MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 840-847
DOI: 10.12659/MSM.897668

Received: 2016.01.20
Accepted: 2016.02.11
Published: 2016.03.14

Pentoxifylline Inhibits Epidural Fibrosis in Post-Laminectomy Rats

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Source of support: Departmental sources

Background: The aim of this experimental study was to investigate the effectiveness of intramuscular pentoxifylline in the prevention of postoperative fibrosis.

Material/Methods: We divided 16 adult Wistar albino rats into 2 equal groups: treatment and control. Both groups underwent L1 vertebral total laminectomy to expose the dura. The intramuscular treatment group received pentoxifylline. Four weeks later, epidural fibrosis was studied in both groups using electron microscopy, light microscopy, histology, biochemistry, and macroscopy.

Results: The evaluation of epidural fibrosis in the 2 groups according to macroscopic ($p<0.01$) assessment and light microscopy revealed that epidural scar tissue formation was lower in the treatment group compared to the control group ($p<0.001$) and the number of fibroblasts was also decreased significantly in the pentoxifylline-treated group ($p<0.05$). More immature fibers were demonstrated in the treatment group by electron microscopy in comparison with the control group. In biochemical analysis, a statistically significant decrease was detected in hydroxyproline, which indicates fibrosis and myeloperoxidase activity, and shows an inflammatory response ($P<0.001$).

Conclusions: Systemic pentoxifylline application prevents postoperative epidural fibrosis and adhesions with various mechanisms. Our study is the first to present evidence of experimental epidural fibrosis prevention with pentoxifylline.

MeSH Keywords: Animal Experimentation • Laminectomy • Pentoxifylline

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/897668

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Background

Although epidural fibrosis is a natural process that occurs following lumbar spinal surgery, it may contribute to 25% of "failed back surgery syndrome". In the present study we show that a xanthine derivative, pentoxifylline, which is used to treat diseases via disturbed vascular perfusion, helps prevent epidural fibrosis by its anti-fibrotic, anti-inflammatory, and anti-proliferative properties in an experimental rat model.

Spinal surgery of the lumbar region is performed in about one million patients all around the world annually [1]. Epidural fibrosis (EF) is a possible result in the process of healing after these procedures [2,3]. However, by causing adhesions on the dura and nerve roots, expansion of epidural fibrotic tissue leads to failed back surgery syndrome (FBSS), which is characterized by permanent pain in the lower back and legs after surgery [4,5]. EF was first reported in 1948 [6]. It is still one of the major problems for surgeons, and treating this situation with reoperation carries high risk due to possible complications, such as dural laceration, root injury, and epidural bleeding [7,8].

The underlying mechanisms of epidural fibrosis formation are complicated. Over-accumulation of extracellular matrix components, such as collagen, fibronectin, dermatan sulphate, and reduction of tissue cellularity result in EF [9,10]. Transforming growth factor-1β (TGF-1β) has been reported to be the key initiating factor of EF [8,11,12].

Pentoxifylline (PTX) is a xanthine derivative. PTX shows its effect by inhibiting phosphodiesterase enzyme. Its therapeutic effect depends on improvement of blood circulation and tissue oxygenation. It is used in the clinic for treatment of peripheral vascular and cerebral diseases [13]. PTX stimulates prostacyclin, secreted from normal endothelial cells, to inhibit cytokine cascades arising from damaged tissue. Also, indirectly, it inhibits the production of thromboxane, which is a strong vasoconstrictor and a stimulator of platelet aggregation. *In vitro* studies showed that PTX increased collagenase activity [14,15]. It was also shown that PTX decreased postoperative peritoneal fibrosis and adhesion formation [16].

The present experimental study, using various parameters, aimed to determine whether PTX inhibits spinal epidural fibrosis.

Material and Methods

This experimental study was performed at the Experimental Animals Laboratory, Maltepe University School of Medicine after receiving approval from the local Ethics Committee. Considering previous studies on this topic, the sham group was removed by the Ethics Committee with the rationale that inclusion of a sham group would not make a statistically significant contribution to the outcome. Therefore, only a control group and a treatment group were allowed. In this study, 16 male Wistar albino rats were used. The weights of rats varied between 300 to 350 g and the average weight was 325 g. All rats were divided into 2 groups: the Pentoxifylline treatment group (n=8) and the Control [Saline] group (n=8). Histopathological examinations were carried out at the Medical Biology and Histology Department Laboratory of Cerrahpasa Medical Faculty at Istanbul University and biochemical tests were carried out at the Biochemistry Laboratory of the same institution.

