

## Clinical management of dural defects: A review

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### Abstract

Dural defects are common in spinal and cranial neurosurgery. A series of complications, such as cerebrospinal fluid leakage, occur after rupture of the dura. Therefore, treatment strategies are necessary to reduce or avoid complications. This review comprehensively summarizes the common causes, risk factors, clinical complications, and repair methods of dural defects. The latest research progress on dural repair methods and materials is summarized, including direct sutures, grafts, biomaterials, non-biomaterial materials, and composites formed by different materials. The characteristics and efficacy of these dural substitutes are reviewed, and these materials and methods are systematically evaluated. Finally, the best methods for dural repair and the challenges and future prospects of new dural repair materials are discussed.

**Key Words:** Dural defect; Cerebrospinal fluid leak; Incidental durotomy; Causes of dural defect; Dural repair

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**Core Tip:** Dural defects are common in spinal surgery and may cause a series of complications, so it is necessary to actively prevent and treat them. In this paper, we reviewed issues related to dural defects and discussed their clinical management.

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## INTRODUCTION

The surface of the brain and spinal cord is covered by three layers of capsular membrane, including the soft membrane, arachnoid membrane, and dural membrane, from the inside to the outside, respectively, with the function of protecting and supporting the brain and spinal cord. The dura, which is the outermost layer of the meninges that protects the brain or spinal cord, can be damaged in situations such as accidental trauma and spinal surgery. In a meta-analysis of 23 studies, the incidence of dural injury related to spinal surgery was 5.8%[1]. Dural damage can result in persistent cerebrospinal fluid (CSF) leakage, which can lead to serious complications including severe headache, pseudomeningocele, nerve root entrapment, and intracranial hemorrhage[2]. In existing research and clinical practice, whether the damaged dura mater should be repaired is debated[3], and research on the repair methods of dural defects has progressed[4,5]. Therefore, this review aimed to summarize the clinical treatment of dural defects, to help doctors better treat dural defects and reduce the occurrence and sequelae of dural injuries.

## ANATOMY OF THE DURA MATER

Although the dura mater spinalis and dura mater encephalin are anatomically continuous, they exhibit several differences. The dura mater encephalin is a thick, tough, double-layer membrane. The outer part of the dura is the periosteum on the inner surface of the skull, which stops at the foramen magnum and becomes the periosteum in the spinal canal. The inner part continues and becomes the dura mater spinalis. In some parts of the dura, the two layers are separated and the inner surface is lined with endothelial cells, known as the dural sinus, which is connected to the extracranial vein by the guiding vein. The dura mater of the spine extends to the dura mater, gradually thinning at the level of the second lumbar vertebra, surrounding the terminal filament, and its lower end is connected to the coccyx. The space between the dura mater and the periosteum of the spinal canal is called the epidural space, which contains loose connective tissue, fat, lymphatic vessels, the venous plexus, and spinal nerve roots. The epidural space is often used for epidural anesthesia in clinical practice. The middle layer of the meninges is referred to as the arachnoid membrane, while the inner layer is referred to as the soft membrane, and CSF is found between these two spaces. The generation, flow, absorption, and circulation of CSF provide the basis for maintaining local homeostasis. Under physiological conditions, CSF fluctuates within a reasonable range. When the dura is torn or damaged, the decrease in CSF pressure leads to a series of clinical symptoms and later complications, such as intracranial hypotension, infectious complications, delayed wound healing, and neurological dysfunction[2,6,7].

