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Topical administration of tranexamic acid for prevention of postoperative epidural fibrosis: insights from a rabbit laminectomy model

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Abstract

Significant advancements in imaging and surgical methodologies have led to more frequent performance of neurosurgical procedures such as laminectomy in both animal and human patients. Epidural fibrosis (EF) is defined as the excessive formation of scar tissue in the epidural space after lumbar laminectomy, often resulting in recurring postoperative pain. Given the association between postoperative hematoma accumulation at the laminectomy site and the development of EF, the present study aimed to evaluate the preventive impact of tranexamic acid (TXA), an antifibrinolytic agent with well-recognized hemostatic properties across various surgical fields. A rabbit laminectomy model was constructed to assess its effectiveness in reducing EF formation. A total number of 18 adult New Zealand White male rabbits were randomly divided into two groups: The control (saline) group and the treatment (topical TXA) group. Each rabbit underwent a two-level laminectomy at L3-L4. The treatment group received 5.00 mL of 100 mg mL^{-1} TXA solution applied topically to the laminectomy site, while the control group received 5.00 mL of saline. Postoperative evaluations included magnetic resonance imaging at week six to assess EF, followed by histopathological examinations to evaluate fibroblast cell density in scar tissue, EF grading and thickness of the dura mater. The analysis of magnetic resonance imaging and histopathologic data revealed significant differences between the two groups indicating that topical administration of TXA might be a promising approach for preventing EF.

Introduction

Epidural fibrosis (EF) is a prevalent complication following spinal surgery. It is described as a non-physiological excessive scar tissue within the epidural space.[1] It potentially extends into the neural canal adhering to the dura mater and nerve roots resulting in compression and tethering of neural structures.[2] This phenomenon is cited as a factor contributing to 20.00 - 36.00% of patients with failed back surgery syndrome ,[3] a complex condition defined as persistent lumbar pain despite surgical intervention or recurring pain emerging after spinal surgery, primarily of neuropathic origin,[4] causing significant social, economic, and medicolegal issues. The EF prevention has been a topic of interest for decades, with numerous studies exploring various pharmacological agents, surgical techniques, biomaterials and nonbiomaterial barriers.[1] However, only modest success has been achieved thus far and a definitive solution remains elusive.

Postoperative hemorrhagic collection at the surgical site is believed to play a crucial role in the formation of EF.[5,6] Although the etiology of EF is complex, the prevailing belief, initially proposed by LaRocca and McNab, is that postoperative scar tissue primarily develops through the infiltration of fibroblasts from traumatized paraspinal muscles into the epidural hematoma. This process ultimately leads to the replacement of the hematoma with excessive and disorganized matrix deposition.[7] This has led to investigations at both clinical and experimental levels aimed at reducing postoperative hematoma either through improved hemostasis or hematoma evacuation with the goal of decreasing the extent of EF.[5,6,8]

Spinal surgeries often involve significant perioperative bleeding and the unique characteristics of the spine hinder the effectiveness of mechanical hemostatic techniques

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such as direct pressure and ligatures. Due to thermal complications and limitations in addressing diffuse hemorrhage associated with electric coagulation, neurosurgeons have increasingly explored the use of topical hemostatic agents. These agents are sought not only for the management of bleeding but also for the prevention of EF in complex spinal operations.[8,9]

Tranexamic acid (TXA) is an antifibrinolytic agent that reduces bleeding by inhibiting the activation of plasminogen to plasmin, thereby, preventing degeneration of blood clots.[10] Primarily administered intravenously, TXA has been demonstrated to significantly reduce perioperative hemorrhage and the need for blood transfusions across various procedures including cardiac, orthopedic, and spinal surgeries.[10,11] Nonetheless, concerns about complications such as convulsive seizures and systemic thrombogenicity have prompted investigations into its topical administration with the aim of achieving a safer and more precisely targeted intraoperative hemostatic approach.[12,13]

Besides its established use in cardiac and orthopedic surgery, topical TXA is now gaining increased attention for spinal procedures. Recent reviews indicate that topical TXA effectively reduces perioperative bleeding during spinal surgeries,[14-16] bringing forward the hypothesis that TXA, with its known hemostatic efficacy, could reduce the amount of postoperative epidural hematoma and thereby mitigate the development of EF.