Surgical procedure

For infection prophylaxis, ceftriaxone [Rocephine, Roche, Turkey] was administered intraperitoneally (i.p.) in a single dose (50 mg/kg) 30 min before surgery. Sedation was achieved by hydrochloride [Rompun] (10 mg/kg i.m. additional dose) after administration of ketamine hydrochloride [Ketalar, Pfizer, Istanbul] (60 mg/kg, i.m.). After the animals were fixed on an operating table, the surgical area was disinfected with povidone iodine solution [POVIOD; 10% polyvinylpyrrolidone-iodine complex Saba, Turkey] after cleaning for 10 min with a povidone iodine scrub [MEDICA brush, 4% chlorhexidine soap, MEDICA BV, The Netherlands]. After the surgical area was covered with sterile drapes, paraspinous muscles were detached subperiosteally with blunt dissection after a vertical midline incision was made from Th11 to L3 to expose the L1 vertebra. After dura mater was revealed by performing total laminectomy on the L-1 vertebra under a surgical microscope [Mentor II, Japan], the wound was closed by apposing the tissue layers following hemostasis. All animals of both groups were placed in individual cages. Control and experimental groups received 2 ml of 0.9% physiological saline solution and 50 mg/kg pentoxifylline [Trental, Aventis-Pharma, Istanbul] i.m. for 7 days. After 4 weeks, they were sacrificed intra-peritoneal injection of high-dose (75–100 mg/kg) thiopental sodium [Pentothal Sodium, Abbott, Italy]. Related vertebral columns were removed totally and examined macroscopically. Animals with tears in the dura, injury to the nerve root during the operation, or infection during decapitation were excluded from the study.

Macroscopic assessment

Macroscopic assessment was performed 4 weeks after surgery. Eight rats were randomly selected from each group and anesthetized. With the help of assistants, the epidural scar adhesion underwent double-blind evaluation and the results were classified based on the Rydell classification (Table 1) [17].

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Table 1. Macroscopic evaluation according to Rydell classification [17].

Grade 0	No scar tissue in the dura mater
Grade 1	Scar tissue in the dura mater but dissected easily
Grade 2	Scar tissue in the dura mater, difficult dissection and impaired dura mater
Grade 3	Adhered scar tissue in the dura mater and cannot be dissected

Light microscopy

The tissue samples were immediately fixed in 10% buffered formaldehyde [37%, Merck, 1.04002] at room temperature for 48 h. Then they were processed according to routine light microscopy tissue processing technique. They were dehydrated in ascending degrees of ethanol, cleared in xylene, and embedded in paraffin [Merck, 1.07337.9020]. Serial sections of 5 micrometers were cut and stained with hematoxylin-eosin. Sections were evaluated using an Olympus BX61 light microscope [Olympus, Tokyo, Japan] and photographed with the Olympus DP71 camera [Olympus, Tokyo, Japan].

Ultrastructural imaging by electron microscopy (EM)

The tissue samples were fixed in 4% glutaraldehyde [G5882; Sigma, St. Louis, MO, USA] in a 0.1 M phosphate buffer solution, post-fixed in 1% OsO_4 prepared in the same buffer, dehydrated with graded ethanol [Merck, Darmstadt, Germany], and embedded in araldite [G4901; Sigma, St. Louis, MO, USA]. They were cut into ultra-thin sections 50-nm–thick using an ultramicrotome [Reichert UM 2 and UM 3, Austria] and positioned on cupper grids (200 mesh) stained with uranyl acetate and lead citrate. Sections were analyzed with a transmission electron microscope [JEM-1011, Jeol Tokyo, Japan] and the Olympus Soft Imaging camera system [Tokyo, Japan].

