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Research Article

Efficacy of Topical Tranexamic Acid in Reducing Blood Loss after Laminectomy and Posterolateral Fusion of the Spine: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial

Moslem Shakeri[1], Mansour Valaie[2], Farhad Mirzaei[3], Ramyar Hariri[4], Ehsan Jangholi[5], Kamkar Aeinfar[6,*]

[1] Associate Professor, Department of Neurosurgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Neurosurgeon, Department of Neurosurgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Assistant Professor, Department of Neurosurgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran
[4] General Practitioner, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[5] Resident, Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[6] Assistant Professor, Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

[*]Corresponding author: Kamkar Aeinfar; Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-9144460372, Email: kamkar_a3336@yahoo.com

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Abstract

Background: Multi-level spine surgeries are associated with high bleeding during and after surgery. A majority of studies have previously evaluated the effect of tranexamic acid (TXA) in reducing bleeding with a focus on intravenous (IV) administration. The aim of the study was to evaluate the efficacy of topical TXA in decreasing bleeding after laminectomy and spinal fusion.
Methods: In this randomized, double-blinded, placebo-controlled clinical trial, 80 patients were enrolled from January 2017 to January 2019. The patients were eligible for laminectomy (2 or more levels) and posterolateral fusion with a pedicle screw. Patients were randomly divided into two equal groups; single-dose TXA (1 g/50 ml) and normal saline. Intergroup comparison was performed for the amount of bleeding during and after surgery, received packed cells, and the number of hospitalization days.
Results: The mean age of the patients was 55.51 ± 10.27 years, and 50 of them were women. 18 and 20 patients in control and TXA groups had intraoperative bleeding more than 400 ml, respectively (P >0.05). The only significant difference was observed in the first and second 12 hours, and total bleeding after surgery in patients who had bleeding above 400 ml (P = 0.011, P = 0.039, P = 0.015, respectively).
Conclusion: The application of topical TXA was effective in patients with high amount of hemorrhage during spine surgery for reducing the bleeding rate in the first and second 12 hours, as well as the mean total bleeding rate after surgery. It had no significant effect on total intraoperative hemorrhage, total packed cells, and total hospitalization length.

Keywords: Bleeding; Laminectomy; Spine; Tranexamic Acid

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Background

Degenerative spinal canal stenosis and spinal instability, which require multi-level spine surgery, are associated with high blood loss during and after surgery (1). Many factors affect the rate of bleeding, including duration of surgery, surgical technique, patient height, concurrent anterior and posterior surgical procedures, number of fusion sites in surgery, and antifibrinolytic drug use (2-4). Many studies have shown that using antifibrinolytic drugs during surgery successfully reduces postoperative bleeding. The three most commonly-used compounds based on potency are aprotinin, tranexamic acid (TXA), and aminocaproic acid, respectively (5). Using TXA is associated with lower side effects compared with other antifibrinolytic drugs. Although it has been frequently used in cardiac, bone, joint, and liver surgeries, its application in neurosurgery is uncommon (6).

Intravenous (IV) TXA is a lysine analog that blocks the placement of lysine on plasminogen and prevents it from converting to plasmin, resulting in inhibition of fibrin degradation (7). TXA is used in IV, intramuscular (IM), oral, and topical forms to control bleeding. The topical form of the drug is associated with lower serum levels and fewer side effects (8). The bioavailability of the IM form is fast and complete. If taken orally with an empty stomach, its bioavailability is 34% compared to the IV drug (9).

Yang et al. in the meta-analysis study with nine studies (total sample size of 581 patients) revealed that the amount of blood loss in patients who received preoperative IV injection of TXA was markedly reduced; also requiring blood transfusion following spine surgery decreased (10). Morgan and Jeffrey-Smith indicated that the use of TXA in patients with upper gastrointestinal (GI) bleeding was not sufficient (11). Molloy et al. studied patients undergoing knee arthroplasty and showed that the reduction in bleeding in patients receiving fibrin spray was not significantly different from patients receiving IV TXA (12). In 2018, Shakeri et al. used preoperative single doses of IV TXA (15 mg/kg) in patients undergoing laminectomy and posterolateral fusion of the spine. The method resulted in a significant reduction in intraoperative and immediate postoperative blood loss, fewer packed red blood cells transfusion, and shorter hospitalization duration after complex spinal surgeries (13).

