Prevention of failed back surgery syndrome with applications of different pharmacological agents: A review article

Ymer Mekaj¹, Agon Mekaj²

¹Institute of Pathophysiology, Faculty of Medicine, University of Prishtina, Kosovo. Prishtina 10000, Kosovo
²Clinic of Neurosurgery, Faculty of Medicine, University of Prishtina, Kosovo. Prishtina 10000, Kosovo

Correspondence: Agon Mekaj
e-mail: agon.mekaj@uni-pr.edu
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Failed back surgery syndrome (FBSS) is a severe, long lasting and very common complication of lumbosacral spine surgery. FBSS can result from a variety of factors, such as an incorrect level of surgery, inadequate surgical decompression, recurrent disc herniation and epidural nerve fibrosis. The primary objective of this study was to present the recent data from animal and clinical studies regarding a variety of biological, pharmacological, and different synthetic materials used to prevent scar formation after spine surgery. There are a substantial number of substances that are topically used on the dura mater to prevent epidural fibrosis; however, we have primarily selected the substances that are used most often, such as hyaluronic acid (HA) and its derivatives, mitomycin C (MMC), 5-fluorouracil (5-FU), tacrolimus, melatonin (MLT), and nonsteroidal anti-inflammatory drugs (NSAIDs). Other biological and synthetic materials are also presented, which are used locally in the dura mater but act as mechanical barriers, such as Adcon-L, amniotic membrane (AM), carboxymethylcellulose and polyethylene oxide (CMC/PEO), polytetrafluoroethylene (PTFE), chitosan, collagen dural matrix, polyethylene glycol hydrogel, and fibrin sealant-based medicated adhesion barrier. As indicated in this review paper, the results regarding the use of these substances and barriers in animal models and humans are different; their effects have not always been successful, and they may have even caused adverse effects. However, it is necessary to identify adequate chemical, biological, and synthetic substances that are more successful in the prevention of epidural fibrosis, which is considered one of the main causes of FBSS.

Keywords: Epidural fibrosis; Failed back surgery syndrome; Mechanical barriers; pharmacological agents


Introduction

Failed back surgery syndrome (FBSS) is a condition characterized by persistent back pain after lumbar spine surgery [1]. FBSS occurs in approximately 8-40% of patients that undergo lumbar disc surgery, including many types of spine procedures; however, FBSS is not always the reason for chronic low pain [2, 3]. According to many authors, epidural fibrosis and scar formation are the most common and problematic complications after lumbar disc surgery [4, 5]. However, these factors could be related to another cause independent of the initial mechanical problems [3]. The formation of epidural scar tissue is an expected consequence of spinal surgery. Epidural fibrosis can cause extra-dural compression or dural tethering, which manifests with persistent back and leg pains [6]. To prevent postoperative epidural fibrosis, which is the major contributor of FBSS, various methods have recently been developed that are used to prevent or reduce the amount of scar formation. These methods are based on the topical application of many pharmacological agents, which inhibit the formation of fibrous tissue via different mechanisms. The use of both
techniques and materials to prevent the formation and adherence of the tissues’ neural elements is therefore important to improve surgical outcome [7]. Some of the most commonly used topical agents are hyaluronic acid (HA), nonsteroidal anti-inflammatory drugs (NSAIDs), gelfoam, Gore-Tex, carboxymethylcellulose (CMC), Adcon-L, autogenous adipose grafting, mitomycin, Tacrolimus, melatonin (MLT) and other substances. In previous decades, these pharmacological agents and several materials have been investigated as potential treatments for the prevention of scar formation after spine surgery [8].

The purpose of our review was to analyze the mechanisms of action of a variety of pharmacological, biological and synthetic materials to prevent or limit the formation of fibrous tissue.

Pharmacological agents

There are many pharmacological agents with anti-inflammatory effects, which have been demonstrated in animal experimental studies after different surgeries (Table 1). Here, we will present the common pharmacological agents that are applied locally after laminectomy to prevent epidural fibrosis, which is the major contributor to FBSS.