Biochemical evaluation

The tissues were weighed and washed in 0.9% NaCl. A piece of tissue sample was stored at –80°C until assayed for levels of myeloperoxidase (MPO) and hydroxyproline (HP).

Preparation of tissue samples

About 190–200 mg of each tissue sample was weighed and diluted 20% w/v in 20 mL of ice-cold Tris HCl, pH 7.4, and homogenized with a Bosch Scintilla SA device [Switzerland]. The homogenate was centrifuged at 5000×g for 10 min, and biochemical parameters were performed in the supernatant fraction. All biochemical parameters were studied on the same day.

Measurement of myeloperoxidase (MPO)activity

MPO has an important role in inflammation. MPO activity was measured with a commercially available kit [MPO, Rat, ELISA kit cat. no. HK105-02, Hycult Biotech Frontstraat 2A5405 PB Uden, The Netherlands]. The coefficients of intra-and inter-assay variations were 4.0% (n=15) and 5.1% (n=15), respectively.

Measurement of hydroxyproline (HP) level

HP level is considered as one of the most important signs of fibrosis. HP level was measured with a commercially available kit [Hydroxyproline Assay Kit, cat. no. MBS162747, My Bio Source, San Diego, CA 92126 USA]. The coefficients of intra- and inter-assay variations were 3.6% (n=15) and 4.8% (n=15), respectively.

Histopathological analysis

All histopathological analyses were done by an independent histopathologist. The amount of epidural fibrosis in laminectomy region and its relationship with dura mater was compared according to histopathological classifications and then the statistical analyses of the results were performed. For histopathological examination, the removed vertebra was fixed with 10% formaldehyde buffer for 4 days and then was decalcified for 5 days (Shanden TBD-2). Spinal cord tissues were obtained from 3 parts (middle, proximal, and distal) of the laminectomy region and each 2-mm cord segment was taken and placed in sampling casettes. These samples were washed with tap water for 3 h to eliminate acidic remnants. Afterwards, a follow-up process was carried out in a tissue processor [Shanden excelsior ES] for 13 h. In this process, tissues were treated twice with formaldehyde for 30 min each time, alcohol 6 times for 60 min each time, xylene 3 times for 60 min each time, paraffin for 60 min once, and paraffin twice for 80 min each time. After the follow-up process was completed, each segment was embedded in paraffin tissues and 3-µm–thick coronal sections were made by microtome [Shanden Fine SSE 325]. Hematoxylin and eosin staining was performed for histopathological examinations and trichrome staining was performed for evaluating epidural fibrosis.

Epidural fibrosis, fibroblast intensity, and granulation tissue in the laminectomy region were examined under a light microscope [OLYMPUS CX31; 1 HPF=0.228 mm^2]. Grading of histopathological epidural fibrosis was done according to the definitions of He et al., as shown in Table 2 [18].

Grading of histopathological epidural fibrosis was done as described by Hinton et al. [19] according to the predominance of fibroblasts. According to this classification, it was graded as grade 1 (less than 100 fibroblasts), grade 2 (between 100 to 150

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Table 2. Histopathological classification of epidural fibrosis, according to the He et al. criteria [18].

Grade 0	No fibrosis influencing the dura mater
Grade 1	Fine fibrous bands between fibrous tissue and the dura mater
Grade 2	Continuous adhesion in less than 2/3 of the laminectomy defect
Grade 3	Adhesion of the fibrous tissue in more than 2/3 of the laminectomy defect and/or fibrous tissue reaches to the nerve roots

Table 3. Fibroblast classification according to the Hinton criteria [19].

Grade 1	<100 fibroblasts
Grade 2	100–150 fibroblast
Grade 3	>150 fibroblasts

fibroblasts), and grade 3 (more than 150 fibroblasts) (Table 3). The average number of fibroblasts was calculated by counting 3 regions under a light microscope at 40× magnification.

Statistical analysis

Values are expressed as mean ±SD. Levels of hydroxyproline, myeloperoxidase activity, and fibroblast counts of groups were compared using the Kruskal-Wallis one-way ANOVA and Friedman two-way ANOVA tests using UNISTAT 5.0 for Windows (Istanbul University). P <0.05 was considered as statistically significant. Multiple post hoc comparisons were also carried out among the groups and within each group, and the Dunn test was performed.

