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Evaluation of efficacy and biocompatibility of a new absorbable synthetic substitute as a dural onlay graft in a large animal model

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Background: Numerous dura substitutes are commercially available, but no absorbable synthetic dura repair product has been used for both onlay and suture applications.
Objective: The safety and effectiveness of a new absorbable synthetic substitute composed of Poly-L-lactide microfibers as onlay dural graft were evaluated.
Methods: Physical properties and performance of the microfibrous synthetic dural substitute implanted as an onlay or suturable grafts were compared with these commercial products, including CODMAN ETHISORB™ Dura Patch and DuraGen™ Dural Graft Matrix, in a canine duraplasty model. The cerebrospinal fluid (CSF) leakage, macroscopic and microscopic observation at 30 and 90 days after implantation were investigated.
Results: The absorbable synthetic dural substitute exhibited good wettability and conformability. When implanted as an onlay graft, it can prevent CSF leakage and integrate with the surrounding tissue to repair dural defects, indicating its good efficacy and biocompatibility as an onlay graft.
Conclusion: Based on the excellent physical properties and performances mentioned above, the new absorbable synthetic substitute can be applied as a dural graft for both onlay and suturable applications.

Keywords: Absorbable synthetic dural substitute, Dural repair, Biomimetic, Onlay, Suturable

Introduction

Numerous dura substitutes are commercially available,[1–3] absorbable synthetic dura repair products have recently gained more and more attention because they pose no risk of disease transmission compared with autologous fasciae, allografts, and biological materials,[4–6] and they can be absorbed completely after guiding the regeneration of the dura mater without the risk of leading to long term, continuous inflammatory reactions or infections compared with non-absorbable materials.[7–11] Of these synthetic dura substitutes, onlay grafts appear promising as sutureless dural repair has several advantages over conventional techniques in which the graft is sutured to cover dural defect, including reduce surgery time, facilitate application of small patches in difficult-to-reach locations, and overcome difficulties related to the presence of fragile or ossified dura mater.[12] DuraGen™ Dural Graft Matrix and Durepair® Dura Regeneration Matrix are xenogeneic collagen-based onlay dural grafts on the market,[13–16] belonging to the category of biological materials with the limitations aforementioned. The only commercially available synthetic dura substitute which can be implanted with or without sutures is Synthecel® Dura Substitute. However, it is a non-degradable graft biosynthesized from cellulose, and is associated with limitation mentioned above.[17] Although a variety of absorbable synthetic dura substitutes, such as CODMAN ETHISORB™ Dura Patch consisting of polyglactin 910 (vicryl) and poly-p-dioxanone (PDS),[18] SEAMDURA Bioabsorbable Artificial Dural Substitute consisting of copolymers of L-lactide and ε-caprolactone [P(LA/CL)] and polyglycolic acid (PGA),[19,20] have been widely applied in the clinic, these products are very stiff with poor adherence to surrounding tissues, thus cannot be applied as onlay grafts.

To overcome these limitations, a new biodegradable synthetic substitute with biomimetic design (the 'biomimetic substitute') has been developed recently.[21] This

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biomimetic substitute is composed of PLLA fibers with open, highly interconnected pores, creating a unique 3D structure which resembles the extracellular matrix (ECM) of human dura mater.[22] Our previous work demonstrated that the biomimetic substitute had good biocompatibility and tensile strength to hold the sutures, and prevented CSF leakage when used as a suturable graft, it could also facilitate cell infiltration and tissue generation and degraded at a proper rate that matches the rate of new tissue formation during biological dural reconstruction.[21]

This biomimetic substitute is hydrophobic and does not absorb water due to the hydrophobic PLLA component. Until recently we have found a new feature of this patch due to its microstructure of the biomimetic design, namely it can absorb saline by applying manual pressure when submerged in saline for 2–5 mins. Under this condition, the new substitute becomes hydrophilic, transparent and exhibits good conformability. Based on this new feature of the biomimetic absorbable graft, it is hypothesized that it can be used as an onlay graft, performing similarly to a suturable graft or other commercial onlay grafts. To the best of the authors' knowledge, there is no one absorbable synthetic dural substitute on the market, which can be used as both an onlay and suturable graft for dural defect repair.

To observe the safety and effectiveness of this synthetic biomimetic substitute as an onlay graft, the wettability, conformability, flexibility, and adhesive strength of the biomimetic substitute were characterized *in vitro*. Moreover, the biomimetic substitute was used as an onlay and suturable graft in a canine duraplasty model and was compared with two commercial products: CODMAN ETHISORB™ Dura Patch and DuraGen™ Dural Graft Matrix ™. CSF leakage, adhesion of graft to cerebral cortex, and microscopic investigation were observed at 30 and 90 days after implantation to evaluate the safety and effectiveness of this new absorbable biometric substitute as an onlay graft.

