THE USE OF VARIOUS MATERIALS AND DRUGS FOR THE PREVENTION OF THE DEVELOPMENT OF POSTOPERATIVE LUMBAR EPIDURAL FIBROSIS: LITERATURE REVIEW

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The paper is a review of the current literature data on the use of various materials and drugs for the prevention of the development of postoperative lumbar epidural fibrosis. Literature searches were performed in the Pubmed, Medline, EMBASE, Cochrane Library and eLibrary databases. The formation and growth of fibrous tissue in the epidural space, followed by tissue adhesion to the dura mater, is the leading cause of pain afferentation in the lumbar spine and/or lower extremities. Several molecular and cellular mechanisms play an important role in the pathophysiology of connective tissue formation in the epidural space. An analysis of experimental and clinical studies examining the effectiveness of various materials and drugs is presented. The authors present the current data on new therapeutic approaches to the prevention of postoperative epidural fibrosis. Topical, unresolved issues which necessitate further research on the pathophysiology of epidural fibrosis are indicated.

Key Words: postoperative epidural fibrosis, adhesion, laminectomy, materials, drugs, prevention.

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Firstly described by LaRocca and MacNab [1] in 1974 as a so-called laminectomy membrane, epidural fibrosis is an urgent issue of modern spinal surgery and orthopedics. Many experimental and clinical papers have been focused on the study of various ways to prevent the connective tissue growth in the epidural space. The main purpose of these studies is the prospect for improving the clinical results of the spinal surgery [2]. A failed back surgery syndrome has been proven to be caused by epidural fibrosis [2–4]. According to a systematic review by Clancy et al. [3], which combined 6 clinical studies of a total of 663 respondents, the formation of connective tissue in the epidural space is the third most common cause (at least 8 %) of the development of the failed back surgery syndrome. Only spinal disc herniation and spinal stenosis are ahead. Regardless of the low prevalence of epidural fibrosis as a reason for the development of a failed back surgery syndrome in patients who have had surgery, this pathological condition requires a detailed examination both from the fundamental and clinical medicine. The advancement of surgical technologies and techniques for the perioperational prevention of the epidural fibrosis does not decrease the prevalence of connective tissue formation in the epidural space after spinal surgeries, and still leaves this indicator high (from 4 to 50 %) [5]. An epidural fibrosis is associated with an inevitable adhesion process of connective tissue to the dura mater, which can result in compression of the dural sac and/or spinal cord roots with the development of appropriate clinical and neurological symptoms (Fig.) [6, 7]. Surgical revision interventions on the spine are associated with a high frequency of adverse effects, as well as with a decrease in the personal satisfaction of the patients with the performed surgeries [7].

Today, several therapeutic methods have been studied for epidural fibrosis, including the drug efficacy. The most effective treatment methods in patients with epidural fibrosis were the following: epidural administration of glucocorticoid hormones, adhesiolysis, radiofrequency ablation, neuromodulation, as well as the use of antiepileptic drugs, non-steroidal anti-inflammatory drugs, antidepressants and opioid analgesics [8]. However, only gabapentin, adhesiolysis and the epidural administration of glucocorticoid hormones have the evidence grade I in the treatment of clinical implications of epidural fibrosis [9]. There are experimental data studying the effectiveness of methylprednisolone, dexamethasone, promethazine, human fibrinolysin, mitomycin C and a number of other agents in the prevention of the epidural fibrosis [10, 11]. There are papers aimed at studying the effectiveness of barrier methods for preventing the connective tissue formation in the epidural space (adipose self-tissue, bioresorbable gelatin sponge, cellulose mesh, hyaluronic acid) [12].

Immunosuppressive and antitumor drugs are essential for the of the post-

operative epidural fibrosis. For example, tamoxifen, an estrogen antagonist and a highly active antitumor agent, has proven its high antifibrotic activity against perivascular fibrosis, lung fibrosis, kidney fibrosis, as well as epidural fibrosis [13]. Etanercept is an anti-tumor necrosis factor agent α (TNF α). It also has a pronounced antifibrotic activity [14]. A tacrolimus is a immunosuppressive agent. Due to the inhibition of fibroblast proliferation and migration, it can effectively prevent the epidural fibrosis development [15].