The TXA has been found effective in reducing EF in rat models, with only two published studies investigating its effect solely through histopathological evaluations.[17,18] This study was the first to explore its preventive effect in rabbits, uniquely incorporating magnetic resonance imaging (MRI) to evaluate total amount of fibrosis alongside histo-pathological evaluations, taking an important step forward in a long way to fully understanding and advancing the potential application of TXA for preventing EF.

Materials and Methods

Animals. All procedures were approved by the Ethical Committee of the Islamic Azad University, Karaj Branch (Approval Number: IR.IAU.K.REC.1401.020, Date: 2022-02-23). A total number of 18 clinically healthy adult New Zealand White male rabbits (Razi Institute, Karaj, Iran), weighing between 1.60 and 2.40 kg, were utilized for this study. The rabbits were individually housed in suspended cages and randomly divided into two groups: The control (saline) group and the treatment (topical TXA) group. One hour before surgery, all rabbits received an intramuscular injection of tramadol (Caspian Tamin, Rasht, Iran) at a dose of 10.00 mg kg^{-1}. The anesthetic protocol for all patients included ketamine (Alfasan, Woerden, The Netherlands) at 50.00 mg kg^{-1} and xylazine (Alfasan) at 20.00 mg kg^{-1} through intramuscular injection.

Surgical procedure. The rabbits were positioned prone and then the back area, extending from the thoracic region to the sacral region, clipped, sterilized with povidone-iodine and draped. A midline incision between L2 and L5 was made, the fascia was incised to expose the tip of spinous processes and the paraspinal muscles were separated subperiosteally from the processes and the laminae of L3 and L4, then retracted bilaterally with Gelpi retractors. The surgery was performed with the aid of a 2.50 × magnification loupe. Hemostasis was achieved using bipolar coagulation. The exposed spinous processes were removed using a rongeur and a two-level laminectomy was performed at L3 - L4 using a power burr and 1.00 mm Kerrison punch, creating a defect of approximately 50.00 mm^2. The ligamentum flavum and dural fat were meticulously removed, leaving clean dura exposed for the full extent of each L3 - L4 laminectomy (Fig. 1). Following irrigation of the defect with sterile saline solution and achieving satisfactory hemostasis, 5.00 mL of saline solution was poured onto the paraspinal muscles and laminectomy defect in the control group (n = 9) and 5.00 mL of 100 mg mL^{-1} TXA solution was poured onto the same area in the treatment group (n = 9). To prevent bias, the operating surgeon was blinded to the choice of rabbit group and solution type. Subsequently, the muscles, fascia and skin were closed in a standard manner. No incidents such as dural tears, lacerations or spinal cord bleeding were occurred during any of the procedures. All rabbits received a prophylactic intramuscular injection of enrofloxacin (Hipra, Girona, Spain) at a dose of 15.00 mg kg^{-1} 30 min before surgery and again at 24 and 48 hr after surgery. Postoperative analgesia was provided by intramuscular injection of tramadol (10.00 mg kg^{-1}) every 8 hr during the first day.