Materials and methods

Materials

The biomimetic substitute, a uniquely designed web of biocompatible PLLA fibers that can be gradually absorbed by the body, was provided by Medprin Biotech GmbH (Germany). An electrodynamic(EHD) jet printing procedure had been developed[23] in which dissolved PLLA was sprayed from specialized jets, as described previously.[21] Briefly, the PLLA fibers were deposited layer by layer in a fleece-like structure, and the fiber microstructure resembles that of the ECM of human dura mater.[22] Two controls were selected: DuraGen™ Dural Graft Matrix (Integra Life Sciences, Plainsboro, NJ, USA), an onlay graft composed of a collagen matrix derived from the bovine Achilles tendon; CODMAN ETHISORB™ Dura Patch (Codman & Shurtleff, Inc. Paramount, MA), a suturable graft which consists of polyglactin 910 (vicryl) and poly-p-dioxanone (PDS).

Characterization of the biomimetic substitute

Wettability & conformability testing

Biomimetic substitute samples were wetted first by submersion in saline. Pressure was applied with gloved fingers to ensure absorbance of saline (2–5 mins). Once transparent, the sample was removed from the saline and cut aseptically into appropriately sized and shaped sections. Samples of dry and wet biomimetic substitute were placed onto a brain model. Photographs were taken using a Panasonic DMC-LX5 camera (Japan), and the conformability of dry and wet biomimetic substitute was assessed.

Flexibility testing

Biomimetic substitute and DuraGen™ Dural Graft Matrix of 2.5 cm × 2.5 cm were cut and then wetted in saline for 2–5 min before testing. The two samples were placed on to an iron rod separately. Photographs were taken using a Panasonic DMC-LX5 camera (Japan). Observations were made to qualitatively assess the flexibility as indicated by the angle formed between a horizontal line and the tangent line of the biomimetic substitute ($n = 5$) and DuraGen™ Dural Graft Matrix ($n = 5$).

Adhesive strength testing

To evaluate the adhesive strength of biomaterials for selective leak closure, a cube-shaped Plexiglas chamber (length 20 cm, volume 8 l) was constructed[24] with one inlet on one of the side walls for air supply and another inlet for pressure measurement (Fig. 1A). A flange was integrated into the removable cover plate (Φ6 cm) upon which a membrane can be mounted and fixed in an airtight round frame, secured by thumbscrews. Rubber ring was then mounted on the flange and the round frame to ensure a tight closure (Fig. 1B).

Porcine dermal was used as the membrane material. Porcine dermal samples were drained of blood, rinsed with physiological saline, and processed as following immediately: samples of 2–3 mm thickness were cut to square shape (width: 9–12 cm) with scissors, then frozen at −81 °C for 48 h. Samples were thawed completely at room temperature before use, and then laid, without any tension, into the flange on the cover plate. The round frame was made airtight and a metal puncher was used to punch out a Φ1 cm defect at the center of the membrane (Fig. 1B).

The biosimulator was connected to a digital pressure gauge (PTB708 Liquid-gas pressure sensor, Guangzhou compass sensor instrument Co., Ltd, China) and a manual pressure generator (JC-702, Hercules). The experiments were carried out under normal conditions (room temperature, moderate air humidity). A 2.5 cm × 2.5 cm patch of biomimetic substitute ($n = 5$) and DuraGen™ Dural Graft Matrix ($n = 5$) was cut and then wetted in saline for 2–5 min before testing. After positioning of the patch on the standardized membrane defect (Φ1 cm), compression was applied for 1 min. Pressure was then applied in the

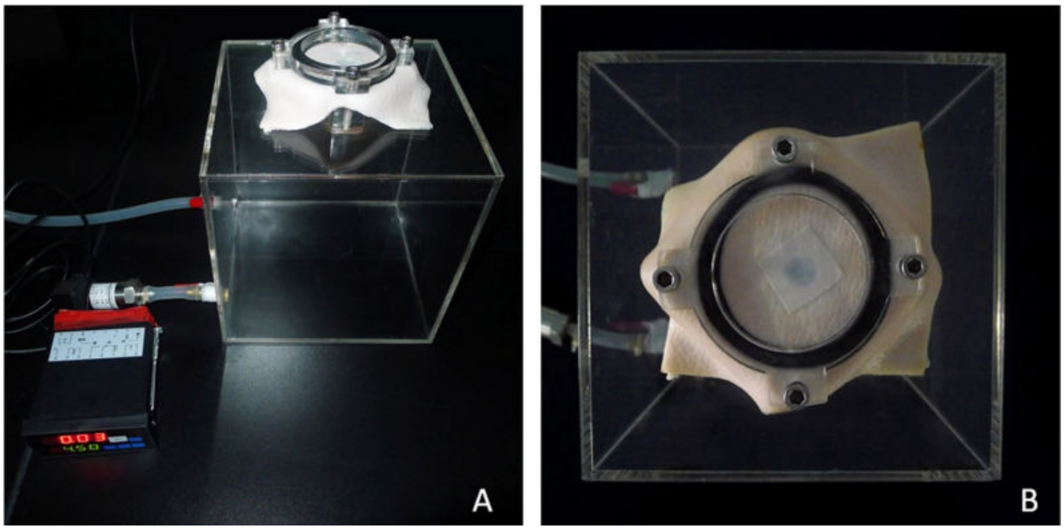

Figure 1 Simulation model used to test the adhesive strength of biomaterials

chamber, resulting deflection of the membrane. The pressure in the chamber drops when the graft being tested lifts off or is destroyed (Fig. 1B). The maximal pressure (Pa) reached in the chamber reflects the adhesive strength of biomimetic substitute or DuraGen™ Dural Graft Matrix.

