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Research Article

The dose-dependent effect of tranexamic acid on epidural fibrosis after laminectomy: an experimental study on rats

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ABSTRACT

Objective: This study aimed to evaluate the dose-dependent efficacy of tranexamic acid (TXA) in preventing epidural fibrosis in a rat laminectomy model and explore its potential as a therapeutic intervention for postoperative fibrosis in spinal surgery.

Methods: In this experimental animal study, 32 female Wistar-Albino rats were randomized into four groups (control, 10 mg/kg TXA, 30 mg/kg TXA, and 100 mg/kg TXA; n=8 per group). Following a standardized laminectomy procedure, TXA was administered intravenously as a loading dose through the tail vein prior to surgery. The rats were sacrificed at the 4th-week post-surgery, the lumbar vertebrae were excised en bloc, and epidural fibrosis, inflammatory cell density, and fibroblast density were assessed histologically.

Results: High-dose TXA (100 mg/kg) significantly reduced epidural fibrosis compared to the control (p=0.004), 10 mg/kg (p=0.002), and 30 mg/kg TXA groups (p=0.03). While the 30 mg/kg group showed lower epidural fibrosis grades compared to the control, the difference was not statistically significant. No significant differences were observed in inflammatory or fibroblast densities across groups.

Conclusion: High-dose TXA (100 mg/kg) effectively reduced epidural fibrosis in a dose-dependent manner, demonstrating potential as a systemic therapeutic option to improve postoperative outcomes in spinal surgery.

Introduction

Laminectomy is a surgical procedure performed by spine surgeons as a treatment for various lumbosacral problems. However, following laminectomy, epidural fibrosis and related adhesions, which develop as a result of the normal wound-healing process, may result in postsurgical compression.[1] The majority of surgical patients develop tissue adhesions during physiologically normal healing processes. However, when this reaction is extreme, excessive tissue formation can cause compression of the nerve root and discomfort.[2] This is called epidural fibrosis, which is defined as non-physiologic scar formation at the surgical access site to the spinal canal.[3]

The pathophysiology of epidural fibrosis is complex, but as with other inflammatory processes, certain cytokines and growth factors take part.[4] One of them is the pro-inflammatory cytokine tumor necrosis factor,[5] which is also implicated in other fibrotic diseases such as myelofibrosis.[6]

Epidural fibrosis is thought to be a contributing factor for failed back surgery syndrome, in which the back pain remains persistent, either with or without leg discomfort, and affects approximately 40% of patients.[7] The diagnosis of epidural fibrosis can be done with contrast-enhanced magnetic resonance imaging[8] or epiduroscopy.[9]

There are currently no known effective treatments for failed back surgery syndrome associated with epidural fibrosis.[10,11] The lower success rate of further surgical and revision procedures and the higher likelihood of scarring account for the unsatisfying outcomes seen in nearly 20% of patients.[12]

Numerous methods have been investigated to prevent excessive epidural fibrosis, including the creation of a physical barrier through the implantation of biocompatible materials between the dura mater and posterior tissues.[13] There are experimental studies using in vitro fibroblast culture and in vivo animal models to prevent the formation of epidural fibrosis in the literature. Previously, pharmacotherapy was primarily used to alleviate inflammation; however, it is now used to significantly impact various cell parameters, including angiogenesis, apoptosis, and energy metabolism.[2] In summary, although there are studies to prevent the formation of epidural fibrosis using different methods, there are currently no methods that have been universally accepted in clinical practice.

Preventing excessive proliferation and activation of fibroblasts at the surgical site, which contributes to the formation of epidural fibrosis, is a promising line of research. In the first 3-5 days following surgery, there is a local inflammatory response that mostly includes coagulation, hemostasis, and the release of chemokines.[14] These local factors recruit inflammatory cells

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to the injury area. Furthermore, the hematoma creates a necessary environment for the maturation of fibrous tissue. Confined bleeding will help prevent excessively increased fibrous tissue formation. As a result, the careful control of fibroblast proliferation has gained popularity as a research topic for reducing fibrosis.

