http://www.cjmb.org doi 10.34172/cjmb.2025.3789

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 12, No. 3, July 2025, 150–156
eISSN 2148-9696

Antifibrotic Efficacy of Topical Tranexamic Acid: Macroscopic and Molecular Evidence in a Rabbit Model of Epidural Fibrosis

Arian Rahmani[1], Soroush Mohitmafi[1*], Fariborz Moayer[2], Mohammad Molazem[3]

Abstract

Objectives: Epidural fibrosis (EF), characterized by excessive scar tissue formation in the epidural space, is a significant complication following spinal surgery, often causing persistent postoperative pain. Given the association between postoperative hematoma accumulation at the laminectomy site and EF, this study aimed to investigate the preventive effect of tranexamic acid (TXA), an antifibrinolytic agent known for its hemostatic properties, on EF formation.

Materials and Methods: Twenty-six adult male New Zealand White rabbits were randomly assigned to either a control group (saline) or a treatment group (topical TXA). Each rabbit underwent a two-level laminectomy at the L3-L4 vertebrae. The treatment group received 5 ml of 100 mg/mL TXA solution topically at the laminectomy site, while the control group received 5 ml of saline. At postoperative week 6, macroscopic adhesion assessment and histopathological analysis were performed to quantify inflammatory cells, vessel density, and collagen concentration in scar tissue at the laminectomy site. Additionally, TGF-β and VEGF expression were evaluated in IHC-stained sections.

Results: Macroscopic evaluation showed significantly reduced adhesion in the TXA-treated group compared to the control. Histopathological analysis revealed lower collagen concentration and TGF-β expression in the TXA group, while inflammatory cell count, vessel density, and VEGF expression showed no significant differences between groups.

Conclusions: These findings provide evidence of the efficacy of topical TXA in preventing EF in a rabbit model of spinal surgery. The topical use of TXA appears to be a promising therapeutic strategy for preventing EF and warrants further investigation to evaluate its effectiveness and potential clinical applications.

Keywords: Epidural fibrosis, Laminectomy, Rabbit, TGF-β, Tranexamic acid

Introduction

Laminectomy is a widely performed procedure for spinal canal decompression, yet postoperative epidural fibrosis (EF) remains a significant complication, posing ongoing challenges for surgeons. EF is characterized by excessive scar tissue formation within the epidural space, which can invade the neural canal, leading to dura mater and nerve root compression and tethering (1,2). This undesirable healing process is a major contributor of failed back surgery syndrome, a life-altering condition marked by persistent or recurring lumbar pain despite surgical intervention, affecting 10% to 40% of patients undergoing lumbar spinal surgery (3-5). For decades, preventing EF has been a critical area of research. Various studies have investigated different pharmacological agents, surgical techniques, and interpositional barriers (1,3,6). However, despite extensive efforts, a definitive solution remains elusive.

The healing process of a laminectomy begins with a hematoma that occupies the laminectomy defect and contacts adjacent epaxial muscles (7). Inflammatory and pro-fibrotic cytokines released in the epidural hemorrhagic collection lead to excessive proliferation and differentiation of local fibroblasts and subsequent extracellular matrix overproduction, resulting in epidural scar tissue formation (8,9). TGF-β, a key cytokine, plays a central role in this process, with its excessive activity strongly linked to increased epidural scarring and adhesion (10,11). Based on the etiopathogenesis of EF, reducing epidural hematoma volume and inflammatory processes, as well as inhibiting cytokines such as TGF-β, are hypothesized to be effective strategies for preventing the formation of EF (8-13).

Tranexamic acid (TXA), an antifibrinolytic drug, reduces bleeding by inhibiting plasminogen activation, thereby preventing blood clot lysis (14). Additionally, by inhibiting plasmin, TXA decreases the production of kinins and other pro-inflammatory peptides that increase vascular permeability (15). Plasmin promotes TGF-β activation (16), and studies have shown that TXA, as a plasmin inhibitor, can inhibit TGF-β activation, with some suggesting it may also suppress its expression

Received 3 February 2025, **Accepted** 27 May 2025, **Available online** 14 July 2025

[1]Department of Clinical Science, Karaj Branch, Islamic Azad University, Karaj, Iran. [2]Department of Pathobiology, Karaj Branch, Islamic Azad University, Karaj, Iran. [3]Department of Surgery and Radiology, Faculty of Veterinary, University of Tehran, Tehran, Iran.
*Corresponding Author: Soroush Mohitmafi, Email: mohitmafi@kiau.ac.ir

Key Messages

- TXA is widely used to reduce surgical bleeding and has shown potential anti-fibrotic effects in experimental models.
- In this experimental rabbit model of laminectomy, topical TXA application led to lower macroscopic adhesion grades, decreased collagen density, and suppressed TGF-β expression.
- These findings suggest a therapeutic potential for intraoperative topical TXA as a simple, low-cost strategy for preventing epidural fibrosis.

