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Use of pimecrolimus to prevent epidural fibrosis in a postlaminectomy rat model

Laboratory investigation

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Object. Epidural fibrosis is the scar tissue formed over the dura mater after a laminectomy. Extensive epidural fibrosis may be an important underlying cause of failed back syndrome. Pimecrolimus, an ascomycin derivative, is one of the new classes of immunomodulating macrolactams and was specifically developed for the treatment of inflammatory diseases. This study examined the preventive effects of the local application of pimecrolimus in minimizing spinal epidural fibrosis in a rat laminectomy model.

Methods. Thirty Wistar rats were divided into 3 equal groups: control, mitomycin C (MMC), and pimecrolimus groups. Each rat underwent a laminectomy at the L-3 lumbar level. In the experimental groups, a cotton pad soaked with MMC (0.5 mg/ml) or 5 mg pimecrolimus was placed on the exposed dura mater. No treatment was performed in the control group rats. Thirty days after surgery, the rats were killed and the dura mater thickness, epidural fibrosis, and arachnoidal involvement were quantified.

Results. The mean dura thickness was measured at 9.28 ± 3.39 μm in the MMC group and at 8.69 ± 2.32 μm in the pimecrolimus group, compared with 14.70 ± 4.14 μm in the control group. In addition, the epidural fibrosis and arachnoidal involvement were reduced significantly in the treatment groups compared with the control group.

Conclusions. In this animal model, it was shown that locally applied pimecrolimus effectively reduces epidural fibrosis and dural adherence in rats that underwent lumbar laminectomy. Mitomycin C was equally effective as pimecrolimus in reducing epidural fibrosis and dural adherence in this study. *(DOI: 10.3171/2009.6.SPINE08580)*

Key Words • epidural fibrosis • failed back syndrome • laminectomy • mitomycin C • pimecrolimus

Postlaminectomy epidural fibrosis, the formation of a dense scar tissue adjacent to the dura mater following posterior lumbar surgery, characterizes the normal response of the body to surgery.[8] The mechanical tethering of nerve roots or the dura by the epidural adhesions may be a contributing factor for a significant subset of patients suffering from persistent back and leg pain following lumbar laminectomy, the so-called "failed back syndrome."[34] Failed back syndrome is a source of difficulty in the daily activities of patients,[14] and reoperation for failed back syndrome is usually unsuccessful.[7] In addition, an increased occurrence of dural tears, nerve root injuries, and bleeding have been noted is association with revision spine surgery.[2] Biological and nonbiological materials have been studied on animals to prevent epidural fibrosis.[3,9,16,20,35] Some of these materials have been applied in humans, and spinal membrane adhesion barrier gels are the most widely accepted materials in current practice, although each is associated with certain drawbacks, such as requiring repeat surgery and a significant cost.[23]

Mitomycin C is an alkalizing antibiotic substance that potentially suppresses fibroblast proliferation after surgery.[10] It has been used with a high success rate in glaucoma filtration surgery to promote the patency of the trabecula as well as in the treatment of tracheal cicatrix after tracheal reconstruction.[19,26,27,39] The local application of MMC prevents epidural fibrosis in rat and rabbit laminectomy models.[8,22]

Abbreviations used in this paper: IL = interleukin; MMC = mitomycin C.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Pimecrolimus is a macrolactam derivative specially designed for the treatment of inflammatory skin diseases as an alternative to corticosteroids. Pimecrolimus belongs to the family of calcineurin inhibitors.[12] Topical pimecrolimus proved to be highly effective in patients with atopic dermatitis.[11,37] Moreover, early clinical trials have shown that orally applied pimecrolimus was very effective in the treatment of psoriasis and atopic dermatitis.[32]

In the current literature, pimecrolimus has not been used for prevention of epidural fibrosis formation after lumbar laminectomy. In this study we aimed to demonstrate the effect of pimecrolimus in epidural fibrosis and to compare its effect with MMC.

Methods

Animal Population

The study population included 30 male Wistar rats, with a mean age of 8 months, and a mean weight of 300 g. The approval of the Ankara University Ethics Committee was obtained to conduct this study.

Surgical Procedure

Ketamine hydrochloride (35 mg/kg; Eczacıbası) and xylazine (5 mg/kg; Bayer) were used intramuscularly for anesthesia. After the lower back of each rat was shaved, the surgical site was sterilized with povidone. The L2–4 laminae were exposed and a total laminectomy was performed at the L-3 level. The ligamentum flavum and epidural fat tissue were cleared away from the surgical site. Hemostasis was provided by using a bipolar coagulator. The rats were then randomly divided into 3 groups, with 10 rats in each group. In the control group, only a laminectomy was performed. In the MMC group, 5 mg MMC was diluted 1:10 in 0.9% NaCl and topically used with a cotton pad soaked with 0.5 ml of the solution for 5 minutes. The cotton pad was then removed. In the pimecrolimus group, 0.5 ml of pimecrolimus cream (Novartis Pharma), which contains 5 mg pimecrolimus, was placed over the epidural space at the laminectomy site for 5 minutes. After 5 minutes, the agent was cleaned up using a cotton pad.

