New Dried Human Amniotic Membrane Is Useful as a Substitute for Dural Repair after Skull Base Surgery

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J Neurol Surg B 2012;73:302–307.

Abstract

Keywords

- ▶ amniotic membrane
- ▶ cerebrospinal fluid (CSF) leakage
- ▶ dural repair
- ▶ dural substitute
- ▶ skull base surgery

Objectives Cerebrospinal fluid (CSF) leakage is an undesirable complication of skull base surgery. We used dried human amniotic membrane (AM) as a patch graft for dural repair to determine its efficacy in preventing CSF leakage.

Design Frontoparietal craniotomy and removal of dura were performed in 20 Wistar rats. A dried AM was placed to cover the dural defect without suturing in 16 animals. In four animals, an expanded polytetrafluoroethylene was implanted. At 2 weeks and 1, 3, and 6 months, histological examination was performed. Dried AM was also used as a substitute in 10 patients who underwent skull base surgery, after approval by the Ethics Committee of the University of Toyama.

Results At 2 weeks after implantation, thick connective tissue completely enclosed the dried AM. At 1 month after implantation, the connective tissue became thin and the implanted AM shortened. At 3 and 6 months after implantation, histological examination revealed disappearance of the dried AM and formation of membranous tissue. In the clinical study, neither CSF leakage nor clinical adverse reactions directly related to the dried AM were observed.

Conclusion Dried human AM appears to be an ideal substitute for dura, since it is replaced by natural tissue.

Introduction

Although primary dural closure with sutures is the preferred method of preventing cerebrospinal fluid (CSF) leakage, tissue loss or injury sometimes makes this procedure impossible. When primary closure of the native dura is not feasible, neurosurgeons must select one of several types of biomaterials as a patch graft for dural repair, including allografts, xenografts, and synthetic materials. Autologous tissues such as fascia lata, pericranium, and temporal fascia have the

obvious advantage of no risk of transmission of infectious diseases¹ but may require an additional incision. Lyophilized cadaveric human dura mater has never been used as an alternative to autologous tissue for dural repair, since it has been implicated in the transmission of prion diseases such as Creutzfeldt-Jakob disease.^{2,3} Most synthetic materials have been rejected due to excessive local tissue reaction, which can result in irritation of the underlying brain, excessive scar formation or encapsulation of the graft, meningitis, and hemorrhage.^{4–6}

received

January 12, 2011

accepted after revision

April 25, 2011

published online

July 30, 2012

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1321506>.
ISSN 2193-6331.

We recently developed a novel dried human amniotic membrane (AM, hyperdry amnion) that is processed using far-infrared and microwave irradiation and then sterilized by gamma-ray irradiation.⁷ We have already begun to apply it to ophthalmic treatment such as patch grafting on the ocular surface in patients with corneal perforation and glaucoma filtering bleb leaks.⁸

In this study, we used dried human AM as an alternative to autologous tissue for dural repair. We employed a rat model to examine whether dried AM can be used for dural repair by assessing histological changes in the implanted dried AM and surrounding tissue over time. Additionally, the dried AM was used for dural repair after skull base surgery to determine its efficacy in preventing CSF leakage. This is the first report of clinical application of amniotic membrane as an intracranial substitute for dura.

Material and Methods

Preparation of Dried Human Amniotic Membrane

Preparation of dried AM was as follows: fresh human AM was obtained with the informed consent from donors who had seronegative results for syphilis, human immunodeficiency virus, human T-cell lymphoma virus type-1 (HTLV-1), and hepatitis B and C viruses after caesarian sections performed in Toyama University Hospital. The AM was washed with sterile phosphate-buffered saline. The amniotic epithelial cell layer was not removed. The AMs were dried consecutively under low-air-pressure conditions, far-infrared, and microwave irradiation at temperatures of less than 60°C using a hyperdry device (Sakura, Nagano, Japan). Thereafter, the AM was cut into 10-cm squares and vacuum packaged. For sterilization, the packages were subjected to gamma-ray (25-kGy) irradiation (► Fig. 1).