## CAUSES OF DURAL DEFECTS

Dural tears are common in spinal and neurosurgery. Depending on the course of the disease, dural tears can be classified as either acute or chronic and primary or secondary. Most dural tears are accidental, while others are intentional. Intentional dural tears, including diagnostic lumbar puncture, therapeutic puncture, removal of intradural tumors or cysts, and selective shunt among others are often required for treatment and diagnosis of various disorders of the brain and spinal cord[8]. Meanwhile, accidental dural tears may be caused by trauma, neurosurgery, or spinal surgery. Multiple studies have shown that patients with a history of lumbar surgery tend to be more prone to dural tears[1,9-12]. For example, Telfeian *et al*[13] found that patients who underwent secondary minimally invasive lumbar surgery were more likely to develop dural defects. Takahashi *et al*[14] found that patients with degenerative lumbar spondylolisthesis and juxtafacet cysts were more likely to undergo an unintended durotomy. In addition, Lukas reported a case of a dural defect caused by a positioning needle during spinal surgery, indicating that caution is needed during needle placement in unilateral surgery[15]. Our research team also found a case of dural damage caused by continuous negative pressure suction after spinal laminectomy in daily clinical work. In addition, dural defects have many risk factors, including obesity. Therefore, we comprehensively summarized the causes and risk factors of dural breakage in Table 1. The clinical symptoms vary by the type of dural defect, and dural defects may cause destruction of the arachnoid membrane and CSF leakage.

## COMPLICATIONS OF DURAL DEFECTS

Dural tears can cause CSF leakage and increase the risk of infection; therefore, they are often associated with acute or chronic complications. Due to CSF leakage, dural tears may cause a persistent decrease in intracranial pressure, leading to symptoms of low cranial pressure, including postural headache[2]. Persistent low cranial pressure can also cause adult migraine, nausea, photophobia, and ataxia, and

Table 1 Etiology of dural defect

Relationship	Classification	Etiology
Immediate factors	Operation	Lumbar anesthesia, puncture[8]
		Analgesia in labor[8]
		Chiropractic[82]
	Trauma	Negative pressure suction
		Skull fracture[83]
		Spinal burst fracture[84]
		Subdural hematoma cleared[85]
	Surgery	Discectomy/artificial disc replacement[86-88]
		laminectomy[86-88]
		Late-presenting dural tear[89]
		minimally invasive surgery[90]
		Secondary intervention after surgical intervention[9,10,14,92]
		Intradural mass resection/cyst removal[9,14]
Indirect factors	Connective tissue disorders	Marfan syndrome[91]
		Ehlers-Danlos syndrome type II[92]
	Miscellaneous	Dural ossification[86]
		Spontaneous fistula
		The use of bone morphoprotein 2[93]
		Older age[1,10,14]
		Diabetes[1]
		Obesity (Body mass index $\geq 30$ )[87]
		Corticosteroid use[87]
		Ankylosing spondylitis[87]

severe low cranial pressure can even cause pseudomeningocele, nerve root entrapment, and intracranial hemorrhage, among other symptoms[2,6,16]. Furthermore, the patient's life is at risk when low pressure in the damaged dural area causes the spinal cord or brain tissue to protrude from the injured opening, resulting in spinal or brain herniation. When dural defects lead to long-term CSF leakage, CSF accumulation in the tissue space can form pseudocysts, sinuses, or fistulas, increasing the risk of infection[6,7,17,18]. Intradural infections caused by dural defects from spinal surgery include meningitis, adhesive arachnoiditis, and dural annulus fibrosus. A high index of suspicion for meningitis should be maintained in patients with a clinical triad of fever, neck stiffness, and disturbance of consciousness after spinal surgery[7]. The spread of the infection can also lead to complications such as sepsis, pneumonia, urinary tract infections, thromboembolism, and acute kidney injury[8]. Moreover, damage to the dura can lead to prolonged bed rest, which may result in a series of long-term bed complications such as bedsores, pendant pneumonia, skin ulcers, and deep venous thrombosis of the lower extremities.

## CLINICAL MANAGEMENT OF DURAL DEFECTS

### **Direct suture**

The common techniques of direct suture are summarized as follows: (1) Direct suture for dural tears or small dural defects; (2) Continuous suture or figure-8 suture; (3) Leaving a small suture hole using GORE-TEX suture material; and (4) Making the distance between two sutures  $< 3$  mm and placing each suture line 1 mm from the edge[19]. One-stage repair is the first choice of treatment, because if it is successful, it can obtain ideal long-term clinical outcomes[20,21]. However, direct suture has a high failure rate of 5%–9%[22]. Failure is affected by many factors, including the surgeon's treatment experience, the size of the defect, the location of the defect, minimally invasive spinal surgery that

increases the challenge of suturing, and brittle surgical dural tissue. Long-term exposure of the dura during operation, irradiation with surgical light, and other factors also lead to dural contraction caused by dural dehydration[23,24]. Several reports have described the development and use of a new device called DuraStat, which deploys a double-armed suture in a controlled manner through the dura to facilitate repair in difficult clinical scenarios. Compared to traditional techniques, this new dural repair device allows surgeons at all levels of training to quickly and successfully repair simulated dural tears [25]. In summary, in clinical settings, primary sutures are mainly used as a basic technique for repairing dural injury combined with other repair methods, rather than simple sutures. Among 11 published reviews of different methods of repairing dural injuries found on PubMed, primary closure was the basis for repairing all 148 intentional durotomies[4].

