF analysis further suggest that the implant material did not induce neurotoxic or inflammatory responses in regional cortical tissue. Draining lymph nodes were explanted and analyzed with H&E staining to detect signs of regional infection or inflammation in response to dural repair. All draining lymph nodes appeared normal, confirming that the implant material did not result in infection or inflammation beyond the local implant site.

### *3.3. Histological / Histopathological Analysis of Implant Sites*

Histopathological evaluation of implant sites 4 weeks after surgery confirmed the Cerafix® graft material was effective in healing both small and large dural defects through induced neoduralization (Fig. 3). In all animals the implant site consisted of vascularized connective tissue spanning the dural defect. The thickness of the regenerated fibrous tissue was similar regardless of defect size, with fibrous capsule thickness of  $324 \pm 185 \mu\text{m}$  in small defects and  $358 \pm 76 \mu\text{m}$  in large defects.

Scoring of the histopathological evaluation provided quantitative analysis of tissue reactions including cortical adhesions, vascularization, and neoduralization within the implant site 4 weeks after surgery (Fig. 4). No adhesions to the pia mater were observed at 4 weeks after surgery, with the exception of one implant site in an animal receiving a small defect that exhibited greater than 75% of the implant field adhering to the pia mater. Minimal vascularization (<25% of the implant field) was seen in 5/6 implant sites for both small and large defects, with one implant site for each defect size exhibiting no vascularization. Neoduralization was evident in the majority of the implant sites, including 3/6 implant sites for small dural defects and 5/6 implant sites for large dural defects. The degree of neoduralization varied from 25-100% of the implant field in small defects and from 0-50% of the implant field in large defects. Resorption of the implant was marked in all animals at 4 weeks post-operatively, with the graft material found within the cytoplasm of macrophages and multinucleated giant cells at the implant site. Quantitative analysis demonstrated no significant differences in the tissue reaction to Cerafix® Dura Substitute when used to repair small or large dural defects.

Histopathological evaluation of implant sites 13 weeks after surgery revealed comparable healing in implant sites involving both small and large dural defects (Fig. 5). At 13 weeks after surgery

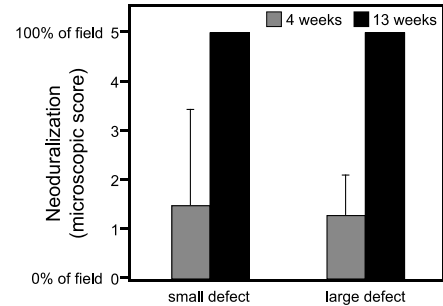


**Figure 3:** Hematoxylin & Eosin-stained sections obtained from injury sites involving small dural defects repaired with Cerafix® Dura Substitute material (A,B) and large dural defects repaired with Cerafix® Dura Substitute material (C,D) 4 weeks post-operatively. B = Bone, F = Fibrous tissue, CA = Control article, TA = Test article, ND = Neodural tissue, D = Dura mater.

histopathological evaluation of the tissue response to the graft material was similar in both small and large dural defects. Neoduralization and fibrous connective tissue spanned the defect and by week 13 regenerated tissue contained lower numbers of macrophages and no multinucleated giant cells. By week 13 the thickness of regenerated fibrous tissue had increased, with fibrous capsule thickness of  $799 \pm 377 \mu\text{m}$  in small defects and  $539 \pm 176 \mu\text{m}$  in large defects. Graft material was found only within the cytoplasm of macrophages at the implant site 13 weeks after surgery, suggesting near complete resorption of the implanted graft material.

Histopathological scoring of the tissue response at the implant sites evaluated cortical adhesions, vascularization, and neoduralization at the implant site 13 weeks post-operatively (Fig. 4). Adhesions to the pia mater increased at 13 weeks after surgery. Animals receiving small defects and large defects exhibited comparable adhesion to the pia mater, with the extent of adhesions varying from 0-75% of the implant site. Minimal vascularization (<25% of the implant field) was observed in all implant sites for both small and large dural defects, except in one implant site in an animal receiving a small defect having vascularization in up to 50% of the implant field. Complete neoduralization was observed in all implant sites at 13 weeks after surgery, such that new dura tissue completely bridged the dural defect. Quantitative histopathological analysis confirmed that the tissue response to implanted grafts material was consistent between 4 and 13-week timepoints in both small and large dural defects. Changes in tissue reaction did, however, occur between 4 and 13 weeks after surgery including increases in neoduralization and new tissue formation.