The animals were killed on postoperative Day 30 using a lethal dose (150 mg/kg) of pentobarbital (IE Ulagay).

Evaluation of Epidural Fibrosis

The bones of the lumbar area were removed en bloc in a manner that included the paraspinal muscles. The specimen was immersed into 10% buffered formalin. The spine was then further cut axially through the upper L-2 to lower L-4 levels to isolate the laminectomy site. All specimens were sent for histological evaluation. Histological evaluation consisted of decalcification, dehydration, and preparation of paraffined blocks. Sections of 10 μm were obtained on the axial plane and stained with Masson trichrome. Sections were examined using a Leica DM 6000B microscope and photographed using a Leica DFC 490 camera (Leica Microsystems). All laminectomy sections were evaluated in a blinded manner by 1 histologist who analyzed the dura thickness, density of fibrosis, and arachnoidal involvement. Quantitative morphometric analysis was performed on sections using the Leica Application Suite Digital Analyzing System. Measurements were conducted at a magnification of 40.

The dura mater thickness was measured at 3 points. The first sample was harvested from the midpoint of the laminectomy defect, the second sample was obtained 2 mm from the right side of the first sample, and the third sample was obtained 2 mm from the left side of the first sample. Mean values were used for statistical evaluation. Subsequently, epidural fibrosis was graded based on the scheme devised by He et al.[15]: Grade 0 = dura mater is free of scar tissue; Grade 1 = only thin fibrous bands are observed between the scar tissue and dura mater; Grade 2 = continuous adherence is observed in < two-thirds of the laminectomy defect; and Grade 3 = scar tissue adherence is large, affecting > two-thirds of the laminectomy defect, or the adherence extended to the nerve roots. The presence of arachnoidal involvement was also noted.

Statistical Analysis

The Kruskall-Wallis and Mann-Whitney tests were used to analyze the dura mater thickness. In addition, the epidural fibrosis and the presence of arachnoidal involvement were statistically analyzed using a standard chi-square test. Probability values < 0.05 were considered statistically significant.

Results

In the surgical wounds, no superficial or deep infection was seen. In addition, erythema, hematoma, and CSF leakage was not observed.

The results of the thickness of the dura are shown in Fig. 1. The mean dura thickness was measured at 9.28 ± 3.39 μm in the MMC group and at 8.69 ± 2.32 μm in the pimecrolimus group, compared with 14.70 ± 4.14 μm in the control group. When dura mater thickness was compared, a statistically significant difference was found between the experimental groups and the control group ($p < 0.05$). Conversely, results of dura mater thickness indicated that the MMC and pimecrolimus groups were not statistically significantly different from each other ($p > 0.05$). In axial sections stained with Masson trichrome, 7 of the control group rats showed Grade 3 epidural fibrosis (Fig. 2). Grade 1 epidural fibrosis was found in 7 rats in the MMC group (Fig. 3) and in 8 rats in the pimecrolimus group (Fig. 4). The results of epidural fibrosis grades (Table 1) indicated that the MMC and pimecrolimus groups were not significantly different ($p > 0.05$). Conversely, there were statistically significant differences in the epidural fibrosis grades among the experimental groups and the control group ($p < 0.05$). The results of arachnoidal involvement are shown in Table 2. When the arachnoidal involvement results were evaluated, statistical significance was found among the experimental groups and the control group ($p < 0.05$). However, statistical significance was not found between the MMC and pimecrolimus groups ($p > 0.05$).