### **Biomaterials**

**Grafts:** Large dural defects often occur in patients undergoing skull base surgery. When the dural defect is too large to be repaired directly, it can be repaired by transplanting other tissues in autotransplantation, allotransplantation, or xenografts. Autografts used to repair dural defects include fat, muscle tissue, fascia, and the periosteum. Neurosurgeons often prefer fascia lata transplantation to repair the dura mater, as it is convenient for dural reconstruction[5]. The transplanted free fascia lata is highly tolerant to infection and can be nourished not only through the scalp, but also through the surrounding dura. Nakano *et al*[26] used fascia lata transplantation to treat postoperative infection of an artificial dura mater and achieved good results. Dural tears from spinal endoscopic surgery are often treated by autologous muscle or fat transplantation using a piece of muscle or fat beside the spine the same size as the damaged dura. To reduce the risk of CSF-related complications after intradural tumor surgery, Arnautovic *et al*[27] used autologous fat transplantation to fill the dead space and close the dura during the operation, and no postoperative CSF-related complications were observed in patients who underwent this procedure. The use of autogenous skull periosteum has been reported to effectively prevent CSF leakage and is feasible in terms of preventing further complications, as well as the time and cost of operation[28]. However, the uses of the periosteum are limited, as it is hard, fragile, and difficult to manage, and it is not suitable for repairing large dural defects. Autologous tissue used to repair dural defects has the advantages of no disinfection, rejection, transmission of disease, or burden on patients; however, additional surgery with local materials increases the surgical trauma, operation time, and risk of adhesion.

Previously, surgeons have used allogeneic materials, including the cadaveric dura, for dural repair [29]. The use of a cadaveric dura reduces pathogens to the greatest extent through freeze-drying and inactivation, but its clinical effect is not optimistic. Moreover, due to limited sources and ethical limitations, this material is no longer common in current clinical practice. At present, the amniotic membrane (AM) is the primary allogeneic material used in clinical settings[30]. The guiding role of the AM as a material for dural repair is based on its non-immunogenicity, anti-inflammatory properties, and promotion of collagen remodeling. The AM promotes the proliferation and migration of epithelial cells and reduces scar formation, thereby playing a role in dural repair. Furthermore, previous studies have compared the use of the AM and an autograft (fascia) in dural repair. They found that in dural repair, the AM could perfectly combine with autologous dura, accompanied by the disappearance of the epithelium and the formation of new connective tissue, fibrous tissue lamina, no inflammatory reaction or necrosis, and no adhesion[31]. In addition, clinicians have used acellular human dermis for dural repair and found no significant difference in the incidence of complications between the use of this material and autografts[32].

Xenogeneic biomaterials from animals, such as the pericardium, mesentery, and peritoneum can also be used to repair dural defects. These heterogeneous biomaterials must be treated by removing the antigen and adding a cross-linking agent before they can be used in medical products. Bovine pericardium was used earlier in clinical settings and welcomed by surgeons. At present, pigs and horses are animal sources of pericardial[32,33]. In animal experiments, He *et al*[34] found that the small intestinal submucosa can stimulate the response of connective and epithelial tissue to dural regeneration and functional recovery without immune rejection, which can provide long-term dural repair and prevent complications. However, the incidence of complications in dural repair, including pseudomeningocele and meningitis, was significantly higher with xenografts than with autografts[32].