A search of literature sources in the Pubmed, Medline, EMBASE, Cochrane Library and eLibrary proved the presence of a large number of experimental and clinical studies focused on the effectiveness of various biomaterials and drugs in the prevention of postoperative lumbar epidural fibrosis. It should be noted that the results of these studies are confusing and contradictory in many ways.

The aim of this review is to analyze modern literature sources focused on the study of the effectiveness of various biomaterials and drugs in the prevention of postoperative lumbar epidural fibrosis.

Natural Polymers

Hyaluronic acid and its compounds. Hyaluronic acid is a bio-friendly heteropolysaccharide and has been actively used in a wide clinical practice for many years. The hyaluronate effectively reduces the proliferation of fetal fibroblasts and cicatrization in the early stages of wound healing [16]. As an anti-adhesive agent, the hyaluronic acid is used in abdominal surgery, traumatology and orthopedics, as well as in ophthalmic surgery [17]. The studies carried out at the beginning of the last decade revealed a high antifibrotic activity of both isolated hyaluronate and its various compounds in connection with postoperative epidural fibrosis. For example, in the work of Isik et al [18] it was observed that the use of high-molecular hyaluronic acid (gel) contributes to a decrease in the intensity of connective tissue formation in the epidural space, and also downgrades the density of the already formed tissue. Meanwhile, the authors argue that no significant differences in the effectiveness of hyaluronate and its high-polar compound were found either in pathomorphological or biochemical analyses of connective tissue samples. At the same time, Cencetti et al. [19] consider that the use of hyaluronic acid gel can delay the hydrolytic cleavage of the latter and slightly prolong (no more than 7 days) its antifibrotic effect in the epidural space. The report by Chen et al. [20] has shown that gelatin based on hyaluronic acid is capable of effectively preventing the process of adhesion of connective tissue and dura mater in rabbit models that underwent lumbar laminectomy.

The aggregate state of hyaluronic acid is of fundamental importance in achieving a full antifibrotic effect. For example, the use of semi-solid and solid forms of hyaluronate compounds can significantly prolong its antifibrotic effect, in comparison to the liquid forms. Kato et al. [21] have observed that the use of solid forms of hyaluronic acid compounds enables to avoid material migration, to create a direct barrier between the dura mater and the musculoaponeurotic layer, as well as to protect neural structures from compression effects. The paper by Hahn et al. [22] proved that the application of semi-solid and solid forms of hyaluronate compounds prolongs the antifibrotic effect up to 29 days. However, this duration of antifibrotic action of hyaluronic acid compounds does not ensure full protection of the dura mater from the process of connective tissue adhesion, since the duration of fibrogenesis is on average 4-6 weeks [23].

Fibrin glue and its forms. A fibrin is a high-molecular non-globular protein formed from fibrinogen synthesized in the liver and blood plasma under the enzyme thrombin. It has the shape of smooth or cross-banded fibers, clots of which form the basis of a blood clot during the coagulation [24]. Today, various types of fibrin are used in clinical practice. One of these forms is a platelet-