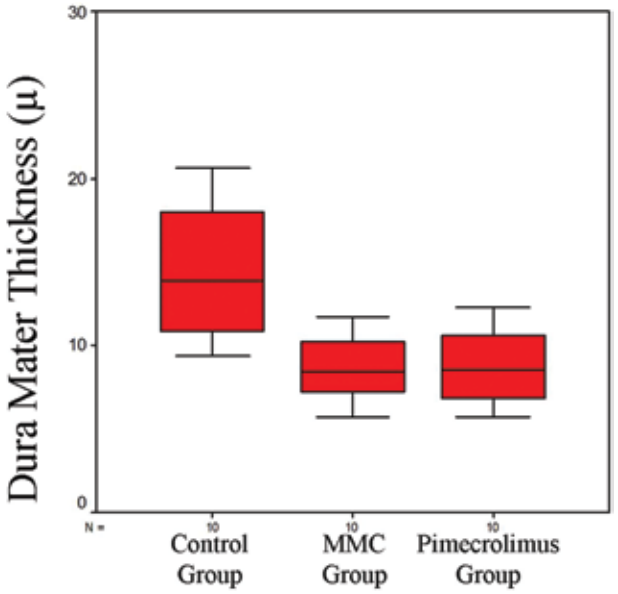

Fig. 1. Box-plot graph demonstrating the differences in dura mater thickness among the pimecrolimus group, MMC group, and control group. Differences between experimental groups and the control group were statistically significant ($p < 0.05$). Conversely, a statistically significant difference was not found between the MMC and the pimecrolimus groups.

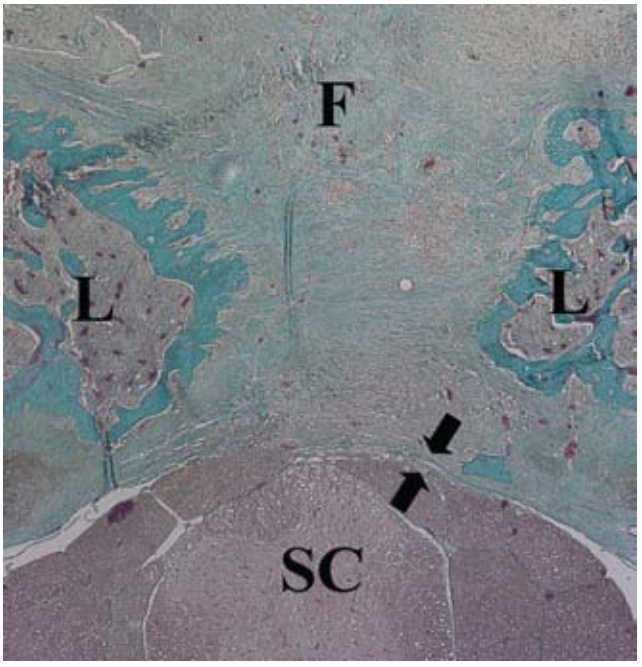

Fig. 2. Photomicrograph showing Grade 3 fibrosis as observed in the control group. The epidural fibrosis (F) was adhered to the underlying dura mater *(arrows)* and spinal cord (SC). L = lamina. Masson trichrome, original magnification × 5.

Discussion

Epidural fibrosis occurs when there is a deposition of fibrous tissue in the epidural space surrounding the nerve root. Formation of the epidural fibrosis is often initiated by injury or trauma to the epidural space, related either to epidural exploration or to surgical procedures involving the disc.[1,5] Fibrosis often produces adhesions tethering the nerve root to adjacent tissues. The tethering may then impede nerve mobility and increase tension on the nerve during motion, leading to nerve injury. Postlaminectomy epidural fibrosis significantly increases the hazards of revision spine surgery and may contribute to the occurrence of failed back syndrome.[33,34]

Numerous biological and synthetic materials used to prevent scar formation have been evaluated, such as hemostatic sponges,[16] fat grafts,[9] hyaluronic acid,[35] carboxymethylcellulose gels,[20] a mixture of dextran sulfate and gelatin (Adcon-L, Gliatech), 5-fluorouracil, cyclosporine,[40] and radiation therapy.[3] However, the results of these studies have demonstrated only moderate success, whereas clinically, their use is yet to be successful.

After lumbar laminectomy, the formation of dense and thick epidural scar tissue and significant adhesions between dura mater fibrous tissues were shown in all control group rats (Fig. 2). It was remarkable that the epidural fibrosis grades were lower in the experimental groups compared with control group; this result was statistically significant as well. In the literature, dura thickness has not previously been used to evaluate epidural fibrosis. During epidural scar formation, the dura mater is the most affected tissue. Thus, we planned this study to evaluate dura mater thickness and demonstrate the postlaminectomy epidural fibrosis intensity. The mean dura mater thickness of the control group was measured at 14.70 ± 4.14 μm. Comparison of the measurements of the dura mater thickness of the control group and the experimental groups showed that the measurements of the control group were higher than the other groups (Fig. 1).