HA and its derivatives

HA is a naturally occurring biopolymer that has important biological functions. It is naturally synthesized by a class of integral membrane proteins referred to as hyaluronansynthetases, and it is degraded by hyaluronidases [9]. HA is known to reduce the extent of scar formation via the inhibition of lymphocyte migration, proliferation and chemotaxis of granulocyte phagocytosis and degranulation, and macrophage motility [10]. HA has also been successfully used in peripheral nerve surgery to reduce nerve adhesions during wound healing after nerve injury, which occur during ophthalmological, cardiovascular, and dermatological procedures [9, 11]. Exogenous HA enhances chondrocyte HA and proteoglycan synthesis, reduces the reproduction and activity of proinflammatory mediators, such as matrix metalloproteinases, and alters the behavior of immune cells. These functions are manifested during scavenging of reactive oxygen-derived free radicals, the inhibition of immune complex adherence to polymorphonuclear cells, the inhibition of leucocyte and macrophage migration and aggregation and the regulation of fibroblast proliferation [12]. Shabanet al. have demonstrated that HA applied in rats significantly reduced post-laminectomy epidural fibrosis [13]. There are various commercial preparations of HA in different forms, such as films, microspheres, liposomes, fibers and hydrogels, which have been used for more than 20 years worldwide [9]. Although HA has mainly been used in animal studies, it also provides useful information regarding the effect of hyaluronate in the prevention of postoperative peridural scar adhesion after laminectomy; however, additional clinical trials regarding the use of HA based gels should be performed to confirm its effects in human subjects [14, 15]. Isiket al. have investigated the effects of cross-linked high molecular weight HA and its derivatives, such as HA gel, on the prevention of epidural fibrosis using histopathological and biomechanical parameters; the authors demonstrated that granulation tissue and epidural fibrosis were significantly lower in the HA and HA gel groups compared with the sham group [15].

Mitomycin C (MMC)

MMC is an alkylating chemotherapeutic agent. It is isolated from Streptomyces caesposus or Streptomyces levenduelae, and it can suppress fibroblast proliferation after

Table 1. Application of topical pharmacological agents at the site of epidural in animals

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Pharmacological agents</th>
<th>N of Animals and it’s type</th>
<th>Site of application</th>
<th>Rout of administration</th>
<th>Effect on FBSS</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaban et al.</td>
<td>2013</td>
<td>Hyaluronic acid</td>
<td>32 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2014</td>
<td>Hyaluronic acid</td>
<td>12 rabbits epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Isik et al.</td>
<td>2014</td>
<td>Hyaluronic acid</td>
<td>56 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2004</td>
<td>Mitomycin C</td>
<td>5 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>16</td>
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<tr>
<td>Lee et al.</td>
<td>2006</td>
<td>Mitomycin C</td>
<td>24 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>22</td>
<td></td>
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<tr>
<td>Yildiz et al.</td>
<td>2007</td>
<td>Mitomycin C</td>
<td>32 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>19</td>
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<tr>
<td>Ismailoglu et al</td>
<td>2011</td>
<td>Tacrolimus</td>
<td>20 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Yan et al.</td>
<td>2012</td>
<td>Tacrolimus</td>
<td>72 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>30</td>
<td></td>
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<tr>
<td>Erol et al.</td>
<td>2012</td>
<td>Melatonin</td>
<td>36 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>4</td>
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</tr>
<tr>
<td>He et al.</td>
<td>1995</td>
<td>NSAID*</td>
<td>32 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Sandoval et al.</td>
<td>2008</td>
<td>NSAID*</td>
<td>24 rabbits epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

FBSS* Failed back surgery syndrome PEF* Preventing epidural fibrosis NSAID* Nonsteroidal anti-inflammatory drugs
surgery. Lee et al. have investigated the effect of MMC via topical application on spinal epidural fibrosis in a rat laminectomy model; the authors determined that it reduced epidural fibrosis, which thereby completely avoided dural adherence [16]. MMC has been used extensively and successfully not only after laminectomies but also in ophthalmologic and otolaryngological surgeries [17]. Experimental studies have evaluated the effectiveness of MMC in the prevention of epidural fibrosis in rats after craniotomy, and according to some authors, topical application of MMC may be successful in the prevention of epidural fibrosis following a craniotomy [18]. The topical effects of mitomycins are dependent on the dose because the administration of 0.01 mg/ml MMC has resulted as not effective compared to higher doses, although it resulted in markedly less epidural fibrosis compared with the sham group [16]. But, MMC may cause different complications related to doses, especially if it is applied topically [19]. Various complications associated with its use have been reported in ophthalmologic surgery [20, 21]. In an experimental study, locally applied MMC at a concentration of 1 mg/ml effectively reduced epidural recurrence fibrosis without side effects after reaped spinal surgery in a laminectomy model in rats [22]. Experimental studies have demonstrated that MMC and Adcon-L have the equivalent effect in the prevention of peridural fibrosis, and both compounds have been demonstrated to be more effective than aprotinin [23].