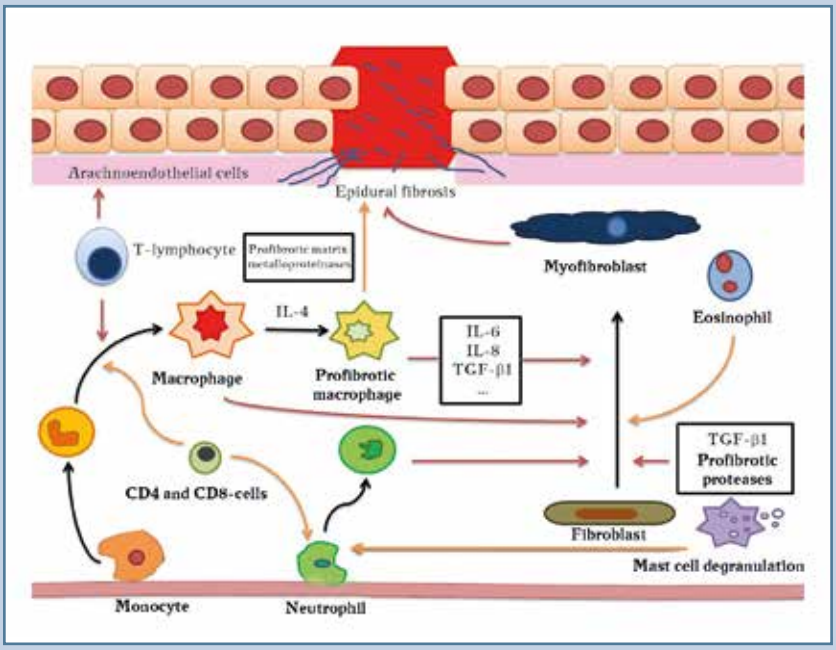

Fig.
The scheme of molecular and cellular mechanisms of epidural fibrosis development: IL – interleukins; TGF – a transforming growth factor; CD – a cluster of differentiation [71]

rich fibrin gel, which can hold the remnants of white blood cells and cytokines secreted by them, which are formed in response to the centrifuge process. According to Demirel et al. [25], a platelet-rich fibrin glue contains a number of anti-inflammatory cytokines, (IL-1 , IL-6, TNF-β), an anti-inflammatory mediator (IL-4), as well as an angiogenesis stimulator (VEGF).

Due to its membrane structure, a platelet-rich fibrin glue serves as a direct barrier between the dura mater and soft tissues and prevents the process of their adhesion. The adhesive may also control the activity of collagenase and the actual synthesis of collagen. Being saturated with platelets, a fibrin glue is a general-purpose hemostatic agent to ensure a quick control of bleeding and inhibition of the migration of fibroblasts from the blood to the wound. It also has a high degree of biocompatibility and does not trigger hypersensitivity reactions. Furthermore, single white blood cells, which are part of the adhesive, prevent the development of infections of the surgical site [25, 26]. The antifibrotic and anti-adhesive effects of the platelet-rich fibrin glue have been clearly proven in a number of experimental studies. For example, Demirel et al. [25] showed that the use of fibrin-platelet adhesive in an experiment on rats ensures a full hemostasis in the wound. It also prevents the flow of fibroblasts from the vascular bed, downgrades the intensity of the inflammatory process due to the anti-inflammatory cytokines. That particular prevents the development of connective tissue in the epidural space. Anitua et al. [27] also confirmed the antifibrotic and anti-adhesive effect of the platelet-rich fibrin glue.

An isolated fibrin glue is an adhesive system of fibrin which initiates the last stage of physiological blood clotting. The transition of fibrinogen to fibrin is carried out by splitting fibrinogen into fibrin monomers and fibrinopeptides. The aggregation of fibrin monomers results in the formation of a fibrin clot. An activated transglutaminase bonds fibrin strands together. The ions of Ca^{2+} are essential both for the transformation of fibrinogen and for the cross-connection of fibrin. As the wound heals, plasmin causes increased fibrinolytic activity of plasma, because of which the decomposition of fibrin to fibrin degradation impurities is initiated [28]. Vaquero et al. [29] and Cekinmez et al. [30] have proved the effectiveness of isolated fibrin glue in the prevention of epidural fibrosis. Vaquero et al. [29] observed that the antifibrotic and anti-adhesive effect of fibrin glue remains for two weeks after laminectomy. Cekinmez et al [29] obtained the similar results during their study. Yet, today there are no studies comparing the effectiveness of isolated fibrin glue and fibrin-platelet glue.

