



Hemostasis Versus Immunosuppression in Preventing Postlaminectomy Epidural Fibrosis: An Experimental Study in Rats

Vaner KOKSAL¹, Tolga MERCANTEPE², Levent TUMKAYA³

¹Samsun University, School of Medicine, Department of Neurosurgery, Samsun, Türkiye

²Recep Tayyip Erdogan University, School of Medicine, Department of Histology and Embryology, Rize, Türkiye

³Ondokuzmayıs University, School of Medicine, Department of Histology and Embryology, Samsun, Türkiye

Corresponding author: Vaner KOKSAL ✉ vaner.koksal@samsun.edu.tr

ABSTRACT

AIM: To compare haemostasis induced with tranexamic acid (TXA) and immunosuppression induced with infliximab (INF) as strategies to reduce epidural fibrosis (EF) in rat laminectomy model.

MATERIAL and METHODS: Twenty-one male Sprague–Dawley rats were randomly assigned into control group (no treatment), TXA treatment group and INF treatment group (n=7 per group). TXA (10–20 mg/mL) and INF (1 mg/mL) were topically applied following L1–L3 laminectomy. Histopathological evaluation involving haematoxylin–eosin and Masson–Goldner’s Trichrome staining was conducted eight weeks postoperatively. EF severity, fibroblast density, inflammatory cell infiltration and neovascularisation were analysed.

RESULTS: Histopathological analysis showed that fibrosis scores were significantly lower in the TXA treatment group than in the control and INF treatment groups (p<0.05). Moreover, TXA reduced fibroblast proliferation, inflammatory cell infiltration and collagen deposition. While INF exhibited moderate anti-fibrotic effects, it was less effective than TXA. No systemic side effects were observed in either treatment group.

CONCLUSION: This study demonstrates that TXA prevents EF more effectively than INF following laminectomy. The findings also underscore that TXA is superior over INF in reducing EF. These results suggest that compared with INF-induced immunosuppression, TXA-induced haemostasis is the more effective strategy to minimise postoperative fibrosis in spinal surgery.

KEYWORDS: Epidural fibrosis, lumbar laminectomy, tranexamic acid, infliximab, fibroblast proliferation, postoperative adhesion, wound healing, haemostasis, spinal surgery, TNF- α inhibition

INTRODUCTION

Lumbar disc herniation surgery is a common procedure, but its success is significantly influenced by post-surgical complications, such as adhesion, fibrosis and scar formation (7,15). Among these complications, epidural fibrosis (EF) is a major concern because it can become a contributory factor to failed back surgery syndrome (1,6). Characterized by excessive fibrotic tissue formation around the dura mater, EF

may compress or put tension on nerve roots, leading to severe pain and functional impairment, often requiring revision surgeries (1,9,14,30). Therefore, developing effective strategies that could prevent EF remains a critical goal in spinal surgery.

The current EF prevention methods include refined surgical techniques—such as meticulous hemostasis, minimization of dural sac manipulation, avoidance of dead space formation, and preservation of epidural fat—as well as the use of bio-



materials and pharmacological agents (4,14). However, no pharmacological agent has been universally adopted in clinical practice (22). Recent studies emphasise the importance of understanding the underlying pathophysiology, particularly fibroblast proliferation, inflammation and haemostasis, to effectively prevent EF (4,14,22). In this context, pharmacological agents inhibiting fibroblast activity (migration) or those modulating inflammatory pathways have gained attention (12,30,32,35).

Tranexamic acid (TXA) and infliximab (INF) treatments represent two distinct pharmacological approaches to EF prevention: TXA acts primarily through haemostasis by stabilizing fibrin and reducing postoperative bleeding (8,10), whereas INF acts via immunosuppression by targeting tumour necrosis factor- α (TNF- α) to suppress inflammation (11). Although both agents have shown potential in reducing fibrosis, no direct comparative study has ever evaluated their topical effects in preventing EF.

This study aims to compare the effectiveness of TXA and INF in reducing EF following laminectomy and to determine whether haemostasis or immunosuppression provides superior protection against postoperative fibrosis. The findings may contribute in the development of safer and more effective pharmacological strategies for EF prevention in spinal surgery patients.

■ MATERIAL and METHODS

Ethical Statement

This study was approved by the Recep Tayip Erdogan University Local Ethics Committee for Animal Experiments (Decision No: 2016/41, 42; Date: 22.12.2016) and was conducted in compliance with the institution's ethical standards for animal research. All experimental procedures adhered to international, national and institutional guidelines for the care and use of laboratory animals. A copy of the ethics approval letter (2016/41, 42) is available upon reasonable request.