Results

Macroscopic evaluation of EF

Surgical operations performed were well tolerated by all rats. None of them had wound infection, neurologic deficit due to nerve injury, or cerebrospinal fluid leakage. All rats healed well after this operation.

In the PTX treatment group, weak fibrotic adhesions were dissected in the epidural region where the laminectomy had been performed. In the control group, rigid and intensive epidural adhesions were observed and dissection of these adhesions was difficult. This was accompanied by deformations in the dura mater. This situation was evaluated according to Rydell classification [17] and it was found that results were statistically significant (p<0.01) (Table 4).

Table 4. The grades of epidural fibrosis on macroscopic evaluation according to Rydell classification.

Grade	Control group (n=8)	Treated group (n=8)
Grade 0	0	2 (25.0%)
Grade 1	1 (12.5%)	5 (62.5%)
Grade 2	2 (25.0%)	1 (12.5%)
Grade 3	5 (62.5%)	0

Histopathological evaluation

In the control group, we observed intensive epidural fibrosis tissue, full thickening of dura, and adhesion of fibrotic tissue, including many irregular blood vessels to the dura at the laminectomized side with spinal cord compression (Figure 1A, 1B). In the treatment group, partial adhesion of compact fibrotic tissue to the dura was detected, but there was less spinal cord compression in the laminectomized region (Figure 1C, 1D).

Light microscopy examination revealed that in the control group 1 was at grade 2 and 7 were at grade 3, according to specifications of He et al. [18]. However, in the treatment group we found that 2 were at grade 1, 4 were at grade 2, and 2 were at grade 3. EF in rats in the PTX treatment group was lower compared to the control group and this difference was statistically significant (p<0.001).

We calculated the number of microscopic fibroblasts according to the average fibroblast numbers in groups (Figure 2). Fibroblast cell counting in the control group determined that 3 were at grade 2 and 5 were at grade 3, according to Hinton criteria [19]. However, in the treatment group, 3 were at grade 3, 4 were at grade 2, and 1 was at grade 1. We found significantly fewer fibroblasts in the treatment group compared to the control group (p<0.05).

Ultrastructural imaging by electron microscopy assessment (EM). In the control group, mature and regular collagen fibers were observed. More immature collagen fibers were observed in the pentoxifylline group compared to the control group. Active fibroblasts were seen in both groups (Figure 3).

Determination of hydroxyproline (HYP) and Myeloperoxidase (MPO) content

In epidural scar tissue, HYP and MPO levels were measured in tissues from both groups (Figure 4). The HYP level in the pentoxifylline group was 9594.56±1072.4 ng/gr and 14 312.97±2899.2

