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Review Article

Epidural Fibrosis Prevention in Failed Back Surgery Syndrome

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ABSTRACT

Peridural fibrosis is considered cause of recurrent pain after lumbar laminectomy and discectomy (FBSS): it occurs in direct consequence of surgery and interests peridural and periradicular space both posterior and anterior. Its extension is directly proportional to the size of the bone defect and the area of surgical dissection: Incomplete hemostasis with presence of large epidural hematoma favors its extension over the limits of the bony defect. The fibrosis would derive from the damaged annulus during the excision of disk, from the inferior surface of the muscles overlying the dura, from the retention of cotton fragments in the operating field or from irritating material coming from residual of the nucleus pulpous.

Advanced hypotheses about the role of the peridural fibrosis in pain genesis are the neuromechanic, the intraneural fibrosis and demyelination, the release of chemical mediators from residues of nucleus pulpous. The prevention of scar formation is based on two factors: correct surgical technique and employment of materials of interposition. Materials of interposition may be biologic and no biologic. Biologic materials used are free fat graft, pedicle fat graft, ligamentum flavum and dura. No biologic materials are porous (gelatine sponge, avitene, bone wax) and non-porous (dacron, polymethylmethacrylate, espanded polytetrafluoroethilene, hyaluronic acid, carbohydrate polymer gel and carboxymethylcellulose gel).

Keywords: Failed Back Surgery Syndrome (FBSS); Periradicular fibrosis; Interposition materials

INTRODUCTION

The formation of scars around the dura mater and roots is one of the most common complications of intervertebral disc surgery and is an important cause of Failed Back Surgery Syndrome (FBSS). The exploration of the roots after previous interventions for herniated disc removal invariably highlights the presence of a well-organized fibrotic tissue that overhangs the dura mater and sometimes binds them to the posterior surface of the disk and adjacent vertebral bodies [1]. The purpose of this work is to discuss factors determining the formation of the scar and its role in the genesis of pain and methods to prevent its occurrence.

EPIDEMIOLOGY AND ETIOLOGY OF FBSS

About 40% patients after lumbar laminectomy suffered from FBSS and 4%-9% patients suffered from the second surgery [2].

Although the etiology of FBSS is not clearly understood, several reports are in agreement that its origin is multifactorial and that the causative factors may be categorized into preoperative, operative, and postoperative factors [2]. Preoperative factors may be further divided into patient-related factors as psychological [3] and social and surgery-related factors [4] as poor candidate selection, revision surgery and improper planning. Operative factors are inadequate decompression of lateral recesses [5] and foramina instability with excessive decompression [5], and incorrect level surgery (2.1%-2.7%). Postoperative factors are

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recurrent disc herniation (6%-23%) [6,7], adjacent segment disease [7], sagittal balance-related problems [8], pelvic incidence and lumbar lordosis mismatch [9], battered root syndrome (20%-36%) [3], and nerve root entrapment syndrome. Extension of scar tissue into the neural canal and adhesion to the dura mater are the major reason for leg and back pain [10].

PATHOPHYSIOLOGY OF EPIDURAL FIBROSIS

The formation process of scar tissue can be classified into three phases [11]: the first phase, from 3th to 5th day after the surgery, is local inflammatory reaction, mainly including hemostasis and coagulation process and chemokine release such as phospholipase A2, which causes aggregation of macrophagocytes, fibroblasts, mastocytes and endotheliocytes [12]. A hematoma completely occupies the bone breach of the laminectomy and is in contact with the deep surface of the muscle. The hematoma surrounds the posterior and lateral surfaces of the dura and extends for a variable distance below the intact neural arcs above and below the defect surgery. After 1 week we note an intense fibroblastic activity on the deep surface of muscle and fibroblasts seem to follow the extension of hematoma. The second phase lasts about 2-3 weeks: fibroblasts proliferate and differentiate into fibrocytes, secrete collagenous fibers in the defect lesion and form granulation tissues gradually, regulated by various cytokines, such as transforming growth factor (TGF)-b1, interleukin-6 (IL-6) and fibroblast growth factor (FGF). Fibroblasts could also secrete TGF-b1, IL-6 and FGF-2 to improve fibroblast proliferation and extracellular matrix synthesis [13]. In animal studies there were indeed released inflammatory mediators contained in the disk such as interleukin 6, interleukin 8 and TNF [14]. At 15 days they have a thick fibrous scar from the erector muscle that extends along the lateral wall of the dura to the spinal roots. If the laminectomy is extended up to the conjugation foramen the scar extends into the latter. A thick and resistant membrane fills in such way the bone defect, adhering tenaciously to the dura and root below. The third phase is tissue reconstruction which lasts months to years with fibrillary connective tissues deposition around the defect lesion and its transformation into scar tissues [15]. There are four theories proposed in literature to explain the origin of fibrosis:

- Key and Ford [16] were the first to study this problem and they concluded that the fibrosis derives mainly from the fibrous ring of disc damaged during the surgical procedure of removal of the herniated disc. They claimed instead that the main source of the scar was the anterior region: the curettage of the annulus would induce an activation of the fibroblasts which would extend along the hematoma that invariably forms in anterior part of the canal in response to discectomy (anterior-lateral fibrosis). This anterior hematoma resolves usually more quickly than posterior: for such reason the scar formation in anterior region resulting in adhesion of roots and dura on the surface of the annulus is generally less extensive.
- LaRocca and Macnab [17] considered the major source of fibrosis is the inferior interested surface of erector muscle of spine that is into contact with the dura through surgical bone defect. Fibroblasts in the deep layer of sacrospinalis proliferate and form the "laminectomy membrane", thick and durable membrane that fills the surgical opening from sacrospinalis to the side of dura mater (posterior-lateral fibrosis).
- Hoyland [18] considered that retention of cotton fragments detached from the swabs used during the surgery is responsible for the appearance of fibrosis. At the polarizing microscope the samples of epidural scar taken from patients reoperated, presence of a bi-reflective crystalline material which, in some areas, is phagocytized by macrophages were observed; around these birefringent deposits there were few chronic infiltrates of inflammatory cells. With histochemical techniques and enzyme histochemical tecniques it was demonstrated that this material birefringent corresponds to cotton fragments and also to pure cellulose, so it derives from the swabs used during surgery.
- Songer and Ghosh Spencer [19] proposed a three-dimensional theory: the scar tissue around the dura originates not only from the front of the sacrospinalis muscle, but also from behind the annulus fiber and posterior longitudinal ligament. The hyperplasia of fibrous tissue around the ventrolateral nerve root causes epidural adhesion. Songer expecially supports that the irritant material from residues of nucleus pulposus stimulates formation of fibrosis.

The majority of authors believe that main source of fibrosis is represented by the surface of the paravertebral muscles which is into contact with the dura after laminectomy; the factors that promote the extension of the scar are the size of surgical bone defect and the presence of blood collection in the epidural space [20]. Recently more attention has been given to scar tissue which shape in the anterior or anterolateral epidural space and on role that irritant material coming from the nucleus pulposus through surgical defect in the annulus fibrous and in the Longitudinal Posterior Ligament (LLP) can play in its formation [21]. The nucleus pulposus contains high levels of A2 phospholipases which, by activating the cascade of arachidonic acid, produce prostaglandins E1, E2 and leukotrienes B. These substances considerably lower the stimulation threshold of C fibers, which are abundant in nerve root and generate a situation of the inflammation. After the discectomy, through the defect in the annulus and the LLP, the residues of nucleus pulposus containing high rates of phospholipase A2 may come into contact with dura and root causing a chronic inflammation at the level of discectomy, producing PGE with subsequent liberation of the cytokines from leukocytes. The cytokines induce proliferation of fibroblasts, collagen production and consequently scar tissue formation at the level of the anterior-lateral epidural space. The scar tissue formation may also be directly induced by PGE2. From the above, it can be concluded that formation of epidural scars is both posterior and anterior for each approach interlaminate (laminectomy and discectomy): Its extension is directly proportional to the diameter of the surgical bone defect and the area of surgical dissection. Imperfect hemostasis with presence of large hematoma promotes tissue fibrotic epidural extension beyond the limits of the bone defect.