A majority of studies evaluating the effect of TXA in reducing bleeding during and after spinal surgeries have focused on IV injections of this drug. Regarding the less attention to the use of topical TXA in spinal surgeries and discrepancy among previous studies, we aimed to evaluate

the efficacy of topical form of TXA in reduction of bleeding after laminectomy and posterolateral fusion.

Methods

Study Design: This randomized, double-blinded, placebo-controlled clinical trial study was performed on elective patients aged 20-70 years who were candidates for two or more levels of laminectomy and pedicle screw fusion (PSF). The study was performed in the Department of Neurosurgery at Imam Reza Hospital, Tabriz, Iran, from January 2017 to January 2019. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.1012) and registered in the Iranian Registry of Clinical Trials Center (IRCT20120527009878N6). Written informed consent was obtained from all patients. The study was in accordance with the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) (12).

We enrolled the patients based on the inclusion and exclusion criteria listed in table 1.

Table 1. Study criteria

Inclusion criteria
Age from 20 to 70 years
Being a candidate for laminectomy surgery of > 2 spaces and posterolateral fusion with pedicle screw
Patient's informed consent
Exclusion criteria
Elevated PT, PTT, INR for any reason
History of thrombotic events such as CVA and MI
History of bleeding disorder
History of traumatic brain injury and CPR
Cancer, or any other serious illness that affects treatment evaluation
Renal failure with GFR lower than 60 ml/min
Use of anticoagulants such as aspirin and dipyridamole
OCP consumption, pregnancy, or lactation

PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; CVA: Cerebrovascular accident; MI: Myocardial infarction; CPR: Cardiopulmonary resuscitation; GFR: Glomerular filtration rate OCP: Oral contraceptive pill

Eighty patients were studied according to the number of hospital visits (Figure 1). Patients were randomly divided into TXA (n = 40) and placebo (n = 40) groups. The patients were matched in both groups according to the factors that may be effective in reducing bleeding, including surgical technique, the surgical team (including surgeon and surgeon's assistance), the number of surgeries performed, and comorbidities. Both physicians and patients were blinded to the type of treatment.

Surgery: All surgeries were performed by one surgical team with the same technique. Forty syringes were filled with TXA (1 g/50 ml, Caspian Tamin Pharmaceutical Co., Iran) as a single dose, and the other 40 were filled with placebo (0.9% normal saline/50 ml). The blinding was performed by preparing syringes by the supervisor before the surgery, and the syringes were administrated by the technician of the operating room. Surgicel or gelfoam was not used during surgery to avoid confounding bias.

After laminectomy and fusion, the surgical and fascia sites were initially packed with gauze. During the surgery, hemostasis was performed with packing, or in severe cases with cautery. After complete hemostasis, one of the prepared syringes was administered to the surgery site for 10 minutes. Then, we inserted drains and sutured the layers.

Data Collection: After patients were transferred to the neurosurgery ward, the blood volume from the Hemovac drain was monitored in the first and second 12 hours after the surgery. Also, we recorded the amount of blood collected after the drain removal, the blood loss during surgery (based on suctioned blood and gauze count), the need for blood transfusion, the length of hospital stay, and drug complications in both groups.

The data collection form was completed by the person in charge of the patients' follow-up, who was also unaware of the patients' group allocation.

Statistical Analysis: The data were analyzed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA). The independent samples t-test, chi-square test, and Fisher's exact test were used to compare qualitative data. All P-values less than 0.05 were considered statistically significant.

Results

A total number of 80 patients were included (50 women and 30 men). The mean age of the patients was 55.51 ± 10.27 years (range: 24-69 years). Preoperative weight, hemoglobin (Hb), and hematocrit (HCT) did not show significant differences among the two groups. Table 2 presents a summary of study variables.