Evaluation of Efficacy of Dried Human AM as Substitute for Dura

Twenty adult male Wistar rats 14 weeks of age were studied after anesthesia had been induced by intraperitoneal administration of sodium pentobarbital. In addition, local anesthesia was maintained by infiltration of 1% lidocaine solution. Following a midline sagittal incision, a right frontoparietal craniotomy was performed using a surgical microscope and a

microdrill. A 5 × 7 mm square piece of dura mater was carefully excised so as not to injure the underlying cortex. An appropriate size of dried human AM was placed on the cortex covering the dural defect sufficiently without suturing in 16 animals (Dried AM group). In four animals, an expanded polytetrafluoroethylene (PTFE) was implanted as a substitute for dura in the same fashion (Control group). A piece of bone wax was placed as bone substitute and the skin was sutured with 2-0 silk.

At 2 weeks (four animals in the Dried AM group), 1 month (four animals in the Control and four animals in the Dried AM group), 3 months (four animals in the Dried AM group), and 6 months (four animals in the Dried AM group) after implantation, immediate perfusion fixation were performed in 4% formalin solution after deep anesthesia had been induced by intraperitoneal administration of an overdose of sodium pentobarbital. The bone margin of the craniotomy, the dural graft zone, and the subjacent brain were removed en bloc for histological examination. The tissues were decalcified with formic acid and stained with hematoxylin-eosin and azan after sectioning in thin layers. The care and use of experimental animals was in accordance with institutional guideline.

Clinical Studies

Between December 2008 and May 2010, dried human AM was used as a substitute for dura in 10 patients who underwent skull base surgery at the Department of Neurosurgery, University of Toyama, Toyama, Japan. Background patient data are summarized in ►Table 1. All surgical procedures were performed after patients had been informed of the risks and alternative treatments, and each patient gave informed consent. This study was approved by the Ethics Committee of the University of Toyama.

Dried AM was cut to appropriate size and shape to fit the dural defect at the skull base. Several pieces of dried AM were placed in the dural defect (underlay technique) to cover the inner surface of the dura. An overlay patch was then placed over the dural defect (overlay technique). Fibrin glue was used to stick the dried AM to that placed in the dural defect and the native dura mater. After packing the dead space with autologous fat grafts, vascularized fascial or pericranial flaps, and fibrin glue, the craniotomy bone flaps were fixed in position with titanium plates.

Figure 1 Macrographic (A) and histologic (B) appearance of the dried amniotic membrane (hematoxylin and eosin).

Table 1 Clinical Characteristics of Ten Patients Treated with Dried Human Amniotic Membrane

	Age/Sex	Pathology	Approach	Follow-Up (Month)	Cerebrospinal Fluid Leakage
1	70/F	Chondrosarcoma	Anterior transpetrosal approach	19	None
2	38/M	Meningioma	Orbitozygomatic approach	16	None
3	5/M	Chordoma	Anterior transpetrosal approach	6	None
4	54/M	Chondrosarcoma	Anterior transpetrosal approach	6	None
5	71/F	Cavernoma	Lateral suboccipital approach	5	None
6	59/M	Meningioma	Orbitozygomatic approach	5	None
7	46/F	Meningioma	Anterior transpetrosal approach	4	None
8	70/F	Craniopharyngioma	Orbitozygomatic approach	3	None
9	67/M	Meningioma	Orbitozygomatic approach	2	None
10	69/F	Meningioma	Frontobasal approach	2	None

Results

Experimental Studies

No infection or CSF leakage was observed in any rats during the follow-up period. At 2 weeks after implantation of dried AM, thick connective tissue, which extended from the native dura mater and the periosteum, completely enclosed the dried AM without adhesion between the implant and cortex. Several inflammatory cells were noted in the connective tissue (►Fig. 2A). At 1 month after implantation, the connective tissue became thin. A few inflammatory cells were noted in the connective tissue (►Fig. 2B). The implanted AM shortened (►Fig. 2B, arrowheads). In the animal with PTFE implanted, growth of connective tissue was sparse, and cyst formation beneath thin connective tissue expanding from the

pericranium was observed (►Fig. 2C). The PTFE had not fused with surrounding native tissue. At 3 and 6 months after implantation, histological examination revealed disappearance of the dried AM and formation of membranous tissue in the Dried AM group (►Fig. 2D).

