PREVENTION OF POSTOPERATIVE EPIDURAL FIBROSIS: CURRENT STATUS OF THE ISSUE

A.P. Zhivotenko[1], Z.V. Koshkareva[1], V.A. Sorokovikov[1, 2]
[1]Irkutsk Scientific Center of Surgery and Traumatology, Irkutsk, Russia
[2]Irkutsk State Medical Academy of Postgraduate Education, Irkutsk, Russia

Epidural fibrosis is a common cause of a failed back surgery syndrome. The current scientific literature proposed many methods for prevention of epidural fibrosis, however, universal methods to fully solve the problem was not found. Prevention tasks in the preoperative period include the identification of risk factors for the development of epidural fibrosis with the correction of the revealed violations. Intraoperative prevention involves the development of barriers in the form of natural and synthetic polymeric materials that impede the formation of epidural fibrosis after laminectomy. The complex of measures to prevent the development of epidural fibrosis in the postoperative period is supposed to include a list of manipulations consisting of epidural blockades with a common complex anti-inflammatory drug therapy. The study presents an analysis of 63 literary sources from PubMed, EMBASE, Cochrane Library, and eLIBRARY databases most fully reflecting the pathogenetically substantiated prevention of the epidural fibrosis development in the preoperative, intraoperative and postoperative periods.

Key Words: spine, osteochondrosis, laminectomy, complications, Failed Back Surgery Syndrome (FBSS), epidural fibrosis, prevention, treatment.

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In the framework of our study, we have analyzed 63 literature sources from the following data bases: PubMed, EMBASE, Cochrane Library, eLIBRARY, most fully reflecting the pathogenetically substantiated prevention of the epidural fibrosis development in the preoperative, intraoperative, and postoperative periods.

The spine surgery develops rapidly. Thanks to the improvement of the quality of diagnostics and surgical techniques, the number of spinal surgeries increases annually. In the USA, the number of lumbar decompression surgeries, involving the stabilization of spinal motion segments, increased from 77,682 to 210,407 in 1998–2008. The rate of laminectomies without stabilization increased by 11.3 %, from 92,390 to 107,790 patients.

In 2002, the total number of spinal surgical interventions exceeded one million [1, 2]. The incidence of pain syndrome in the lumbar spine increases with age, consequently, the number of surgeries to treat degenerative diseases increases in accordance with demographic aging of population [3]. Thus, in the USA, the average age of operated patients increased from 48.5 to 52.2 years [3, 4]. At this age, spinal stenosis of degenerative genesis often develops with different degree of manifestations of neurovascular compression syndrome; that is why minimally invasive surgical techniques are not always acceptable, and more traumatizing decompression surgical interventions involving/not involving the spine stabilization dominate [5]. According to the literature data [6–9], failed surgical interventions make up 10–40 %.

The principal symptom of the failed back surgery is recurrence of pain syndrome in the postoperative period [10]. New concepts and terms, such as postlaminectomy syndrome and failed back surgery syndrome (FBSS), have appeared [11, 12]. FBSS encompasses a heterogeneous group of disorders that have in common a complex of symptoms, the main of which is a persistent or recurrent chronic pain in the lumbar spine and lower extremities after the spinal surgery that seemed to be anatomically successful. Consequently, the operating surgeon and patient not always receive the expected positive results of the surgical treatment. Approximately 95 % of FBSS patients can be provided with an ethiopathogenetically substantiated diagnosis [10]. In 5 % of cases, it is difficult to determine the real cause of pain because of the existing surgical and ethiological reasons causing pain syndrome [10, 13]. It is known that a repeat surgery is necessary in nearly half of the FBSS cases [10], but every next spinal surgery decreases the percentage of satisfactory results. Thus, more than 50 % of primary spinal surgeries are successful, at the same time, no more than 30 %, 15 %, and 5 % of the patients have successful outcomes after the second, third, and fourth surgeries, respectively [1, 7].

One of the main surgical reasons of the pain syndrome recurrence in the postoperative period is the formation of epidural fibrosis, thus making the repeat surgery more difficult and risky [5, 14]. The role of epidural fibrosis in the pain syndrome development in the postop-

erative period is controversial [15, 16], whereas there is no doubt that it worsens outcomes of the repeat spinal surgery. Postoperative cicatricial epiduritis develops in 100 % of cases in presence of aseptic inflammation as a reaction to the injury during surgical interventions, involving various clinical neurological manifestations and morphological changes in tissues, and these manifestation do not always correlate in the postoperative period [17].