Mitomycin C is an alkalizing antibiotic isolated from *Streptomyces caespitosus*. It prevents postoperative fibroblast proliferation.[10] Mitomycin C is safely used topically

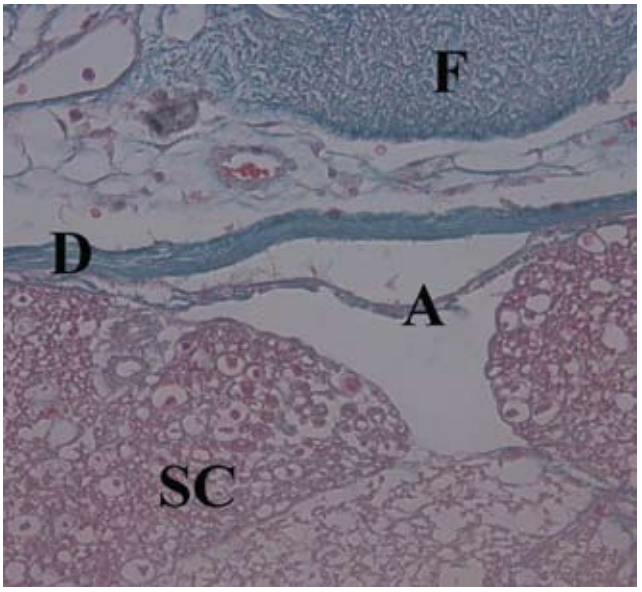

Fig. 3. Photomicrograph showing Grade 1 fibrosis as observed in the MMC group. Direct contact between the underlying spinal cord (SC) and arachnoid mater (A) with the epidural fibrosis (F) was demonstrated. D = dura mater. Masson trichrome, original magnification × 40.

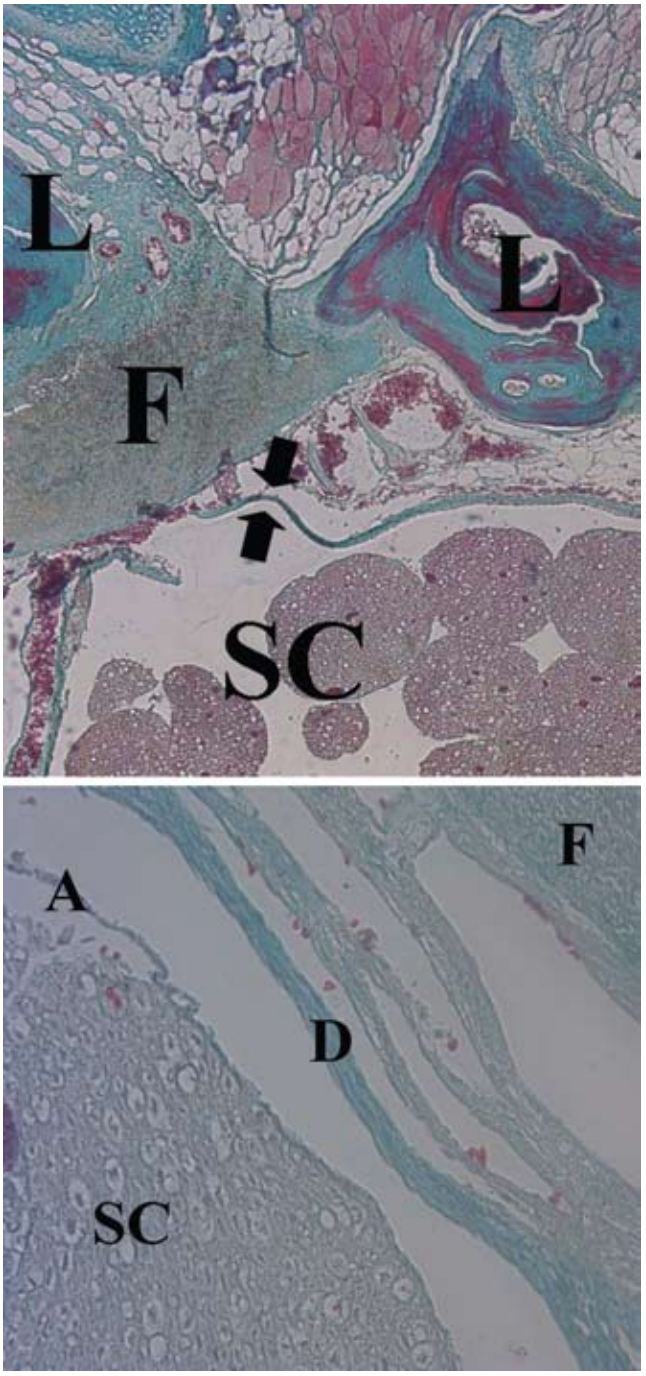

Fig. 4. Photomicrographs demonstrating Grade 1 fibrosis in the pimecrolimus group. *Upper:* No direct contact between the underlying spinal cord (SC) and the epidural fibrosis tissue (F) is evident. L = lamina; *Arrows* = dura mater. *Lower:* No direct contact was observed between the underlying spinal cord and arachnoid mater (A) with the epidural fibrosis tissue (F). D = dura mater. Masson trichrome, original magnification × 2.5 *(upper)* and × 40 *(lower)*.