Animal experiments

Animal selection

Adult Chinese domestic dogs were provided by Suibei Medical Animal Testing Center (Guangzhou, China).This study was designed in full compliance with Declaration of Helsinki and the policies and procedures set by Institutional Animal Care and Use Committee of the Tiantan Hospital of Capital Medical University (Beijing, China). The health and growth of the experimental dogs were monitored for at least two weeks before surgery. The animal housing room temperature and relative humidity were monitored daily and maintained at 18–28 °C and 30–70% humidity. The light cycle was controlled using an automatic timer (12 h light, 12 h dark). A total of 12 healthy adult dogs weighing 25–30 kg and within the age range of 1.5–2 years were randomly divided into two groups of six animals. Bilateral dural defects were created in all animals. In the suturable group, the biomimetic substitute and ETHISORB™ Dura Patch were sutured to the surrounding dura. In the sutureless group, the biomimetic substitute and DuraGen™ Dural Graft Matrix were implanted as an onlay graft on bilateral defects.

Surgical technique

All experimental animals were injected intravenously with 3% pentobarbital sodium (1 mL/kg) for general anesthesia after premedication with intramuscular injection of atropine. The hair of each dog was shaved, and the animal was placed on the operation table in a prone position. A midline incision was made through the skin from the level of the right and left orbits to the external occipital protuberance (inion). The temporalis muscles were subperiosteally elevated from the frontal and parietal bones and retracted bilaterally. A nitrogen-powered drill attached with an appropriate burr was used to create the starting holes for the craniotomy. A 1.7 mm × 12 mm side-cutting burr was used with a laminectomy burr guard (a burr with a protective tip) to create a rectangular defect in the bone, measuring approximately 3 cm × 2 cm. The defect was created just lateral to the sagittal suture and approximately 3 cm cranial to the apex of the inion. The portion of removed skull was immersed in sterile saline and saved for later closure. A durotomy was performed at the craniotomy by removing a section of approximately 1 cm × 1.5 cm of the exposed dura. The durotomy was centrally located within the craniotomy to retain a native dural border of approximately 3–4 mm. Similar to the orientation of the craniotomy, the durotomy was oriented in the rostral direction and parallel to the sagittal sinus.

To ensure conformability of the biomimetic substitute before implantation, the substitute was cut to size and hydrated in saline as previously described, ensuring the substitute can cover over 15–20 mm of the animal's remaining dura mater around the edge. In the suturable group, the sample was sutured in place using an appropriate non-absorbable suture in a simple continuous pattern (Fig. 2). In the sutureless group, the sample was implanted without suture as an onlay graft to cover dural defects (Fig. 2).The dural repair was observed for CSF leakage, handling and suturability of the samples were recorded. The cranial bone flap was placed back to its normal position and secured in place using bone plates and screws. The wound was then closed in layers using an appropriate suture in a simple continuous pattern. The skin was closed with an appropriate suture and/or stapled. This procedure was then repeated on the contralateral side with the defect treated with the same type of sample. In the case of intraoperative cortical edema, the

