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Current developments in dural repair: a focused review on new methods and materials

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1. ABSTRACT

The dura mater, the outermost layer of the meninges covering the brain and spinal cord, is a collagenous connective tissue consisting of numerous collagen fibers, fibroblasts, and few elastic fibers arranged in a parallel form. The dura mater may be damaged by trauma or excising during intracranial or spinal surgery., To date, cerebrospinal fluid leakage followed by dura damage is still an intractable complication due to its various secondary complications , dural repair has recently garnered increased attention with the progress of the spinal surgery and neurosurgery. In this review, we discuss commonly used methods including the addition of sealants, the use of substitutes, and other effective methods and materials.

2. INTRODUCTION

The dura mater is the toughest and outermost layer of the three meninges that surrounds the brain and spinal cord and covers and supports the dural sinuses and carries blood from the brain toward the heart (1). However, the dura mater can be damaged by trauma or excising during intracranial or spinal surgery. As cerebrospinal fluid (CSF) is an integral part of the central nervous system (CNS), effective CSF containment following dural closure is imperative to prevent CSF leakage and facilitate dura regeneration (2, 3). Thus, advances in surgical techniques and dura repair materials are critical to improve the duration and functionality of artificial dura mater repairs. Although the grading system used to evaluate dural healing

Table 1. Grading system for histopathological evaluation of extent of healing

	0	1	2	3	4
Epithelialization	None to very minimal	Minimal to moderate	Completely epithelialized; thin layer	Completely epithelialized; thick layer	Thick epithelium
Cellular content	None to very minimal	Predominantly inflammatory cell; few fibroblasts	More fibroblasts with inflammatory cells	Predominatly fibroblasts	Several fibroblasts in dermis
Granulation tissue	None to sparse amount at wound edges	Thicker amount at wound edges; None to thin layer at wound center	Thicker amount at wound edges; thick at wound center in various degrees	Uniformly thick at wound center	Uniformly thick at wound center
Collagen deposition	None	Few collagen fibers	Few to moderate collagen fiber	Moderate to extensive collagen deposited	Dense, organized , oriented collagen fibers
Vascularity	None	Few capillaries	Few to moderate capillaries	Moderate to extensive neovascularization	Few well-defined capillary systems

can be modified from the criteria set forth by Lasa *et al.* (4) (Table 1) and considerable dura repair materials and methods have been applied to the clinical ,the optimal choice of materials for use in dura repair procedures still remains unclear. In this review, we predominantly focus on the characteristics of the most commonly used and recently developed methods and materials for dural repair with a focus on the addition of sealants, the use of substitute materials, and under-used methods.

3. SEALANTS

CSF leakage is one of the intractable complications of neurosurgery and spinal surgery because the dura has no inherent self-sealing capacity. Possible sequelae of CSF leaks include bacterial meningitis delayed wound healing, airway obstruction, cutaneous CSF fistula, and pseudomeningocele.. Direct repair is certainly optimal management in most cases of dural tear with a resultant CSF leak however, exposure is often inadequate to facilitate direct repair. Moreover, the pinhole-sized tears from suture needles that allow CSF to leak through the dura. The potential risk of using primary suture closure for small incidental dural tears is conversion of a low-pressure defect to highpressure pinholes from suture needles (5). Given these reasons, the addition of chemical sealant has been proposed as a mechanism to overcome the problem of CSF leak from the suture holes .

3.1. The DuraSeal Sealant System

Tissue glues provide a final sealant layer and aid in the reinforcement of CSF leak repair (6). The DuraSeal Sealant System is a dural sealant product containing polyethylene glycol hydrogel and indicated for use in CSF leak repairs (7). As approved by the Federal Drug Administration (FDA), DuraSeal is applied to freshly closed dura to hold it closed for 4—8 weeks while healing occurs. Leng *et al.* (8) described a "gasket technique" employing DuraSeal to the fascia to close defects of the skull base with or without a CSF leak. By analyzing a database of endoscopic skull-base cases between 2007 and 2009 that involved CSF leaks repaired with DuraSeal, Chin *et al.* (9) reported successful endoscopic repairs of CSF leaks in four of five cases. Another study also demonstrated that patients undergoing spinal surgery using DuraSeal, when compared to suturing with or without fibrin sealant, showed a decrease in the absolute risk of CSF fistula with no increased risk of complications (10). However, the use of DuraSeal in lumbar spine surgery has shown varied results. For example, in 37 of 86 patients, the use of DuraSeal decreased the frequency of postoperative radiculitis from 20.4% to 5.4% and there were no ''compressive'' complications reported (11). In another lumbar study involving laminotomy/discectomy with durotomy, DuraSeal-induced migration and/or swelling, not its use in an enclosed space, led to a case of postoperative cauda equina syndrome (12). A similar study by Osbun *et al.* (13) analyzed the use of DuraSeal in head surgeries and reported that compared to suturing with or without fibrin sealant, patients undergoing head surgery using DuraSeal showed no reduction in the absolute risk of neurosurgical or incisional complications, including CSF leakage.