	Small defect		Large defect	
	<i>4 weeks</i>	<i>13 weeks</i>	<i>4 weeks</i>	<i>13 weeks</i>
Defect size (cm <sup>2</sup> )	1.8	1.7	4.2	3.9
Implant vascularization <sup>a</sup>	0.8	1.2	0.8	1.0
Neoduralization <sup>b</sup>	1.5	5.0	1.3	5.0
Pia mater adhesion <sup>c</sup>	0.7	1.0	0.0	1.8
Fibrosis <sup>d</sup>	3.2	4.0	3.7	3.8
Fibrous capsule (μm) <sup>e</sup>	324	799	358	539



**Figure 4:** Average histopathological scoring of tissue response at the implant site for small and large dural defects repaired with Cerafix®, 4 and 13 weeks after surgery (Left). (a) Scored from 0 (absent) to 5 (>75% of implant field). (b) Scored from 0 (absent) to 5 (100% of the implant field). (c) Scored from 0 (absent) to 5 (100% of the implant field). (d) Scored from 0 (no measurable fibrous capsule) to 5 (fibrous capsule thickness > 300 μm). (e) Measured at three locations at each implant site. Comparison of neoduralization at the implant site for small and large dural defects repaired with Cerafix®, 4 and 13 weeks after surgery (Right).

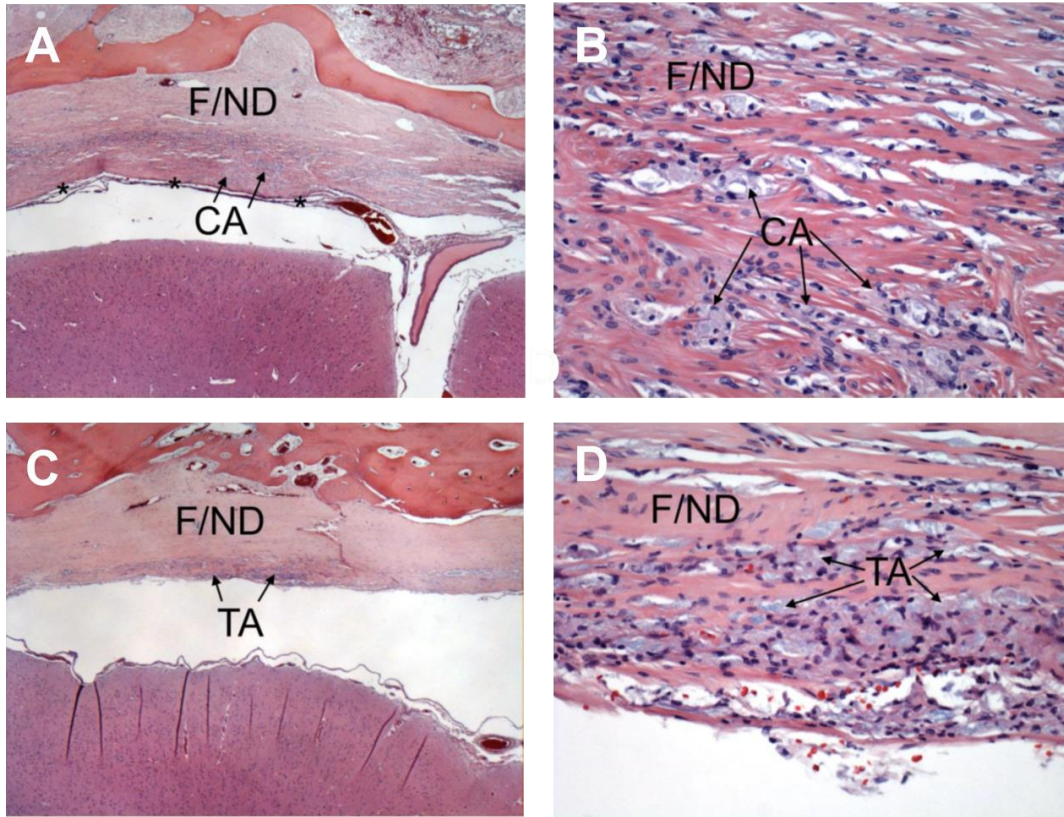
Histopathological evaluation of underlying and proximal cortical tissue was further performed to examine the effect of the surgical procedure and the implanted graft material on local neural tissue. Local brain tissue appeared normal in H&E, LFB, and GFAP sections in the majority of animals implanted with Cerafix®. Mild astrocytosis, neuronal necrosis, and microgliosis were observed across implant sites involving both small and large dural defects and were attributed to the surgical procedure rather than to the graft material.

#### 4. Discussion

The present study aimed to examine whether a fully-resorbable non-biologic dura substitute (Cerafix® Dura Substitute) is effective in repairing large-area dural defects where the time course of neoduralization may be prolonged. Prior studies demonstrated the ability of Cerafix® graft material to effectively repair induced dural defects and prevent CSF leakage in vivo. Large animal testing demonstrated equivalent performance of the Cerafix® material to gold-standard collagen-matrices widely used in contemporary neurosurgical clinics. Histopathological analysis further demonstrated that Cerafix® exhibited distinct advantages in local tissue response compared to existing biologic matrices, including reduced fibrosis / fibrous capsule formation and decreased cortical adhesions, and greater neoduralization. Yet, prior studies failed to address whether rate of graft resorption would allow the Cerafix® graft material to support dural regeneration in cases where neoduralization may be prolonged due to the size of the dural defect.