**Protein-based adhesives:** In addition to dural repair materials directly derived from human or animal tissues, those made of collagen and fibrin from human or animal tissues are also useful as dural substitutes. Collagen exhibits good biocompatibility and low antigenicity. Currently, DuraGen® (Integra, NJ, United States) and TissuDura® from bovine and equine Achilles tendon collagen respectively are commonly used. DuraGen® is a chemically cross-linked collagen sponge composed of collagen type 1 in the Achilles tendon. Clinical trials have reported that DuraGen® can be used in patients with significantly larger dural defects and can prevent postoperative epidural effusion to ensure that the dura is completely sealed[35]. However, because DuraGen® is mainly placed on the damaged dura using a "mosaic" technique without suture, it can easily lead to complications such as CSF leakage and infection[36]. TissuDura® is an elastic, chemically inert, and adaptable collagen-based biological matrix [37]. In a rat model experiment, glial hyperplasia and inflammation in the bone and parenchyma foreign

bodies were significantly decreased in the TissuDura® group, indicating that this material is more biocompatible in dural meningeoplasty[38]. Based on the previous use of collagen, researchers added fibrinogen, which results in blood coagulation and a better repair effect. Generally, fibrinogen is extracted from the blood and is an important protein involved in blood coagulation and hemostasis. At present, fibrin glue products contain two main components: fibrinogen and thrombin, which are mixed to form fibrin clots in a liquid glue or dry patch[39]. The first fibrin glue product used was Tisseel/Tissucol glue (Baxter, Deerfield, IL, United States). Later, researchers developed Evicel (Ethicon US, LLC) and dry patch products such as TachoSil (Baxter) and Tachocomb (CSL Behring, Tokyo, Japan). TachoSil, whose fibrinogen product is made from horse collagen, bovine thrombin, bovine aprotinin, and human fibrinogen, is widely used in clinical practice. To eliminate the risks associated with bovine materials, TachoSil has gradually replaced all bovine materials with those of human origin[40]. TachoSil, which was approved for clinical use long ago, is widely used for surgical hemostasis. Later studies also found that TachoSil not only acts as a mechanical barrier between surfaces during mesothelial recovery, but also reduces adhesion by inhibiting the level of plasminogen activator inhibitor-1, which can effectively prevent intra-abdominal, gynecological, and pleural adhesions. Therefore, TachoSil can repair dural defects, prevent postoperative dural adhesions, and provide good satisfaction among surgeons[40,41]. An analysis of 35 patients with spinal intradural tumors using TachoSil to treat dural defects showed that only 1 patient had CSF leakage, and no other complications were observed[42]. Gazzeri *et al*[43] successfully treated CSF leakage with TachoSil after anterior cervical discectomy and fusion. While the effectiveness of TachoSil in spinal surgery has been well established, this material poses potential risks of infection, including human parvovirus B19, alloimmunity, and allergic reactions. Thus, surgeons are developing fully autologous fibrin glue as a dural sealant[44]. To treat 17 patients with CSF leakage, Taniguchi *et al*[44] simultaneously prepared cold precipitates and thrombin from the patient's own blood within 90 min before surgery and did not add any allogeneic components or other exogenous additives. Fully autologous fibrin glue was prepared to repair and prevent CSF leakage. Full autologous fibrin glue can eliminate the risk of virus or prion transmission and alloimmunity; however, this material comes from patients themselves. Thus, patients must meet the requirements to prepare a sufficient amount of autologous fibrin glue.

**Bacterial cellulose membrane:** Researchers have also noted the excellent mechanical and biological properties of the bacterial cellulose (BC) membrane, including good biocompatibility and low host inflammatory response. Therefore, this material has been employed for dural repair[45]. Xu *et al*[45] found that the BC membrane could repair dural defects in rabbits, and the inflammatory response was lower than that of traditional materials (NormalGEN, biological dural repair patch in Guangzhou, China). Through mouse experiments, Lima *et al*[46] verified that BC membranes showed suitable biocompatibility in repairing the dura without inducing an immune response, chronic inflammatory response, or loss of neurotoxic signals. Jing *et al*[47] developed a new type of electrospun BC (EBC) membrane. Compared with BC, the inflammatory reaction was lower, more collagen fibers were uniformly distributed on the outside of the EBC membrane, and brain tissue adhesion and epidural scarring were reduced in the EBC group. Additionally, through animal experiments, Xu *et al*[48] found that the continuous release of vancomycin BC could effectively improve central nervous system infection after implantation. Moreover, BC is strong in the hygroscopic state, exhibits good biocompatibility, is relatively simple and cost-effective, and has the ability to carry drugs or growth factors. Therefore, the BC membrane can be used as a new artificial dural material, but the long-term effects of BC on dural repair remain to be studied[49,50].