The role of epidural fibrosis in the pain syndrome formation has not yet been clearly identified, nevertheless, it is known that scar tissue forms adhesions between neurovascular anatomical structures of the spinal canal, compresses them and increases sensibility of the nerve root during the formation of recurrent herniation and foraminal spinal stenosis because of the restriction of the spine movement. Moreover, atrophia of neurons and demyeliniation of axons take place under the scar tissue [18].

A direct correlation is observed between the rise in frequency of various intraoperational complications (injuries of the dura mater, nerve roots and vessels) accompanied by bleedings into the epidural space and development of postoperative liquorrhea after repeat surgeries in the setting of epidural fibrosis [19]. The prevention of cicatricial epiduritis is nowadays an important and unsolved problem in the spine surgery. In case of repeat surgeries and persistent pain syndrome, epidural fibrosis is not always the main reason; there is a combination of several reasons causing a complex of clinical neurological disorders that determine the surgeon's decision whether a repeat surgery is necessary [14]. According to the literature data [5], surgeons are not satisfied with outcomes of spinal surgeries in case of repeat surgeries, when the diagnosis of epidural fibrosis is made. The prevention of the epidural fibrosis development is a recommended alternative aimed to reduce the frequency of complications in case of repeat surgical interventions and to improve their outcomes [20].

Methods of the epidural fibrosis prevention. The prevention of cicatricial epiduritis foresees the following three periods: preoperative, intraoperative and postoperative. The prevention tasks in the preoperative period include the identification of risk factors and predictors for the epidural fibrosis development, prognostication of the development, and the revealed problems correction. There are known methods of prognostication of the epidural fibrosis development in the preoperative period based on the coagulogram data with the assessment of fibrinolytic activity of blood and the subsequent correction of the found disorders [21, 22]. The estimation of the epidural fibrosis development was carried out taking into account anthropometric, immunologic, and immunogenetic parameters [23–25]. The preoperative prognostication and the performed prevention of cicatricial epiduritis do not always reflect the real situation of the epidural fibrosis development. That is why the prevention should be considered as a complex of measures on the organism, organ, tissue, and cellular levels [17, 26]. One of these measures is the intraoperative prevention aimed to reduce nonspecific aseptic inflammation process in the epidural space, to create a barrier isolating the dura mater and neurovascular structures, to minimize traumatization of tissues on the basis of the microsurgery principles (careful attitude to tissues, meticulous hemostasis, removal of all necrotically changed tissues, minimization of ischemia, up-to-date non-immunogenic suture materials, prevention of ingress of infection and foreign bodies into the wound, elaboration of minimally invasive technologies in order to reduce traumatization of surgical interventions), as well as to reduce the surgery duration [27, 28]. There are methods of prevention of the epidural fibrosis development by creating a barrier with the use of autologous tissues (adipose, dorso-lumbar fascia, and yellow ligaments) [29–32]. The disadvantage of autografts is their biodegradation due to their atrophy or necrosis, often with the formation of a seroma; so they do not impede the epidural fibrosis development [31, 32]. The cases of the migration of adipose transplants into the spinal canal with the subsequent development of caudal syndrome are described in the literature [31, 32].

Different methods of laminoplasty are used to create a bone barrier, but they increase the surgery duration and a risk of purulent-septic and thromboembolic complications in the postoperative period. These surgeries are known for massive blood losses that complicate the cause of concomitant chronic cardiorespiratory diseases [33].

One of the measures of the intraoperative prevention of cicatricial epiduritis is the development of barriers in the form of natural and synthetic polymer materials that impede the epidural fibrosis formation after laminectomy [34]. Strict requirements are imposed on the choice of ideal barrier materials. They must be effective, biocompatible [35], completely bio-degradable in the organism during a certain period of time, they must be attached to damaged surfaces without additional fixation, they must remain active in the presence of exudate [36, 37], become integrated into the tissues of the recipient (do not encapsulate).