5-Fluorouracil (5-FU)

5-FU is a chemotherapeutic agent that exerts its antiproliferative effect by antagonizing pyrimidine metabolism. Experimentally, 5-FU is a very effective inhibitor of fibroblast growth [19]. In addition to its broad use in cancer chemotherapy and glaucoma surgery, it has some efficacy in the treatment of keloid scars that overgrow the boundaries of the original wound [24]. Many growth factors have a role in wound repair, such as platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), and TGF-β, which can promote small increases in granulation tissue mass or incisional wound breaking strength [24]. Yildiz et al. and Lama et al. have demonstrated that 5-FU is an effective inhibitor of fibroblast growth. However, the long-term effects of the local application of 5-FU in the prevention of epidural fibrosis require further investigation [19, 25].

Tacrolimus

Tacrolimus (FK-506) is a novel macrolide immunosuppressant drug discovered in 1984, which is isolated from a strain of Streptomyces and is currently used for transplantation. FK-506 was discovered after cyclosporine and has a similar mechanism of action; however, it is 50-100 times more potent [26]. Tacrolimus can modulate the immune system and inhibit T cell function by binding to FK binding proteins (FKBP), and it mediates immunosuppression via the inhibition of calcineurin, calcium- and calmodulin dependent phosphatase [27]. FK506 can promote peripheral nerve regeneration through a reduction in scar formation; however, little is known regarding how FK506 reduces scar formation [28]. Recently, some studies have demonstrated the effect of FK506 on the reduction of epidural scar formation. Ismailoglu et al. reported that FK506 is an effective chemical agent in the prevention of post-laminectomy epidural fibrosis in rats [29]. Additionally, Yan et al. determined that topical application of FK506 could inhibit fibroblast proliferation and prevent epidural scar adhesion after laminectomy in a rat model [30].

Melatonin (MLT)

MLT is the main hormone of the pineal gland. In recent years, the neuroprotective, free radical scavenging, antioxidative, and analgesic properties of MLT have received significant attention [31]. It is known that exogenous MLT can prevent neuropathy development via the inhibition of lipid peroxidation in renal tissue and the inhibition of TGF-β, which limits the effects against fibrosis [32]. MLT can prevent increased hydroxyproline in fibrous tissue. The mechanisms by which MLT limits fibrosis are currently unclear; however, based on an experimental model, Erol et al. reported that MLT used for the prevention of epidural fibrosis after laminectomy exhibited a positive impact [4].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit inflammatory and fibroblastic responses. NSAIDs inhibit cyclooxygenases, which are responsible for the synthesis of prostaglandins [33]. In addition to the inhibition of prostaglandin synthesis, NSAIDs can also modify the synthesis of leukotrienes, the generation of superoxides, the release of lysosome enzymes and the aggregation and adhesion of neutrophils [34]. The effects of NSAIDs have been evaluated through a quantitative model of epidural post-laminectomy fibrosis in rats. This model allowed local or systemic trial administrations as a preventive treatment for post-laminectomy scar formation [35]. Sandoval et al. have reported that aceclofenac inhibits the presence of inflammatory cells in fibrous scars during the early stages after lumbar laminectomy in rabbits. These authors have suggested NSAIDs are capable of reducing the fibrous area and inhibiting the presence of inflammatory cells during fibrous scarring [36]. It is worth noting that the same authors did not identify a significant difference regarding the presence of fibroblasts in animals treated with aceclofenac compared with control animals in other experimental rabbit.
Table 2. Demonstration of the application of mechanical barriers in dura mater after surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Pharmacological agents</th>
<th>N of Animals and it’s type</th>
<th>Site of application</th>
<th>Rout of administration</th>
<th>Prevention of FBSS</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Richter et al.</td>
<td>2001</td>
<td>Adcon-L gel</td>
<td>398 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>41</td>
<td></td>
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<tr>
<td>Hiebert et al.</td>
<td>2001</td>
<td>Adcon L</td>
<td>27 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Tao et al.</td>
<td>2009</td>
<td>Amniotic membrane</td>
<td>56 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>43</td>
<td></td>
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<tr>
<td>Choi et al.</td>
<td>2011</td>
<td>Amniotic membrane</td>
<td>20 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>45</td>
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<tr>
<td>Kurt et al.</td>
<td>2009</td>
<td>CMC/PEO*</td>
<td>30 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>8</td>
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<tr>
<td>Kim et al.</td>
<td>2003</td>
<td>CMC/PEO*</td>
<td>23 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>47</td>
<td></td>
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<tr>
<td>Kim et al.</td>
<td>2004</td>
<td>CMC/PEO*</td>
<td>18 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>48</td>
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<tr>
<td>Fransen P</td>
<td>2008</td>
<td>CMC/PEO*</td>
<td>396 patients epidural</td>
<td>Topically</td>
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<td>49</td>
<td></td>
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<tr>
<td>Kurt et al.</td>
<td>2009</td>
<td>PTFE*</td>
<td>30 rats epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>8</td>
<td></td>
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<tr>
<td>Kim et al.</td>
<td>2013</td>
<td>Chitosan</td>
<td>41 rabbits epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>53</td>
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<td>Keskinet al.</td>
<td>2010</td>
<td>Chitosan</td>
<td>21 rabbits epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>54</td>
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<tr>
<td>Arrotegoi I</td>
<td>2011</td>
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<td>200 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
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<td>Narotame et al.</td>
<td>1995</td>
<td>Collagen</td>
<td>102 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
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<tr>
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<td>57</td>
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<tr>
<td>Oskinet al.</td>
<td>2012</td>
<td>Polyethylene glycol hydrogel</td>
<td>237 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>58</td>
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<tr>
<td>Richards et al.</td>
<td>2010</td>
<td>Fibrin Sealant-BMAB*</td>
<td>27 Sheeps epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>60</td>
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<tr>
<td>Savamurraet et al.</td>
<td>1999</td>
<td>Fibrin sealant</td>
<td>500 patients epidural</td>
<td>Topically</td>
<td>Through PEF*</td>
<td>61</td>
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</table>