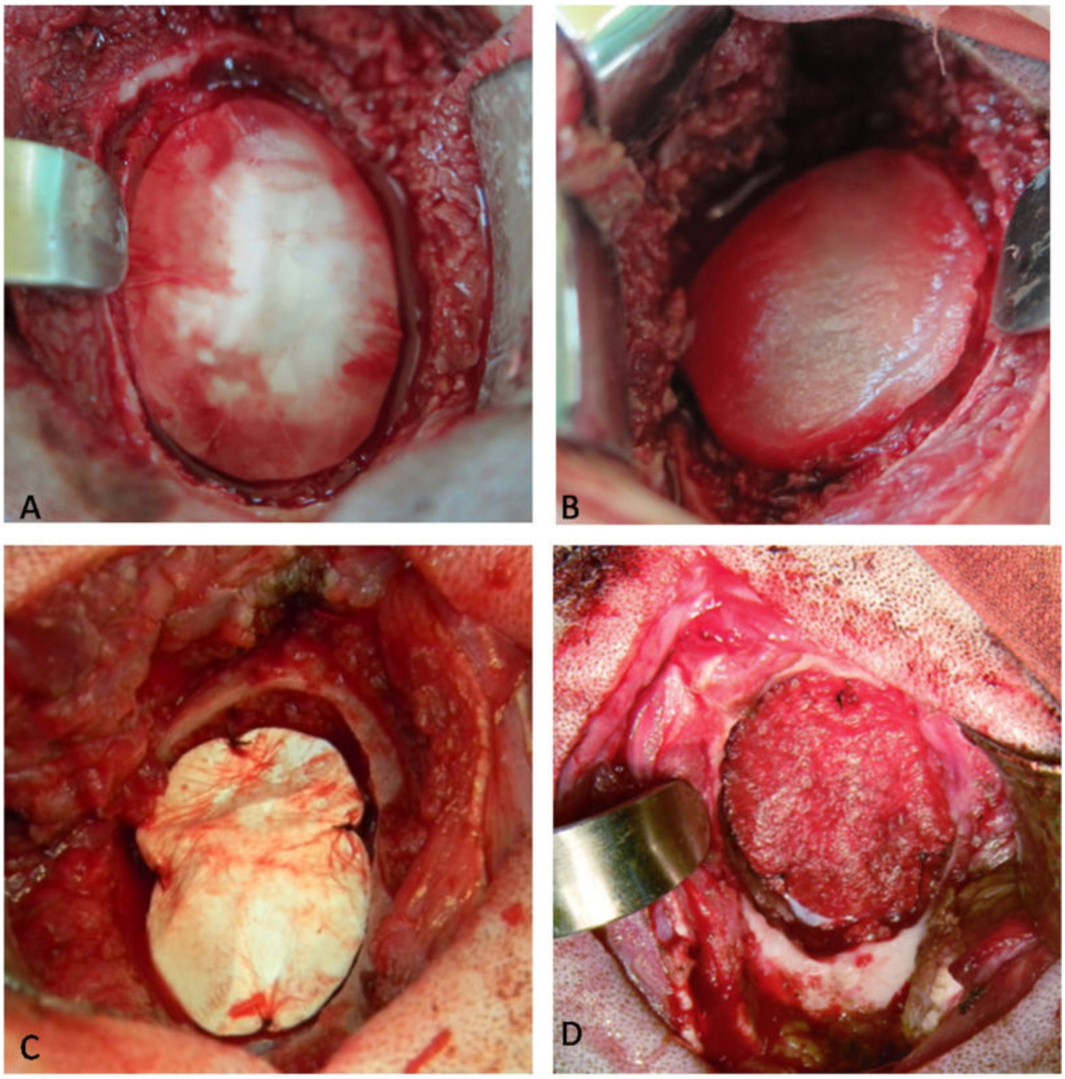

Figure 2 Canine duraplasty model (A: biomimetic substitute sutureless, B: Duragen™ Dural Graft Matrix sutureless, C: biomimetic substitute suturable, D: ETHISORB™ Dura Patch suturable)

veterinarian appropriately treated the condition following standard of care.

Postoperative observation

The animals were monitored daily and signs and symptoms of CSF leakage including rhinorrhea, otorrhea, head pressing, head tilting, photophobia, cranial vault swelling, excessive sub-dermal fluid collection at surgical site, dehiscence, focalized neurological symptoms (Focal Seizures), anorexia, and somnolence(drowsiness) were recorded. The surgical incisions were assessed for signs of infection, inflammation, and general integrity once daily for the first 14 days after surgery or until healed. After 30 and 90 days, three animals from each group were sacrificed and the implanted samples were retrieved separately. In brief, after the skull was surgically opened, macroscopic investigation recorded the presence of any seroma formation, CSF leakage, adhesion, and overall healing of the dural defect at the surgical site. The implants and surrounding tissues were collected, and fixed in 10% formalin solution for histological analyses using hematoxylin and eosin (H&E) staining.

Grading system

A quantitative grading system was used to score the tissue response to the implants, as previously described.[10,11,25] Macroscopic assessment of CSF leakage, adhesions to cerebral cortex, and inflammation of the graft were graded as following: 0 = none, 1 = minimal, 2 = moderate, and 3 = extensive. Integration of the grafts with surrounding tissue was graded from 0 = no integration, 1 = ingress of fibroblasts into the device, 2 = only parts of the graft remained detectable, to 3 = complete integration.

Statistical analysis

Statistical analysis was performed using SPSS version 17 (IBM Corporation, USA), and group data were compared using the independent sample *t*-test. Differences were considered to be significant at $p < 0.01$.

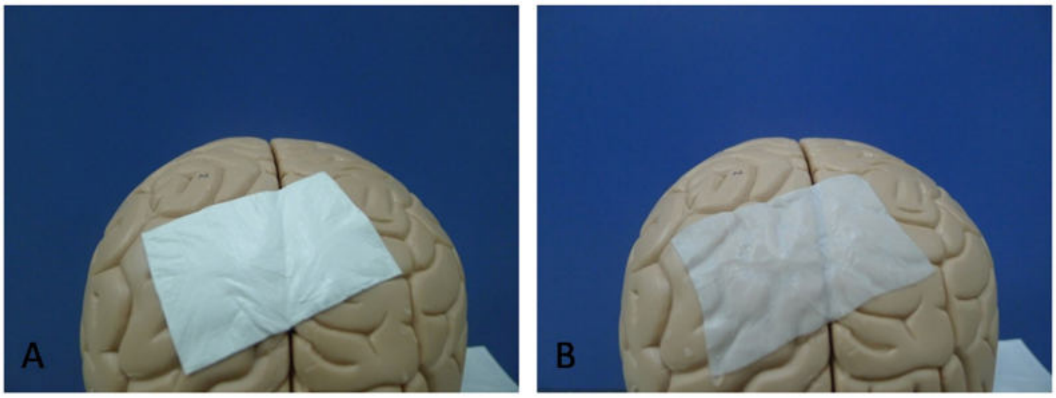

Figure 3 **Wettability of the biomimetic substitute. Biomimetic substitutes (4 cm × 6 cm) were tested on a brain model: A: Dry, B: Wet**