3.2. BioGlue Surgical Adhesive

BioGlue is an organic surgical adhesive indicated for use as an adjunct to standard materials, such as sutures and staples, to achieve hemostasis in adult patients in open surgical repair of large vessels. It is composed primarily of bovine serum albumin and glutaraldehyde and is commonly used in vascular and cardiopulmonary repair surgery, but has also been recently used in neurosurgical procedures, in which the risk of a CSF leak is high (14). In several neurosurgical studies, BioGlue was successfully used as a dural sealant to prevent postoperative CSF fistulas (15). Yuen *et al.* (16) reported that BioGlue was a useful adjunct for repair of a lumbar dural tear. Despite persisting fragments after 2 years, no complications of the Bioglue itself were noted (16). In a study using BioGlue for 32 transsphenoidal procedures, postoperative CSF fistulas were avoided, again without complications (14).

3.3. EVICEL

As a fibrin glue, FDA-approved EVICEL is approved by FDA and known to facilitate hemostasis in surgery when standard methods of controlling hemorrhage are not effective (17). EVICEL is a plasma cryoprecipitate-based sealant that consists of 2 components: (1) biological active component-2, also called human clottable protein, which consists predominantly of fibrinogen and (2) thrombin (18). In one study involving the application of EVICEL to peripheral nerve tissues, Bivalacqua *et al.*

concluded that EVICEL is safe in an experimental rat model of erection physiology, with no detrimental effects on neuroregulatory control of erection (17). Another study in the mongrel dog durotomy model also showed that EVICEL was safe and effective in achieving and maintaining a watertight seal of the dura (19). However, no large clinical studies that document the safety/efficacy of EVICEL in neurosurgery.

3.4. Tisseel

Tisseel, a human fibrin sealant, is another pooled human plasma-based fibrin glue consisting of a two-component fibrin biomatrix that offers highly concentrated human fibrinogen and thrombin to seal tissues and stop diffuse bleeding. Among the benefits of Tisseel are its adhesiveness, hemostatic action, and promotion of wound healing (20). Although not FDA-approved for use in neurosurgery, Tisseel is widely adopted in "off-label" uses. For example, Sekhar *et al.* (21) demonstrated that Tisseel was an excellent option for hemostasis in the epidural space (200 patients), anterior cavernous sinus (46 patients), and vertebral venous plexus (20 patients). The safety/efficacy of Tisseel for anterior cervical dural repair is also documented by two clinical studies: in the first (22), 30 pairs of matched patients (experimental vs. controls) undergoing anterior cervical fusions involving more than two levels, the application of Tisseel at the end of multilevel anterior cervical fusion significantly decreased postoperative drain output and length of hospitalization, whereas in the second, Epstein *et al.* (23) showed that of 82 patients undergoing multilevel anterior corpectomy for multilevel ossification of the posterior longitudinal ligament/kyphosis, five developed intraoperative dural lacerations that were successfully managed with a complex dural repair involving wound-peritoneal and lumboperitoneal shunting procedures.

3.5. TissuePatchDural (TPD)

TPD is a synthetic sealing film that is mainly used to repair pleural defects during lung surgery and has been introduced in neurosurgery for the management of dural defects to avoid postoperative CSF leaks (24). As a synthetic film made up of a multilaminated structure of glycolic acid, TPD works as a sealant because of two intrinsic characteristics: adhesiveness and impermeability. Della *et al.* (25) first used this sealant to treat 12 patients with a high risk of developing postoperative CSF leakage and reported no evidence of CSF leakage or specific adverse events attributed to the sealant. The use of TPD has reduced repair time and improved the final surgical results. von der Brelie *et al.* (26) evaluated the application of TPD in 25 patients, who underwent intradural neurosurgery and exhibited CSF effusion after dural suturing due to circumscribed defects, and concluded that TPD was effective in achieving watertight closure of the dura mater and prevented CSF leakage in 92% of patients.