Tranexamic acid (TXA) is a synthetic lysine derivative that prevents the interaction of plasminogen and fibrin. This action prevents clot breakdown, which in turn decreases bleeding in patients.[15,16] Introduced during the 1960s, TXA has since been used for diminishing bleeding associated with surgery and trauma, alongside reducing the necessity for blood transfusions across various medical specialties.[17] Particularly in the realm of orthopedic surgery, TXA's effectiveness is notable in joint replacement surgeries and spinal operations where there is a high expectation of blood loss.[18]

It has been hypothesized that TXA will reduce epidural hemorrhage, which may lead to a reduction in fibrous tissue and ultimately lessen epidural fibrosis. In an experimental study, it has been shown that TXA is effective in preventing the formation of epidural fibrosis.[19] Although the effectiveness of TXA in preventing epidural fibrosis formation is hypothesized, the effectiveness of the drug at different doses remains unknown. In this study, the aim was to evaluate the dose-dependent effects of TXA on the formation of epidural fibrosis.

Material and methods

32 mature female Wistar-Albino rats with a mean weight of 282 ± 39 grams and a mean age of 6 months were included in the study. In constrained laboratory settings, the rats were provided standard food and unlimited access to water. The room was maintained between 20°C and 24°C and 50% and 60% humidity with a 12-hour light/darkness cycle. The care of the animals was carried out in accordance with national and international standards. Bagcilar Training and Research Hospital Institutional Animal Care and Use Committee (Approval no: HADYEK/2023-03 Date: 27.03.2023). was obtained to authorize the entire protocol of the study.

Each rat received a unique identifier for differentiation. Anesthesia was achieved through intramuscular injections, using xylazine (5 mg/kg; sourced from Rompun, Bayer, Istanbul, Türkiye) combined with ketamine hydrochloride (35 mg/kg; obtained from Ketalar, Pfizer, Istanbul, Türkiye). The rats were then divided into 4 random groups, with each subject undergoing a laminectomy procedure. Prior to the surgery, the rats had the fur around the operation area trimmed. The skin around the site was disinfected with povidone-iodine (manufactured by Batticon, Adeka Pharmaceuticals, Istanbul, Türkiye). A surgical incision was then made along the midline, stretching from the T12 to the L3 vertebrae. With the aid of a microscope with 2.5 times magnification (World Precision Instruments, Sarasota, FL, USA), a bilateral laminectomy was executed at the L1 and L2 levels of the vertebrae, allowing clear visibility of the nerve roots and dura mater as depicted in Figure 1.

No drug was injected in Group I (Control Group, n=8). Group II (10 mg TXA drug group, n=8) received 10 mg/kg of TXA (Herajit, Vem, Ankara, Türkiye), Group III (30 mg TXA drug group, n=8) received 30 mg/kg of TXA, and Group IV (100 mg TXA group, n=8) received 100 mg/kg TXA. These doses were administered intravenously through the tail vein during the same session as the surgery prior to laminectomy.

Following meticulous hemostasis, the incisions were closed with 3-0 sutures. An intraperitoneal injection of 10 mg/kg of enrofloxacin (Baytril-K, Bayer HealthCare AG, Leverkusen, Germany) was used for preoperative and postoperative antibiotic prophylaxis. Fentanyl 0.02 mg/kg (Fentanyl; Janssen-Cilag Pty Ltd, North Ryde) was administered intraperitoneally for postoperative analgesia. There were no indications of systemic disease or wound infection, and the motor functions of the rats were normal.

Rats were sacrificed in the 4th week following the protocol of Circi et al[19] using 100 mg/kg of the anesthetic ketamine hydrochloride (Ketalar, Pfizer, Istanbul, Türkiye). The rats were thoroughly dissected, and the lumbar spines were removed entirely.

Tissue samples were placed in a 10% neutral buffered formalin solution and then decalcified in 10% formic acid for 7 days in order to facilitate sectioning. After decalcification, axial slices of the laminectomy site were obtained. Processing, paraffin embedding, and 3 mm sectioning were performed on the fixed tissues. A histopathologic analysis was carried out in a blinded fashion.

Dural thickness was determined by taking 3 measurements roughly equally spaced at the laminectomy site (Figure 2A). Masson's trichrome (MTK) staining was applied to assess epidural fibrosis. Epidural fibrosis was evaluated in accordance with the literature

HIGHLIGHTS

- The dose-dependent effects of tranexamic acid (TXA) on epidural fibrosis were assessed in a rat laminectomy model.
- TXA at a high dose (100 mg/kg) significantly reduced epidural fibrosis, showing its potential efficacy in preventing this complication.
- Lower doses of TXA (10 mg/kg and 30 mg/kg) did not yield statistically significant results in reducing epidural fibrosis compared to the control group.
- This study suggests that systemic high-dose TXA could be a valuable tool in spinal surgery for reducing postoperative epidural fibrosis and potentially improving surgical outcomes.