Experimental Animals

A total of 21 male Sprague–Dawley rats aged 4–6 months and weighing 250–300 g were obtained from the university's Animal Care and Research Unit. The animals were reared in accordance with the guidelines outlined in the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Study Design

The rats were randomly assigned to three groups, namely, INF treatment group, TXA treatment group and control group, each group comprising seven rats.

The rats were maintained under controlled environmental conditions: a constant temperature of $21^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and a 12-hour light/dark cycle. Throughout the experimental period, the rats were fed ad libitum with standard pellet chow containing 21% crude protein (Purina) and were given free access to drinking water. The groups were homogeneous with respect to physiological characteristics. Monitored physiological parameters

included body weight, food and water intake, grooming activity, locomotion, and general physical condition.

Experimental Procedures

The experiment was initiated under general anaesthesia induced via intramuscular administration of ketamine hydrochloride (25 mg/kg; Ketalar, Pfizer, Istanbul, Turkey) and xylazine (5 mg/kg; Rompun, Bayer, Istanbul, Turkey). The rats were placed in the prone position and had their backs shaved. The surgical site was subsequently sterilized with povidone-iodine (Batticon; Adeka Pharmaceuticals, Istanbul, Türkiye).

Midline skin incision and dorsal fascia dissection were performed from T12 to L4. The paravertebral muscles were bilaterally dissected over the laminae. A total laminectomy from L1 to L3 was performed using magnifying surgical loupes and fine, sharp-tipped instruments.

The surgical site was irrigated with sterile saline solution for 5 min to induce haemostasis. In cases where bleeding persisted beyond this period, the irrigation time was extended. No additional haemostatic agents or bipolar cautery was used in any of the groups. Macroscopic haemostasis was confirmed prior to TXA and INF administration.

To ensure both efficacy and safety, we administered TXA topically at a literature-supported dose suitable for small animal models such as rats (16). A 10–20 mg/mL TXA solution (Transamin[®], Daiichi Sankyo Co., Ltd., Tokyo, Japan) was applied on the laminectomy site for 5 min using a soaked surgical pad.

As for INF, no experimental studies have ever investigated its use in the lumbar epidural area of rats. Thus, dosing was determined based on previous studies; the dose range applied in different experimental settings was 3–5 mg/kg (10,16). On this basis, a lower dose of approximately 1 mg/mL was applied on the laminectomy site for 5 mins using a soaked surgical pad (Remicade[®], Janssen Biotech, Inc., Horsham, PA, USA) (26,42).

Following each treatment, the incision site was closed in layers. The subcutaneous tissue was sutured using 3/0 Ethicon-Vicryl, (Ethicon, Inc., Somerville, NJ, USA) Rapide with a minimum of two stitches, followed by skin closure with 3/0 Prolene sutures, ensuring anatomical integrity.

No wound complications or neurological deficits were observed in any of the rats postoperatively. The animals were provided with appropriate diet and were reared under standardised conditions for eight weeks. Then, they were sacrificed via cervical dislocation.

Histopathological Analysis

Spinal cord tissue specimens were harvested and fixed in 10% neutral-buffered formalin (Sigma-Aldrich, St. Louis, MO, USA) for 48 hours prior to histological processing. Paraffin-embedded spinal cord sections 4–5 μm in thickness were obtained using a rotary microtome (Leica RM2125RT, Germany). The sections were stained with haematoxylin and eosin (H&E) (Harris Haematoxylin, Merck, Germany; Eosin G, Merck, Germany) and Masson-Goldner's Trichrome stain

(Merck, Darmstadt, Germany) for histopathological evaluation. The samples were examined under a light microscope (Olympus BX51, Olympus Corporation, Tokyo, Japan), and high-resolution images were captured using an Olympus DP71 (Olympus Corporation, Tokyo, Japan) camera for further analysis.

Semi-Quantitative Analysis

The histopathological changes observed in the samples were scored according to the EF scoring method described by He et al. (13,28) (Table I). This scoring system was independently applied by two blinded histopathologists (TM and LT), who evaluated 40 different areas in each sample (13,28).

Table I: Epidural Fibrosis Grading

Grade	Amount of fibrosis	
Grade 0	No	Dura mater is free of scar tissue
Grade 1	Mild fibrosis without dural adherence	Thin fibrous bands between scar tissue and dura mater
Grade 2	Moderate fibrosis with partial dural adherence	Continuous adherence in less than two-thirds of the laminectomy defect
Grade 3	Dense fibrosis with complete adherence to dura	Widespread adherence of scar tissue affecting more than two-thirds of the laminectomy defect and/or adherence to nerve roots

Statistical Analysis

Data were analyzed using SPSS version 18.0 (IBM Corp., Armonk, NY, USA). Non-normally distributed variables were expressed as median and interquartile range (IQR), along with minimum and maximum values. Between-group comparisons were performed using the Kruskal–Wallis test, followed by Tamhane’s post-hoc test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the control group, the spinal cord tissue sections exhibited EF that adheres to the underlying dura mater (epidural fibrosis grade median: 2.00 ± 0.54 ; Figures 1A, B; Table I).