EVALUATION OF EPIDURAL FIBROSIS

There are three main aspects to evaluate the fibrosis: macroscopic analysis, histological analysis and Magnetic Resonance Imaging (MRI) analysis. Macroscopic analysis evaluates a space between the dura and surrounding soft tissues about the quality of wound healing, possible adverse effects and epidural adhesion [11]. Adhesion tenacity is evaluated using Rydell and Balazs's standard score. Grade 0: No adhesion between dura and scar; Grade 1: scattered and slight adhesion between dura and scar which is easily separable; Grade 2: extensive and compact adhesion between dura and scar, where it is difficult to separate adhesion surrounding the dura while keeping the dura mater complete; Grade 3 severe adhesion between dura mater and scar, and separation means destroying the dura [21]. Histological analysis is based on Hematoxylin and Eosin (H&E) staining (that represented cell activity) and Masson's trichrome staining (that shows inflammatory factor and fibrin). Modified Henderson's grading system is based on epidural fibrosis, abscess, acute inflammation and necrosis, dividing into Grade 0 (no fibrosis, no inflammation, no abscess and no necrosis), Grade 1 (mild interstitial fibrosis, mixed inflammation (25%), abscess area 2 and necrosis area >2), Grade 3 (marked fibrosis collagen formation, mixed inflammation (75%), marked abscess and marked necrosis) and Grade 4 (massive fibrosis, massive inflammation, massive abscess and massive necrosis) [22-24]. MRI observations of implant materials after lumbar laminectomy show the size of the material and the remodeling of the material according to the dura mater in relation to the postoperative transient shrinkage and expansion of the dura. MRI can monitor the state of implant to evaluate the function of implant based on the signal and diameter [25,26].

ROLE OF EPIDURAL FIBROSIS IN PATHOPHYSIOLOGY OF FBSS

Epidural adhesion is one of the most important causes of FBSS. The exact role of epidural fibrosis in the genesis of pain of the FBSS is not yet clearly defined, but many authors believe that it constitutes a fundamental and important factor in the FBSS. Three hypotheses have been proposed: neuro-mechanics hypothesis, intra-neural fibrosis hypothesis and demyelination, hypothesis of release of chemical mediators from nucleus pulpous residues.

Neuro-mechanic hypothesis

In healthy people the movements of flexion-extension and abduction of the lower limbs and of flexion, extension and lateral flexion of the trunk on the pelvis involve a flow of the nerve roots into the foramen and an upward and/or downward movement of the spinal cord. These actions put in traction the roots and the dura, which does not cause pain. In presence of epidural fibrosis, the dura and the roots are tenaciously adherent to the scar tissue: the movements of the limbs and the trunk therefore involve a deformation on the roots and on the dura with appearance of pain. Moreover, even if scar was not directly responsible for the pain, its presence in the epidural space would create a situation of relative stenosis of the canal or the foramen for which also small protrusions or osteophytes would become symptomatic [21,27]. Then we can say that "the epidural scar is more extended so as the patient has pain". MRI studies with gadolinium instead showed that there are no significant differences in the amount and extension of scar tissue between symptomatic and asymptomatic people. Moreover, this mechanical theory does not explain why another surgery of neuro-lysis of scars results in only transient improvement of pain.

Hypothesis of intra-neural fibrosis and demyelination

The chronic root compression due to disc herniation first and then fibrosis causes a rupture of the blood-brain barrier in the endoneural space with subsequent root edema and increased endoneural liquor pressure: this results in the appearance of dura fibrosis and arachnoid thickening, fibrosis intra radicular and demyelination of large diameter fibers [28,29].