4. DURAL SUBSTITUTES

The standard methods of dura mater repair consist of the application of sealants and the use of dura mater replacement materials (duraplasty) to expand or replace the resected dura mater during a neurosurgical procedure (27). Dural substitutes are used as patches to prevent CSF leakage and infection and foster regrowth of dura-like tissue across the defect. Native autologous tissue grafts, such as the fascia lata, temporal fascia, and pericranium, can perform well as dural substitutes because they do not provoke severe inflammatory or immunological reactions, but potential drawbacks, such as difficulty in achieving a watertight closure, formation of scar tissue, insufficiently accessible graft materials to close large dural defects, and additional incisions for harvesting the graft, remain problematic (28-30). Off-the-shelf dural substitutes have been developed as alternatives to autologous transplantation and various xenografts have been studied, including bovine and ovine pericardium (31, 32), porcine small intestinal submucosa (33, 34), and processed collagen matrices (27, 35-37). However, these xenografts are often associated with adverse effects, such as graft dissolution, encapsulation, foreign body reaction, scarring, and adhesion formation. Permanent and bioresorbable synthetic polymer membranes have also been tested as dural substitutes (38, 39). Although many efforts have been made, the challenge to develop a suitable dural substitute has been met with limited success.

4.1. Nanofibrous matrices

Nanofibrous matrices composed of biodegradable nanoscale fibers have vast potential as scaffolds for tissue engineering and wound repair because they can mimic the natural fibril structure of the extracellular matrix. Electrospinning is an enabling technique used to produce nanoscale fibers from > 100 different polymers, which, in turn, are used to produce nanofibrous matrices for the creation of micro- and nanoscale fibrous matrices with tunable macroscale geometries and nanofiber architectures (40, 41). To promote cell migration from the surrounding tissue to the center of a dural defect and shorten the time for healing and regeneration of dura mater, a surface patterned with radially aligned, nanoscale features would be highly desirable as an artificial dural substitute.

Although nanofibrous matrices have been previously investigated for applications in soft tissue repair (42, 43), few studies have attempted to use such a scaffold for healing of the dura mater. However, several studies have shown that electrospun membranes composed of oriented nanofibers can be used to influence cell alignment and cellular processes *in vitro* (44-46). For example, Xie *et al.* (47) reported the fabrication of electrospun nanofiber scaffolds composed of radially aligned fibers and its potential application as a dural substitute. Recently, Kurpinski *et al.* (48) demonstrated a novel electrospinning method using an *in vivo* canine duraplasty model to produce a unique synthetic nanofibrous dural substitute with two integrated layers: one with predominantly aligned fibers and the other with predominantly random fibers.

4.2. Silk fibroin

Silk protein spun by the silkworm, *Bombyx mori*, has been used as a surgical suture because of its excellent mechanical and biological properties, which include biocompatibility and a low host inflammatory reaction (49).

As the main component of silk protein, fibroin has been characterized by its good water vapor and oxygen permeability (50, 51), blood compatibility (52), and ability to accelerate collagen formation and proliferation of cultured human skin fibroblasts (53). Kim *et al.* (54) reported that they prepared a transparent, silk fibroin–based artificial dura mater for the first time, which was found to be safe for neurosurgical applications and effectively inhibited inflammation without inducing side effects. Although the long-term effects need to be determined in larger animals, this transparent artificial dura mater material no doubt has a huge potential in neurosurgical applications.

4.3. Dural grafts

Dura mater replacement materials used internationally are numerous and all have distinct disadvantages. Although the advent of high-molecular weight biomaterials offers a consistent and reliable source of easy-to-use artificial dura mater materials, they are difficult to suture, can not always be inserted accurately, and are associated with poor infection resistance, thus limiting their wide-spread use. Therefore, autologous or xenogeneic grafts have become an area of interest. Dural grafts have been in use for > 30 years and autologous tissues were commonly accepted as dural replacements 10 years ago, as autologous membranes are from the patient's own tissue, thus they do not have the problems of tissue incompatibility and immunorejection. In an experimental study, Chaplin *et al.* (55) showed that autologous pericranium was ideal for dural replacement and a study evaluated by Tachibana *et al.* (56) showed that free fascial grafts can heal with durable fibrous tissue without the presence of a blood supply from an overlying vascularized flap. However, the disadvantages of autologous tissues are limited supply, surgical complexity, and involvement of additional trauma. Some studies have reported that adhesions can form between autologous membranes and brain tissue, which may result in epilepsy in brain-injured individuals (57). Compared with autologous tissues, xenogeneic biomaterials have the advantages of relatively good infection-resistance and mechanical properties similar to those of the host dura mater (58). Filippi *et al.* (59) reported that xenogeneic bovine pericardium was a flexible and easily suturable, safe, and cost-effective material for duraplasty as a dural substitute. Using an animal model of xenogeneic dura mater transplantation, Shi *et al.* (60) recently showed that a modified dura mater implant retained good tissue compatibility and ideal mechanical characteristics that facilitated host cell invasion and permitted gradual replacement by new biological tissue with functions of normal dura mater.