(17,18). TXA effectively reduces perioperative bleeding and the need for blood transfusions in various surgeries, including cardiac, orthopedic, and spinal procedures, both intravenously and topically (14,19). Recently, topical TXA has gained attention among neurosurgeons, with reviews indicating its efficacy in reducing perioperative bleeding in spinal surgeries (20,21).

Therefore, based on the etiopathogenesis of EF, we hypothesize that intraoperative topical TXA, with its proven hemostatic properties in spinal procedures, could reduce postoperative epidural hematoma and limit the release and activation of cytokines such as TGF-β, potentially serving as an effective strategy for EF prevention.

We aimed to evaluate the effect of topical TXA in preventing EF in a rabbit model six weeks post-surgery through macroscopic adhesion assessment, inflammatory cell count, collagen and vessel density measurement, and immunohistochemical analysis of VEGF and TGF-β expression. Previous studies have explored TXA's effectiveness in reducing EF in rat models, with only two published studies (22,23). However, this study is the first to investigate TXA's impact on EF in a rabbit model and the first to assess in vivo macroscopic adhesion, collagen density, and TGF-β and VEGF expression in this context. These findings represent a significant step toward understanding TXA's potential for EF prevention and provide novel insights into its therapeutic applications.

Materials and Methods

Animals

For this study, 26 adult male New Zealand White rabbits (Razi Institute, Karaj, Iran) with an average weight of 2 ± 0.4 kg were used. The rabbits were housed individually in suspended cages and randomly divided into two groups: the control (saline) group and the treatment (topical TXA) group. The anesthetic regimen for all subjects included 10% ketamine (Alfasan Inc., Utrecht-Netherlands) at 50 mg/kg and 2% xylazine (Alfasan Inc., Utrecht-Netherlands) at 20 mg/kg.

Surgical Procedure

The rabbits were positioned prone, and the back area from the thoracic to the sacral region was clipped, sterilized with povidone-iodine, and draped. A midline incision was created between the L2 and L5 vertebrae. The fascia was incised to reveal the tips of the spinous processes. The paraspinal muscles were separated from the spinous processes and the laminae of L3 and L4 in a subperiosteal manner and retracted bilaterally using Gelpi retractors. The exposed spinous processes were excised using a rongeur, followed by a two-level laminectomy at L3-L4 performed with a power burr and a 1 mm Kerrison punch, resulting in a defect of approximately 5 × 10 mm^2. The ligamentum flavum and dural fat were carefully removed to expose the clean dura for the entire length of the L3-L4 laminectomy (Figure 1). After irrigating the defect with sterile saline and achieving satisfactory hemostasis, 5 mL of saline solution was applied to the paraspinal muscles and laminectomy defect in the control group (n=9), while the treatment group (n=9) received 5 mL of 100 mg/mL TXA solution in the same area. To eliminate bias, the operating surgeon was blinded to the rabbit group assignments and the type of solution used. The muscles, fascia, and skin were then sutured in the usual manner. No complications, such as dural tears, lacerations, or spinal cord bleeding, occurred during any of the procedures.

All rabbits received a prophylactic intramuscular injection of enrofloxacin (HIPRALONA Enro-I, Hipra, Girona, Spain) at a dosage of 15 mg/kg, administered 30 minutes before surgery and then again at 24 and 48 hours post-surgery. Postoperative pain was managed with intramuscular tramadol injections (10 mg/kg) every 8 hours for 24 hours.

Macroscopic Assessment

At six weeks post-operation, macroscopic evaluations of epidural adhesions were performed. To ensure unbiased selection, four rabbits from each group were randomly chosen using a number-based random selection tool. The selected rabbits were then coded by an independent

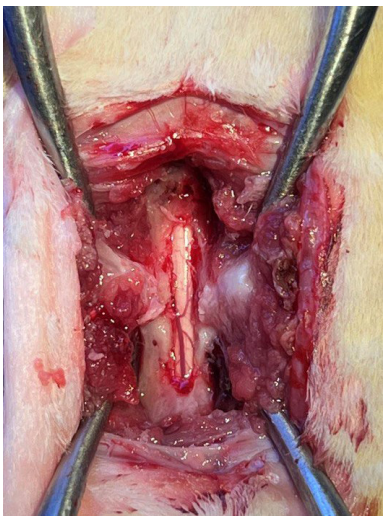

Figure 1. Intraoperative Image of L3-L4 Laminectomy in Rabbits.

researcher not involved in the evaluation. Two professional pathologists, blinded to the coded assignments, assessed the degree of epidural adhesions at L3-L4 using the Rydell standard (24) as follows: Grade 0, epidural scar tissue was not adherent to the dura mater. Grade 1, epidural scar tissue was adherent to the dura mater, but easily dissected. Grade 2, epidural scar tissue was adherent to the dura mater but could be dissected with difficulty without disrupting the dura mater. Grade 3, epidural scar tissue was firmly adherent to the dura mater and could not be dissected. Inter-rater reliability was assured through weighted Cohen's kappa, and in cases of disagreement, a consensus was reached through discussion.