A canine duraplasty model was selected to compare the ability of the Cerafix® material to repair either small or large dural defects induced via microdissection. Post-operative and terminal observations confirmed that Cerafix® successfully facilitated acute dural closure in both size small and large defects, as the implanted graft material prevented CSF leakage, infection, and damage to the proximal cortical tissue. These results largely correlate with previous studies demonstrating the ability of the Cerafix® material to successfully repair defects in multiple rabbit, pig, and canine models. Histopathological analysis of the repair sites further revealed equivalent tissue reaction to the resorbable graft in both small and large dural defects. In either case, the graft material experiences significant tissue ingrowth in concert with graft resorption, and replacement with pristine dural tissue consisting of fibrous vascularized connective tissue. The thickness of regenerated fibrous tissue increased from 4 weeks to 13 weeks after surgery, and was shown to be equivalent between surgical sites involving small and large dural defects. Evidence of graft resorption was equally apparent in both small and large dural defects as Cerafix® was found only within the cytoplasm of macrophages infiltrating the fibrous tissue at the implant site.





**Figure 5:** Hematoxylin & Eosin-stained sections obtained from injury sites involving small dural defects repaired with Cerafix® Dura Substitute material (A,B) and large dural defects repaired with Cerafix® Dura Substitute material (C,D) 13 weeks post-operatively. F = Fibrous tissue, CA = Control article, TA = Test article, ND = Neodural tissue.

Quantitative analysis of histopathological observations permitted quantitative comparison of the tissue reaction between small and large dural defects at 4 and 13 weeks after surgery. Adhesion of neodural tissue, or associated fibrous tissue, to the pia mater was observed both 4 weeks to 13 weeks after surgery. Yet, adhesions did not induce any changes in proximal neural tissue and thus were not believed to have any negative effect on the performance of the graft material at the implant site.

Vascularization of the implant site was also shown to be similar in the majority of implant sites. Both small and large dural defects exhibited minimal vascularization at 4 weeks and 13 weeks after surgery. Minimal vascularization is expected as a necessary component of regenerating tissue that heals the dural defect as the graft is resorbed. Similar vascularization between small and large dural defects at both time points confirmed that Cerafix® induced similar processes of tissue regeneration at the implant site, independent of defect size.

The most striking outcome in the study were observations of consistent and progressive neoduralization – seen at equivalent rates in both large and small dural defects - throughout the course of the study, resulting in complete repair of induced dural defects by 13 weeks post-operatively. Neoduralization was observed in the majority of implant sites at 4 weeks after surgery. 13 weeks after surgery, all implant sites in animals receiving both small and large dural defects exhibited neoduralization in 100% of the implant field, such that regenerated native dura completely bridged the original defect. Complete and successful neoduralization of both small and large dural defects at both time points confirmed the ability of Cerafix® to heal induced dural defects independent of defect size. Furthermore, effective neoduralization confirms that the rate of graft resorption is suitable to support dural regeneration in cases where neoduralization may be prolonged due to the size of the dural defect.



In total, Cerafix® Dura Substitute was shown to effectively repair large dural defects through the induction of consistent and progressive neoduralization. Cerafix® was also shown to effectively facilitate both immediate closure of the dura mater as well as progressive tissue regeneration and gradual resorption, optimally balanced by cellular infiltration and neoduralization. These results confirm that Cerafix® Dura Substitute is equally suited for the repair of small and large dural defects and is a desirable graft material applicable in multiple neurosurgical settings involving dural repair.

## 5. Conclusions

Cerafix® Dura Substitute is a novel non-biologic, fully-resorbable dural graft material possessing a nanoscale architecture that mimics the extracellular matrix of natural tissue. This unique architecture promotes cellular infiltration, encourages regeneration of the native dura, provides mechanical strength for suturability, and endows malleability for ease of handling. In the present study, Cerafix® effectively repaired induced dural defects independent of defect size in a canine duraplasty model. Cerafix® achieved a balanced rate of graft resorption and neoduralization that appropriately healed both small and large dural defects equivalent to 1.9 in<sup>2</sup> and 4.4 in<sup>2</sup> dural defect in humans. All dural defects were completely bridged by regenerated native dura by 13 weeks after surgery. Cerafix® thus provides a unique alternative to existing biologic grafts and dura substitutes in multiple neurosurgical settings.

## 6. References

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