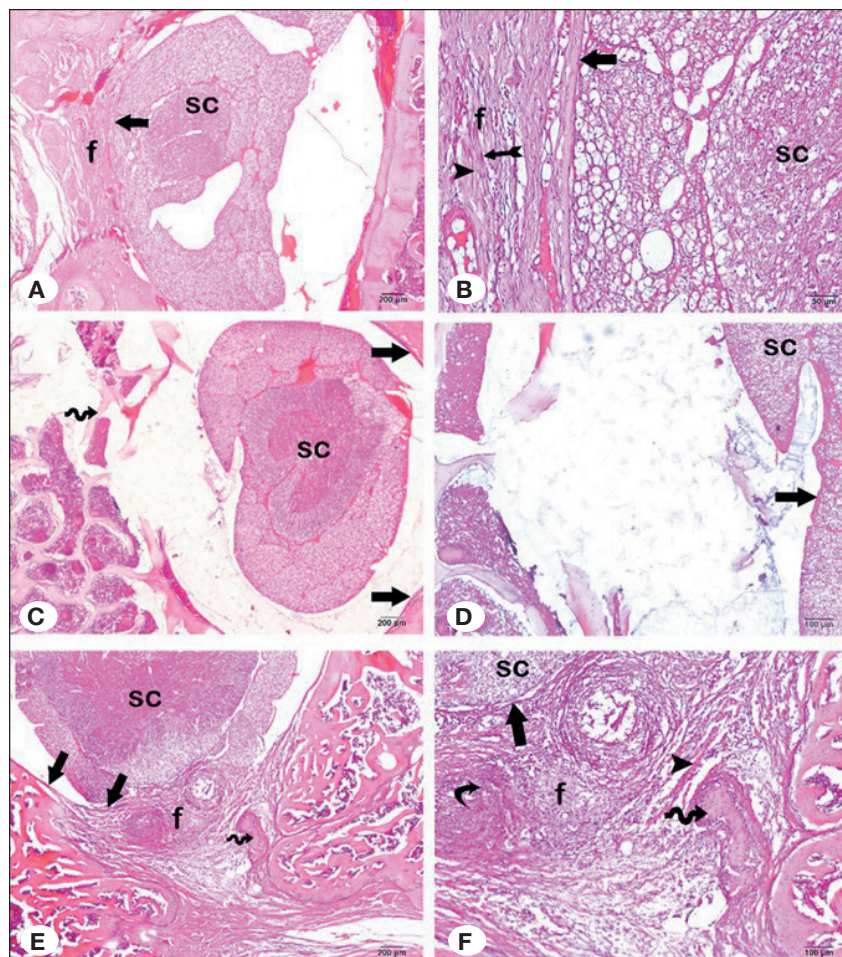


Figure 1: Representative photo micrographs of spinal cord tissue sections stained with Hematoxylin and Eosin. **A** ($\times 40$), **B** ($\times 20$): Sections from the control group showing epidural fibrosis (f) adhering to the underlying dura mater (arrow) (epidural fibrosis grade median: 2.00 ± 0.54). **C** ($\times 4$), **D** ($\times 10$): Sections from the INF treatment group exhibiting epidural fibrosis (f), dura mater adherence (arrow) and inflammation (curved arrow). Osteoblastic activity and new bone formation were observed but to a lesser extent (spiral arrow) (epidural fibrosis grade median: 3.00 ± 0.35). **E** ($\times 4$), **F** ($\times 10$): Sections from the TXA treatment group showing a thin fibrous band adhering to the underlying dura mater (arrow). Moreover, new bone formation was widespread compared with that in the control and INF treatment groups (epidural fibrosis grade median: 0.50 ± 0.53).

In the INF treatment group, EF with dura mater adhesion and inflammation was observed. Additionally, osteoblastic activity and new bone formation were observed to a lesser extent (epidural fibrosis grade median: 3.00 ± 0.35 ; Figures 1C, D; Table II).

In the TXA treatment group, a thin fibrous band adhering to the underlying dura mater was observed. Moreover, this group exhibited widespread formation of new bone tissue compared with the two other groups (epidural fibrosis grade median: 0.50 ± 0.53 ; Figures 1E, F; Table II).

DISCUSSION

Fibrosis Formation in the Epidural Space

The formation of fibrosis in the epidural space, which is a common consequence of surgical procedures—particularly lumbar discectomy, laminectomy, foraminotomy, and spinal fusion—is closely linked to the wound healing process (30,32). In the skin, keloid formation results from fibroblast hyperproliferation and excessive accumulation of extra cellular matrix (ECM), particularly collagen types I (COL1) and III (COL3) (7,31). Similarly, during lumbar laminectomy, fibroblasts originating from paravertebral muscles and infiltrating blood cells contribute to ECM overproduction, leading to postoperative adhesion and potential complications (15,19,22,27,33,36).