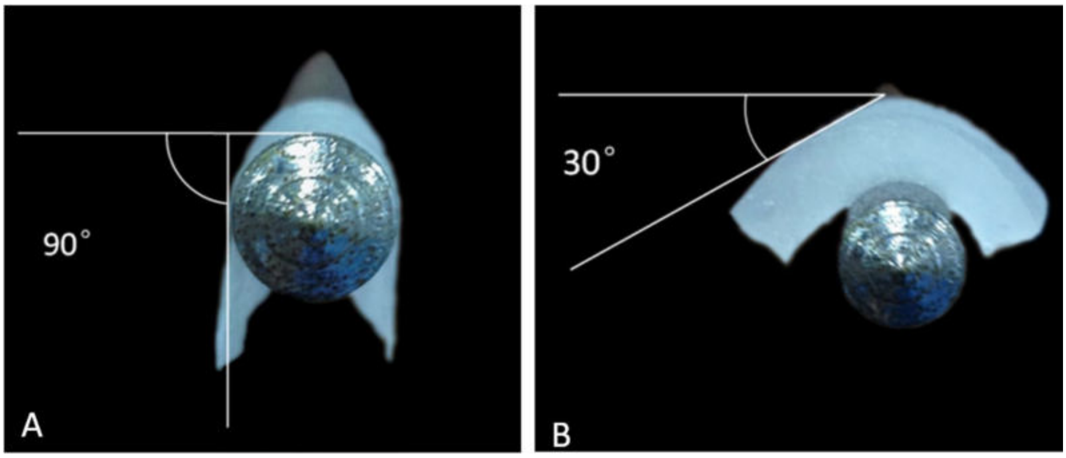

Figure 4 **Flexibility of the biomimetic substitute and Duragen™ Dural Graft Matrix on an iron rod. A: biomimetic substitute, B: Duragen™ Dural Graft Matrix**

Results

In vitro characterization of biomimetic dural substitute

Wettability & conformability testing

Under the dry condition, the biomimetic substitute was hydrophobic by nature and could not absorb water because of the hydrophobic PLLA component. However, when submerged in saline, in particular when manual pressure was applied for 2–5 mins, the substitute could absorb water, and become 'hydrophilic' and transparent. Under the wet condition, the substitute conformed and adhered to curved surfaces better (Fig. 3).

Flexibility testing

The flexibility of the biomimetic substitute was compared with that of DuraGen™ Dural Graft Matrix both in wet state on an iron rod (Fig. 4). The angle between the horizontal line and the tangent line of the biomimetic substitute and DuraGen™ Dural Graft Matrix were 87.4° ± 1.8° and 29.2° ± 2.4°, respectively. Qualitative bench testing demonstrated that the biomimetic substitute exhibited greater conformability and flexibility than the DuraGen™ Dural Graft Matrix.

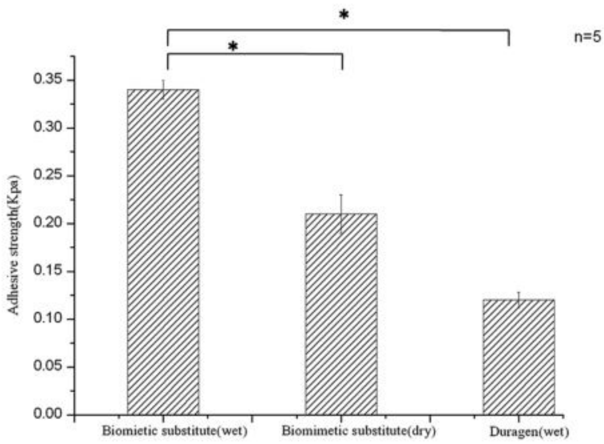

Figure 5 **The adhesive strength of wet biomimetic substitute was compared with that of dry biomimetic substitute and Duragen™ Dural Graft Matrix separately (*$p < 0.01$)**

Adhesive strength testing

The adhesive strength of the wet biomimetic substitute, dry biomimetic substitute, and DuraGen™ Dural Graft Matrix were 0.34 kPa ± 0.01 kPa, 0.21 kPa ± 0.02 kPa, 0.12 kPa ± 0.008 kPa, respectively. The adhesive strength