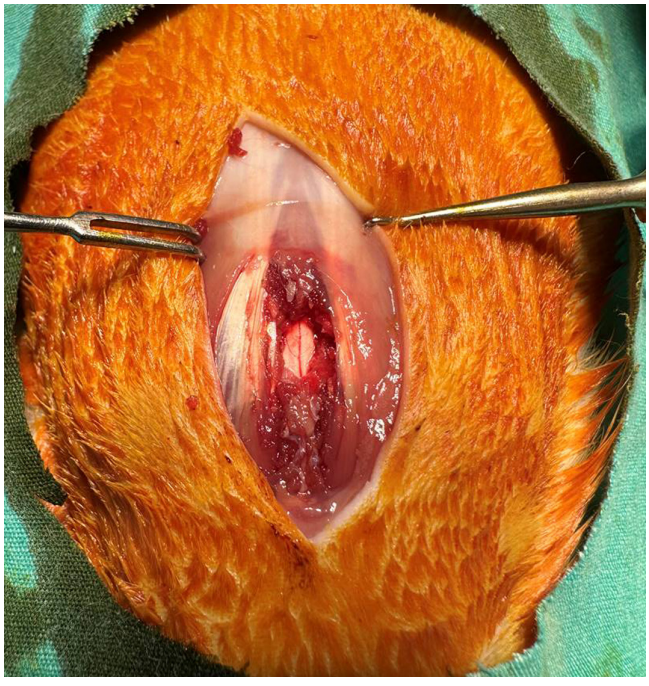

Figure 1. Exposed spinal cord following laminectomy. The top is cranial.

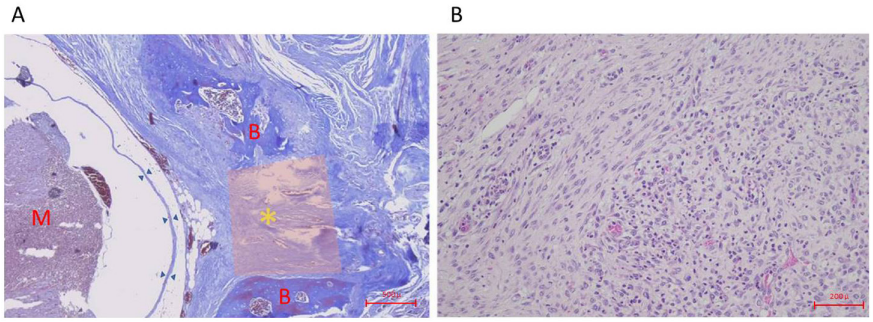

Figure 2. A. The average dura thickness for each specimen was calculated using 3 different measurements at the laminectomy site. The transparent red area shows the defect created by laminectomy. Solid triangles: Dura mater. *, Laminectomy defect; B, Bone; M, Medulla (Specimen 100 mg/kg group, 40x, MTK). B. Example of co-presence of Grade 3 inflammatory cells and fibroblasts from the defect area in the same specimen (Specimen from Control Group, 100x, HE).

data.[8] Grade 0: The dura mater is free of scar tissue; Grade 1: Only thin fibrous bands between the scar tissue and the dura mater are seen; Grade 2: Continuous adherence is seen in less than two-thirds of the laminectomy defect; and Grade 3: Scar tissue adherence is significant, affecting more than two-thirds of the laminectomy defect, or the adherence extended to the nerve roots.[20]

To evaluate inflammatory cell density and fibroblast density, the tissue sections were stained with hematoxylin-eosin (HE). The cells in 3 separate places (2 borders and the center of the laminectomy defect) (fibroblasts and inflammatory cells) were counted, and the mean was determined (Figure 2B). The following categories were used to grade the fibroblast and inflammatory cell densities: Grade 1: Up to 100 fibroblasts or inflammatory cells per 400-meter field; Grade 2: 100-150 fibroblasts or inflammatory cells per 400-meter field; and Grade 3: More than 150 fibroblasts or inflammatory cells per 400-meter field.[21] The grading was done by one of the authors (HIO), who is an experienced attending pathologist, in a blinded fashion.