Histological and Immunohistochemical Analysis

The remaining 18 rabbits were humanely euthanized with a lethal dose of intramuscular ketamine (200 mg/kg) and xylazine (40 mg/kg). The spinal columns from L2 to L5, along with adjacent muscles, were removed en bloc and fixed in 10% neutral buffered formalin for one week, followed by decalcification in an EDTA/hydrochloric acid solution for six weeks. After decalcification, an independent researcher not involved in the evaluation coded the specimens to ensure blinding. The laminectomy area, including the L3-L4 segment, was then dehydrated, embedded in paraffin, and sectioned into 3-5 μm thick cross-sectional slices, which were stained with H&E and Masson's trichrome. Histopathological analyses were performed using a semi-automated image system consisting of a computer equipped with image analysis software (ImageJ, National Institutes of Health, Bethesda, MD, USA) and a high-resolution color monitor. Quantitative evaluation of epidural scar tissue post-laminectomy included measuring: 1) the number of inflammatory cells in the scar tissue at the laminectomy site (cells per mm^2), 2) collagen density (percentage per mm^2), and 3) blood vessel density (microvessels per mm^2). Two professional pathologists independently conducted all assessments, with inter-rater reliability evaluated using the intraclass correlation coefficient (ICC). Final values were calculated by averaging the measurements from both raters.

For the evaluation of TGF-β and VEGF expression, immunoreactivity was assessed under light microscopy using a semi-quantitative scoring system based on the percentage of TGF-β and VEGF positive cells (25), as described in Table 1.

Table 1. Scoring System for Expression of TGF-β and VEGF Based on IHC Positivity

Score	Results
0	None
1	<5%
2	Involvement 5%-25%
3	>25%-50%
4	>50%

Statistical Analysis

Data analysis was performed using SPSS for Windows, version 25 (SPSS, Inc., Chicago, IL, USA). Inter-rater reliability for continuous variables was assessed using the ICC, based on a two-way random-effects model with absolute agreement. For macroscopic adhesion grading, inter-rater agreement was evaluated using the weighted Cohen's kappa statistic. The normality of continuous variables was assessed using the Shapiro–Wilk test, and variance homogeneity was checked with the Levene test. Student's t-test was employed to compare mean variables (inflammatory cell count, new vessel density, collagen density) between experimental and control groups, as variances were homogeneous. The Mann-Whitney U test was used to analyze macroscopic assessment between the two groups. The chi-square test was applied to examine relationships and compare qualitative indicators (TGF-β, VEGF expression) between groups.

Results

All animals remained in good health following surgery, with no instances of infection or mortality. They were housed individually in cages with unlimited access to food and water. Additionally, the rabbits were not immobilized and remained ambulatory throughout the postoperative period.

Macroscopic Assessment of Epidural Scar Adhesion

In the laminectomy sites of the control group, severe and dense epidural scar adhesions were observed, making dissection attempts risky due to potential bleeding, dura mater disruption, or nerve root injury. Complete re-exposure of the dura mater was not feasible. In contrast, rabbits treated with TXA exhibited significantly softer and less extensive epidural scar adhesions, facilitating easier dissection and highlighting the ameliorative effect of TXA. Inter-rater reliability for the macroscopic evaluation was assessed using weighted Cohen's kappa, revealing substantial agreement between the two pathologists (quadratic weighted $\kappa = 0.68$, $p = 0.046$). Discrepancies between raters were resolved through discussion, and the final agreed-upon adhesion grades (Table 2) were used for group comparisons, which revealed a statistically significant reduction in the TXA group ($P = 0.047$).

Histological Analysis

Table 2. Grades of Epidural Scar Adhesion in Rabbits, According to Rydell Standard

Group	Grade			
	0	1	2	3
Control	0	0	1	3
TXA	0	2	2	0

Inflammatory Cell Count

The inter-rater reliability for inflammatory cell count showed an ICC of 0.985 (95% CI, 0.961–0.994), indicating excellent agreement. At six weeks postoperatively, the number of inflammatory cells was not significantly different between the two groups ($P = 0.12$), although the mean count was lower in the TXA group (217 cells/mm²) compared to the control group (291 cells/mm²).

Vessel Density

The inter-rater reliability for vessel density measurements showed an ICC of 0.862 (95% CI, 0.631–0.949), indicating good agreement. There was no statistically significant difference in mean vessel density between the TXA group (22.78/mm²) and the control group (23.11/mm²) ($P = 0.916$), suggesting that TXA treatment had no significant effect on vessel density.

Collagen Density

The inter-rater reliability for collagen density measurements showed an ICC of 0.883 (95% CI, 0.694–0.956), indicating good agreement. The mean collagen density was 26.1%/mm² in the TXA group and 36.3%/mm² in the control group, demonstrating a statistically significant reduction in collagen density following TXA treatment ($P = 0.012$) (Figure 2). Since collagen concentration increases during fibrosis, this suggests that TXA reduced epidural adhesion and fibrosis after surgery.