Factors Influencing EF Formation

Foreign materials such as glove powder and cotton fibres worsen inflammation in the epidural space, highlighting the need for thorough irrigation to reduce fibrosis (23,31). Meanwhile, excessive bipolar coagulation can lead to peripheral tissue carbonization, further increasing EF (21).

Mechanisms of Fibrosis Prevention

The mechanism of EF prevention involves blocking fibroblast migration into the epidural space or suppressing inflammation by targeting fibrosis-promoting cytokines.

Inhibition of Fibroblast Migration

The use of various materials, including fat grafts, gel foam, Silastic, Zenoderm and carboxymethylcellulose, have been explored for EF prevention (23,30,32). Despite the promising results in animal models, their widespread clinical application remains limited due to high cost, surgical feasibility and inconsistent outcomes.

Table II: Semi-Quantative Analysis Results (Median±Standart Deviation)

Group	Description	Epidural Fibrosis Grading Score
1	INF+LM	3.00±0.35^a
2	TXA+LM	0.5±0.53^{b,c}
3	Control	2.00±0.54

^a*p*=0.007 versus to Control group, ^b*p*=0.00 versus to Control group, ^c*p*=0.00 versus to INF+LM group, Kruskal Wallis -Tamhane's T2 test.

Various physical barriers, such as polyethylene oxide, sodium hyaluronate and carboxymethylcellulose, have been used to limit fibroblast infiltration into the epidural space. Haemostasis, or bleeding control, can also be considered part of this strategy (8,29). However, not all haemostatic methods are equally effective. An experimental study on Ankaferd Blood Stopper, a haemostatic agent, showed that instead of reducing EF, it promoted erythrocyte aggregation by forming an encapsulated protein network, potentially contributing to fibrosis formation (3,41). However, the clinical application of haemostatic agents in EF prevention remains limited due to variability in efficacy, surgical feasibility, and cost constraints.

Suppression of Fibrosis-Promoting Inflammatory Pathways

Pharmacological agents targeting pro-fibrotic cytokines, such as TNF-α and TGF-β, have been investigated. Curcumin, known for its anti-inflammatory properties, has been investigated in two studies; etanercept has also been investigated in two experimental studies (7,18). Etanercept, a TNF-α inhibitor, reduces fibrosis by blocking pro-inflammatory cytokine activity at the site of injury (7,20). Given their potential for EF prevention, temozolomide—an immunosuppressive agent—has been evaluated in one study, tacrolimus in three studies, mitomycin-C—commonly used in ophthalmic surgery—in two studies and bevacizumab in one study (2,11,22,40). While TNF-α inhibitors such as INF and vascular endothelial growth factor inhibitors such as ranibizumab have shown promise in reducing fibrosis, their role in EF prevention remains underexplored (13,39).

Effect of INF on EF

INF is a TNF-α inhibitor with anti-fibrotic and anti-angiogenic properties. INF limits fibrosis formation by reducing fibroblast activity, collagen production and neovascularisation (11). Experimental studies have demonstrated INF's efficacy in reducing fibrosis in ophthalmic and glaucoma surgeries (11,26). However, the potential of INF for EF prevention has not yet been evaluated. Our findings indicate that topical INF is safe, as no systemic adverse effects were observed over the eight-week treatment period. While INF did reduce fibrosis, its effect was inferior to that of TXA, suggesting that TNF-α inhibition alone may not be sufficient to control fibrosis and that haemostasis plays a more dominant role in wound healing (34,42).

Effect of TXA on EF

Although TXA is widely used to induce haemostasis, its role in fibrosis prevention in various surgical procedures has been evaluated in eight studies only (3,5,23). A 2004 study investigated for the first time the effects of TXA on intra-peritoneal adhesion, whereas a 2021 study demonstrated reduced inflammation following knee arthroplasty (16,25,37,38). To date, only two studies have examined TXA's role in EF prevention. Haemostasis appears to play a crucial role in reducing EF, as shown in studies where surgical drains minimise fibrosis formation (9,24). This view is supported by studies showing the EF-reducing effects of various haemostatic agents in experimental models (3,17).

TXA inhibits fibrinolysis by preventing plasminogen activation, thereby reducing intraoperative bleeding and subsequent fibrosis formation (3,8,19). Erdogan et al. reported that topical TXA significantly reduced fibrosis, fibroblast density and inflammatory cell infiltration in a rat laminectomy model (9). Circi et al. found that systemic TXA alone and systemic TXA combined with topical TXA significantly lowered fibrosis and inflammation scores compared with the control (5). These findings reinforce the potential utility of TXA in EF prevention.