### **Non-biological materials**

Biological materials have many advantages in dural repair; however, they are difficult to prepare, limited in shape and size, differ among batches, and lack mechanical strength. In contrast, synthetic materials are easier to prepare than biological materials, can be repeatedly synthesized in large quantities and adjusted according to demand, and are relatively cheaper than natural materials. Two main types of synthetic materials can be used for dural repair[5]: (1) Non-degradable polytetrafluoroethylene and polyurethane; and (2) Degradable polyglycolic acid, polycaprolactone, and poly (L-lactic acid) (PLLA). Although these sealants are effective for watertight dura, a number of retrospective analyses have found no significant difference in CSF leakage between the sealant and suture groups. Nevertheless, some studies suggest that the use of sealant can reduce infection[51], while others suggest no significant difference in the infection rate[52].

Therefore, in recent years, researchers have derived a variety of new dural repair materials on this basis and achieved good repair results in human or animal models (Table 2). Under the condition that the dura could not be repaired directly after craniocerebral surgery, four patients underwent dural reconstruction with a new graft material, CerafixDura, a synthetic porous polymer matrix composed of spun poly (lactic acid-glycolic acid) and poly (p-dioxane). Satisfactory results were obtained without complications[53]. Researchers often combine various polymers to experiment with their characteristics [54-56]. For example, Chuan *et al*[57] prepared a three-dimensional composite nanofiber membrane based on enantiomeric polylactic acid and poly(d-lactic acid)-grafted tetracalcium phosphate. The