5. OTHER METHODS

5.1. Phenytoin sodium

Phenytoin is the oldest non-sedative anticonvulsive drug commonly used for the treatment of primary and secondary epilepsy, migraine, trigeminal neuralgia, some psychotic disorders, cardiac arrhythmias, digital intoxication, and following myocardial infarction by blocking neuronal depolarization via blockade of sodium flow into the cell and neuronal re-excitation via calcium flow blockade (61-65). Given these effective characteristics of phenytoin, Ergun *et al.* (66) attempted to use phenytoin to heal dura mater and found that the systemic use of the low-cost drug as an antiepileptic before and after neurosurgical procedures had favorable effects on dura mater healing, but further clinical studies are needed to determine effective dosages and duration of use.

5.2. Fibroblast growth factor (FGF)

FGFs have been shown to induce DNA synthesis, cell migration, blood vessel growth, and dermal wound closure *in vivo* (67). In addition, up-regulation of endogenous FGF seems to be an important mechanism to stimulate repair of damaged epithelia as demonstrated in the skin, bladder, and kidney (68). Other studies have demonstrated that different FGF concentrations promote mitosis of keratinocytes and smooth muscle cells, and wound granulation. Furthermore, FGFs may promote wound healing in diabetes and radiotherapy (69, 70) (figure 1). In an animal model, Nurata *et al.* (71) showed that FGF-2 facilitated dura mater healing in both the early and late phases of wound healing and the quality of the dura mater healing remained time-dependent because there was a significant difference between the FGF-2 groups after 3 and 6 weeks. Wu *et al.* (72) further demonstrated that the use of FGF for spinal cord injury was safe and feasible in their clinical trial and reported significant improvements in American Spinal Injury Association (ASIA) motor and sensory scale scores, ASIA impairment scales, neurological levels, and functional independence measurements 24 months postoperatively. Therefore, further large-scale, randomized, and controlled investigations are warranted to evaluate the efficacy and long-term results of FGF to promote wound healing of the dura mater.

5.3. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF is a multipotent cytokine which may lead to enhanced keratinocyte growth, selective recruitment of Langerhans cells into the dermis, and enhanced wound healing of the prepared site (73). The use of GM-CSF in experimental animal models and preclinical studies has revealed that it facilitates wound healing (74, 75). Using a rat model, Kurt *et al.* (76) evaluated the effects of GM-CSF on dural healing after experimentally induced CSF leakage and reported that the local application of GM-CSF to the site of CSF leakage facilitated dural healing and prevented complications.

5.4. Laser beam

Surgical incisions can be bonded by heating with a laser beam (77). Several earlier studies evaluated the use of laser bonding for primary dural closure. Foyt *et al.* (78) published a report on the use of a diode laser with albumin plus indocyanine green solder for the closure of dural cuts. Desiccation of brain tissue was observed in this report, possibly because no temperature control was used and because of the deep penetration of diode laser radiation into the brain tissue. Hadley *et al.* (70) conducted laser welding experiments on the dura, but they did not obtain complete laser dural closure resulting in intraoperative CSF leaks.