Additionally, while preventing EF, TXA does not inhibit new bone formation, which is particularly advantageous in spinal surgery. This characteristic ensures that TXA does not interfere with spinal fusion, a critical factor for successful postoperative outcomes. Unlike some immunosuppressive or anti-inflammatory agents, which may impair osteogenesis, TXA allows for optimal bone healing while minimising fibrotic adhesions, making it a promising adjunct treatment in spine surgery.

Study Duration and Methodological Considerations

The optimal duration for fibrosis evaluation varies; four weeks is the minimum period to observe fibrotic changes, whereas six to eight weeks are needed to assess mature fibrosis (17,23,26,30). Similar to a research investigating the use of haemostatic agents for EF prevention, our study employed an eight-week observation period (8).

To ensure an objective fibrosis assessment, we used histopathological grading as the primary method to evaluate fibrosis severity, fibroblast density and inflammatory cell in-

filtration. This approach allowed for a standardised and reliable comparison between the study groups. However, immunohistochemical staining was not performed in this study (14,34,38,40).

Comparison between TXA and INF in terms of EF Prevention

No prior studies have directly compared TXA and INF in terms of EF prevention. Our results indicate the superior efficacy of TXA in reducing EF compared with INF, suggesting that haemostasis plays a more critical role in spinal wound healing than immunosuppression alone. These findings highlight the importance of intraoperative haemostasis in minimising postoperative fibrosis and support TXA's potential clinical utility for EF prevention. Further studies are needed to validate these results, to optimise treatment strategies and to explore combination therapies for more effective fibrosis management (Table III).

INF inhibits osteoblast proliferation, leading to reduced bone formation and potential delays in bone healing. Given that TNF- α plays a key role in regulating osteoclast activity and bone turnover, its suppression can disrupt the natural balance of bone remodelling, impairing early bone regeneration. Additionally, long-term TNF- α blockade has been linked to decreased bone mineral density and slower bone regeneration, which may pose challenges in surgical settings where successful fusion and bone healing are critical (13).

Table III: This Table Compares Tranexamic Acid (TXA) and Infliximab (INF) in Terms of Mechanism, Effectiveness, and Clinical Applicability, Incorporating Our Experimental Findings

Feature	Tranexamic Acid (TXA)	Infliximab (INF)
Mechanism of Action	Inhibits fibrinolysis by preventing plasminogen activation	TNF- α inhibition, suppresses inflammatory pathways
Primary Effect	Hemostasis, reduces postoperative bleeding	Anti-inflammatory, immunosuppression
Route of Administration	Topical, Systemic (IV)	Topical, Systemic (IV)
Fibrosis Reduction Effectiveness	High – Reduces fibroblast proliferation and collagen deposition	Moderate – Reduces inflammation but less effective in fibrosis prevention
Histopathological Fibrosis Score (Experimental Findings)	0.50 \pm 0.53 (Significantly lower fibrosis vs. INF & Control)	3.00 \pm 0.35 (Moderate reduction but less effective than TXA)
Hemostatic Effect	Strong	None
Anti-inflammatory Effect	Moderate	Strong
New bone formation	Widespread new bone formation	New bone formation were observed to a lesser extent
Cost & Availability	Low cost, widely available	High cost, limited availability
Clinical Application Potential	High – Commonly used in various surgeries, potential for epidural fibrosis prevention	Moderate – Potential in fibrosis reduction but costly and less accessible
Potential Side Effects	Minimal, but risk of thrombosis with systemic use	Immunosuppression, increased infection risk

The strength of this study lies in the simultaneous evaluation of the therapeutic efficacy of TXA and INF. In previous studies, these molecules were analysed separately, and they have never been evaluated together in an experimental setting. Moreover, a histological assessment to compare the effect of an immunosuppressive agent and a haemostatic agent on fibrosis prevention has never been performed. Our study addresses this research gap by providing novel evidence on the potential efficacy of topical tranexamic acid (TXA) in preventing epidural fibrosis.

Study Limitations and Future Directions

While our study provides valuable insights, certain limitations should be acknowledged. The sample size was limited, and future studies with larger cohorts are warranted to confirm and generalize our findings with greater statistical confidence. The doses used were based on prior studies, but dose–response studies could further optimise the efficacy of TXA and INF. While histopathology was our primary method, incorporating electron microscopy or immunohistochemistry to investigate TNF- α , TGF- β or CD105 can provide deeper mechanistic insights.

Additionally, while an eight-week post-treatment follow-up period is adequate for fibrosis assessment, longer-term studies can evaluate the functional impact of fibrosis prevention strategies—such as reductions in neuropathic pain, improved nerve root mobility, or enhanced locomotor recovery—and assess potential late-onset complications, including chronic inflammation, delayed scar maturation, or recurrent adhesions.