Amniotic sac. The amniotic sac forms the reservoir wall filled with the amniotic fluid in which the fetus is located. The main function of the amniotic sac is the production of amniotic fluid, which provides an environment for the developing organism and protects it from mechanical abnormality. The amniotic sac epithelium, turned into its cavity, not only secretes amniotic fluid, but also takes part in their reabsorption. The amniotic fluid keeps the essential composition and concentration of salts until the end of pregnancy. The amniotic sac also has a protective function, preventing hazardous agents from entering the fetus [31]. The effectiveness of the amniotic sac in the prevention of epidural fibrosis is shown in several experimental studies. For example, Choi et al. [32] showed that the application of a freshly frozen amniotic sac to the dura mater in rats undergoing laminectomy can prevent the connective tissue formation in the epidural space. At the same time, in the paper by Tao et al. [33] it was shown that the use of a freshly frozen amniotic sac does not promote the long-term preservation of the dura mater from the process of adhesion of the muscular aponeurotic layer owing to the rapid degradation of the sac by enzymes. The authors of this study argue that the use of an amniotic sac soaked in a 0.25 % solution of glutaraldehyde effectively suppresses the connective tissue formation in the epidural space after performing surgeries on the spine for 12 weeks. This technique is recommended for the clinical practice of spinal surgeons and orthopedists.

Chitosan. Chitosan (aminosaccharide), a derivative of a linear polysaccharide, macromolecules consist of randomly connected β-(1-4)-D-glucosamine units and N-acetyl-D-glucosamine. The chitosan is derived only from chitin, which is naturally found in the cell walls of fungal of Zygomycota (in complex with chitin) and crustacean shells [34]. Carvalho et al. [35] and Li et al. [36] have proved the effectiveness of chitosan and its compounds in experimental studies. For example, Carvalho et al. [35] have graphically proved that the application of the chitosan membrane to the dura mater in rabbits effectively decreases the epidural fibrosis severity. Li et al. [36] also proved the high antifibrotic activity of local application of the chitosan compound in combination with L-glutamic acid in rabbits which underwent laminectomy. Furthermore, the authors of this study pointed out that the use of chitosan/L-glutamic acid combination gives an opportunity to reduce the adhesion of the dura mater and the musculoaponeurotic layer. Moreover, it is also necessary to reduce the severity of scar tissue compression on the neural structures (according to the MRI study) 24 weeks after spinal surgery.

Synthetic Polymers

Copolymer of lactic and glycolic acids. The membrane, consisting of a copolymer of lactic and glycolic acids, is of good biocompatibility, pronounced barrier properties and a long resorption period. The antiadhesive activity of the copolymer of lactic and glycolic acids is similar to the application of adipose self-tissue [37]. The study by Li et al. [36] reported that the use of this copolymer can effectively reduce the degree of connective tissue formation in the epidural space in rabbits after laminectomy. The main disadvantage of the copolymer of lactic and glycolic acids is its rapid resorption. Following complete resorption of the copolymer, a free cavity is formed between the dura mater and soft tissues.

ADCON-L. ADCON-L by Gliatech (USA) is a non-toxic biodegradable carbohydrate polymer gel consisting of polyglycan ester and gelatin in a phosphate-salt buffer. ADCON-L was widely applied in the clinical practice of spinal surgeons and orthopedists to prevent the development of postoperative epidural fibrosis and the failed back surgery syndrome [38, 39]. For example, Kim and Lim [40] showed that the local use of ADCON-L gel in patients after lumbar microdiscectomy considerably downgrades the degree of epidural fibrosis and the pain severity in the postoperative period. In the paper by Demirel et al. [25] a comparative analysis of the antifibrotic and anti-adhesive activities of platelet-rich fibrin gel, ADCON-L and hyaluronic acid was performed. The authors concluded that the studied polymers decrease the epidural fibrosis severity and adhesion of the dura mater and soft tissues, but the fibrin-platelet gel has the most pronounced effect. It should be noted that the use of ADCON-L is associated with the development of adverse events, among which the most common were a decrease in the activity of bone block formation in the operated spinal motion segment and an impaired healing of the musculoaponeurotic layer [41]. The development of these complications has resulted in a considerable decrease in demand for this polymer and its further phase-out.

Polytetrafluoroethylene membrane. It is a porous, stable synthetic polymer providing a barrier function and preventing the migration of fibroblasts into the epidural space. According to the anti-adhesive properties, the polytetrafluoroethylene membrane is several times superior to adipose self-tissue [42]. In the clinical series of Lada et al. [43] it was clearly proved that polytetrafluoroethylene membrane implantation is highly effective in preventing the development of postoperative lumbar epidural fibrosis in patients after laminectomy. The same results were found in the study of Ivanic et al. [44]. Nevertheless, some authors consider that the polytetrafluoroethylene membrane serves as a foreign body in the epidural space and only sustains the inflammatory process and the connective tissue formation [45]. Undoubtedly, it is essential to conduct further experimental and clinical studies of the effectiveness of this synthetic polymers in the prevention of epidural fibrosis.