Hypothesis of release of chemical mediators by the nucleus pulpous

Hypothesis of release of chemical mediators by the nucleus pulpous remained *in situ* after discectomy. After the discectomy through the fenestration in the annulus the residues of the nucleus pulpous are located closely to the dural sac and the roots. Such residues contain high A2-phospholipase concentrations that activate into the epidural space the arachidonic acid cascade making prostaglandins El, E2 and leukotrienes B. These substances reduce the threshold of stimulation or stimulate directly the small diameter fibers type C present inside the roots and responsible for the transmission of pain [27,29].

PREVENTION OF LUMBAR EPIDURAL FIBROSIS

The possible mechanism of the epidural scar formation is that the fibroblasts around the surgical environment are transported into the operative area by blood [30]. Therefore, the main strategy for preventing epidural fibrosis is to restrict the migration of fibroblasts, ensure thorough hemostasis in the surgical area, and isolate the contact of the spinal dura mater and fibrous tissue. The prevention of the formation of epidural scars is based on two fundamental factors: a correct surgical technique and the use of interposition materials. Essential prerequisite for preventing the scar formation of the scar is a correct surgical technique consisting of a maintaining periradicular fat, careful curettage of the intersomatic space, accurate hemostasis of the space and anatomical reconstruction of the periradicular space [30,31]. Limited retraction of the nerve root, use of bipolar coagulation and good hemostatic control are crucial [32]. The current methods used clinically include the usage of drugs such as Mitomycin C, dexamethasone, hydroxycamptothecine, rosuvastatin and no-steroidal anti-inflammatory drugs, low dose radiation, traditional Chinese drugs and biomaterials such as autologous

tissue and biodegradable polymeric materials [11]. The placement of inert substance between dura, muscles and annulus prevents or reduces the formation of fibrotic tissue in the epidural space. Various interposition materials have been studied: Some of them have been used only for experimental purposes, while others have been used in clinical practice [33-45]. These materials are divided into biological (for example free or pedunculated graft of fat, flavum ligamentum and dura mater) and non-biological materials (porous or not porous materials). The porous materials are Gelfoam, Avitene, bone wax, the non-porous materials are divided into solid as Dacron, Poly-methyl-methacrylate, membrane of expanded polytetrafluoroethylene, and viscous as hyaluronic acid, carbohydrate polymer gel or carboxy-methyl-cellulose gel.

Biological materials: The free or pedunculated fat grafts are widely used in surgical practice to prevent or reduce the formation of epidural scar [39,41]. There are, however, some problems as a result of their use: the fat does not adequately cover the opening of the laminectomy and so the fibrotic tissue invades the space through its edges. If you use too much fat, his saponification may compress the cauda. It was proposed to create the peduncle of the flavum ligament and to reposition between the two hemilaminas at the end of the surgery [31]. Dural patches have been used in laminectomy, but they need to be fixed with stitches at the bone edges otherwise their dislocation is very common. However, all materials used do not prevent the formation of scars in the anterior epidural space.

Non-biological materials: The porous materials (Gelfoan, Avitene) are not an efficacy system of interposition because it seems that they act as scaffolding material for the growth of fibrotic tissue or even seem to stimulate it [39,41]. Non-porous materials, on the other hand, constitute an effective anti-fibrous barrier. In the case of non-porous solid materials, the majority of them exist in form of membranes and they need to be fixed at margins of the laminectomy: A problem can therefore be constituted by the invasion of the epidural space by the scar tissue through the existing gap between membrane and edges of the operated bone [33,45]. Moreover, these solid materials have no effect on the prevention of the anterior epidural fibrosis that is associated with annulus fenestration and discectomy because they are interposed between dura and muscle. The ideal material are probably viscous materials [21,40,42-44,46]. For their viscosity, they can be injected at the level of the bone defect anteriorly to the dura and the roots, laterally in the lateral recess and posteriorly in the bone defect between the dura and the posterior spinal muscles, reaching both the anterior and posterior epidural space: In this way they prevent formation of fibrosis both anterior-laterally and posteriorly to the dura and roots. They are also biocompatible because they are completely absorbable even if slowly (average time 4 weeks). They also influence extracellular regulation of migration of inflammatory cells: *in vitro* they inhibit the migration of lymphocytes, macrophages and granulocytes, mobility and multiplication of fibroblasts and the production of cytokines. It can possible classify the polymeric materials into natural polymeric materials and synthetic polymeric materials. The natural polymeric materials (chitosan, fibrin gel, hyaluronate and amniotic membrane) have been proved, but the success is limited, for example gelatin sponge can form a hematoma after the expansion in blood absorption and then it would transform into scar tissue with epidural adhesion [47].