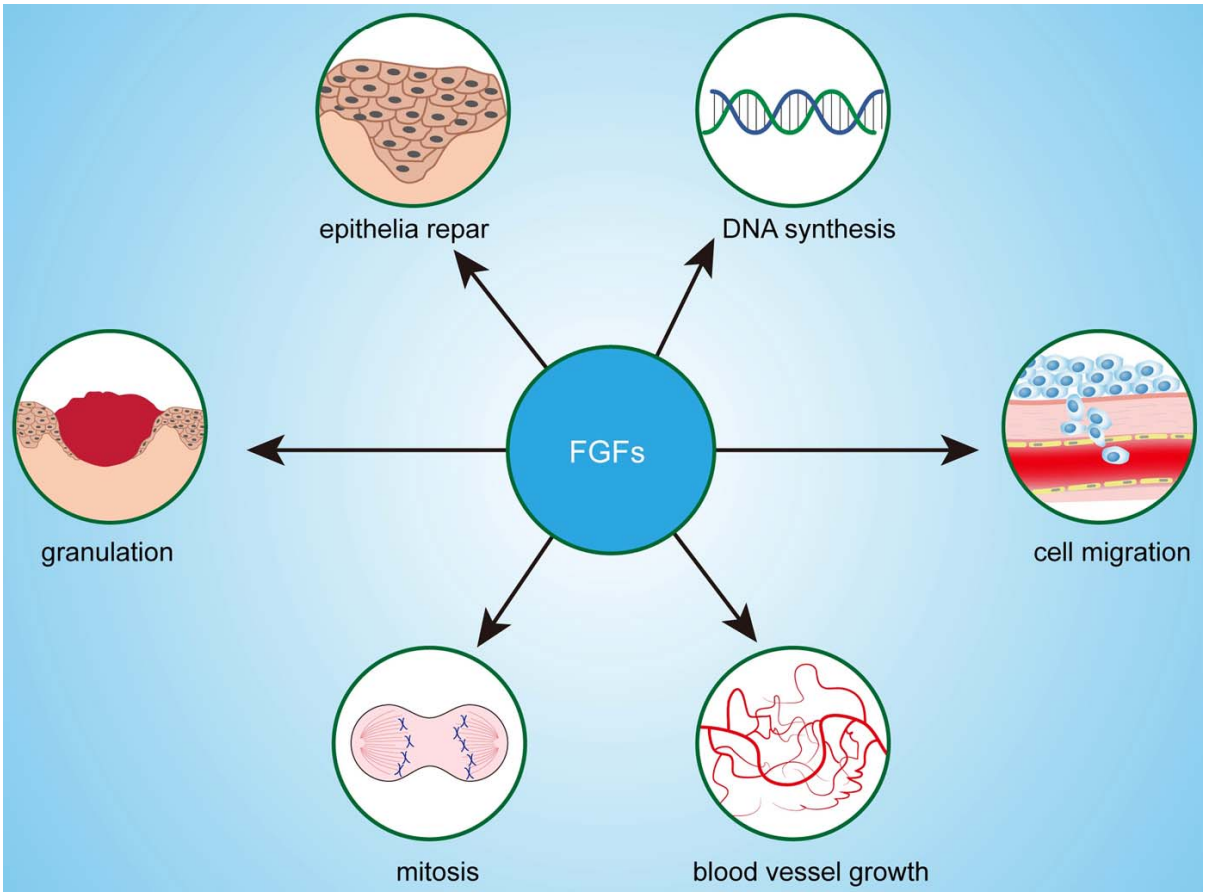

Figure 1. Fibroblast growth factors (FGFs) promote wound healing. FGFs have been shown to induce DNA synthesis, cell migration, blood vessel growth, and dermal wound closure *in vivo*. In addition, up-regulation of endogenous FGF seems to be an important mechanism to stimulate repair of damaged epithelia. FGF could promote mitosis of keratinocytes and smooth muscle cells, and wound granulation.

Thus, an immediate watertight seal was not achieved. Menovski *et al.* (80) used a relatively low energy CO_2 laser and applied egg white as a solder, as they were mostly interested in understanding the mechanism of the structural changes in the irradiated dura mater and the role of the solder in the process, whereas Forer *et al.* (81) demonstrated the actual potential of a temperature-controlled CO_2 laser system in dural surgery and reported that the laser tissue soldering procedure promised to be a safe and reliable technique, which may find numerous applications in neurosurgery and in many other surgical fields.

6. CONCLUSIONS

In the present review, we introduced and compared characteristics of the most commonly used and newly developed dural repair procedures and materials regarding of the addition of sealants, the use of substitutes, and other effective methods. Although, most newly developed methods focused on animal models, large clinical studies to document the safety and efficacy of new methods in dural repair need to be conducted in the future.

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Abbreviations: ASIA, American Spinal Injury Association; CSF, cerebrospinal fluid; FDA, Federal Drug Administration; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; TPD, TissuePatchDural.

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