Immunohistochemical Analysis

TGF-β Expression

The percentage of TGF-β positive cells was significantly lower in the TXA-treated group compared to the control group (Figure 3A, B). In the TXA group, 2 rabbits exhibited grade 1 TGF-β expression, while 7 exhibited grade 2. In contrast, the control group had 3 rabbits with grade 2 TGF-β expression, 4 with grade 3, and 2 with grade 4. A statistically significant reduction in TGF-β expression was observed in the TXA group ($P = 0.022$).

VEGF Expression

The percentage of VEGF positive cells did not differ significantly between the groups (Figure 3C, D). In the TXA group, 5 rabbits exhibited grade 2 VEGF, while 4 exhibited grade 3. Similarly, in the control group, 4 rabbits exhibited grade 2 VEGF expression, and 5 exhibited grade 3. The difference in VEGF expression between the TXA and control groups was not statistically significant ($P = 0.637$).

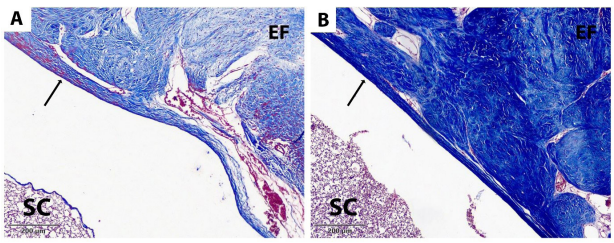

Figure 2. Photomicrographs of epidural scar tissue at laminectomy sites in rabbits, stained with Masson trichrome to analyze collagen density. The collagen density in sections from TXA-treated rabbits (A) was significantly lower than that in sections from the control group (B). SC: Spinal Cord, Black arrow: Dura mater, EF: Epidural Fibrosis

Discussion

This study evaluated the effect of topical TXA on EF formation in a rabbit post-laminectomy model. Our findings indicate that TXA has an anti-fibrotic effect, demonstrated by reduced macroscopic epidural adhesion, decreased collagen density, and lower TGF-β expression in histopathological evaluations.

Erdogan et al (22) were the first to investigate TXA's efficacy in preventing EF, reporting reduced epidural adhesion scores, fibroblast cell density, inflammation, and microvessel density in TXA-treated rats. Similarly, our study observed decreased epidural adhesions, supporting their findings. However, unlike Erdogan et al, we did not find statistically significant differences in inflammatory cell and vessel densities. These discrepancies may stem from differences in evaluation methods. Erdogan et al used a semi-quantitative approach, assessing specific areas at 400x magnification, while our study employed a more comprehensive analysis of a larger scar tissue area (1 mm²). This broader approach may capture a wider range of cellular and vascular changes but could overlook localized alterations, potentially explaining the observed discrepancies.

Circi et al (23) also evaluated TXA's efficacy in rats using a qualitative grading system for scar tissue characteristics,

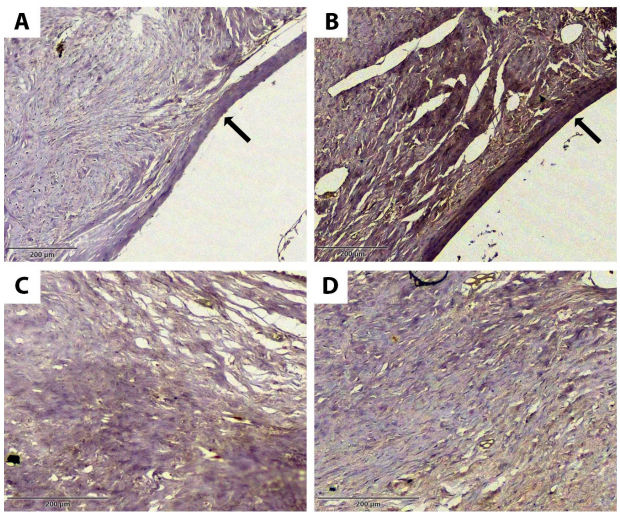

Figure 3. Photomicrographs of immunohistochemical staining depicting the expression of studied markers in epidural scar tissue of rabbits. (A) TGF-β expression in a TXA-treated rabbit, showing significantly lower staining compared to (B) TGF-β expression in a control group rabbit. (C) VEGF expression in a TXA-treated rabbit, and (D) VEGF expression in a control group rabbit, indicating no significant difference in expression levels. Black arrow: Dura mater.

including inflammation, vascular proliferation, and epidural adhesion. Similar to our findings, they reported no significant differences in inflammation and vascular proliferation between the topical TXA and control groups. Although they observed lower adhesion grades in the TXA group, the difference was not statistically significant. In contrast, our study demonstrated significant reductions in macroscopic adhesion grades and collagen density in TXA-treated rabbits.