Clinical Relevance and Future Applications

Widely in haemostasis induction, TXA may serve as a cost-effective adjunct treatment in spine surgery once its anti-fibrotic effects have been confirmed. While INF shows potential in fibrosis reduction, its high cost limits its routine use. Future research should include larger sample size, investigate varied dosages and compare systemic and topical administration. Molecular analyses, including evaluation of TGF- β and TNF- α expression, could clarify fibrosis mechanisms. Ultimately, randomised clinical studies are needed to validate TXA's role in preventing EF.

CONCLUSION

This study is the first to compare TXA and INF treatments as strategies in EF prevention. The findings suggest that TXA significantly reduces EF more effectively than INF, indicating that haemostasis plays a dominant role in reducing postoperative fibrosis. TXA may have strong clinical potential as an adjunct treatment in spinal surgery for EF prevention. Further large-scale experimental and clinical trials are necessary to validate these findings, to optimise fibrosis prevention strategies and to explore novel treatment approaches for improving postlaminectomy outcomes.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: VK

Data collection: TM, LT, VK

Analysis and interpretation of results: TM

Draft manuscript preparation: VK

Critical revision of the article: VK

Other (study supervision, fundings, materials, etc...): TM, LT

All authors (VK, TM, LT) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Abdou MS, Hardy RW Jr: Epidural fibrosis and the failed back surgery syndrome: History and physical findings. *Neurol Res* 21 Suppl1:S5-8, 1999. <https://doi.org/10.1080/01616412.1999.11758603>
2. Aydincak O, Yilmaz MB, Emmez H, Kurt G, Sepici A, Memis L, Baykaner K: The effect of temozolomide on the prevention of epidural fibrosis developing after lumbar laminectomy in rats. *Turk Neurosurg* 22:706-11, 2012. <https://doi.org/10.5137/1019-5149.JTN.5966-12.1>
3. Bozkurt I, Kazanci A, Gurcan O, Gurcay AG, Arikok AT, Bavbek M: Spinal epidural fibrosis following hemostatic agent employment. *Br J Neurosurg* 37:137-41, 2023. <https://doi.org/10.1080/02688697.2021.1950627>
4. Brito-García N, García-Pérez L, Kovacs FM, Del Pino-Sedeño T, Pérez-Ramos J, Imaz-Iglesia I, Serrano-Aguilar P: Efficacy, effectiveness, safety, and cost-effectiveness of epidural adhesiolysis for treating failed back surgery syndrome: A systematic review. *Pain Med* 20:692-706, 2019. <https://doi.org/10.1093/pm/pny233>
5. Circi E, Atici Y, Baris A, Senel A, Leblebici C, Tekin SB, Ozturkmen Y: Is tranexamic acid an effective prevention in the formation of epidural fibrosis? Histological evaluation in rats. *J Korean Neurosurg Soc* 66:503-510, 2023. <https://doi.org/10.3340/jkns.2022.0249>
6. Costa F, Oertel J, Zileli M, Restelli F, Zygorakis CC, Sharif S: Role of surgery in primary lumbar disk herniation: WFNS spine committee recommendations. *World Neurosurg* X 22:100276, 2024. <https://doi.org/10.1016/j.wnsx.2024.100276>
7. Demirel C, Turkoz D, Yazicioglu IM, Cokluk C: The preventive effect of curcumin on the experimental rat epidural fibrosis model. *World Neurosurg* 145:e141-e148, 2021. <https://doi.org/10.1016/j.wneu.2020.09.140>
8. Erdogan H, Kelten B, Tuncdemir M, Erturkuner SP, Uzun H, Karaoglan A: Hemostasis vs. epidural fibrosis?: A comparative study on an experimental rat model of laminectomy. *Neurol Neurochir Pol* 50:323-330, 2016. <https://doi.org/10.1016/j.pjnns.2016.05.002>