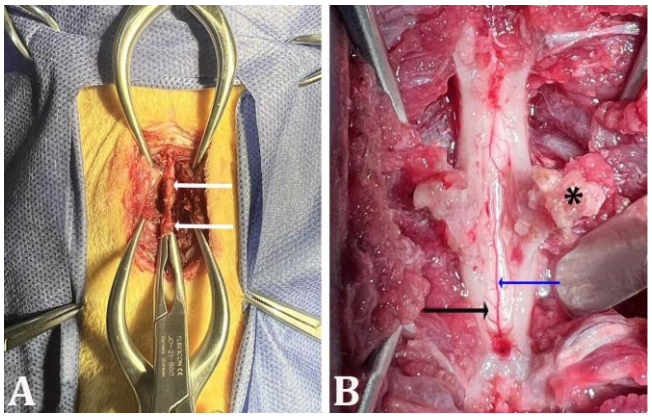

Fig. 1. Intraoperative images of the rabbit laminectomy procedure. **A)** Paraspinal muscles are separated and retracted from the spinous processes (white arrows) of L3 and L4, with the processes being removed by a rongeur. **B)** The laminectomy site at the L3-L4 level after excision of the laminae and ligamentum flavum, revealing the exposed spinal cord with intact dura (black arrow). The black asterisk indicates the facet joint and the blue arrow indicates the posterior median spinal vein.

Magnetic resonance imaging. Under general anesthesia, MRI was conducted at week six following surgery on all rabbits using 3T scanner (Siemens Magnetom Trio, Erlangen, Germany) with a knee coil receiver. The MRI examinations included axial T1-weighted fast spin echo sequence (repetition time msec/echo time msec: 500/10) with a 2.00-mm section thickness. The MRI was employed to identify EF in the epidural cavity following spinal surgery with a radiologist grading EF according to the modified Ross method.[19,20] Ross *et al*.,[20] described a method for estimating EF in a single axial MRI slice by dividing the lumbar spinal canal into four quadrants, drawing lines perpendicular to the central point of the thecal sac (Fig. 2). However, this technique was limited by its planar quantification and did not provide comprehensive volume information about the extent of the pathology. Lubina *et al*. proposed a modified Ross method which facilitates the estimation of the total amount of EF in a specific segment of the spinal canal post-surgery.[19] This method is straightforward to implement and does not require any additional software or hardware. In this study, our observation areas comprised the two quadrants on the dorsal side of the dural sac across five continuous axial sections centered on the L3 - L4 inter-vertebral disc level encompassing the laminectomy site.

Histopathology. Following MRI scans, the rabbits were humanely euthanized using intramuscular injection of 200 mg kg^{-1} ketamine and 40.00 mg kg^{-1} xylazine. Spinal columns from L2 - L5, along with adjacent muscles were resected en bloc and fixed in 10.00% neutral buffered formalin for 1 week followed by decalcification for 6 weeks in EDTA/hydrochloridric acid solution. The laminectomy area, encompassing the L3 - L4 segment, underwent dehydration, paraffin embedding, and sectioning into 3.00 µm thick cross-sectional slices followed by staining with Hematoxylin and Eosin. Histo-pathological analysis, conducted by a blinded professional pathologist upon light microscopy examination included assessing fibroblast cell density in epidural scar tissue following Hinton *et al*.'s and grading of EF based on He *et al*.'s system.[21,22] Dural thickness was measured *via* ViewPoint Software (version 1.0.0.9628; PreciPoint Group, Munich, Germany) according to the method described by Cemil *et al*.[23]

Statistical analysis. Data analysis was performed using SPSS Software (version 25.0; IBM Corp., Armonk, USA). The Shapiro-Wilk test was used to determine where the distribution of continuous variables was normal. The Levene test was used to evaluate the homogeneity of the variations. Additionally, Student's *t* test (in the case of nonhomogeneity of variance) was used to compare the average variables in the two experimental and control groups. Furthermore, the chi-square test and eta coefficient were used to assess relationships and compare qualitative indicators between the experimental and control groups.