These discrepancies may stem from the dose of topical TXA application. The total dose and concentration used in the present study have proven effective in previous research. Specifically, the topical application of 5 mL of TXA at 100 mg/mL in the abdominal cavity of rabbits has been shown to safely reduce postsurgical intra-abdominal fibrotic adhesions (26). Wiseman et al reported an inverse correlation between TXA's dose and the incidence or severity of fibrotic adhesions, identifying 100 mg/mL as the most effective concentration (27). Additionally, an in vitro study found that TXA concentrations of 50 mg/mL and 100 mg/mL inhibited fibroblast proliferation, collagen secretion, and cell adhesion, while lower doses lacked these effects, indicating a dose-dependent response (28). These findings align with the present study, which also demonstrated reduced macroscopic adhesion and collagen concentration in TXA-treated rabbits.

Circi et al reported using a total of 30 mg of TXA but did not specify the concentration or volume of the solution, leaving this aspect of their study unclear. Previous research has identified 300 mg/kg as the maximum effective dose for hemorrhage control in rodents (29), far exceeding the dose used by Circi et al. Moreover, studies indicate that TXA's antifibrinolytic efficacy is dose-dependent, with higher doses reducing blood loss more effectively (14). Based on this, we hypothesize that the dose used in our study may have contributed to the more pronounced effects observed.

Our study is the first to evaluate the TXA's impact on TGF-β expression in epidural scar tissue, demonstrating lower TGF-β levels in the TXA-treated rabbits. Previous research has shown that TGF-β levels decrease alongside EF reduction (30), consistent with our findings of reduced collagen density and adhesion grades in the TXA group. These results further indicate that topical TXA effectively mitigated the fibrotic response and suppressed TGF-β expression.

TGF-β, a key cytokine in fibrosis, is secreted in two stages within the wound microenvironment: first by platelets during blood clotting and later during plasmin-mediated clot lysis (31). TXA may affect both stages by controlling perioperative bleeding and potentially reducing the population of platelets, the primary source of TGF-β. Additionally, by inhibiting plasmin, TXA prevents clot lysis and the subsequent release of retained TGF-β. This dual mechanism suggests that TXA's hemostatic effect may simultaneously reduce TGF-β levels and epidural hematoma volume.

In addition to inhibiting TGF-β secretion, TXA may also affect its activation. Plasmin promotes the activation of TGF-β (16), and since TXA primarily inhibits plasmin, it may suppress TGF-β activation in vivo (17,18). Given the proposed positive feedback loop in TGF-β autostimulation (12,32), inhibiting its activation may reduce both its active form and overall expression. Hiramoto et al. demonstrated that TXA treatment suppressed plasmin activity and lowered plasma levels of TGF-β in aging mice (18). Similarly, Suzuki et al. found that TXA not only reduced TGF-β activation but also unexpectedly decreased its mRNA expression (17). This suggests that topical TXA, by inhibiting the activation of TGF-β in the early stages of the inflammatory phase, could trigger suppressive changes in TGF-β-mediated pathological processes that can persist into later stages. However, as this is the first study to examine these effects in the context of EF, further research is needed.

Several studies have successfully reduced experimental scarring by inhibiting TGF-β with topical agents (33-36). Ding et al (13) demonstrated that exogenous TGF-β promotes fibroblast proliferation in a dose-dependent manner, while Decorin, a TGF-β inhibitor, significantly reduced collagen deposition and epidural adhesion based on Rydell classification. Similarly, intraoperative topical administration of pirfenidone, which inhibits TGF-β production and TGF-β pathways, resulted in reduced adhesions and lower collagen density (36). These findings are consistent with our study, where TXA-treated rabbits exhibited lower collagen density and adhesion grades.

Limitations of the Study

While this study offers valuable insights into the potential effects of topical TXA on fibrosis prevention, certain limitations should be acknowledged. One limitation is the relatively small sample size. Although it was sufficient to detect key differences in fibrosis severity, it may have limited the statistical power to identify more subtle histological and molecular changes, such as inflammatory cell count and vessel density. Future studies with larger sample sizes are warranted to confirm and expand upon these findings, providing a more comprehensive understanding of TXA's effects on EF.

This study used a single postoperative time point of 6 weeks, a period commonly adopted in EF research as it represents an optimal window to evaluate scar tissue formation before significant bone regeneration, thereby minimizing potential confounding factors (37,38). While beneficial for generating preliminary data on the short-term efficacy of TXA, additional follow-up assessments in future studies will be essential to better understand its long-term effects and safety in spinal surgery.

Although studies on systemic absorption of topically applied TXA remain limited, available evidence generally indicates minimal absorption, with some studies reporting

undetectable levels (39-41). However, the possibility of some degree of absorption cannot be entirely ruled out. Moreover, most existing data are based on single time-point measurements, which limits the ability to determine peak concentrations and precluding a comprehensive pharmacokinetic evaluation. Future studies should incorporate serial blood sampling and pharmacokinetic modeling to better characterize systemic exposure following topical TXA application.

Despite TXA's widespread use to reduce perioperative bleeding, no consensus exists regarding the optimal route of administration or dosing regimen, whether systemic or topical (23,42). Experimental studies have employed a wide range of doses across various surgical contexts. To our knowledge, this is the first study to evaluate the use of TXA in spinal procedures in a rabbit model. The selected dose was based on evidence from previous experimental models in other surgical fields (26,27), as no established guidelines exist for spinal applications in rabbits.