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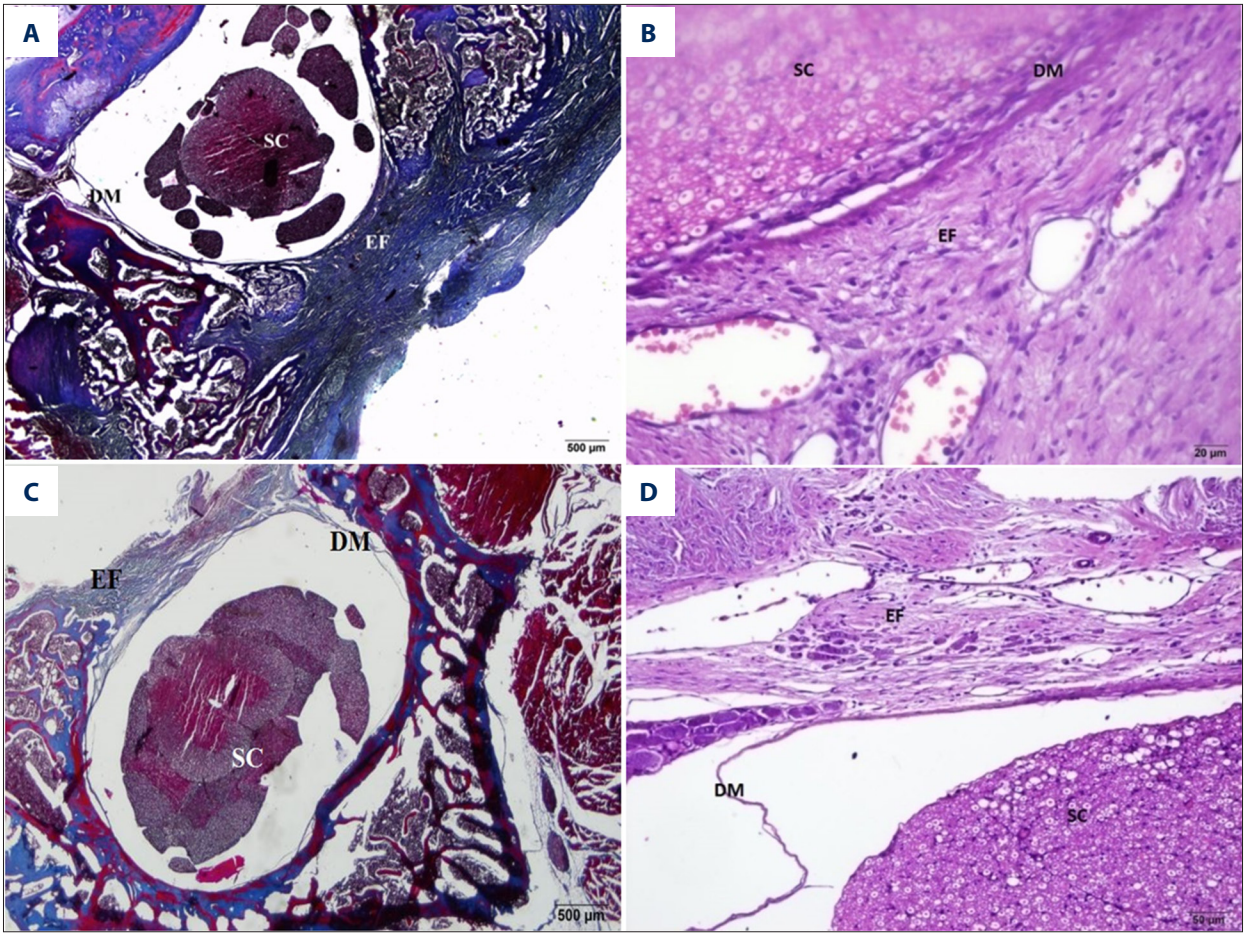

Figure 1. Histopathological examination of the epidural fibrosis. Control group: Existence of dense epidural scar tissue in the laminectomy sites (**A**, trichrome) and scar tissue adhering to the dura mater were observed (**B**, H&E). Treatment group (Pentoxifylline): Loose epidural scar tissue in the laminectomy sites (**C**, trichrome) and partial adhesion of fibrotic tissue to the dura mater were observed (**D**, H&E). SC – spinal cord; DM – dura mater; EF – epidural fibrosis.

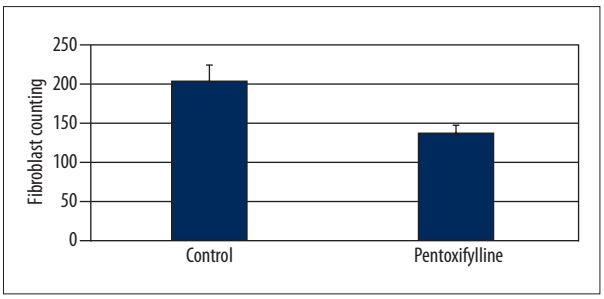

Figure 2. The pentoxifylline group had fewer fibroblasts than the control group (P<0.05).

ng/gr in the control group, showing a statistically significant difference (P<0.001). The MPO level was 13 705.06±2023.1 ng/gr in the treatment group and 18 144.63±4609.0 ng/gr in the control group. This lower level in the treatment group was significantly different when compared to control group (P<0.001).