Clinical Studies

Postoperatively, subcutaneous collection of CSF was observed in one patient (Case 2), but the fluid disappeared spontaneously. One patient experienced a wound infection and subcutaneous abscess at 1 month after surgery (Case 4). The abscess was surgically removed, and intraoperative examination showed that the abscess was remote from the site of dural defect anterior to the petrous apex where dried AM had been implanted.

Figure 2 Histologic appearance. (A) Two weeks after implantation of dried amniotic membrane. Note that thick connective tissue, which extended from the native dura mater and the periosteum, completely enclosed the dried amniotic membrane (arrowheads) without adhesion between the implant and cortex. (B) At 1 month after implantation of dried amniotic membrane. Note that the connective tissue became thin, and the implanted amniotic membrane shortened (arrowheads). (C) At 1 month after implantation of expanded polytetrafluoroethylene (PTFE). Note that the PTFE (arrow) had not fused with surrounding native tissue. (D) At 6 months after implantation of dried amniotic membrane. Note that the amniotic membrane is not observed.

Figure 3 Preoperative (A) and postoperative (B) T2-weighted magnetic resonance images in Case 1. Note that the tumor is mainly located in the middle cranial fossa, and extends into the posterior cranial fossa with compression of the brainstem.

The mean follow-up period after use of dried human AM was 6.8 months (range, 2 to 19 months). No CSF leakage requiring surgical repair was observed during the follow-up period. No clinical adverse reactions directly related to the dried AM were observed.

Case Presentation (Case 1)

A 70-year-old woman with left oculomotor paresis was referred to our department for removal of a tumor in the left middle cranial fossa (►Fig. 3A). The tumor extended into the posterior cranial fossa and compressed the brainstem. She

underwent tumor removal by the extradural subtemporal and anterior transpetrosal approach. The tumor penetrated the dura and extended into the intradural space of the posterior cranial fossa. After removal of the tumor (►Fig. 4A), dried AM cut to appropriate size and shape to fit the dural defect at the skull base was implanted. A piece of the dried AM was placed in the dural defect, and then the overlay patch was placed over the dural defect (►Fig. 4B). Fibrin glue was used to stick the dried AM to the native dura mater (►Fig. 4C). After packing the dead space with autologous fat grafts and fibrin glue (►Fig. 4D), the craniotomy bone flaps were fixed in position with titanium plates. The

Figure 4 Intraoperative photographs in Case 1. (A) Dural defect of the posterior cranial fossa after removal of the tumor. (B) Implantation of dried human amniotic membrane (arrow). (C) Sealing with fibrin glue. (D) Packing the dead space with autologous fat grafts.

postoperative course was uneventful. Her oculomotor paresis remained unchanged postoperatively. No CSF leakage was observed during a 19-month period after surgery.

Discussion

The ideal dural substitute should be immunologically inert, nontoxic, and unable to spread infectious disease.^{9–11} It should unite with the native dura but not adhere to the brain. It should be degradable and replaced by natural tissue while providing a sufficient patch until then.¹²

Sheets of PTFE have been used as an alternative material for dural repair.¹³ PTFE does not unite with the surrounding natural tissue and thus requires watertight suturing. Since PTFE is a nonabsorbable synthetic material, it may cause a chronic foreign body reaction. Recently, a bioabsorbable artificial dura mater has been developed and used clinically.^{14,15}

Collagen sponge has been reported to be a favorable dural substitute in both experimental and clinical settings.^{10,16} The collagen matrix is immediately hemostatic, initiating clot formation that results in a chemical seal, and then provides a chemical signal for fibroblast infiltration, which commences after 3 to 4 days and becomes established over the next 10 to 14 days. The fibroblasts use the pores in collagen matrix as a scaffold to lay down new collagen. Over 6 to 8 weeks, the collagen matrix is resorbed as the new dura is constituted. It also forms a separate layer between the brain and the overlying tissues to minimize adhesion formation.