Results

The average thickness of dura among the specimens was 39.96 μm (±14.64). The mean thickness among groups was not statistically significant ($P > .05$) (Figure 3). Table 1 presents the average grade values for inflammatory cell density, fibroblast density, and epidural fibrosis grades in the 4 different groups (control, 10 mg/kg, 30 mg/kg, and 100 mg/kg). Table 2 shows the pairwise comparison of groups

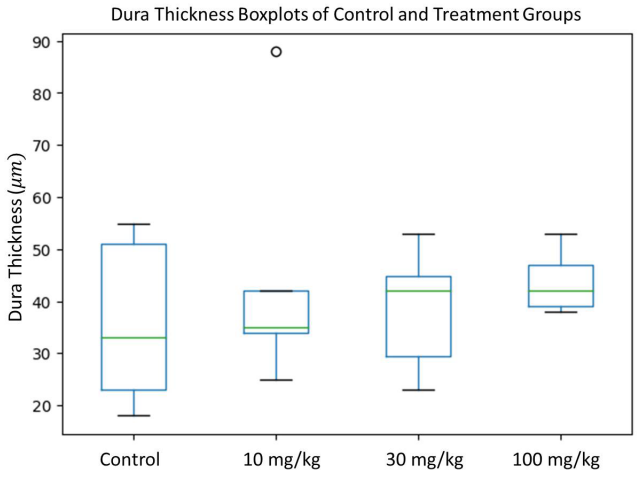

Figure 3. Comparison of dura thickness between control and treatment groups.

for statistical significance in terms of these grades. For inflammatory cell density, no significant differences were found among the pairwise comparisons of groups (1 vs 2 (P=.597), 1 vs 3 (P=.597), 1 vs 4 (P=.397), 2 vs 3 (P=1.0), 2 vs 4 (P=.077), and 3 vs 4 (P=.077)). In terms of fibroblast density, the comparisons were also not statistically significant among the pairs (1 vs 2 (P=.070), 1 vs 3 (P=.070), 1 vs 4 (P=.174), 2 vs 3 (P=1.0), 2 vs 4 (P=.096), and 3 vs 4 (P=.096)).

For the epidural fibrosis grade according to He et al,[20] statistically significant differences were observed in the pairwise comparisons (1 vs 4 (P=.004*), 2 vs 4 (P=.002*), and 3 vs 4 (P=.03*)). Figure 4A represents the grade distribution between the groups. Figure 4B shows the average epidural fibrosis grade of the groups with corresponding ranges. No significant differences were found between other groups. Figure 5A and B show representative specimens from the control and 100 mg/kg groups demonstrating different He grades.

These results suggest that TXA was statistically effective at a 100 mg/kg dose in preventing epidural fibrosis. Although statistically insignificant, the 30 mg/kg TXA group also had a lower average epidural fibrosis grade compared to the control and 10 mg/kg group.

Statistical analysis

Mean, SD, median, minimum, maximum, frequency, and ratios were used in the descriptive statistics of the data. The distribution of the variables was assessed with the Kolmogorov–Smirnov test. For the examination of quantitative independent data, the Kruskal-Wallis and Mann–Whitney *U* tests were utilized. The analysis was conducted using the SPSS 28.0 program (IBM SPSS Corp.; Armonk, NY, USA).

Discussion

Epidural fibrosis is a significant complication that leads to unsatisfying results after laminectomy procedures. The absence of bony support for the posterior column results in substantial fibroblast growth and scarring that follow laminectomy, and postoperative epidural fibrosis occurs when this response is excessive.[1,10,11] Prevention of

Table 1. Mean and range inflammatory cells, fibroblast density, and epidural fibrosis grades of groups

Groups Parameters	Control	10 mg/kg	30 mg/kg	100 mg/kg	*P*
Inflammatory cell density	2.3 (1-3)	2.1 (2-3)	2.1 (2-3)	2.6 (2-3)	>.05
Fibroblast density	2.1 (1-3)	3 (3)	3 (3)	2.6 (2-3)	>.05
Epidural fibrozis grade according to He et al[20]	2.6 (1-3)	2.6 (1-3)	1.85 (1-3)	0.75 (0-2)	<.05