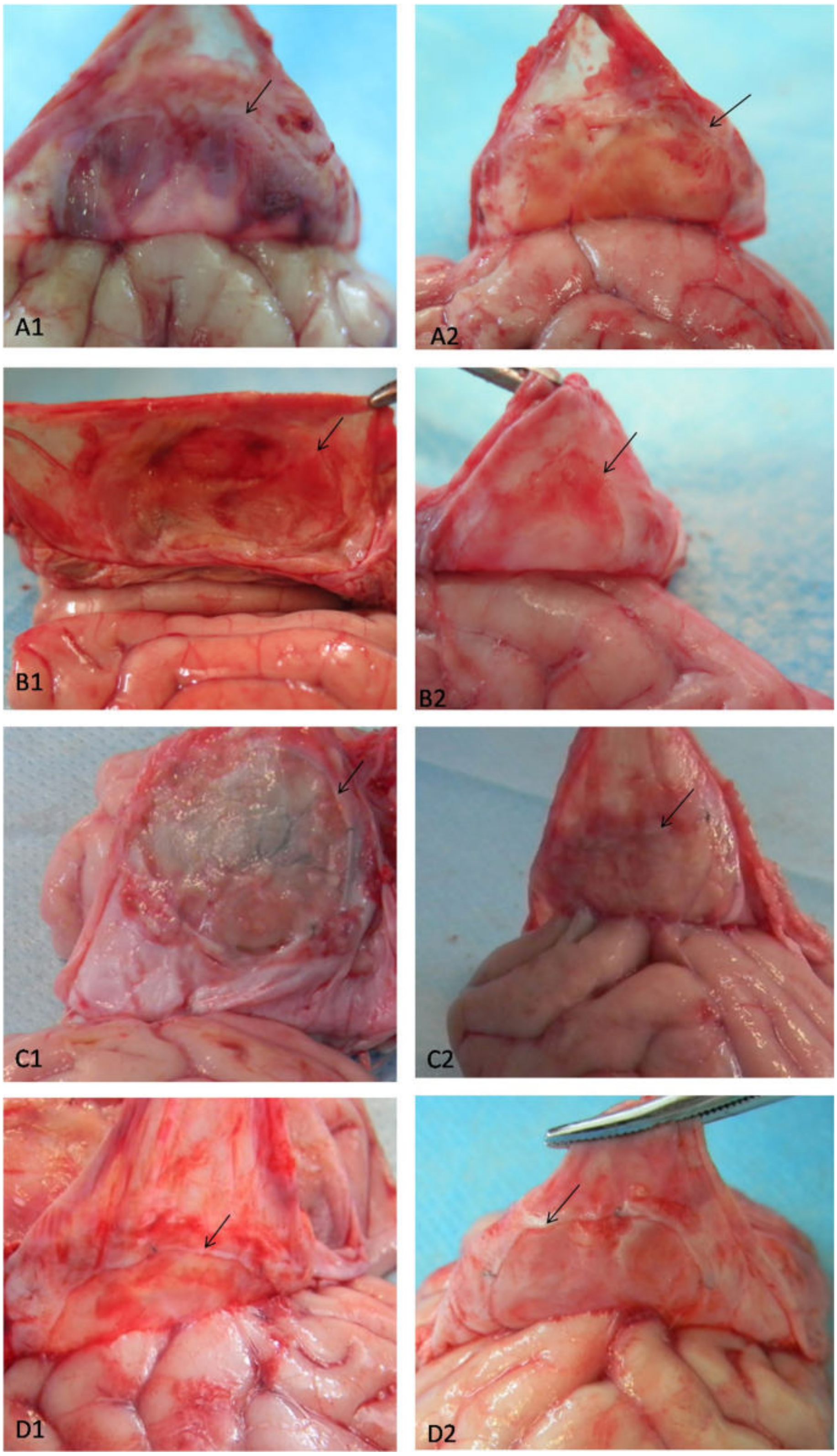

Figure 6 Macroscopic investigation of dural healing with dural substitutes at 30 and 90 days after implantation: Biomimetic substitute sutureless at 30 days (A1) and 90 days (A2), B: Duragen™ Dural Graft Matrix sutureless at 30 days (B1) and 90 days (B2), C: biomimetic substitute suturable at 30 days (C1) and 90 days (C2), D: ETHISORB™ Dura Patch suturable at 30 days (D1) and 90 days (D2)

of dry DuraGen™ Dural Graft Matrix was too weak to be tested. The adhesive strength of the wet biomimetic substitute was significantly greater than that of the dry biomimetic substitute (Fig. 5, $p < 0.01$). Moreover, the adhesive strength of wet biomimetic substitute was significantly higher than that of DuraGen™ Dural Graft Matrix (Fig. 5, $p < 0.01$). Higher adhesive strength may allow the dura to withstand higher intracranial pressure and prevent CSF leaks.

Animal study

We compared the feasibility of repairing dura mater with suturable and onlay surgical technique in a canine duraplasty model. Animals were assigned to two groups: in the suturable group, biomimetic substitute and ETHISORB™ Dura Patch were used as suturable grafts, and in the sutureless group, biomimetic substitute and DuraGen™ Dural Graft Matrix were implanted as onlay grafts.

Macroscopic investigation

Thirty or 90 days after implantation, all animals in the two groups had good recovery without complications or signs of discomfort or neurological impairment. There were no signs of infection or abnormality in the major organs and no graft failure or adverse brain tissue reaction in any of the 24 duraplasty sites. No visible fluid collection was observed under the scalp.