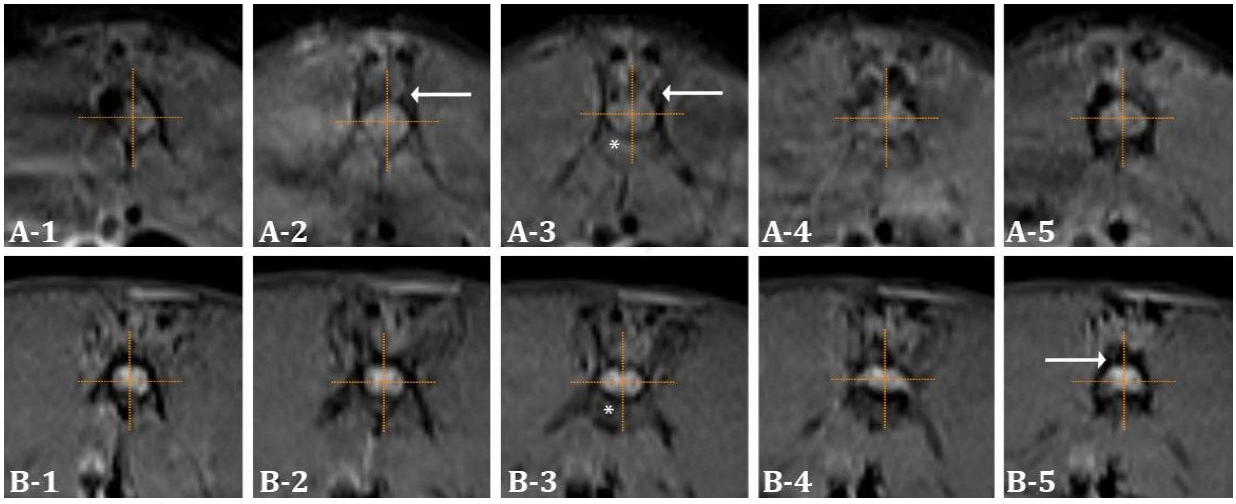

Fig. 2. Magnetic resonance imaging (MRI) observation of epidural fibrosis in rabbits 6 weeks postoperatively. Five consecutive T1-w axial MRIs of two rabbits, centered on the L3 - L4 disc level (indicated by asterisks in both panels). Perpendicular orange dotted lines are drawn to indicate quarters according to the grading system proposed by Ross *et al*. [20]and modified by Lubina *et al*.[19] The upper panel (A) depicts a control group rabbit, showing a relatively greater amount of EF and adhesion (white arrow) to the dura mater in the dorsal quarters. In (A-1), a pseudomeningocele caused by scar tissue regression is observed. In (A-2, A-3), scar tissue and adhesion are visible in more than 75.00% of both dorsal quarters consistent with a grade 4 Ross score.[20] In (A-4), scar tissue and adhesion are visible in 25.00-50.00% of both dorsal quarters, consistent with a grade 2 Ross score. In (A-5), despite the absence of epidural fibrosis in the left dorsal quarter, scar tissue is visible in more than 75.00% of the right dorsal quarter, consistent with a grade 4 Ross score.[20] The bottom panel (B) illustrates a TXA group rabbit with relatively less EF and adhesion to the dura mater in the dorsal quarters. In (B-1), there is no adhesion despite scar tissue formation. In (B-2, B-5), minimal scar tissue adhesion to the dura mater is observed in the left dorsal quarter while the other quarter remained free of adhesion. In (B-3), a lacuna between the epidural scar tissue and the dura mater at the disc level shows a large amount of epidural scar tissue in both dorsal quarters.

Results

All animals maintained good health after surgery with no reports of mortality, seizure, infections or post-operative neurologic deficits. They were individually housed in cages with free access to food and water, not immobilized and were ambulatory throughout the entire postoperative period.

Magnetic resonance imaging. The MRI observations revealed that rabbits in the TXA group exhibited a smaller amount of epidural scar tissue and adhesion to the dura mater at laminectomy sites (Fig. 2). Despite the formation of scar tissue in the epidural space, a narrow gap was visible between the fibrosis and dura in most slices of the TXA group indicating less adhesion. Also, the dura mater was not obviously compressed. In contrast, rabbits in the control group exhibited noticeable epidural scar tissue adhering to the dura mater with dense scar tissue compressing the dural sac. The mean values for the total amount of fibrosis were 51.00 ± 7.00% in the TXA group and 74.00 ± 3.00% in the control group. This represented the extent of the dorsal epidural space affected by fibrosis at the laminectomy site indicating a statistically significant difference.