Discussion

One of the most common complications of lumbar spinal surgery with posterior approach is EF; it causes failed back surgery (FBC) and then adversely affects the result of this surgery. In the literature, failed back surgery occurs in 8-40% of all back surgery patients [20]. In 25% of them, complaints were thought to be related to the EF [21]. Fibroblasts have an important role in the healing process. After fibroblasts are activated by inflammatory factors, they produce collagen fibers and spread them around as part of the healing process. However, exaggerated inflammatory response and fibrotic process cause over-accumulation of local collagen. In conclusion, overgrowth of scar tissue, which is transformed from fibrous tissue, causes compression of the dura or nerve root, which can cause spinal stenosis, limited movement of the nerve root, and dural compression. Thus, it has been accepted that EF is characterized by accumulation of extracellular proteins and fibroblasts by deformation of normal tissue structure with inflammation [22].

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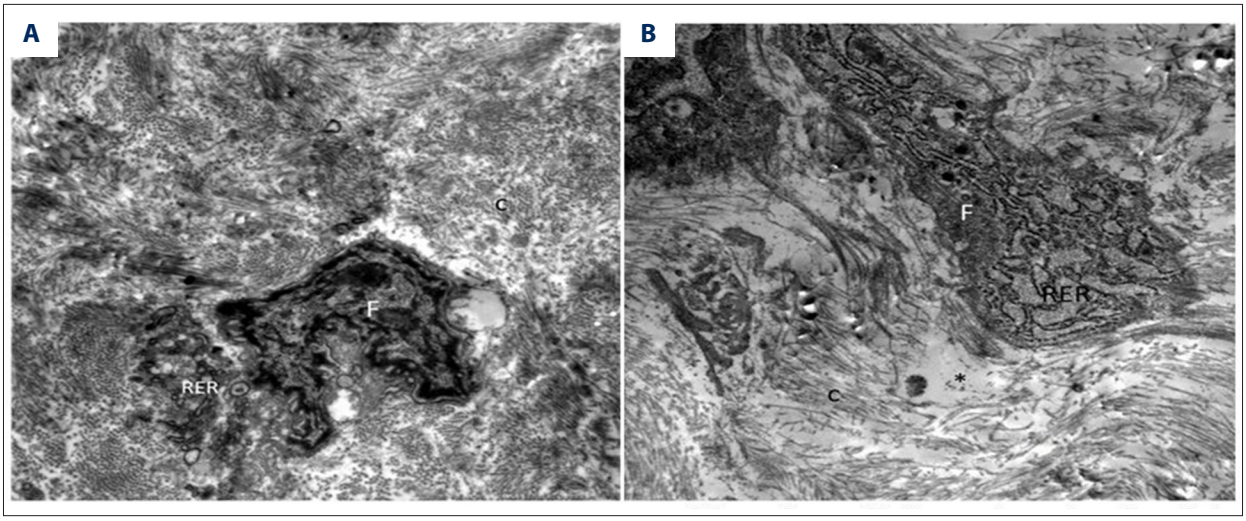

Figure 3. Electron microscopic evaluation of the epidural fibrosis. Active fibroblast between the collagen fibers located in various directions in the control group (**A**). Expanded RER in the active fibroblast cytoplasm. Collagen fibers are immature and located in various directions surrounded by edema in the Pentoxifylline group (**B**). (Magnification: A, B ×15 000). F – fibroblast; C – collagen fibers; * edematous areas; RER – rough endoplasmic reticulum.

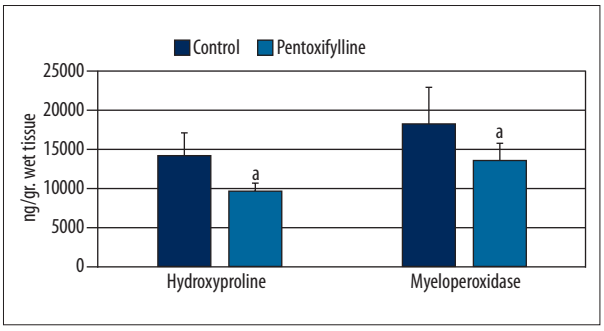

Figure 4. Hydroxyproline and myeloperoxidase levels expressed as the mean ± standard deviation of wet tissue. The pentoxifylline group showed the lowest level. P<0.001, compared with the control group.

This situation is challenging for surgeons if it leads to reoperation due to the elevated risks of dural tear, severe bleeding, or nerve root injury.