Thirty days after surgery, implanted grafts in both the suturable and sutureless groups exhibited good integration and ingrowth into the autologous dura. No pore or crack was observed around the dural defect edge, and the pinhole was filled with fibrous tissue in the suturable group (Fig. 6).The transition between the graft and autologous dura was noticeable, but the defect was completely closed without cerebrospinal fluid leakage. After the dura was peeled off and brain tissue was exposed, no cerebral hemorrhage or cerebral edema was observed. To determine whether the patch adhered to the brain tissues, the interfaces between the implant and the cerebral cortex were examined. Figure 6 and Table 1 indicate that in the suturable group (biomimetic patch and ETHISORB™ Dura Patch), most areas exhibited no adhesion with a clear and smooth surface between the graft and cerebral cortex, and only a few spots were observed, indicating mild adhesions. These adhesions could be easily separated by slightly detaching the implant from the brain tissue (Table 1). Besides, no adhesion between the graft and cerebral cortex was observed in the sutureless group (biomimetic substitute and DuraGen™ Dural Graft Matrix).

Ninety days after surgery, the edges between the graft and autologous dura merged well and could not be distinguished in either group. The newly formed connective dura-like tissue was soft and covered the dural surface. After the dura was peeled off and the brain tissue was exposed, no cerebral hemorrhage or cerebral edema was observed. Biomimetic substitute and DuraGen™ Dural Graft Matrix did not adhere to brain tissue, and ETHISORB™ Dura Patch exhibited a thin wispy adhesion to brain tissue.

Microscopic investigation

For histological analyses, the implants and the surrounding tissues were isolated and observed. Figure 7 and Table 1 show the results of histological evaluation using H&E staining of suturable and sutureless group at 30 and 90 days after implantation.

Thirty days after surgery, all the grafts were tightly wrapped by surrounding tissues and extensively infiltrated by fibroblasts. Neovascularization was observed, and new subdura presented and extended to the dural defect. In the biomimetic substitute and DuraGen™ Dural Graft Matrix group, abundant fibroblasts and capillaries had infiltrated. In the ETHISORB™ Dura Patch group, abundant fibroblasts were found, but a few capillaries were observed. Among which, lymphocytic infiltration and massive capillary proliferation were visible with local calcification and hemorrhage. The inflammatory reactions in both groups were determined to be mild and involved only a few lymphocytes and foreign-body giant cells. However, the inflammatory reactions of the suturable group were a little more severe than those observed in the sutureless group due to the presence of suture line (Table 1). Pia mater, cortical cells, and other tissues also exhibited no degeneration nor necrosis, and cerebral tissue edema and hemorrhage was not seen.

Ninety days after surgery, the wounds of both groups exhibited a reduced number of inflammatory cells, including macrophage and lymphocytes (Fig. 7 and Table 1). All three materials were tightly wrapped by the surrounding tissues and replaced with connective dura-like tissue, which was extensively infiltrated by fibroblasts, and exhibited massive neovascularization (Table 1). The biomimetic substitute materials were separated into several fragments and approximately 30–40% of the residual materials were retained. The ETHISORB™ Dura Patch and DuraGen™ Dural Graft Matrix were almost completely fragmented. The inflammatory reactions observed in the three groups were similar and determined to be mild, involving only a few lymphocytes and foreign giant cells (Table 1).

Table 1 Summary of grades stratified by macroscopic and histological findings at 30 and 90 days after surgery

	Sutureless group				Suturable group			
	Biomimetic substitute		DuraGen™ *Dural Graft Matrix*		Biomimetic substitute		ETHISORB™ Dura Patch	
	30 days	90 days	30 days	90 days	30 days	90 days	30 days	90 days
CSF leakage	0	0	0	0	0	0	0	0
Adhesion of graft to cerebral cortex	0.2	0.3	0.1	0.2	0.3	0.4	0.4	0.4
Inflammation	1.5	0.8	0.7	0.3	1.8[†]	1.0	1.6	0.5
Integration of the device	1.0	2.0	0.8	2.8	1.0	2.0	0.8	2.7

[†]Suture material increases inflammation.