Histopathologic examinations. As shown in Figure 3, regarding fibroblast cell density, the control group exhibited more abundant fibroblasts with 77.00% of rabbits showing grade 3 and 22.00% showing grade 2 compared to the TXA group, where, 22.00% were grade 1, 66.00% grade 2, and 11.00% grade 3. The difference between the groups was statistically significant (p = 0.014). Regarding EF grading, dense epidural scar tissue with widespread adhesions to the dura mater and dorsal muscles was observed at the laminectomy sites in the control group. Conversely, the laminectomy sites in the TXA group exhibited loose or minimal adhesions. In the control group, 77.00% of the rabbits were graded as 3, and 22.00% graded as 2. In the TXA group, 11.00% were graded as 0, 33.00% graded as 1, and 44.00% graded as 2, with only one case graded as 3, representing 11.00%. The difference in EF grading between the control and TXA groups was statistically significant (p = 0.027) indicating less EF and epidural adhesion in the TXA group. The mean thickness of the dura mater was 27.7 µm in the control group and 21.24 µm in the TXA-treated group with the differences being statistically significant (p = 0.0153). This result suggested that inflammation in the dura after surgery was reduced in the TXA group.

Discussion

For almost half a century, EF has been remained a significant challenge in spine surgery, driving a surge in research efforts in recent years. However, the research for effective interventions to address this issue remains unfulfilled.

The MRI examination in our study demonstrated a significant decrease in EF in the TXA group supporting the potential role of TXA in reducing EF through the reduction of postoperative epidural hematoma. This finding was consistent with MRI results from studies by Mohi Eldin and Abdel Razek.[5] and Kotil,[6] using Ross *et al.*'s[20] grading, which revealed that the removal of postoperative hematoma via suction drains obtained similar results.