The collagen matrix is used with an overlay or underlay technique that does not require additional fixation if the overlap between graft and dura is sufficient.^{11,12,17,18} Sutureless dural repair reduces the time required for surgery and facilitates application of small patches in anatomically difficult locations.

AM is a tissue of fetal origin and is composed of three major layers: a single epithelial layer, a thick basement membrane, and an avascular mesenchyme.⁷ AM has been considered suitable for allotransplantation, based on its anti-inflammatory effects and low immunogenicity.^{19–28} There was no evidence of tumorigenicity in humans when isolated amniotic cells were transplanted into human volunteers to examine immunogenicity or into patients in an attempt to correct lysosomal storage diseases.^{20,29,30} Because the AM is discarded after parturition, it is easy to obtain without harming mothers or infants, as long as approval of the local institutional Ethics Committee and written informed consent from mothers has been obtained. Cryopreserved human AM is currently being used for a wide spectrum of ocular surface disorders.³¹ AM reportedly suppresses inflammation and neovascularization, inhibits scarring, and promotes re-epithelialization on the ocular surface. AM is used not only as a substitute but also as a scaffold upon which cells can migrate and regenerate, forming new and healthy tissue.⁷

We recently developed a novel dried human AM that is processed under low-air-pressure conditions using far-infrared and microwave irradiation and is then sterilized by gamma-ray irradiation.⁷ Gibbs et al reported the difficulties

in destroying the infective particles known as prions by gamma-ray irradiation.³² For rejection of Creutzfeldt-Jakob disease, donors were checked by medical staff's interview of medical examination. Those items of sentence were selected and modified from that of diagnosis by asking questions of the blood donation, which had been authorized by the Ministry of Health and Welfare of Japan. Our dried AM possesses several advantages: it can be preserved in a dry state at room temperature, and can easily be cut to desired size and shape with scissors just before application.⁸

In this experimental study involving the repair of dural defects in rats with dried human AM, connective tissue extended from the surrounding tissue of the dried AM and enclosed it by 2 weeks after implantation. The dried AM subsequently shortened and was absorbed within 6 months, and a membranous structure reformed.

Postoperative CSF leakage is an undesirable complication of neurosurgical procedures. It occurs relatively frequently after skull base surgery, since complete watertight closure of the basal dura mater is not always possible and a graft is often required to secure complete closure. Depending on the surgical approach, the rate of CSF leakage reported in the literature ranges between 5% and 20%.^{33–37} Musculo-fascial or vascularized pericranial flaps are of great importance for sealing the dead space left by removal of lesions.^{38–40} Packing the dead space with autologous fat grafts, muscle, fascia lata, or fibrin glue is also a very important technical adjunct that decreases the likelihood of CSF leakage and enhances healing of the postoperative dural defect.

In this study, dried AM was applied using both the underlay and overlay techniques. Because the dried AM could be cut easily to the desired size and shape with scissors, we could always design the pieces of dried AM to fit complex and deep-seated dural defects at the skull base and place them in the dural defects (underlay technique). Dried AM was then placed with fibrin glue over the defect (overlay technique). When dried AM absorbs water, it returns to a layered structure similar to that of fresh AM. The strength of the membrane and its water resistance are thus guaranteed. In our series, no CSF leakage requiring surgical repair was observed following the use of dried AM in skull base procedures. No clinical adverse reactions directly related to the dried AM were observed.

One limitation of this study was the small number of patients who underwent dural repair after skull base surgery using the dried human AM. In addition, appropriate indications for use of AM are lacking, as is scientific evidence from randomized comparative studies demonstrating that its use is better than that of other alternatives.

Conclusion

We successfully repaired dural defects and prevented CSF leakage after skull base surgery using dried human AM as a substitute for dura. This sutureless dural repair with dried AM and tissue adhesive is an alternative method of repair of dural defects after skull base surgery.

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