CMC/PEO* Carboxymethylcellulose/polyethylene oxide PTFE* Polytetrafluoroethylene MBAB*Based Medicated Adhesion Barrier studies [37].

Implantation of materials to prevent epidural fibrosis

A large variety of materials, including several bioabsorbable barriers, have been implanted on the dura mater and nerve structures in experimental and clinical studies to prevent epidural fibrosis after laminectomy [38]. In 1974, LaRocca and MacNab were the first authors to describe laminectomy membranes that are composed of various biological and synthetic materials used to prevent scar formation. These materials have been evaluated, and hemostatic sponges, free fat grafts, silastic, hyaluronic acid, polyactic acid, carboxymethylcellulose gels, Adcon-L and other implanting materials are worth noting (Table 2).

Adcon-L

Adcon-L is a pharmacological gel prepared from a mixture of a dextran sulfate and gelatin, which serves to reduce the incidence and severity of scarring during spinal surgery. There are opposing opinions regarding the effects of Adcon L. Vogelsang et al. reported a reduced incidence of heavy scarring after the application of Adcon-L in a clinical study that included 100 patients [39]. However, in a prospective study that involved 54 patients, Nyagaard et al. reported that after twelve months, there was no connection detected via magnetic resonance imaging (MRI) between peridural scarring and clinical results [40]. In addition, Richter et al. found no positive effect on the prevention of epidural fibrosis with Adcon-L gel in patients undergoing one-level lumbar discectomy [41]. Nevertheless, Adcon L is widely used, and there are some reports of side effects, such as late-onset headaches and associated leakage of cerebrospinal fluid from dural injuries secondary to delayed healing and foreign body reactions [42]. Based on these data, further investigation is necessary to identify the role of Adcon-L in the prevention of epidural fibrosis after spinal surgery.

Amniotic membrane (AM)

AM is a promising material composed of the inner fetal membrane. It comprises an inner layer of epithelial cells on a basement membrane [43]. AM can reduce inflammation, inhibit vascularization, treat infection and limit postoperative adhesions. Therefore, AM has considerable use in the treatment of various diseases, such as non-healing skin ulcers, vaginal atresia, and some ocular diseases [44]. Using a rat model, Choi et al. demonstrated that implantation of a human AM after laminectomy significantly reduces epidural fibrosis on macroscopic evaluation; the authors suggested the potential use of human AMs as an adhesion technique in clinical practice [45].

Carboxymethylcellulose and polyethylene oxide (CMC/PEO)
CMC/PEO gel is an anti-adhesion gel that reduces adhesions and interacts with proteins. Since 2002, a synthetic combination of CMC/PEO has been used that contains calcium chloride for stabilization. One trade name is Oxiplex/SP gel, which, in an experimental study in rabbits, reduced epidural fibrosis and did not impair normal healing. Both components of Oxiplex/SP gel (CMC and PEO) are known to reduce adhesion formation and fibrotic scars that form after surgery. Kim et al. have demonstrated a reduction and lower-extremity weakness over a 6-month follow-up period in patients that underwent discectomy. In another study, the same authors reported that a greater benefit in clinical outcome measures was identified over the 12-month follow-up period in gel-treated patients. According to Fransen, the results of his clinical safety assessment of CMC/PEO in spinal surgery were positive.