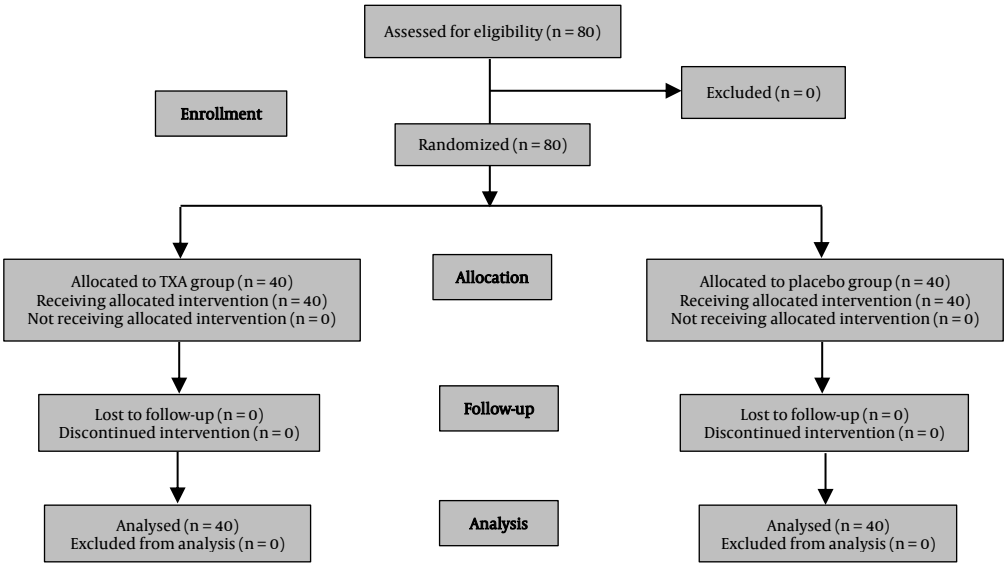

Figure 1. Consolidated standards of reporting trials (CONSORT) flowchart

Table 2. Comparison of the study variables between tranexamic acid (TXA) group and control group

Variables	TXA group (n = 40)	Control group (n = 40)	P-value
Sex			
Male	15	15	
Female	25	25	
Age (year)	56.63 ± 10.82	54.40 ± 9.69	0.330
Weight (kg)	75.20 ± 8.96	78.07 ± 7.07	0.110
Hb (mg/dl)	13.97 ± 1.62	13.95 ± 1.79	0.780
HCT (percentage)	42.55 ± 3.92	42.25 ± 4.35	0.740
Amount of bleeding			
First 12 hours (ml)	108.88 ± 30.09	121.38 ± 43.78	0.120
Second 12 hours (ml)	92.63 ± 37.15	104.13 ± 34.50	0.150
Total postoperative bleeding (ml)	217.25 ± 59.00	243.25 ± 63.82	0.060
Intraoperative hemorrhage (ml)	441.25 ± 152.70	442.75 ± 192.56	0.960

Data are presented as number or mean ± standard deviation (SD)
TXA: Tranexamic acid; Hb: Hemoglobin; HCT: Hematocrit

For subgroup analysis of intraoperative hemorrhage and bleeding in the first 12 hours, the groups were categorized based on a 400 ml cutoff. During the surgery, 22 (55%) patients in control group and 18 (45%) patients in TXA group had bleeding less than 400 ml (P = 0.011). The intraoperative bleeding was more than 400 ml in 18 (45%) patients in control group and 20 (50%) patients in TXA group (not significant).

Based on the new subgroups, intraoperative bleeding and the second 12 hours postoperative bleeding were compared.

The only significant difference was between the subgroup of intraoperative bleeding more than 400 ml in the control group and TXA treatment (P = 0.039). In the comparison of total intraoperative bleeding and postoperative bleeding, the only significant difference was between the intraoperative bleeding more than 400 ml in the control group and TXA group (P = 0.015).

Discussion

In this study, we included 80 patients between the ages of 20-70 years who were candidates for two or more laminectomies and PSF for any reason other than trauma. Since the intervention was performed with 1 g/50 ml TXA at the end of the surgery, there was no significant difference between intraoperative hemorrhage in the control group and the TXA group. In a meta-analysis by Luo et al., the total intraoperative bleeding was between 650 ml and 2839 ml, which was higher than intraoperative bleeding in our study (4). Xu et al. reported 223.8 ± 163.0 ml intraoperative bleeding in posterolateral fusion (14), which was lower than our results.