Table 2 Non-biological materials and their effect evaluation

Ref.	Year	Restorative materials	Object of application	Evaluation of clinical / laboratory effect
Ramot <i>et al</i> [94]	2020	Novel synthetic and fibrous Dural graft: Poly (L-lactic-co-caprolactone acid) and poly (D-lactic-co-caprolactone acid)	Rabbits	12 mo after operation, there was no animal death, and the new dura mater, dura mater injury and upper bone healing were formed at the implantation site. The advantage for this material is favorable local tolerability and biodegradability
Schmalz <i>et al</i> [53]	2018	Cerafix dura substitute: Spun poly (lactic-coglycolic acid) and poly-p-dioxanone	Human: Four patients after resection of brain tumor	In all patients wound healing proceeded without complication. There was no imaging evidence of persistent fluid collection to suggest cerebrospinal fluid leakage or pseudomeningocele formation, nor was there evidence of meningeal enhancement to suggest the development of subclinical chemical meningitis
Li <i>et al</i> [60]	2022	bioactive patch composed of alginate and polyacrylamide hydrogel matrix cross-linked by calcium ions, and chitosan adhesive	<i>In vitro</i> experiment and <i>in vivo</i> experiment in rabbit model	The bioactive patch have the good properties of withstanding high pressure, promoting defect closure, exerting the effects of anti-inflammatory, analgesic, adhesion prevention and inhibiting postoperative infection
Kinaci <i>et al</i> [58]	2021	Liqoseal, a dural sealant patch comprising a watertight polyester-urethane layer and an adhesive layer consisting of poly (DL-lactide-co-ε-caprolactone) copolymer and multi-armed N-hydroxylsuccinimide functionalized polyethylene glycol	Computer-assisted models, fresh porcine dura and <i>In vitro</i> experiment	The mean burst pressure of Liqoseal in the spinal model (233 ± 81 mmHg) was higher than that of Tachosil (123 ± 63 mmHg) and Tisseel (23 ± 16 mmHg). Compared with Adherus, Duraseal, Tachosil, and Tisseel, Liqoseal was able to achieve a strong watertight seal on dura defects in the <i>in vitro</i> model
Yamaguchi <i>et al</i> [56]	2019	Durawave: Polyglycolic acid felt	Human: 36 cases of tumor resection <i>via</i> transpetrosal approach	The cerebrospinal fluid leakage rate of patients treated with polyglycolic acid felt was lower than that of autogenous fascia fixation, and the time of intraoperative dural reconstruction was significantly shortened. Using polyglycolic acid felt to reconstruct dura mater simplifies the operation and may prevent cerebrospinal fluid-related complications after transpetrosal approach
Huang <i>et al</i> [61]	2022	Photo-Crosslinked Hyaluronic Acid/Carb oxymethyl Cellulose Composite Hydrogel	<i>In vitro</i> experiment and <i>in vivo</i> experiment in rabbit model	It has biocompatibility, biodegradability and mechanical strength. By drastically reducing attachment and penetration of adhesion-forming fibroblasts <i>in vitro</i> , HC hydrogel can be used as an anti-adhesion barrier to prevent postoperative adhesion
Zhu <i>et al</i> [95]	2021	Tetra-PEG hydrogel sealants	<i>In vitro</i> experiment and <i>in vivo</i> experiment in rabbit model	It has the advantages of simple operation, high safety, fast solidification time, easy injection, good mechanical strength and strong tissue adhesion. In the liquid environment, the tetra-PEG hydrogel sealants can also instantly adhere to the irregular tissue surface
Chuan <i>et al</i> [57]	2020	Stereocomplex nanofiber membranes based on enantiomeric poly (lactic acid) and poly (D-lactic acid)-grafted tetracalcium phosphate	<i>In vitro</i> experiment	It has heat resistance, stretching similar to human dura mater, non-toxic to cells, and neuron compatibility
Yu <i>et al</i> [62]	2015	Two layers of novel electrospun membranes, dermal fibroblasts and mussel adhesive protein for repairing spinal dural defect. Inner layer: Lactide-co-glycolide other layer: Chitosan-coated electrospun nonwoven poly(lactide-co-glycolide) membrane	Goats	Seamless and quick sealing of the defect area with the implants was realized by mussel adhesive protein. Effective cerebrospinal fluid containment and anti-adhesion of the regenerated tissue to the surrounding tissue could be achieved in the current animal model
Masuda <i>et al</i> [96]	2016	Suture or nonpenetrating titanium clips, followed by reinforcement with a polyglycolic acid mesh and fibrin glue intraoperatively	75 patients (34 males and 41 females; age range, 16e80 years; mean age, 57.1 years)	Only one patient out of 75 (1.3%) required reoperation for dural repair
Terasaka <i>et al</i> [64]	2017	Fibrin glue and polyglycolic acid felt (GM111)	Sixty patients were enrolled. The craniotomy site was supratentorial in 77.2%, infratentorial in 12.3% and sellar in 10.5%	Cerebrospinal fluid leakage and subcutaneous cerebrospinal fluid retention throughout the postoperative period were found in four patients. Adverse events for which a causal relationship with GM111 could not be ruled out occurred in 8.8% of the patients. There were no instances of postoperative infection due to GM111
Liao <i>et al</i> [97]	2021	Triple-layered composite: Poly (L-lactic acid), chitosan, gelatin, and acellular small intestinal submucosa	<i>In vitro</i> experiment	Satisfactory multifunction of leakage blockade, adhesion prevention, antibacterial property, and dura reconstruction potential
Deng <i>et al</i> [66]	2017	Absorbable materials Poly (L-lactic acid) and gelatin	<i>In vitro</i> experiment	More biomimetic to native extracellular matrix than collagen substitute did, together with better cytocompatibility, tissue ingrowth, and neoangiogenesis

PLLA: Poly (L-lactic acid).