Table 2. Pairwise comparison of groups for statistical significance

Groups (*P*) Parameters	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Inflammatory cell density	0.597	0.597	0.397	1.0	0.077	0.077
Fibroblast density	0.070	0.070	0.174	1.0	0.096	0.096
Epidural fibrozis grade according to He et al[20]	0.820	0.145	0.004*	0.131	0.002*	0.03*

*Statistical significance.

epidural fibrosis, which can develop after laminectomy, is important for achieving successful results in spinal surgery. Experimental studies have been conducted regarding many methods that are thought to be effective in preventing epidural fibrosis, but their routine application has not become possible in today's practice.[2,13,20,21]

Tranexamic acid could prevent the progression of epidural fibrosis through 2 mechanisms: decreasing bleeding and hematoma formation, and reducing inflammation. Although these are interrelated, a recent systematic review also found that TXA has a distinct anti-inflammatory effect in patients undergoing orthopedic surgery, such as decreasing C-reactive protein and interleukin-6 levels.[22] However, this study was designed as a morphological observation, and as such, the accuracy of speculation regarding the mechanism of action in this case is limited. Further research into the mediators of TXA's anti-inflammatory effect in the context of epidural fibrosis is warranted.

According to current literature data, TXA reduces blood loss during spine surgery.[18] There is no widely acknowledged guideline for the TXA dose in spine surgery, and the appropriate dose of intravenous TXA is still being debated. In a comprehensive review, it has been reported that the optimal dosage ranges of intravenous TXA are between 0.5 and 5 g, or 10 and 100 mg/kg.[23]

Due to the wide range of doses available, TXA's effects on various surgical procedures and locations require further investigation. In this study, the dose-dependent effects of TXA on epidural fibrosis formation were evaluated. It was anticipated that this work will help clinicians to better understand the doses of TXA necessary for clinical application to prevent epidural fibrosis.

There are studies reporting that high-dose administration of TXA, referred to as a loading dose of 30 mg/kg or 2000 mg, is more effective in controlling bleeding than a low dose.[24] Cheriyan et al[18] hypothesized that high-dose TXA had a superior hemostatic impact compared to low doses. Similarly, recent research reveals that when compared to low-dose TXA, high-dose TXA considerably reduces perioperative blood loss while having no negative effects on perioperative morbidity or mortality.[25] Retrospective case series show that using high-dose TXA during complex spine procedures on adult patients may be both safe and effective.[10] A meta-analysis by Li et al[26] suggested that TXA is safe and effective when administered intravenously to individuals undergoing spine surgery. High-dose TXA decreases total blood loss and the requirement for blood transfusions while not raising the risk of postoperative deep vein thrombosis.

In this study, it was shown that TXA has a dose-dependent effect on epidural fibrosis. Sigaut et al[24] reported that TXA administration of 30 mg/kg and above can be considered a high dose. It has been reported in the literature that high-dose TXA is more effective in limiting surgical bleeding.[18,25,27] The results in this study also suggest that high-dose administration of TXA was effective in limiting the formation of epidural fibrosis. Tranexamic acid was found to be most effective in preventing epidural fibrosis when administered at 100 mg/kg. It was determined that low-dose TXA administered at 10 mg/kg was not different from the Control Group. Therefore, it was concluded that systemic administration of low-dose TXA did not show sufficient efficacy in preventing epidural fibrosis. Also, the 30 mg/kg TXA group had a lower average epidural fibrosis grade; however, it was not significantly lower than the Control Group and 10 mg/kg group.

While systemic high-dose TXA is more effective in preventing surgical bleeding and preventing epidural fibrosis, the risk of thromboembolism is a concern.[28] In a retrospective cohort study evaluating 318 cases, Raman et al[29] reported that high-dose TXA can have important side effects such as pulmonary embolism, deep vein thrombosis, atrial fibrillation, and myocardial infarction. The cases in which side effects were detected were in the group of patients over 70 years of age with a history of cardiovascular disease. Clinicians should be cautious when planning interventions with TXA for patients who have a history of thromboembolic disease or inherited thrombophilia. Use of hormonal oral contraceptives concurrently must also be done with caution.[16]