All the proposed materials are developed to impact different pathophysiological processes in the wound, including reduction of the inflammatory response in the operational area, inhibition of fibroblast proliferation, use of pharmaceutical drugs affecting the fibrin formation/decomposition balance, mechanical separation of damaged tissues from each other with the use of barrier materials. It is also important to block the on-set of autoimmune inflammatory process in the wound, when an intervertebral disc herniation is removed, because the nucleus pulposus is a sequestered tissue, and it is formed in the avascular zone separately from the immune system [38].

The existing and described technologies of using membranes and gels are inconsistent. The advantage of the use of membrane forms (GORE-TEX Preclude Spinal, Dura-Gen, and Reperen) is their handliness and easy modeling in order to match the form of the postlaminectomy defect. Their disadvantages are a loose coupling of membranes to neurovascular structures; impossibility to achieve the

exact and complete covering of the neurovascular structures in the laminectomy area, so fibrous tissue may penetrate into the epidural space through the spacings between the neurovascular structures of the spinal canal and the barrier implant; as well as difficulty in fixing such membranes vertically [19].

Another direction of the prevention of cicatricial epiduritis is the use of gel-type implants (Guardix SG, antiadhesive antibody, Oxiplex/AP, and mesogel). The disadvantages of the gel-type barrier materials are their mobility and fluidity; their fixation in the area of the surgical intervention depends on adhesion properties of the material. Implanted gel material may migrate and drain out of the wound, when active drains are used in wound management. A tighter covering of neurovascular structures of the spinal canal, a complete filling of the formed surgical area with the implant are the advantages of the use of this material. So, a gel barrier makes it possible to cover the whole area of neurovascular structures in the periphery areas regardless the form of the opened area [19].

The following four analytical methods are used in animal research studies to estimate the formed epidural fibrosis: macroscopic analysis, histological analysis, PCR and MRT methods to identify markers of the connective tissue formation in the epidural scar.

Macroscopic analysis is performed in the space between the dura mater and the surrounding soft tissues. It is based on the quality of the wound repair, possible adverse effects, and development of epidural fibrosis. The adhesion strength of the scar tissue is determined according to a standard scale of 0 to 3 [39], where: 0 – no adhesions around the dura mater and there is no obvious adhesion between the dura mater and the onset of scar tissue in the injury area; 1 – thin adhesions observed at the outside of the dura mater, and they can be easily separated; 2 – moderate adhesions appearing around the dura mater, and they are hardly dividable from it; 3 – dense fibrous adhesions tightly adhesive to the dura mater, and they could be divided with strength, causing injury of the dura mater.

Histological analysis is based on the material staining with hematoxylin, eosin, and Masson trichrome. Some authors [40] use criteria of histopathological evaluation of scar tissue according to the classification proposed by He et al. Epidural fibrosis was rated as Grade 0 (the absence of fibrosis on the dura mater), Grade 1 (thin fibrous bands between the scar tissue and dura mater), Grade 2 (continuous fibrous adherence for less than 2/3 of the laminectomy area), Grade 3 (widely spread scar tissue for more than 2/3 of the laminectomy area, with extension to the nerve roots). At histological analysis, some authors [41] estimate the quantity of fibroblasts (density of fibroblasts) in the scar tissue by calculating cells in three different counting areas (one at the center and two at the edges of the laminectomy window). The number of fibroblasts was counted under an optical microscope (400x). The average number of fibroblasts in the three areas was graded as follows: Grade 1 (less than 100 fibroblasts per field), Grade 2 (from 100 to 150 fibroblasts per field), Grade 3 (more than 150 fibroblasts per field). The density of the microvessels development in the zone of the forming epidural fibrosis was also histologically estimated. Microvessels were visualized with immunomorphological staining using anti-CD105 antibodies; microvessels were calculated using 400-fold magnification in three different areas, where the density of neovascularization was the highest. The average number of vessels was calculated in three areas. The density of microvessels was estimated in the following way: Grade 1 (the average number of microvessels was $\leqslant$3); Grade 2 (from 4 to 6 vessels); Grade 3 ($\geqslant$7 vessels) [42].