tensile strength of the composite membrane was close to that of a human dura, and no cytotoxicity was observed. Ligossee, a dural sealant patch composed of a watertight polyester urethane layer and an adhesive layer consisting of poly (DL-lactide-co- $\epsilon$ -caprolactone) copolymer and multiarmed N-hydroxylsuccinimide-functionalized polyethylene glycol, exhibited stronger watertight sealing ability than Adherus, Duraseal, TachoSil, and Tisseel[58]. Other researchers have developed double-layer oxidized regenerated cellulose knitted fabric/poly ( $\epsilon$ -caprolactone) knitted fabric-reinforced composites and compared them with human cadaveric membranes and three commercial dura mater substitutes (two collagen substrates, DuraGenPlus and TissuDura, and a synthetic poly-L-lactide patch, ReDura). Although slightly inferior to human cadaveric membranes, this new composite exhibited better functional properties than typical dural substitutes[59]. Bioactive patches composed of calcium-cross-linked alginate, polyacrylamide hydrogel matrix, and chitosan adhesive have been proven to have anti-inflammatory, analgesic, and anti-adhesive effects[60]. Photo-cross-linked hyaluronic acid/carboxymethyl cellulose composite hydrogels can also be used as a dural substitute to prevent postoperative adhesion[61].

### **Composite materials**

Different materials have different advantages and disadvantages; therefore, the combination of various materials to form composites may result in better dural repair. Yu *et al*[62] developed a package that includes two layers of novel electrospun membranes, dermal fibroblasts, and mussel adhesive proteins to repair spinal dural defects. This compound material effectively curbed CSF leakage and resisted adhesion between regenerated and surrounding tissues in a goat animal model. Additionally, autologous human muscle or fat transplantation can be combined with fibrin glue or fibrin-sealed collagen sponges. Surgeons collected autologous muscles from patients during total endoscopic surgery and transplanted them into several layers of dural defects. The graft was then fixed and sealed watertight with fibrin sealant and a gelatin sponge[63]. In a multicenter clinical trial, a new dura mater substitute (GM111) composed of polyglycolic acid felt and fibrin glue was used for non-suture dural repair. Of the 60 patients in the group, 4 experienced CSF leakage and subcutaneous CSF retention after surgery, and no postoperative infections resulted from the use of GM111. Therefore, GM111 showed good closure ability and safety for dural closure without sutures[64]. Similarly, in a review of 409 patients who underwent reconstruction of the sellar region, a single synthetic dura mater substitute was used to cover the damaged area, and then a dural sealant was applied to the repaired epidural surface. Postoperative results showed that this technique can effectively prevent postoperative CSF leakage[65]. Another composite, named Neodura<sup>TM</sup> (MedprinBiotechGmbH, Germany), was made of absorbable PLLA and gelatin. Compared with the control DuraGen group, the surface properties of the composite substitute were more bionic to the natural extracellular matrix and exhibited better cell compatibility, inward tissue growth, and neovascularization. In clinical trials, this substitute further proved its ideal repair effects without CSF leakage or other adverse reactions[66].

### **Other repair methods**

A non-penetrating titanium clip is commonly used for dural repair in clinics. Compared with the primary suture, the non-penetrating anastomotic clip has the advantages of simple operation, rapid process, reduced dura exposure, no pinhole, and no risk of pinhole leakage. Additionally, compared with the foreign body inflammatory reaction caused by sutures, the use of a titanium clip significantly reduces local acute or chronic inflammation, as well as the risk of postoperative adhesion[67-69]. Shahrestani *et al*[67] used non-penetrating anastomotic clips to repair dural defects in children, and the incidence of postoperative CSF leakage and non-penetrating titanium clip infection was very low. Ito *et al*[70] used non-penetrating titanium clips to prevent postoperative CSF leakage during spinal surgery, and only 1 of the 31 patients exhibited postoperative CSF leakage. These studies suggest that non-penetrating anastomotic titanium clips are a good auxiliary tool in the treatment of dura breakage. However, because they are made of metal, these clips may lead to metal artifacts and affect the discrimination of structure in the future. Nevertheless, some studies think that they are small enough to not produce obvious artifacts[71]. In addition, the use of non-penetrating titanium clips exhibits several issues, including dural tears caused by the clips, displacement and non-reusability of the clips, high medical costs, and non-degradable materials. Additionally, the long-term effects of the use of titanium clips have not been observed. Whether these clips will eventually lead to progressive stenosis of the dural space, among other issues, require further exploration.

Epidural or intrathecal injection of saline has also been considered to alleviate the complications of CSF leakage caused by dural injury. Saline injection can improve the symptoms of intracranial hypotension by restoring CSF pressure in the subarachnoid space, which can immediately improve symptoms. However, this is only a temporary solution[72,73].