In many studies, a great number of materials and drugs have been used to inhibit EF, including adipose tissue, polyvinyl alcohol, hydrogel membrane, polytetrafluoroethylene membrane, polylactic acid membrane, and Vicryl mesh used as solid barriers. Sodium hyaluronate and ADCON-L were used as anti-adhesion gels. Gel recombinant tissue plasminogen activator and urokinase were used as fibrinolytic agents. Gelatin sponge and microfibrillarly collagen were used as hemostatic agents. Methylprednisolone, triamcinolone, prednisolone, ketoprofen, and dexamethasone were used as anti-inflammatory agents. In some studies, it was reported that low-dose radiotherapy and CO_2 laser application decreased formation of EF [23]. In most of the studies successful results have been found in animal experiments, but adequate clinical findings in humans have not demonstrated that these materials and drugs inhibit EF.

PTX is a methylxanthine derivative drug used for vascular perfusion disorder because of its effects on deformity correction in erythrocytes, decrease in blood viscosity, and improvement of capillary blood flow [24,25]. Moreover, it has anti-inflammatory effects leading to accumulation of intracellular cyclic adenosine monophosphate (cAMP), reduction of neutrophil release, and inhibition of oxygen radical production [26].

In vitro studies on fibroblasts have demonstrated that PTX drastically decreases acute cell proliferation, stimulates intestinal collagenase activity, and suppresses secretion and synthesis of fibrillary collagen type 1 and 3, fibronectin and proteoglycan reservoir [27–29]. In recent studies, it was shown that PTX has anti-fibrinogenic effect on liver stellate or myofibroblast cells that are responsible for over-production of extracellular matrix in fibrosis of liver [30–32]. This effect of PTX has been supported by other studies. In previous studies on its direct effects, it was reported that PTX inhibits dermal and hepatic fibroblastic cells in culture [15,33]. It also decreases proliferation of fibroblasts obtained from human skin and production of collagen and matrix proteins [15,29]. Berman et al. reported that PTX decreased the components of extracellular matrix, including type1, type 3 collagen, and glycosaminoglycans in dermal cells, while increasing collagenase activity [14]. Moreover, it was shown by Preaux et al. that PTX inhibits growth and collagen synthesis of cultured human myofibroblasts [34]. Desmoulikre et al. showed that PTX decreased fibroproliferation and myofibroblastic differentiation with inflammatory response in rats with liver fibrosis [35].

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Our study was conducted on laminectomized rats to evaluate the effects of PTX, which has received acceptance by the Food and Drug Administration (FDA). We used multiple parameters for evaluation of its potential properties. Grade 3, representing the most intensive scar tissue according to Rydell classification, was not detected in the treatment group by macroscopic examinations, but it was frequently observed in the control group ($p<0.01$). Examinations of H&E staining by light microscopy and electron microscopy showed that PTX decreased epidural fibrosis compared to the control group and reduced significantly the number of fibroblasts ($p<0.05$). In biochemical analyses, hydroxyproline levels indicate the amount of collagen as the key component of healing wound [36]. Increased hydroxyproline levels are considered one of the most important signs in the process of fibrosis [37,38]. Myeloperoxidase is a lysosomal enzyme released by leukocytes as a response to oxidative stress [39]. MPO plays an important role in fibrosis by producing reactive oxidative molecules [40,41]. These data reveal that HP levels and MPO activity would be reduced with decreased formation of fibrosis. In our study, decrease in hydroxyproline and myeloperoxidase in the treatment group was a valuable result in terms of PTX's anti-fibrotic and anti-inflammatory effects. It was also shown that PTX reduces epidural fibrosis in rats with laminectomy with these features. These findings reveal the importance of our study.

After reviewing several studies, we aimed to conduct the first study that investigates whether PTX has positive effect on epidural fibrosis in an experimental laminectomy model in rats, and our results show that PTX has positive effects. Further studies are required to evaluate its effective dose, possible adverse effects, long-term results, and methods of application before clinical practice.

Conclusions

Our experimental study reveals that pentoxifylline is able to reduce fibroblast proliferation and inflammation, and might thereby prevent epidural fibrosis in post-laminectomy rats.

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