Copolymer of multi amino acids and nano-hydroxyapatite. Compared with other synthetic polymers, this one shows considerably better biocompatibility and an adjustable rate of resorption [46]. The decay products of the copolymer are neutral and do not result in an inflammatory process. It is well known that calcium hydroxyapatite is the main mineral component of bone tissue (about 50 % of the total bone mass) [47]. Therefore, the use of nano-hydroxyapatite, which is part of the copolymer, is one of the prospective methods for preventing the postoperative epidural fibrosis. This is due to its good biocompatibility, a high degree of bone integration and proper barrier properties between the dura mater and soft tissues. Zhao et al. has proved a clinical efficacy of the compound "hydroxyapatite/polyamide-66" [48]. The researchers have proved that the use of the vertebral arch, consisting of the complex "hydroxyapatite/polyamide-66", can effectively prevent the epidural fibrosis and adhesion of the dura mater and soft tissues. Moreover, it enables to maintain normal biomechanical characteristics of the lumbosacral spine and to achieve regression of the existing clinical and neurological symptoms.

Copolymer of lactic and glycolic acids/ polyethylene glycol. The combined use of a copolymer of lactic and glycolic acids and polyethylene glycol has proved its high anti-adhesive activity in abdominal surgery [49]. It worth noting that the anti-adhesive effect of this combination of polymers is achieved both due to the direct barrier mechanism and owing to the support function performed by them. The copolymer of lactic and glycolic acids / polyethylene glycol is distinguished by reduced cytotoxicity, prolonged resorption, as well as moderate antiangiogenic and pronounced anti-adhesive effect [49]. Furthermore, to increase the resorption time of this combination of polymers, a complexation reaction with various metals is carried out [49].

Drugs

Tamoxifen. It is a competitive blocker of estrogen receptors on the surface of target organ cells and has been intensively used in the prevention and treatment of breast cancer for half a century [50]. The antifibrotic action of tamoxifen is a disruption of the transcription process of ribonucleic acid, inhibition of cell proliferation and the production of cellular growth factors (TGF and IGF) [50]. Some clinical studies report that tamoxifen effectively reduces the pulmonary fibrosis severity and the adhesion of peritoneal layers by reducing the synthesis of TGF-β and IGF-1 [51]. In the case of Kim et al. [52] it was shown that tamoxifen effectively suppresses renal parenchymal fibrosis by inhibiting TGF-β1-induced fibroblast proliferation and migration. The oral efficacy of tamoxifen against epidural fibrosis was clearly shown in an experimental study by Ozturk et al. [13]. The authors have proven that oral administration of tamoxifen significantly reduces the epidural fibrosis severity, the adhesion of the dura mater and the musculoaponeurotic layer and the inflammatory process in the epidural space in comparison with the application of the hemostatic sponge "Spongostan" (USA).

Methotrexate. Methotrexate it is an antagonist of folic acid and refers to the group of cytotoxic immunosuppressive drugs [53]. Chen et al. [54] studied the antifibrotic effect of methotrexate in an experiment on 48 rats after laminectomy. They have obtained promising results. However, a study by Wiebe et al. [55], comparing the types and occurrence of adverse side effects associated with taking tamoxifen and methotrexate, proved a significant advantage and safety of tamoxifen. Furthermore, Eckermann et al. [56] have shown that the preventive use of tamoxifen is cost-efficient. All this have resulted in the termination of

further studies on the effectiveness of methotrexate in epidural fibrosis.