Chitosan

One of the most abundant marine-based biopolymers is chitosan, which has a low molecular weight and is a water-soluble hydrolysate of chitosan that has a wide range of biological activities. The trade name of chitin is SuporGel. It is a novel adhesion barrier produced from macromolecular polysaccharides and has a structure similar to human tissue, which enhances epithelial regeneration, prevents fibroblast growth and decreases hemorrhage. Chitosan has exhibited effective anti-adhesive properties comparable to hyaluronic acid-carboxymethylcellulose membranes (HA-CMCs) in a rabbit laminectomy model and has been used as an anti-adhesive agent for spine surgery. Additionally, Keskin et al. demonstrated that chitin is effective in the prevention of epidural fibrosis, and based of their findings, they suggest that chitin is an effective adhesion barrier agent.

Collagen dural matrix

Collagen dural matrix is an adhesion barrier that prevents periradicular lumbar fibrosis following spine surgery. It is a collagen sponge used as an onlay graft to repair cranial and spinal dural defects. It has been used in some experimental and clinical studies as a substitute for dura mater. Collagen dural matrix is the first reported effective and safe onlay dural graft solution for the prevention of symptomatic post-operative epidural fibrosis. In a study using rabbits, it was demonstrated that collagen dural matrix (Duragen) was more effective than a fat graft in the prevention of epidural fibrosis; however, there was no significant difference compared with the control animals. Considering Duragen’s excellent clinical profile, it may be useful as an adhesion barrier, and it can be used successfully in the prevention of epidural fibrosis and, consequently, FBSS.

Polytetrafluoroethylene (PTFE)

PTFE is a synthetic fluoropolymer of tetrafluoroethylene. Its trade name is Gore-Tex, and it represents an anti-adhesive material. The anti-adhesive properties of Gore-Tex have been previously studied in abdominal and vascular surgeries. Gore-Tex is based on thermo-mechanically expanded PTFE and other fluoropolymer products, which are used in a wide variety of applications, such as high performance fabrics, medical implants and filter media. Most experimental studies have focused on its beneficial effects in the prevention of postoperative peridural fibrosis. Gore-Tex and Oxiplex share a similar barrier effect and can be safely used for peridural fibrosis.

Chitosan

Polyethylene glycol hydrogel

Polyethylene glycol hydrogel is known as DuraSeal. The Dural Sealant System was approved by the United States Food and Drug Administration to obtain watertight dural closure when applied after dural suturing. This novel, non-swelling polyethylene glycol-based hydrogel is effective against cerebrospinal fluid (CSF) leakage and also prevents adhesion formation after spine surgery. Polyethylene glycol hydrogel is a dual function material that reduces postoperative leaks and prevents epidural adhesion formation.

Fibrin sealant-based medicated adhesion barrier

The majority of anti-adhesion studies have primarily focused on the contact between dura and invading fibroblasts through the application of various barriers. Previous studies have demonstrated that a fibrin sealant is effective in the prevention of early post-laminectomy scar formation in an experimental laminectomy model. There is no evidence for these effects at the later stages of wound healing when epidural adhesions form. Additionally, the fibrin sealant-based medicated adhesion barriers, such as polyethylene glycol hydrogel, have dual functions. They treat dural tears in craniotomy procedures and have been demonstrated to be effective and safe. According to Richards et al., a fibrin sealant is not sufficient in the prevention of long-term epidural adhesion formation, and a combination with other potential anti-adhesive agents may be required.

Conclusion

The prevention of FBSS via the inhibition of epidural fibrosis after laminectomy represents a major challenge in spine surgery. For this reason, a variety of biological, pharmacological, and different synthetic materials have been used for more than 25 years. Increasing efforts have been
aimed at the identification of the previously described preparations, which are characterized by biocompatibility, biodegradability, the prevention of epidural fibrosis, the lack of complications and the lack of a delay in wound healing. Future studies should be aimed at the identification of appropriate chemical preparations and mechanical barriers that, together with perfections of operative surgical techniques, will decrease the formation of epidural fibrosis and, consequently, FBSS, which will reduce the need for reoperation after spine surgery.

Conflict of Interest

The authors declare that they have no conflict of interest

Authors contributions

YM wrote the manuscript and assisted in editing. AM performed the literature research and editing. Both authors read and approved the final manuscript.

References