While our findings suggest potential efficacy at this dose, without comparing multiple concentrations, it remains uncertain whether lower or higher doses might offer improved efficacy or reduced risk. Future studies exploring dose–response relationships will be crucial for better defining the therapeutic window and identifying optimal dosing strategies that offer the most favorable balance between anti-fibrotic efficacy and safety.

This study focused primarily on histological and molecular outcomes, and the assessment of neurological function was not within the scope of our research objectives. Incorporating behavioral and neurological evaluations in future studies would enhance clinical relevance by allowing better correlation between histological changes and functional outcomes.

While TGF-β and VEGF were analyzed due to their well-established roles in extracellular matrix deposition and angiogenesis, future studies incorporating a broader panel of fibrosis-related cytokines such as TNF-α, MMPs, and PDGF could further clarify the mechanisms underlying TXA's potential anti-fibrotic effects.

Although the rabbit model is widely used in EF research, anatomical and physiological differences from humans may limit direct clinical translation. Variations in spinal biomechanics, tissue healing, and drug metabolism could affect outcomes. Future studies in larger animal models or clinical trials are necessary to validate these findings in more clinically relevant settings.

Conclusion

This study provides novel evidence for the antifibrotic efficacy of topical TXA in the context of EF. Our results demonstrated significant reductions in macroscopic adhesion grades, collagen density, and TGF-β expression in the TXA-treated group. These findings enhance our understanding of TXA's potential therapeutic mechanisms. Future research should aim to optimize dosing strategies, investigate additional fibrosis-related pathways, and evaluate the broader applicability of TXA in preventing post-surgical fibrosis and improving patient outcomes.

Authors' Contribution

Conceptualization: Arian Rahmani, Soroush Mohitmafi, Fariborz Moayer, Mohammad Molazem.
Data curation: Arian Rahmani, Soroush Mohitmafi, Fariborz Moayer, Mohammad Molazem.
Formal analysis: Arian Rahmani.
Investigation: Arian Rahmani, Soroush Mohitmafi, Fariborz Moayer.
Methodology: Arian Rahmani, Soroush Mohitmafi, Fariborz Moayer.
Project administration: Arian Rahmani, Soroush Mohitmafi.
Resources: Arian Rahmani.
Software: Arian Rahmani.
Supervision: Soroush Mohitmafi.
Validation: Soroush Mohitmafi, Fariborz Moayer.
Visualization: Arian Rahmani.
Writing–original draft: Arian Rahmani.
Writing–review & editing: Arian Rahmani, Soroush Mohitmafi, Mohammad Molazem.

Conflict of Interests

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

Ethical Issues

All procedures were approved by the Ethical Committee of Islamic Azad University, Karaj Branch (Approval No.: IR.IAU.K.REC.1401.020, Date: February 23, 2022) and conducted in accordance with relevant ethical guidelines to ensure the humane care and welfare of the animals.

Financial Support

The authors declare that no financial support was received for this study. The research was conducted without external funding or sponsorship.

Acknowledgments

The authors wish to acknowledge Dr. Ahad Muhammadnejad at the Cancer Biology Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, for his invaluable guidance and expertise, which were essential to the success of this study. The authors also thank Dr. Asal Darvishi for her unwavering support and contributions throughout the course of this research.

References

1. Ganesh V, Kancherla Y, Igram CM, et al. Pharmacotherapies to prevent epidural fibrosis after laminectomy: a systematic review of in vitro and in vivo animal models. Spine J. 2023;23(10):1471-1484. doi:10.1016/j.spinee.2023.05.007
2. Rajpal K, Singh J, Bahadur R, Bansal K, Shyam R, Khatri K. Postoperative Epidural Fibrosis Prevention: Which Is Better-Autologous Fat versus Gelfoam. Asian Spine J. 2022;16(3):343-351. doi:10.31616/asj.2020.0268
3. Lewik G, Lewik G, Müller LS, von Glinski A, Schulte TL, Lange T. Postoperative Epidural Fibrosis: Challenges and Opportunities - A Review. Spine Surg Relat Res. 2023;8(2):133-142. doi:10.22603/ssrr.2023-0106
4. Sebaaly A, Lahoud MJ, Rizkallah M, Kreichati G, Kharrat K. Etiology, Evaluation, and Treatment of Failed Back Surgery Syndrome. Asian Spine J. 2018;12(3):574-585. doi:10.4184/asj.2018.12.3.574
5. Thomson S, Jacques L. Demographic characteristics of patients with severe neuropathic pain secondary to failed back surgery syndrome. Pain Pract. 2009;9(3):206-215. doi:10.1111/j.1533-2500.2009.00276.x
6. Li J, Ma Q, Wu J, Zhao P, Li T, Li J. Dose preservation of ligament flavum really help prevent postoperative epidural fibrosis and improve outcome in microdiscectomy?. J Clin Neurosci. 2020;80:331-335. doi:10.1016/j.jocn.2020.06.013
7. Torre AD, La Torre D, Lacroce P, Lavano A. Epidural Fibrosis Prevention in Failed Back Surgery Syndrome. J Pain Manage Med. 2022;8:168. doi:10.35248/2684-1320.22.8.168
8. Çetin E, Eren B, Karagöz Güzey F, et al. Comparison of the effect of