Tranexamic acid can be applied topically or systemically. There are possible drawbacks to the topical application of TXA during full exposure of spinal nerves. Although it has been reported that topical TXA has a limiting effect on the formation of epidural fibrosis in spinal surgery,[19] it has also been reported that topical TXA may have significant side effects.[30] Topical TXA's packaging may resemble that of bupivacaine, and accidental intrathecal injection of TXA can result in myoclonus, seizures, paraplegia, arrhythmias, and death. Patel et al[31] published a review article that included 21 reports of accidental intrathecal administration of tranexamic acid injected during spinal anesthesia. Ten incidents resulting in death were reported, with a mortality rate of just under 50%. The recommendation was that special care should be taken when applying topical TXA during spine

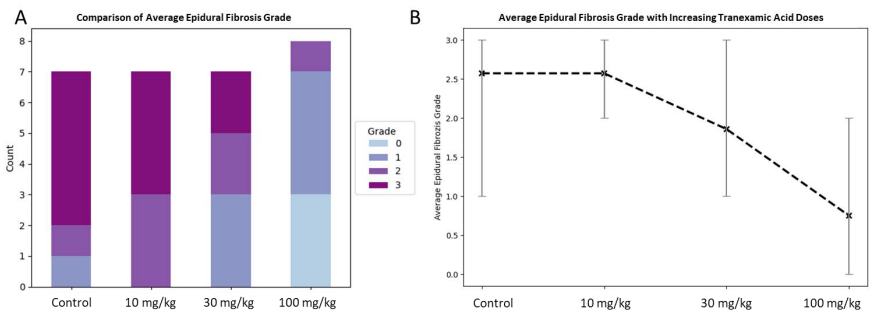

Figure 4. A. Distribution of epidural fibrosis grades among groups. B. Average epidural fibrosis grades between groups with bars denoting range.

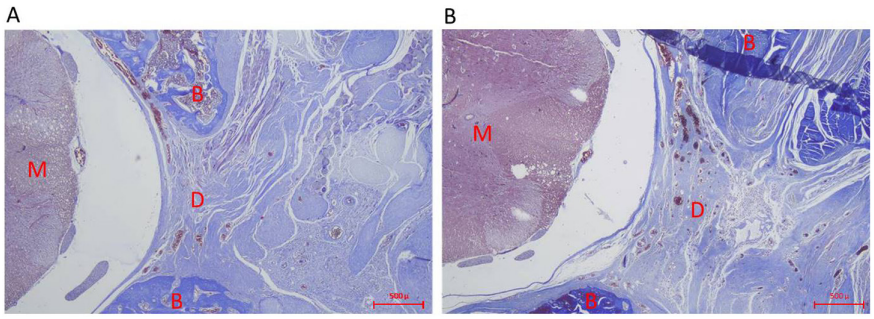

Figure 5. A. Example of Grade 3 epidural fibrosis in which fibrotic tissue over the dura mater covers less than two-thirds of the laminectomy defect (Specimen from Control Group, 40x, MTK). B. Example of Grade 2 epidural fibrosis in which fibrotic tissue over the dura mater covers less than two-thirds of the laminectomy defect (Specimen 30 mg/kg group, 40x, MTK). B,: Bone; D, Defect area; M, Medulla.

surgery. It should not be forgotten that these effects may occur when high doses are used.

The main limitation of this study is the size of the groups. It is possible that a dose lower than 100 mg/kg TXA might have been effective; however, the group size was not sufficient to show the difference. The 30 mg/kg TXA group had a lower epidural fibrosis grade on average; however, it was not significantly different from the Control Group and 10 mg/kg group ($P > .05$). Furthermore, it was significantly different from the 100 mg/kg TXA group but with a relatively high *P*-value ($P = .03$). With groups of this size, this significant difference between the 30 mg/kg and the 100 mg/kg groups might have occurred due to normal statistical variation rather than being a clinically significant difference. Tranexamic acid has a place in future research to prevent epidural fibrosis. Since acute inflammation is present for a few days in the post-operative period, continuing TXA administration in the post-operative period might also be promising to research.

Ultimately, the goal of future studies should be to develop a comprehensive understanding of TXA's role in spinal surgery, enabling clinicians to tailor treatments to individual patient needs, thereby improving surgical outcomes and reducing the incidence of complications such as epidural fibrosis. In this context, these results suggest that high-dose systemic TXA might be an effective tool in the surgeons' armamentarium against epidural fibrosis.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Bagcilar Training and Research Hospital (Approval no: HADYEK/2023-03 Date: 27.03.2023).

Informed Consent: N/A

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