in humans. It is preferred in ophthalmological surgery such as trabeculectomy, excision of pterygium, strabismus surgery, and optic nerve decompression.[17] Mitomycin C is also safely used in otolaryngology procedures such as recurrent subglottic and tracheal stenosis, endoscopic dacryocystorhinostomy, and endolymphatic shunt procedures.[6,13,30] Previously, Dogulu et al.[8] found that topical application of MMC may be a successful method of preventing postlaminectomy peridural fibrosis. Recently, Kurt et al.[21] have reported that aprotinin, MMC, and Adcon-L were effective in preventing peridural fibrosis and dural adhesions in postlaminectomy areas. In the present study, slightly thickened dura mater (Grade 1 [Fig. 3] to Grade 2 fibrotic adhesions to the surrounding epidural scar tissues) was shown in 9 (90%) of the 10 MMC-treated rats. When the extent of epidural fibrosis and the result of arachnoidal involvement were compared between the MMC treated group and the control group, a significant difference was found between the groups. In addition, the mean dura mater thickness of the MMC group was measured at 9.28 ± 3.39 μm, which was lower than the measurement in the control group. When dura mater thickness of the MMC group and the control group was compared, a statistically significant difference was found. The results of the MMC group in our study are well correlated with results in the literature.

TABLE 1: Histological results of epidural fibrosis grades

Group	No. of Rats	Epidural Fibrosis Grade			
		0	1	2	3
control	10	0	0	3	7
MMC	10	0	7	2	1
pimecrolimus	10	0	8	1	1

Pimecrolimus is a chemical modification of ascomycin produced by *Streptomyces hygroscopicus var ascomyceticus* and belongs to the immunomodulatory macrolides. The mode of action of this topical calcineurin inhibitor is more cell-selective than that of corticosteroids. Pimecrolimus blocks the activation of T cells in affected skin by binding with cytosolic binding protein FKBP-12, a 12 kD macrophilin, and forming a complex with calcineurin, calmodulin, and calcium, thereby inhibiting the phosphatase activity of calcineurin. The dephosphorylization of the nuclear factor of activated T-cell protein, a transcription factor necessary for the expression of proinflammatory cytokines such as IL-2, tumor necrosis factor–α, IL-4, and IL-5, is thus inhibited. The most common adverse effect following the application of pimecrolimus is mild to moderate symptoms of irritation such as burning, erythema, and pruritus.[4,18] The pimecrolimus treatment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.[24,28,29,36,38] The US FDA issued a warning about pimecrolimus and tacrilimus in 2005, stating: "Since their approval, the FDA has received reports of lymphoma and skin cancer in children and adults treated with these drugs; whether the reported cancers are associated with these products has not been established."[31]

In the current study, we tested the hypothesis that the use of pimecrolimus after laminectomy would significantly reduce the extent of epidural fibrosis, and prevent the consequent adhesion of this tissue to the dura mater.

TABLE 2: Histological results of arachnoidal involvement

Group	No. of Rats	Arachnoidal Involvement	
		Yes	No
control	10	10	0
MMC	10	2	8
pimecrolimus	10	1	9

The dose of pimecrolimus chosen for this study was 5 mg and was based on the published data in the literature.[25] Microscopic evaluation of tissue showed no evidence of infection or chronic inflammation. In 9 (90%) of the 10 pimecrolimus-treated rats, slightly thickened dura mater showed Grade 1 (Fig. 4) to Grade 2 fibrotic adhesions to the surrounding epidural scar tissues. Comparison of the epidural fibrosis and arachnoidal involvement results of the MMC and pimecrolimus groups showed no statistically significant difference between these groups. The mean dura mater thickness of the pimecrolimus group was measured at 8.69 ± 2.32 μm. No statistically significant difference was found in dura mater thickness measurements between the MMC and pimecrolimus groups. Mitomycin C is an agent that affects fibroblasts and prevents epidural fibrosis. Even if pimecrolimus affects the activation of T-cells, it could prevent epidural fibrosis formation as effectively as MMC.

Conclusions

Our study has revealed that pimecrolimus prevents the formation of epidural fibrosis in an experimental laminectomy model as successfully as MMC does. Both MMC and pimecrolimus could be used for epidural fibrosis. Further studies will help to find different agents which could effectively prevent epidural fibrosis formation.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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