9. Erdogan U, Tanik C, Tanriverdi O, Gunaldi O, Yilmaz I, Arslanhan A, Ofluoglu AE: Immuno histochemical grading of epidural fibrosis with CD105 antibody. *World Neurosurg* 125:e297-e303, 2019. <https://doi.org/10.1016/j.wneu.2019.01.068>
10. Fatima N, Barra M, Roberts R, Massaad E, Hadzipasic M, Shankar G, Shin JH: Advances in surgical hemostasis: a comprehensive review and meta-analysis on topical tranexamic acid in spinal deformity surgery. *Neurosurg Rev* 44:163-175, 2021. <https://doi.org/10.1007/s10143-020-01236-z>
11. Güçlü ES, Sarı AA, Dinç E, Özcan Metin T, Çoşkun Yılmaz B, Taşdelen B. Efficacy of mitomycin-C and infliximab in reducing adhesion and fibrosis following strabismus surgery. *Turk J Med Sci*. 2016 Nov 17;46(5):1401-1406. <https://doi.org/10.3906/sag-1506-45>
12. Haroon NN, Sriganthan J, Al Ghanim N, Inman RD, Cheung AM: Effect of TNF-alpha inhibitor treatment on bone mineral density in patients with ankylosing spondylitis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 44:155-161, 2014. <https://doi.org/10.1016/j.semarthrit.2014.05.008>
13. He Y, Revel M, Loty B: A quantitative model of postlaminectomy scar formation: Effects of a nonsteroidal anti-inflammatory drug. *Spine* 20:557-563, 1995. <https://doi.org/10.1097/00007632-199503010-00010>
14. Heavner JE, Bosscher HA, Wachtel MS: Cell types obtained from the epidural space of patients with low back pain / radiculopathy. *Pain Pract* 9:167-72, 2009. <https://doi.org/10.1111/j.1533-2500.2009.00272.x>
15. Hinton JL Jr, Warejcka DJ, Mei Y, McLendon RE, Laurencin C, Lucas PA, Robinson Jr JS: Inhibition of epidural scar formation after lumbar laminectomy in the rat. *Spine* 20:564-570, 1995. <https://doi.org/10.1097/00007632-199503010-00011>
16. Hunt BJ: The current place of tranexamic acid in the management of bleeding. *Anaesthesia* 70 Suppl 1:50-53, e18, 2015. <https://doi.org/10.1111/anae.12910>
17. Ismailoglu O, Albayrak B, Gulsen I, Tanriover G, Demir N: Topical application of tacrolimus prevents epidural fibrosis in a rat postlaminectomy model: Histopathological and ultrastructural analysis. *Turk Neurosurg* 21:630-633, 2011. <https://doi.org/10.5137/1019-5149.JTN.4954-11.1>
18. Ismailoglu O, Kizilay Z, Cetin NK, Topcu A, Berber O: Effect of curcumin on the formation of epidural fibrosis in an experimental laminectomy model in rats. *Turk Neurosurg* 29:440-444, 2019. <https://doi.org/10.5137/1019-5149.JTN.24773-18.1>
19. Kemaloglu S, Ozkan U, Yilmaz F, Nas K, Gur A, Acemoglu H, Karasu H, Cakmak E: Prevention of spinal epidural fibrosis by recombinant tissue plasminogen activator in rats. *Spinal Cord* 41:427-431, 2003. <https://doi.org/10.1038/sj.sc.3101466>
20. Kizilay Z, Cetin NK, Topcu A, Ismailoglu O, Omurlu IK, Aktas S, Yilmaz A: Effect of etanercept on the formation of epidural fibrosis in an experimental model. *Turk Neurosurg* 28:111-117, 2018. <https://doi.org/10.5137/1019-5149.JTN.18460-16.1>
21. Koksal V, Mercantepe T, Tumkaya L, Oktem IS: Less use of the bipolar cautery can prevent post laminectomy epidural fibrosis: An experimental study in rats. *Turk Neurosurg* 29:874-881, 2019. <https://doi.org/10.5137/1019-5149.JTN.27544-19.2>
22. Kurt G, Aytar MH, Doğulu F, Cemil B, Erdem O, Baykaner MK, Ceviker N: A comparison of the local effectiveness of mitomycin C, aprotinin, and Adcon-L in experimental peridural fibrosis. *Surg Neurol* 70:608-613, 2008. <https://doi.org/10.1016/j.surneu.2007.07.071>
23. Lewik G, Lewik G, Müller LS, vonGlinski A, Schulte TL, Lange T: Postoperative epidural fibrosis: Challenges and opportunities - a review. *Spine Surg Relat Res* 8:133-142, 2023. <https://doi.org/10.22603/ssr.2023-0106>
24. Mirzai H, Eminoglu M, Orguc S. Are drains useful for lumbar disc surgery? A prospective, randomized clinical study. *J Spinal Disord Tech* 19:171-177, 2006. <https://doi.org/10.1097/01.bsd.0000190560.20872.a7>
25. Morris JL, Letson HL, McEwen P, Biros E, Dlaska C, Hazratwala K, Wilkinson M, Dobson GP: Comparison of intra-articular administration of adenosine, lidocaine, and magnesium solution and tranexamic acid for alleviating postoperative inflammation and joint fibrosis in an experimental model of kneearthroplasty. *J Orthop Surg Res* 16:726, 2021. <https://doi.org/10.1186/s13018-021-02871-y>
26. Nikeghbalian S, Vafaei H, Moradian F, Kazemi K, Tanideh N, Shayan L, Nikeghbalian Z: Administration of intravenous infliximab for prevention of peritoneal adhesions formation in rats. *Bull Emerg Trauma* 3:97-103, 2015.
27. Nussbaum CE, McDonald JV, Baggs RB: Use of Vicryl (polyglactin 910) mesh to limit epidural scar formation after laminectomy. *Neurosurgery* 26:649-654, 1990. <https://doi.org/10.1097/00006123-199004000-00014>
28. Ozturk Y, Bozkurt I, Yaman ME, Guvenc Y, Tolunay T, Bayram P, Hayirli N, Billur D, Erbay FK, Senturk S, Bozkurt G: Histopathologic analysis of tamoxifen on epidural fibrosis. *World Neurosurg* 111:e941-948, 2018. <https://doi.org/10.1016/j.wneu.2018.01.004>
29. Opoku-Anane J, Vargas MV, Marfori CQ, Moawad G, Maasen MS, Robinson JK: Intraoperative tranexamic acid to decrease blood loss during myomectomy: A randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 223:413.e1-7, 2020. <https://doi.org/10.1016/j.ajog.2020.02.019>
30. Pereira P, Avelino A, Monteiro P, Vaz R, Castro-Lopes JM: New insights from immuno histochemistry for the characterization of epidural scar tissue. *Pain Physician* 17:465-474, 2014. <https://doi.org/10.36076/ppj.2014/17/465>
31. Reina MA, LópezGarcía A, Aguilar JL, PalaciosMartín R: Electron microscopic analysis of particles from surgical gloves and their possible introduction into the epidural space during epidural anesthesia. *Rev Esp Anesthesiol Reanim* 46:60-66. Spanish, 1999
32. Samy Abdou M, Hardy RW Jr: Epidural fibrosis and the failed back surgery syndrome: history and physical findings. *Neurol Res* 21 Suppl 1:S5-8, 1999. <https://doi.org/10.1080/01616412.1999.11758603>
33. Songer MN, Rauschnig W, Carson EW, Pandit SM: Analysis of peridural scar formation and its prevention after lumbar laminotomy and discectomy in dogs. *Spine* 20:571-580, 1995. <https://doi.org/10.1097/00007632-199503010-00012>