Identification of markers of the connective tissue formation in the epidural scar. Some authors [42, 43] analyze material samplings from the laminectomy areas for the content of hydroxyproline by a spectrophotometric method, because its level in tissues is considered to be an important sign of fibrosis. The material sampling is also examined by real-time PCR using primers to identify markers of connective tissue formation in the epidural scar. The CTGF level (connective tissue growth factor) in the projection of laminectomy is considered to be the key factor at the epidural fibrosis formation, it refers to fibroblasts proliferation promoting factors and production of the extracellular matrix. They also determine other markers of the connective tissue formation: COL I (collagen type I), COL III (collagen type III), α-SMA (alpha smooth muscle actin), and Actb (β-actin) [42, 43].

MRT. The MRT examination plays an important role in assessment of the biomaterial efficacy in preventing epidural fibrosis, and of the implant function based on the signal depending on implant size (diameter) and structure [5, 43]. MRT makes it possible to dynamically monitor barrier materials after laminectomy, to clearly determine their shape and size, which can be changed in the process of remodelling. Moreover, on the basis of the MRT data, it is possible to carry out quantitative estimation of scar adhesion process in the epidural space by analyzing five axial MR images on the level of laminectomy. Each axial image is divided into four quadrants resulting in 20 quadrants for the analysis. The epidural fibrosis formation is graded according to the following scale: Level 0 (none or traces of scar adhesion process); Level 1 (from 0 to 25 % of the quadrant is filled with the scar tissue); Level 2 (from 25 to 50 % of the quadrant is filled with the scar tissue); Level 3 (from 50 to 75 % of the quadrant is filled with the scar tissue); Level 4 (>75 % of the quadrant is filled with the scar tissue) [5].

Characteristics of biomaterials. There are many biomaterials with different characteristics, including high molecular weight, complicated structure, various biological and physico-chemical functions, etc. In recent years, with the rapid development of material science and interdisciplinary communication, biodegradable polymer materials have come into use for the prevention of epidural fibrosis. On the one side, polymer materials may be used as a physical barrier, on the other side, as a carrier for controlled release drugs. Polymer materials are divided into natural and synthetic

materials which in turn can be biodegradable and non-biodegradable [48].

Chitosane, fibrin gel, hyaluronate, and amniotic membranes are natural polymer materials. The experimental use of each of these materials has demonstrated the reduction of the inflammatory process and the epidural fibrosis formation. A certain success of the mentioned biomaterials is determined by immunogenic response induction, which causes an additional local trauma accompanied with aseptic inflammation and short biodegradation time, because it is easily hydrolyzed. Thus, hyaluronic acid with a high molecular weight decreases the fibroblasts proliferation and sedimentation of collagen; that is why a positive effect is observed at the prevention of the epidural fibrosis formation and reduction of the fibrous tissue density [44, 45]. At the same time, a long-term use of hyaluronic acid in the wound is limited because of the tissue-specific enzymatic degradation. In order to overcome this limitation, the researchers have synthesized polygalacturonic acid and hyaluronate composite hydrogel by the Schiff cross linking reaction [46]. The synthesized hydrogel was incompletely decomposed *in vivo* in 4 weeks, and it prevented adhesion and infiltration of fibroblasts [46].

Amniotic membrane is a kind of a natural membrane, which is the inner layer of the embryonic membrane. In term of its function, it can be referred to a physical barrier, because it reduces local inflammatory signs and inhibits vascularization, thus limiting the epidural scar formation, which has been proved on a laminectomy model in rats [47].

Poly(α-hydroxy acids), including polylactic acid (PLA), polyglycolic acid (PGA), poly(ε-caprolactone) (PCL) and their copolymers, polylactic-co-glycolic acid (PLGA) and polylactide-co-caprolactone (PLCL), are synthetic biodegradable polymers functioning as a physical barrier against the ingrowth of connective tissue into the epidural space. Synthetic indecomposable polymers are as follows: silicone, polyacrylonitrile/vinylchloride (PAN/PVC); crosslinked polymers based on methacrylate hydrogels – poly(2-hydrhydroxyethylmethacrylate) (PHEMA), poly[N-(2-hydroxypropyl) methacrylate] (PHPMA), polyethyleneglycol (PEG), polyvinyl alcohol (PVA), and polyacrylimide (PAM) [48]. At the Irkutsk Scientific Center of Surgery and Traumatology, Wistar rats were used in the experiment for prevention of epidural fibrosis with the use of a Reperen plate (a cross-linked polymer of methacrylate oligomers) [49]. The histomorphologic estimation in this study has demonstrated that elements of the intervertebral disc act as triggers of inflammation, causing epidural fibrosis, which is reduced, when a barrier material is used [49].