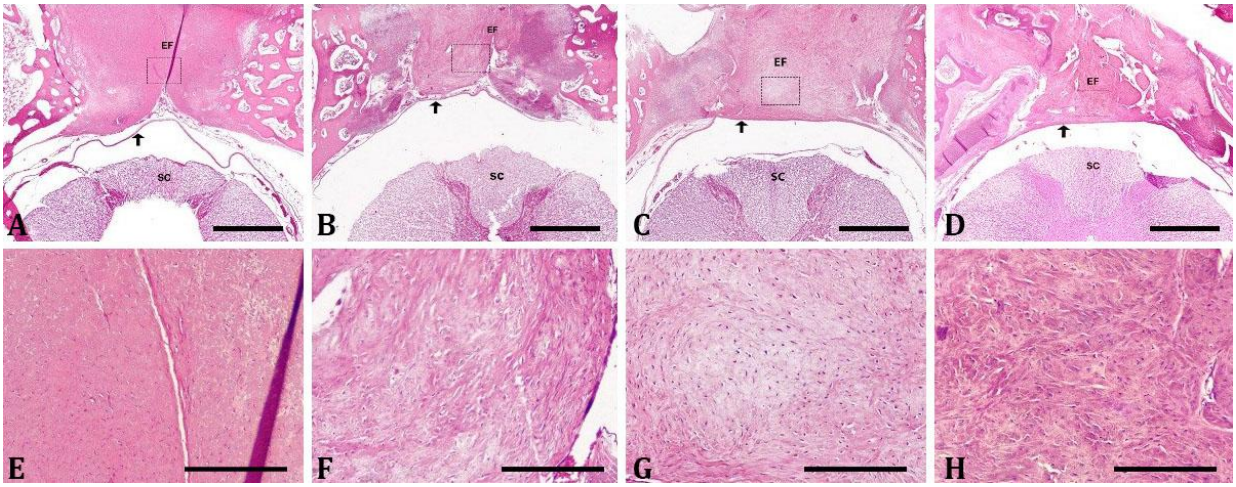

Fig. 3. Photomicrographs of Hematoxylin and Eosin-stained sections of laminectomy sites at 6 weeks post-operatively. **A)** 40 × magnification image of a TXA-treated rabbit demonstrating scar tissue without adherence to the dura mater, compatible with grade 0 EF; **B)** 40 × magnification image of a TXA-treated rabbit demonstrating only thin fibrous bands and minimal adhesion between the epidural fibrotic scar and dura mater, compatible with grade 1 EF; **C)** × 40.00 magnification image of a TXA-treated rabbit demonstrating epidural scar tissue with less than 2/3 adherence with the dura mater, compatible with grade 2 EF; **D)** 40 × magnification image of a control group rabbit demonstrating dense scar tissue adhering to more than 2/3 of the underlying dura mater, compatible with grade 3 EF. The bottom panel shows high-resolution images (400 ×) of the dotted rectangles in each of the upper panel images demonstrating the fibroblast density. **E, F)** Grade 1, **G)** grade 2 and **H)** grade 3 fibroblast density. Arrow indicates the dura mater. SC: Spinal Cord; EF: Epidural Fibrosis.

Cytokines like transforming growth factor beta, released from blood products left in the surgery zone, enhance fibroblast production and proliferation, leading to EF formation.[24] Therefore, minimizing blood in the epidural area is believed to lower the risk of EF formation.[9] In this study, rabbits in the TXA group showed significantly lower fibroblast cell density and EF grades. This was in agreement with findings from other studies using hemostatic agents. For example, fibrillar-structured oxidized cellulose and microporous polysaccharide hemospheres reduced EF grading and also showed decreased fibroblast density within epidural scar tissue.[8,9]

Ozturk *et al*. investigated the effect of tamoxifen, an inhibitor of fibroblast proliferation, on EF in a rat laminectomy model.[25] They analyzed dural thickness and EF grading using the same methods as in the present study. Their findings demonstrated that tamoxifen significantly reduced both dural thickness and EF grading compared to the control group.[25] These results were in agreement with our present study, where, TXA-treated rabbits exhibited reduced fibroblast density, dural thickness and EF grading.

The TXA, discovered in 1960, is now included in World Health Organization Model List of Essential Medicines. According to meta-analyses and a large systematic review conducted by Ker *et al.*, which included 29 RCTs with a total number of 2,612 patients, the use of both intravenous and topical TXA resulted in a one-third reduction in perioperative hemorrhage and the necessity for blood transfusions.[26-29] Investigations by Khadivi *et al*. assessed the effects of topical TXA in patients undergoing posterior cervical laminectomy, and posterior cervical laminectomy and fusion surgery, indicated that topical TXA efficiently reduced intra- and postoperative bleeding.[30]

Erdogan *et al*. initially investigated TXA's effect on EF using TXA-impregnated cotton pads in a rat laminectomy model.[17] Their study, which evaluated fibroblast density and EF grading similarly to our methods, found significantly lower scores in TXA-treated specimens compared to controls, consistent with our findings. Notably, Erdogan *et al*. reported no fibroblast density grades higher than one in the TXA-treated group, and most of our TXA-treated samples had a grade of two.[17]

This disparity could be due to factors such as the larger operative site and osseous defect in our study, increased bleeding, tissue manipulation, and the more time-consuming laminectomy in rabbits compared to rats. Variations between animal models and the small sample sizes in both studies should also be considered.

Circi *et al*. evaluated the role of TXA on EF using an experimental rat model, focusing solely on histological assessments.[18] Their study applied He *et al*.'s[22] grading system for EF and a semi-quantitative grading system to assess acute and chronic inflammation, and vascular proliferation in scar tissue. Circi *et al*. found no significant differences between the control and the topical TXA in any of the individual histological parameters.[18] However, when combining the mean scores of all four histological parameters, the total score for the topical TXA was lower than that for the control. In contrast, our study demonstrated a stronger effect of TXA, with statistically significant reductions in all measured parameters, including fibrosis on MRI, fibroblast density, EF grading and dural thickness in the TXA group. This provides more robust evidence for TXA efficacy. This discrepancy in findings may be due to significant methodological differences between the studies. Except for EF grading, which is the only common parameter, the parameters assessed are essentially different between the studies.