Bevacizumab. Bevacizumab is a VEGF antagonist. It is actively used as a molecular targeted drug in patients with colorectal cancer and high-grade brain gliomas [57]. Karatay et al. [58] noted that bevacizumab contributes to reducing the epidural fibrosis severity in an experiment on rats after laminectomy. Nevertheless, the widespread use of bevacizumab in clinical practice is limited, which is associated with a large number of adverse drug reactions. The most common adverse reactions of bevacizumab are malignant arterial hypertension, anaplastic anemia and myelodysplastic syndrome [59]. At the same time, a number of researchers consider that the use of bevacizumab in short courses (up to 3–7 days) will effectively prevent the postoperative epidural fibrosis without the development of significant adverse drug reactions [60].

Tacrolimus. Tacrolimus refers to a group of immunosuppressive drugs. By its chemical structure, it is classified as a natural macrolide, produced by actinomycete *Streptomyces tsukubaensis* [61]. Its antifibrotic and anti-adhesive effects were considered in the studies of Ismailoglu et al. [62] and Yan et al. [63]. In both cases, tacrolimus was highly effective in epidural fibrosis prevention. The main mechanism of the antifibrotic action of tacrolimus is the suppression of the production of proinflammatory cytokines by cells (IL-2, -4 and TGF-β) and, consequently, inhibition of fibroblast proliferation and migration into the epidural space [63].

Mitomycin C. Mitomycin C is a cytostatic drug from the group of antitumor agents. According to its chemical structure, it belongs to mitosans. This drug has an alkylating action mechanism. Some studies have indicated that the topical use of mitomycin C helps to reduce the epidural fibrosis severity after laminectomy [64, 65]. Lee et al. [66] believe that the high antifibrotic activity of mitomycin C is a direct apoptotic effect on fibroblasts due to the inhibition of the endoplasmic reticulum. Considering the large number of adverse drug reactions associated with the local use of mitomycin C, its widespread use is impossible. Liu et al. [11] and Wang et al. [67] studied the effectiveness of a combination of mitomycin C and polyethylene glycol and persuasively proved that this combination can effectively reduce the migration and proliferation of fibroblasts into the epidural space. As for polyethylene glycol, it promotes the dosed release of mitomycin C, which contributes to the almost complete leveling of the development of adverse drug reactions.

Steroid and non-steroidal anti-inflammatory drugs. In the paper by Lin et al. [68] it was shown that the local use of the combination of ibuprofen/hyaluronate/polygalacturonic acid enables to prevent the epidural connective tissue formation. The released ibuprofen has low cytotoxicity and considerably reduces the prostaglandin E2 synthesis. The histological examination of the formed epidural scar tissue in rats after laminectomy revealed a substantial decrease in the collagen fiber content, as well as a decrease in the migration and proliferation of fibroblasts. Liu et al. [69] also observed that the use of ibuprofen can contribute to the regression of clinical and neurological symptoms in the early postoperative period after lumbar laminectomy. Cekinmez et al. [30] showed that the isolated use of methylprednisolone is as good as the combination of methylprednisolone/fibrin glue in its antifibrotic activity and can be used in a wide clinical practice of spinal surgeons and orthopedists. Haskell et al. [70] have studied the clinical and instrumental efficacy of epidural injections of steroid hormones. They concluded that epidural injections of glucocorticosteroid hormones have high antifibrotic and anti-adhesive activity. These hormones make it possible to grade clinical and neurological symptoms and reduce the compression of the dural sac and spinal cord roots with an average period of postoperative follow-up of at least 12 weeks for the respondents.

Conclusion

The postoperative epidural fibrosis is the leading cause of the failed back surgery syndrome and is an actual challenge of modern spinal surgery and orthopedics. In this review, the authors attempted to introduce up-to-date literature data on experimental and clinical methods for preventing the postoperative lumbar epidural fibrosis. The prior knowledge concerning the pathophysiology of epidural fibrogenesis provides an opportunity to actively develop and introduce into wide clinical practice new anti-adhesive and antifibrotic methods, based on the use of biological and synthetic polymers, and their combination with various drugs. A particularly interesting fact is the use of a combination of polymers with cytotoxic and immunosuppressive agents and the dosed release of the latter into the epidural space. Undoubtedly, further investigation of the pathophysiology of postoperative epidural fibrosis will considerably advance the treatment of this group of patients.

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