bipolar coagulation and fibrillar structured oxidized cellulose on formation epidural fibrosis in rats. Turk J Med Sci. 2021;51(4):2206-2212. doi:10.3906/sag-2002-162
9. Tao L, Wu L, Ge Y. Tubastatin alleviates epidural fibrosis via negatively targeting TGFβ/PI3K/Akt pathway. Cell Mol Biol (Noisy-le-grand). 2024;70(4):231-236. doi:10.14715/cmb/2024.70.4.36
10. Jiang F, Cao J, Kong R, et al. MICAL2 regulates myofibroblasts differentiation in epidural fibrosis via SRF/MRTF-A signaling pathway. Life Sci. 2021;269:119045. doi:10.1016/j.lfs.2021.119045
11. Song Z, Wu T, Sun J, et al. Metformin attenuates post-epidural fibrosis by inhibiting the TGF-β1/Smad3 and HMGB1/TLR4 signaling pathways. J Cell Mol Med. 2021;25(7):3272-3283. doi:10.1111/jcmm.16398
12. Lin CL, Jou IM, Wu CY, et al. Topically Applied Cross-Linked Hyaluronan Attenuates the Formation of Spinal Epidural Fibrosis in a Swine Model of Laminectomy. Sci Rep. 2019;9(1):14613. doi:10.1038/s41598-019-50882-x
13. Ding Q, Wei Q, Sheng G, et al. The Preventive Effect of Decorin on Epidural Fibrosis and Epidural Adhesions After Laminectomy. Front Pharmacol. 2021;12:774316. doi:10.3389/fphar.2021.774316
14. Shi J, Zhou C, Pan W, et al. Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery: The OPTIMAL Randomized Clinical Trial. JAMA. 2022;328(4):336–347. doi:10.1001/jama.2022.10725
15. Maeda K. Mechanism of Action of Topical Tranexamic Acid in the Treatment of Melasma and Sun-Induced Skin Hyperpigmentation. Cosmetics. 2022;9(5):108. doi:10.3390/cosmetics9050108
16. Sakata K, Hara M, Terada T, et al. HCV NS3 protease enhances liver fibrosis via binding to and activating TGF-β type I receptor. Sci Rep. 2013;3:3243. doi:10.1038/srep03243
17. Suzuki K, Yamamoto T, Ito S, Kamimura T, Aizawa Y. Reduction by tranexamic acid of glomerular hypertrophy and increased glomerular expression of extracellular matrix components induced by streptozotocin diabetes in rats. Clin Exp Nephrol. 2001;5(2):90–96. doi:10.1007/s101570170016
18. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T. Ameliorative effect of tranexamic acid on physiological skin aging and its sex difference in mice. Arch Dermatol Res. 2019;311:545–553. doi:10.1007/s00403-019-01938-5.
19. Fatima N, Barra ME, Roberts RJ, et al. Advances in surgical hemostasis: a comprehensive review and meta-analysis on topical tranexamic acid in spinal deformity surgery. Neurosurg Rev 2021;44(1):163-175. doi:10.1007/s10143-020-01236-z
20. Izima C, Sampath SG, Tang AJ, Ambati VS, Chou D, Chan AK. Systematic review and meta-analysis of topical tranexamic acid in spine surgery. Neurosurg Focus. 2023;55(4):E18. doi:10.3171/2023.7.FOCUS23363
21. Mitha R, Colan JA, Hernandez-Rovira MA, et al. Topical tranexamic acid (TXA) is non-inferior to intravenous TXA in adult spine surgery: a meta-analysis. Neurosurg Rev 2024;47(1):48. doi:10.1007/s10143-023-02254-3
22. Erdogan U, Tanik C, Tanriverdi O, et al. Immunohistochemical Grading of Epidural Fibrosis with CD105 Antibody. World Neurosurg. 2019;125:e297-e303. doi:10.1016/j.wneu.2019.01.068
23. Circi E, Atici Y, Baris A, et al. Is Tranexamic Acid an Effective Prevention in the Formation of Epidural Fibrosis? Histological Evaluation in the Rats. J Korean Neurosurg Soc. 2023;66(5):503-510. doi:10.3340/jkns.2022.0249
24. Rydell N. Decreased granulation tissue reaction after installment of hyaluronic acid. Acta Orthop Scand. 1970;41(3):307-311. doi:10.3109/17453677008991516
25. Koksal V, Mercantepe T, Tumkaya L, Oktem IS. Less Use of the Bipolar Cautery can Prevent Postlaminectomy Epidural Fibrosis: An Experimental Study in Rats. Turk Neurosurg. 2020;30(2):217-224. doi:10.5137/1019-5149.JTN.27544-19.2