34. Ucar D, Ocakoglu O, Solakoglu S: Histological evaluation of local TNF alpha inhibition on conjunctiva and tenon fibroblastic activity in surgical wound healing of rabbit eyes (experimental pre study). *Turk J Ophthalmol* 39:197-204, 2009
35. Wang H, Sun W, Fu D, Shen Y, Chen YY, Wang LL: Update on biomaterials for prevention of epidural adhesion after lumbar laminectomy. *J Orthop Translat* 13:41-49, 2018. <https://doi.org/10.1016/j.jot.2018.02.001>
36. Wang X, Ma Y, Gao Z, Yang J: Human adipose-derived stem cells inhibit bio activity of keloid fibroblasts. *Stem Cell Res Ther* 9:40, 2018. <https://doi.org/10.1186/s13287-018-0786-4>
37. Winter S, Santaguida C, Wong J, Fehlings M: Systemic and topical use of tranexamic acid in spinal surgery: A systematic review. *Glob Spine J* 6:284-295, 2015. <https://doi.org/10.1055/s-0035-1563609>
38. Wiseman D, Lyachovetsky Y, Keidan I, Trout JR, Nur I: The effect of tranexamic acid in fibrin sealant on adhesion formation in therat. *J Biomed Mater Res B Appl Biomater* 68:222-230, 2004. <https://doi.org/10.1002/jbm.b.20016>
39. Yilmaz A, Karatay M, Yildirim T, Celik H, Sertbas I, Erdem Y, Caydere M, Isik HS, Bayar MA: Prevention of epidural fibrosis using ranibizumab in a postlaminectomy rat model. *Turk Neurosurg* 27:119-123, 2017. <https://doi.org/10.5137/1019-5149.JTN.14882-15.1>
40. Yilmaz I, Erdogan U, Tanriverdi O, Gunaldi O, Adilay U, Omeroglu M, Tanik C, Tugcu B: Evaluation of bevacizumab for the treatment of epidural fibrosis by immuno histochemical staining for CD105 and osteopontin. *Turk Neurosurg* 28:954-962, 2018. <https://doi.org/10.5137/1019-5149.JTN.22633-18.2>
41. Yilmaz M, Gulabi D, Guclu B, Kaya I, Basak K, Bas A: The effect of ankaferd blood stopper? on epidural fibrosis after laminectomy in rats: An experimental study. *Turk Neurosurg* 27:114-118, 2017. <https://doi.org/10.5137/1019-5149.JTN.14559-15.1>
42. Yukselen V, Vardar E, Yukselen O, Oruc N, Yenisey C, Karaoglu A, Ozutemiz O: Infliximab in experimental alkali burns of the oesophagus in therat. *Acta Gastroenterol Belg* 71:21-26, 2008