A cross-linked hyaluronate for its semifluid condition can fit with the anomalous half ellipse dura mater adequately, Therefore, reducing NIH/3T3 fibroblasts viability, downregulating S100a and P4hb expression in NIH/3T3 fibroblasts and reducing scar tissue formation *in vivo*.

A chitosan-silane membrane: Chitosan-silane membrane improved mechanical strength which makes it suitable to maintain a predefined shape to prevent adhesion [48].

The amniotic membrane: is the inner layer of fetal membrane, which acts as a barrier to reduce inflammation, inhibit vascularization and limit postoperative adhesion. In a rat model, it can be helpful to reduce the adhesion, compared with fat graft; it shows better biocompatibility and capability of existing for a certain period in the body [49].

PLGA (Poly lactic-co-glycolic acid membrane): PLGA is a membrane with good biocompatibility, blood compatibility and slight organization response, exact barrier function and moderate absorption cycle and it was proved on the rabbit, but after PLGA absorption there will be a cavity because PLGA is absorbable material [50]. Exist a compost of PLGA with PEG as thermos-gel that act as effective and well-modulated barrier devices to prevent postoperative adhesion [51,52] and as a support. PEG is biodegradable and the combination with PLGA produces a material that has no cytotoxicity, but good results.

ADCON-L: ADCON-L is a bioabsorbable carbohydrate polymer gel which is composed of a poliglycan estere and porcine derived gelatin in phosphate-buffered saline that reduces postoperative fibrosis as seen on MRI studies [51]; after its use it has been strongly criticized in systematic reviews for negative influence on wound healing and bone fusion, increase rate of CSF leakage, collateral effects as pain, non-CSF fluid collections, tachycardia and erythematous skin reactions.

e-PTFE: Expanded polytetrafluoroethylene membrane (e-PTFE) has excellent biocompatibility and stable structure so that fibroblasts cannot penetrate. It is from porous materials with better biocompatibility and that maintains a stable position [53].

MAACP/nHa multi-amino acid copolymer/ nanohydroxyapatite: HA is a part of osseous tissue, and for this, MAACP-nHA has very good biocompatibility. It has no dislocation of artificial lamina and it does not cause the aseptic inflammation, because the degradative product is neutral [54].

There are a lots of combination strategies of a physical barrier combining the advantages of drugs such as dexamethasone, ibuprofen, mitomycin C, hydroxycamptothecine [55,46].

Gelatin sponge+dexamethasone: Gelatin sponge separates the nervous tissue from the surrounding tissue, performing an interval barrier effect, dexamethasone stops the first and the second process of hematoma as anti-inflammatory, delaying the granulation formation to prevent adhesion, reducing scar formation and preventing adipocyte necrosis [56].

Fibrin glue+methylprednisolone acetate: A macromolecular substance, it can form the network structure to stop the bleeding of the multi-bioactivity protein and it has a faster degradation speed *in vivo* without bacterial infection. It is non-toxic, nonreactive, biologically, compatible material [57].

Mitomycin C+ PEG film/PLGA film: The Mitomycin was associated with PEG or PLGA, in the first case PEG decreases the concentration of hydroxyproline. Mitomycin C –PEG controlled-release film has been showed to inhibit collagen secretion and induces apoptosis of fibroblasts in the early wound of a post-laminectomy rat model [58], only high concentration of mitomycin C is cytotoxic.