The grading system they employed is not an established method in studies investigating EF. It is self-referred, lacks well-studied intra- and interobserver correlation, and lacks precise quantitative measurements as they mentioned before.[31] Furthermore, they did not specify critical details about how this grading system operates, for instance, they did not clarify which parts of the scar tissue were evaluated or the extent of the field of view assessed. In the present study, we evaluated additional parameters that helped interpret and support our results regarding the effect of topical TXA in the prevention of EF. First, we evaluated fibroblast density in scar tissue. Research agrees that fibroblasts are main cells in EF formation, making the inhibition of fibroblast proliferation through various modalities an important potential strategy for preventing EF.[32,33] We aimed to assess the effect of TXA on this fundamental aspect of EF formation using the method of Hinton *et al*.,[21] which has been employed for nearly three decades to evaluate fibroblast density in studies on EF.

We previously discussed how TXA might reduce fibroblast density through its hemostatic efficacy. *In vitro* studies suggest that topical TXA may also inhibit fibroblast proliferation, adhesion, migration and collagen synthesis through additional non-hemostatic effects. However, these effects are observed only at certain concentrations of the solution.[34,35] In the present study, we used a 100 mg mL^{-1} concentration of TXA, which has been effective in reducing bleeding in clinical studies and in inhibiting fibroblast proliferation, migration and collagen synthesis in *in vitro* studies.[34,36] This concentration also demonstrated further anti-adhesive effects in skin models, a result not observed at lower concentrations.[35] Circi *et al*. administered 30.00 mg of TXA at the surgical site but did not specify the volume or concentration of the TXA solution used.[18] This omission raised questions about whether the TXA concentration at their surgical site was sufficient to effectively reduce bleeding or affect fibroblasts. This methodological difference could explain the more significant results

observed in our study and may also account for the reduction in fibroblast density. These findings provide additional evidence supporting the topical use of TXA in spinal surgery and suggest directions for future research to explore optimal concentrations of topical TXA and its potential direct effects on cells for the prevention of EF.

Another contrary aspect between studies is the targeted sites of TXA application. Circi *et al*. reported injecting the solution into the intervertebral space but did not mention applying it to the bleeding muscle surface.[18] Based on the manufacturer's information and the dose used, the volume applied (0.30 - 0.60 mL) would likely be insufficient to cover the entire surgical defect including the muscle surfaces. This is crucial since muscle surface bleeding significantly contributes to blood loss and hematoma formation in spinal surgeries. In contrast, our study applied TXA to the entire dissected muscle surface, exposed bone surface, and osseous defect, thereby, addressing all potential sources of bleeding comprehensively. This approach reduced hematoma formation due to muscle bleeding, which likely contributed to the significant reductions observed in all parameters in our treatment group.

Another dissimilarity between the studies pertains to findings on inflammation. While Circi *et al*.[18] found no significant difference in TXA-treated rats, our observations suggested reduced inflammation in TXA-treated rabbits. This disparity could be attributed to differences in the method of TXA application, as discussed previously, and variations in evaluation methods. Circi *et al*.[18] utilized a semi-quantitative grading system, whereas, we quantitatively assessed inflammation indirectly by measuring dural thickness.

The present study indicated that the topical application of TXA could reduce EF in terms of both adhesion to the dura mater and the total amount of fibrosis after laminectomy in the rabbit model. This suggested that TXA, an effective hemostatic agent could serve as a potential preventive agent for EF formation.

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Conflict of interest

The authors declare no conflict of interest, regarding the authorship or publication of this article.

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