26. Wiseman DM, Meidler R, Lyahovetsky Y, Kurman E, Horn S, Nur I. Evaluation of a fibrin preparation containing tranexamic acid (Adhexil) in a rabbit uterine horn model of adhesions with and without bleeding and in a model with two surgical loci. Fertil Steril. 2010;93(4):1045-1051. doi:10.1016/j.fertnstert.2008.11.026
27. Wiseman D, Lyachovetsky Y, Keidan I, Trout JR, Nur I. The effect of tranexamic acid in fibrin sealant on adhesion formation in the rat. J Biomed Mater Res B Appl Biomater. 2004;68(2):222-230. doi:10.1002/jbm.b.20016
28. Wang F, Wang SG, Yang Q, et al. Cytotoxicity and Effect of Topical Application of Tranexamic Acid on Human Fibroblast in Spine Surgery. World Neurosurg. 2021;153:e380-e391. doi:10.1016/j.wneu.2021.06.125.
29. Walker PF, Foster AD, Rothberg PA, Davis TA, Bradley MJ. Tranexamic acid decreases rodent hemorrhagic shock-induced inflammation with mixed end-organ effects. PLoS One. 2018;13(11):e0208249. doi:10.1371/journal.pone.0208249
30. Wang Z, Wang Y, Xie P, Liu W, Zhang S. Calcium channel blockers in reduction of epidural fibrosis and dural adhesions in laminectomy rats. European Journal of Orthopaedic Surgery & Traumatology. 2014;24:293-298. doi:10.1007/s00590-013-1395-7
31. Karolczak K, Watala C. Blood Platelets as an Important but Underrated Circulating Source of TGFβ. Int J Mol Sci. 2021;22(9):4492. doi:10.3390/ijms22094492
32. Kim SJ, Denhez F, Kim KY, Holt JT, Sporn MB, Roberts AB. Activation of the second promoter of the transforming growth factor-beta 1 gene by transforming growth factor-beta 1 and phorbol ester occurs through the same target sequences. J Biol Chem. 1989;264(32):19373-19378. PMID: 2808430.
33. Zhang C, Kong X, Zhou H, et al. An Experimental Novel Study: Angelica sinensis Prevents Epidural Fibrosis in Laminectomy Rats via Downregulation of Hydroxyproline, IL-6, and TGF-β1. Evid Based Complement Alternat Med. 2013;2013:291814. doi:10.1155/2013/291814
34. Gürer B, Kahveci R, Gökçe EC, Ozevren H, Turkoglu E, Gökçe A. Evaluation of topical application and systemic administration of rosuvastatin in preventing epidural fibrosis in rats. Spine J. 2015;15(3):522-529. doi:10.1016/j.spinee.2014.10.018
35. Yaman ME, Ergül G, Güvenç Y, et al. Evaluation of topical Dexmedetomidine administration in postlamnectomy epidural fibrosis rat model. Int J Surg. 2018;53:80-85. doi:10.1016/j.ijsu.2018.03.032
36. Shi K, Wang F, Xia J, Zuo B, Wang Z, Cao X. Pirfenidone inhibits epidural scar fibroblast proliferation and differentiation by regulating TGF-β1-induced Smad-dependent and -independent pathways. Am J Transl Res. 2019;11(3):1593-1604. PMID: 30972185; PMCID: PMC6456526.
37. Bottegaro NB, Kos J, Pirkic B, et al. Reduction of epidural fibrosis after laminectomy in rabbits by omental free graft. Veterinární medicína. 2013;58(1):25-31. doi:10.17221/6653-VETMED.
38. Park JW, Bak KH, Cho TK, Chun HJ, Ryu JI. Effects of a temperature-sensitive, anti-adhesive agent on the reduction of adhesion in a rabbit laminectomy model. J Korean Neurosurg Soc. 2016;59(3):250-258. doi:10.3340/jkns.2016.59.3.250.
39. Ausen K, Pleym H, Liu J, et al. Serum concentrations and pharmacokinetics of tranexamic acid after two means of topical administration in massive weight loss skin-reducing surgery. Plast Reconstr Surg. 2019;143(6):1169e–1178e. doi:10.1097/PRS.0000000000005620.
40. Winter SF, Santaguida C, Wong J, Fehlings MG. Systemic and topical use of tranexamic acid in spinal surgery: a systematic review. Global Spine J. 2016;6(3):284-295. doi:10.1055/s-0035-1563609.
41. De Bonis M, Cavaliere F, Alessandrini F, et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. J Thorac Cardiovasc Surg. 2000;119(3):575-580. doi:10.1016/S0022-5223(00)70139-5.
42. Wang X, Wang X, Liang F, Yu Y, Han R. Safety and efficacy of intravenous or topical tranexamic acid administration in surgery: a protocol for a systematic review and network meta-analysis. BMJ Open. 2022;12(5):e058093. doi:10.1136/bmjopen-2021-058093.