Ibuprofen-conjugated hyaluronate (HA)/polygalacturonic acid (PGA) hydrogel: the ibuprofen decreases prostaglandin E2 and the production of the lipopolysaccharide, induced in RAW264.7 cells and the compost delayes condensation of scar tissue [59].

Carboxy-methyl-cellulose oly-ethylene oxide: CMC/PEC (Oxyplex) is compost from sodium carboxymethylcellulose and polyethylene oxide, the first one has properties of adhesion to tissues while the second blocks fibrosis by inhibiting the formation of fibrin tissue on the surface it covers. The gel is absorbed from the epidural space in 30 days. This is seeming very safe.

PG (Duraseal exact): PG is a synthetic hydrogel composed mainly of Polyethylene glycol, contains no organics material, acts as a barrier between tissues and is absorbable in two months.

ADSCs are a kind of autologous stem cells. Compared with bone marrow stem cells, they show easy accessibility, relative abundance with proliferation ability and easy differentiation to fat tissue. Meanwhile, the scaffold should fulfil the items listed previously, and the degradable speed should match the proliferation and differentiation speed of ADSCs. The searched property is that the material should reach everywhere the adhesion may happen to block the invasive fibroblast, soft scaffolds may be better than hard scaffolds. Soft scaffolds occupy every space in the defect area and act as the physical barrier in the early stage. After the stem cells differentiate into adipose tissue, the engineered adipose tissue will act as a bio-barrier in the later stage. The engineered adipose tissue is still under study, and further work should figure out more suitable and effective materials and techniques [11].

TREATMENT OF PAIN DUE TO EPIDURAL FIBROSIS

The possible strategies for treatment of pain due to development of epidural fibrosis are medical treatments and surgical treatments. Medical treatments consist of nonsteroidal and steroidal anti-inflammatory drugs, muscle relaxants, opioids and their derivatives, antidepressants and anti-epileptics, spinal infiltrations.

Surgical treatments concern reoperation with removal of epidural scar tissue, spine fusion+grafting for restoring sagittal and coronal spinal balance [3] and Spinal Cord Stimulation (SCS).

Spinal Cord Stimulation (SCS) is believed mediate pain relief *via* activation of dorsal column Aβ fibers, treating the gate control theory of pain, as the pain impulses provoked in the periphery, which are carried by C fibers and A-delta fibers, could be interrupted by stimulating larger A-beta fibers. This interruption is facilitated by the common nerve synapse location in the substantia gelatinosa of the dorsal horn. In other words, stimulation of the touch and vibration nerves "closes the gate" on ascending pain impulses that carry noxious pain stimuli cephalad, resulting in variable effects on sensory and pain thresholds, and measurable alterations in higher order cortical processing. This effect is maximum if it is used chronically and fully implanted devices. The mechanism of action, initially based on the gate control theory, is still imperfectly known. SCS probably acts through inhibition of the nociceptive message transmission and nociceptive neurons hyperactivity in the dorsal horn of the spinal cord and through supra spinal mechanisms including activation of the inhibitory descending pathways. The stimulation electrode is implanted, percutaneously or surgically, in the posterior epidural space, in contact with the spinal cord. The implant of stimulation system is divided into two phases: the first is trial stimulation; the second is definitive implant and chronic stimulation [60-64].

CONCLUSION

The trial stimulation phase, using an external battery for a few days (about 7 or 15 days), is mandatory to assess the efficacy of the therapy (pain intensity decrease >40%-50%) before connecting the electrode to a subcutaneous implanted stimulator. For more than 40 years, only tonic (50-90 Hertz) continuous stimulation, inducing perceptible paresthesia, has been used. Recently, new stimulation modalities have been proposed, as burst stimulation, high-frequency (>1000 Hertz) stimulation or high-density stimulation, to avoid the perception of paresthesia or increase the pain relief. SCS indications have been specified in several consensus recommendations and concern predominantly neuropathic pain with limited topography, excepting the face, after the failure of conventional drug treatments. Most frequent indications are post-operative chronic low back and radicular pain (FBSS), complex regional pain syndromes (CRPS), and peripheral neuropathy pain.

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