In addition, clinical adjuvant treatments, such as fluid replacement, caffeine, sphenopalatine ganglion block, greater occipital nerve block, local pressure bandaging, surgical closure of the space, and short-term bed rest after surgery are reasonable in current clinical practice, as these methods can increase the pressure in the dural defect area and avoid postural low intracranial pressure[74-77]. Through animal experiments, Ahmadi *et al*[78] found that local or systemic supplementation with L-arginine is beneficial for the treatment of dural tears. Systemic supplementation with L-arginine can promote collagen deposition and vascularization and increase the level of granulation tissue formation to accelerate dural healing.

### **Systematic evaluation of dural repair technology**

Many types of dural repair techniques and the continuous emergence of dural repair materials provide clinicians with more choices in the face of dural damage. A Canadian medical questionnaire examined clinicians' choice of repair methods in the face of different dural defects[79]. The results showed that when the diameter of the damage was less than 1 mm, the surgeon often chose sealant or even no treatment. When the diameter of the damaged opening was greater than 1 mm, the combination of suture and sealant was found to be a more popular option. Additionally, the larger the diameter of the damaged opening, the greater the proportion of the combined application. On the other hand, surgeons preferred to use sealants or do nothing when the damage was located in the anterior area, most surgeons chose to use a combination of sutures and sealants in the posterior area, and use more sealants in the nerve root area. However, the results also showed that at least 20% of doctors chose a different repair method than the mainstream for different conditions. Therefore, the combined use of dural repair techniques and materials should be evaluated. Alshameeri *et al*[80] conducted a systematic review and meta-analysis on the management of accidental dural tears during spinal surgery in 2020. A total of 3822 cases of dural tears were included among 49 studies. Compared with different dural repair techniques, the risk of dural tears was 5.2% (4%-6.5%). Regardless of the type of treatment, the total combined proportion of dural tear treatment failure was 6.1%(4.4%-8.3%). In other words, little difference was observed among the different repair methods. Among them, the total failure rate of direct suture repair (with or without any other reinforcing material) was lower than that of indirect repair (with sealant and/or a patch)[80]. In a systematic review in 2021, a summary analysis of 11 studies showed that among the 776 enrolled patients, the most common technique was primary suture, patch, or a combination of graft and sealant (22.7%, 176/776). The incidence of CSF leakage was the lowest in the primary suture plus patch or bone graft group (5.5%, 7/128). In addition, compared with the use of an occluder alone (17.6%, 18/102), sealant as an aid to primary closure (13.7%, 18/131) did not significantly reduce the incidence of CSF leakage. Moreover, regardless of the repair technique, no significant difference was observed in the rate of infection or postoperative neurological deficits[4]. A total of 106 patients with dural tears, CSF leakage, dural incisions, or pseudomeningocele in the online databases of Southampton General Hospital from 2016 to 2019 were enrolled in the study[81]. The authors compared the combination of preliminary suture closure, artificial patch, sealant, autologous repair, and drainage in patients with dural ruptures. By comparing the length of hospitalization, number of readmissions or revision surgeries, time of readmission, postoperative infection rate, and neurological symptoms related to dural tear, the authors concluded that primary suture plus an artificial dural patch was the most effective method for repair.

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## **CONCLUSION**

In summary, one-stage suture is essential for all types of dural damage and partial dural damage repair surgeries, and primary suture plus patch repair is recommended. If the damage is too large for direct repair, indirect repair should be considered. Additionally, as the overall failure rate of spinal dural repair is 6.1%, dural repair materials should be constantly updated in clinical practice. In the development and testing phases, the new repair materials should be further adapted to special occasions, such as when a large, damaged area cannot be directly sutured or when patients with other diseases cannot tolerate secondary surgical sutures. In addition, many of the new repair materials are still in the *in vitro* or animal experiment stage, and further clinical trials are expected to obtain more clinical data.

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## **FOOTNOTES**

**Author contributions:** Dong RP, Zhang Q contributed to this paper with design of the study, literature review and analysis, and manuscript drafting; Yang LL collected relevant information; Zhao JW and Cheng XL guided the writing and reviewing of this paper and put forward suggestions for the article; all authors have read and approved the final manuscript.

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