There are literature data on a simultaneous use of physical barriers in a combination with different medicinal drugs, including steroidal and nonsteroidal anti-inflammatory compounds [50, 51], substances inhibiting specific cytokines or vascular permeability [5, 18, 52], substances selectively inhibiting vessel endothelial growth factor (VEGF), for example, ranibizumab inhibits the process of vascularization in the postoperative injured area, thus reducing the development and formation of scar tissue. This supposition has been proved by experimental studies [53] in Wistar rats and confirmed by histomorphological studies. There are works describing the use of chemico-therapeutic agents and immunodepressants with the aim to prevent the epidural fibrosis formation in the postoperative period [42, 54–56]. Controlled-release Mitomycin C in combination with a polyethyleneglycol film (C-PEG) has proved its effectiveness as a barrier in terms of the decrease of the epidural fibrosis and adhesions development on the spine in the experimental laminectomy model [57]. Because of the pronounced cytotoxicity of high Mitomycin C concentrations, there has been developed a C-PEG film that reduces the intensity of the epidural fibrosis development due to the reduction of the hydroxyproline concentration and the increase of the fibroblasts apoptosis [56]. Controlled-release Mitomycin C in combination with a PLGA film also prevents the epidural fibrosis development after laminectomy, by inducing autophagy of fibroblasts and regulating the expression of miRNAs [58]. Such combined barriers impact pronouncedly the inhibition of the epidural fibrosis formation at the area of the surgical intervention [58]. The authors confirm that the use of a combination of two and more materials decreases the formation of cicatricial epiduritis and improves the outcomes of the postoperative period. The obtained positive effect in using new compounds aimed to prevent the epidural fibrosis formation in animal experiments requires further improvement and study, which would give clinicians a possibility to introduce these compounds in practice [59]. So, a search for new barrier materials, technologies and approaches to the prevention of postoperative cicatricial epiduritis is still relevant.

The prevention of cicatricial epiduritis in the postoperative period means the blocking of the fibrosis formation. For this purpose, lysis of adhesions is used by introducing of hyaluronidase with the hypertonic saline into the epidural space [60–62]. According to Kim et al. [60], hyaluronidase with steroids is more effective and has a long-term effect. Helm et al. [63] used epiduroscopy for mechanical removal of the formed adhesions, this method allows a physician to visualize adhesions in the epidural space and to control the degree of their removal.

Therefore, the prevention of the epidural fibrosis development requires a complex approach, the clinician should apply general principles involving the completeness and stage-by-stage approach of the performed manipulations, their pathogenetic purpose, sparing character, and taking into account individual characteristics of the patient.

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Address correspondence to:
Zhivotenko Aleksandr Petrovich
Irkutsk Scientific Center of Surgery and Traumatology,
Bortsov Revolutsii str., 1, Irkutsk 664003, Russia,
sivotenko1976@mail.ru

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Aleksandr Petrovich Zhivotenko, junior researcher in the Research Clinical Department of Neurosurgery, Irkutsk Scientific Center of Surgery and Traumatology, Bortsov Revolutsii str., 1, Irkutsk, 664003, Russia, ORCID: 0000-0002-4032-8575, sivotenko1976@mail.ru;
Zinaida Vasilyevna Koshkareva, MD, PhD, leading researcher of the Research Clinical Department of Neurosurgery, Irkutsk Scientific Center of Surgery and Traumatology, Bortsov Revolutsii str., 1, Irkutsk, 664003, Russia, ORCID: 0000-0002-4387-5048, zina.koshkareva1941@mail.ru;
Vladimir Alekseevich Sorokovikov, DMSc, Prof., Director, Irkutsk Scientific Center of Surgery and Traumatology, Bortsov Revolutsii str., 1, Irkutsk, 664003, Russia; Head of the Department of Traumatology, Orthopedy and Neurosurgery, Irkutsk State Medical Academy of Postgraduate Education – Branch Campus of the Russian Medical Academy of Continuing Professional Education, Yubilejnyj microdistrict, 100, Irkutsk, 664049, Russia, ORCID: 0000-0002-9008-6383, vasorokovikov@mail.ru;