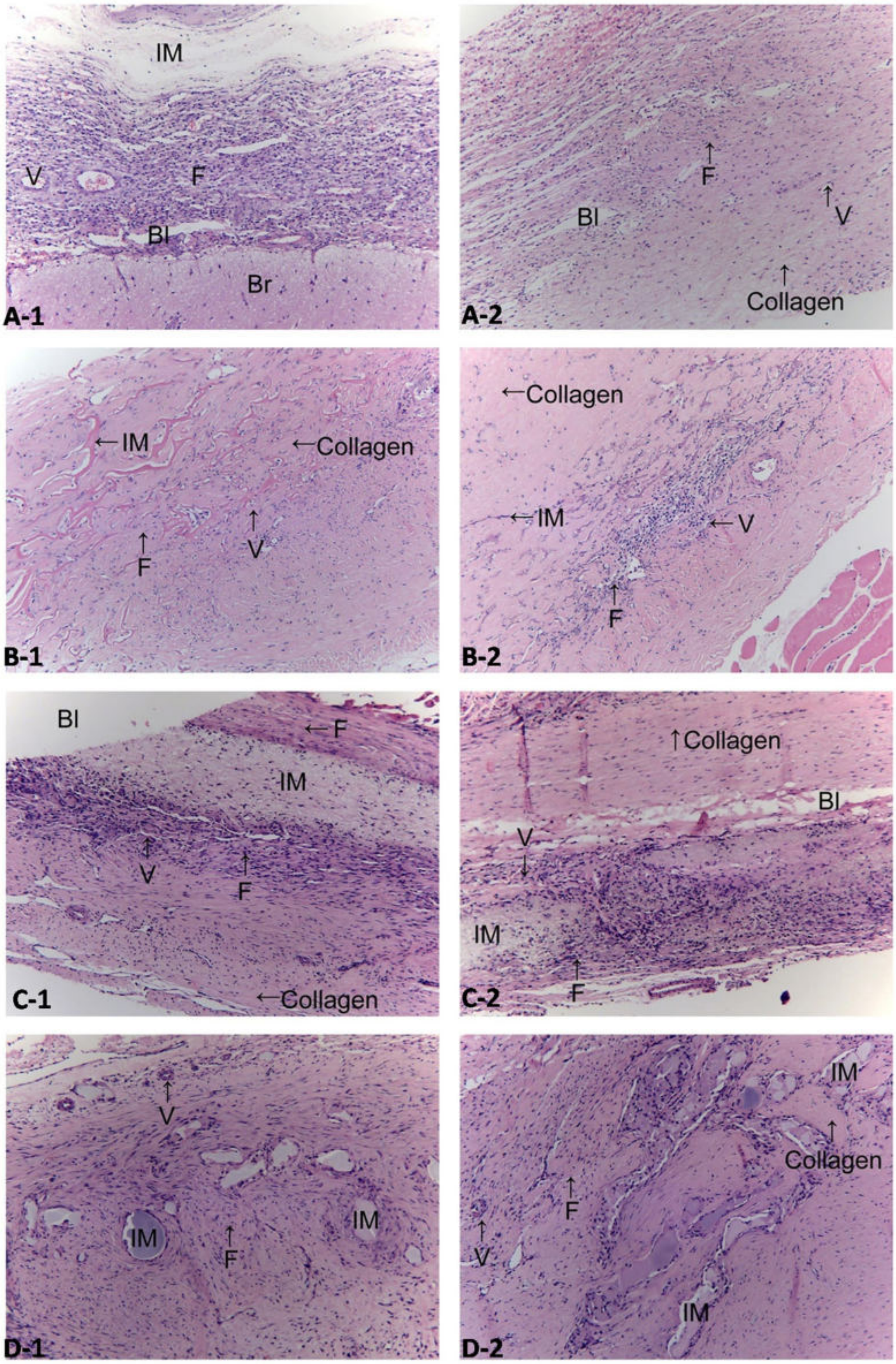

Figure 7 HE staining of the implants at 30 and 90 days after implantation: Biomimetic substitute sutureless at 30 days (A1) and 90 days (A2), B: Duragen™ Dural Graft Matrix sutureless at 30 days (B1) and 90 days (B2), C: biomimetic substitute suturable at 30 days (C1) and 90 days (C2), D: ETHISORB™ Dura Patch suturable at 30 days (D1) and 90 days (D2) (Magnification:×100; IM:implant material; F: fibrocyte; V: vessel; Bl: blank; Br: brain tissue)

Discussion

Sutureless dural repair grafts appear promising because they have several advantages over traditional techniques. For example, sutureless dural repair grafts do not require labor-intensive suturing, reduce surgery time, facilitate application of small patches in surgically difficult-to-reach locations, overcome difficulties related to the presence of fragile or ossified dura mater, and do not cause major reaction of the surrounding tissue.[13,15,26] These advantages are fundamental to the transsphenoidal approach, which has a narrow surgical field [12] and surgeons can only use sutureless dural grafts. Some studies have recently reported that operating time can be reduced with the use of onlay collagen matrix instead of suturable acellular human dermal grafts.[13,27]

In this study, the biomimetic substitute was hydrophobic; when it is pressed in saline, however, the substitute became hydrophilic, transparent, conformed, and adhered to curved surfaces. These features can be attributed to the microstructure of the biomimetic substitute, which is composed of thousands of pores between the microfibers. When the biomimetic substitute was pressed in saline, the 'capillary effect' caused retention of water in the biomimetic substitute. This is a new method for leading the hydrophobic material to absorb water. Furthermore, another possible explanation is that microfibers in the biomimetic substitute have large surface areas to interact with the dura mater, like tentacles, creating an excellent absorption capacity. The adhesive strength of this biomimetic substitute was also higher than that of DuraGen™ Dural Graft Matrix. The conformability, flexibility, and adhesive ability likely support the onlay implantation.

When the biomimetic substitute was implanted in a canine duraplasty model, no significant differences between the sutureless group and suturable group were observed at both the macroscopic and microscopic levels. The biomimetic substitute indicated functionality of the onlay implantation method, good integration with dura mater, no CSF leakage, little to no adhesion, mild inflammation, and no adverse effects to the underlying brain tissue at 30 and 90 days after implantation. To our knowledge, this is the first study to demonstrate that the absorbable synthetic dural substitute can be used as both onlay and stuture grafts for surgical repair of dura mater defects.

Conclusion

In this study, the newly developed biomimetic dura substitute exhibited good wettability and conformability, and was implanted as an onlay graft to prevent CSF leakage in a canine duraplasty model. This new absorbable synthetic dural substitute with biomimetic design shows great potential in supporting both onlay and sutured implantation, which will provide more choices for doctors during neurosurgeries.

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