Our study indicates no statistically significant difference in the amount of bleeding in the first 12 hours, second 12 hours, and total postoperative bleeding in the TXA group. Although many studies have demonstrated the effect of different doses of IV TXA on bleeding in spine and knee surgeries, the topical TXA seems less effective with contradictory results (15). Many studies have shown that topical TXA significantly reduces postoperative bleeding volume (3, 4, 8, 12, 14, 15). Ker et al. investigated 29 randomized clinical trials with 2612 patients for hemostatic effects of topical TXA in different surgical procedures (3). Eighteen clinical trials showed reduced postoperative hemorrhage, of which seven were in the field of cardiac surgery, five in knee arthroplasty, three in spine surgery, and three in other fields. Other trials showed no effect on bleeding (3).

Luo et al. collected the data from both randomized and non-randomized clinical trials from 1966 to 2017. Their meta-analysis showed that topical use of TXA in spinal surgery significantly reduced postoperative bleeding. In addition, the use of TXA did not significantly increase the risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and postoperative infection (4). Xu et al. evaluated 139 patients with posterior spinal fusion surgery and found that topical use of TXA significantly reduced postoperative bleeding without increasing postoperative complications (14). In another meta-analysis by Cheriyan et al., TXA reduced intraoperative, postoperative, and total bleeding rates. Only one case of DVT was reported in this study (16).

In subgroup analysis, we categorized our groups based on the amount of intraoperative bleeding. In the intraoperative bleeding of more than 400 ml, TXA significantly reduced the postoperative bleeding in the first and second 12 hours after the surgery, which shows the benefits of TXA in reducing postoperative bleeding when a higher amount of bleeding exists during surgery. In contrast to our findings, Xu et al. used a single-dose of TXA with a mean intraoperative hemorrhage of 223.8 ± 163.0 ml and it significantly decreased the postoperative bleeding from 204 ml (control group) to 93 ml (TXA group) (14).

In our study, the mean length of hospital stay after surgery in control and TXA groups was 2.8 days and 2.7 days, respectively, which were not significantly different. In a study by Elwatidy et al. on single-dose preoperative IV TXA and a study by Xu et al. on the effect of topical TXA on spinal fusion patients, there was no significant difference in postoperative hospitalization (6, 14).

We found no significant difference between the groups regarding the number of hospitalization days and the number of packed cells received intraoperatively. In accordance with our findings, Neilipovitz reported no significant difference between the TXA and control groups in terms of hospital stay and intraoperative packed cells in major spine surgeries (17). Alvarez et al. showed the efficacy of TXA in the reduction of blood loss and transfusion requirements after knee replacement surgery (18).

Since we used TXA at the end of the surgery, the number of intraoperative packed cells did not differ between the groups. Our results were consistent with previous findings in terms of intraoperative blood loss (14). Shi et al. evaluated the effect of an IV bolus dose of TXA (30 mg/kg) following a maintenance dose of 2 mg/kg/h that had no significant difference in blood transfusion between the TXA and placebo (19). In contrast, in the study performed by Huang et al. on the role of TXA in the reduction of postoperative blood loss and intraoperative blood transfusions in orthopedic surgeries, a significant difference was observed between the groups in the amount of received packed cells (2).

Conclusion

The application of topical TXA was effective in patients with high hemorrhage during spine surgery for reducing the bleeding rate in the first and second 12 hours and the mean total bleeding rate after surgery. It had no

significant effect on total intraoperative hemorrhage, total packed cells, and total hospitalization length.

Conflict of Interest

The authors declare no conflict of interest in this study.

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References

1. Cubillos J, Tse C, Chan VW, Perlas A. Bedside ultrasound assessment of gastric content: An observational study. *Can J Anaesth*. 2012;59(4):416-23. doi: 10.1007/s12630-011-9661-9. [PubMed: 22215523].
2. Huang F, Wu D, Ma G, Yin Z, Wang Q. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: A meta-analysis. *J Surg Res*. 2014;186(1):318-27. doi: 10.1016/j.jss.2013.08.020. [PubMed: 24075404].
3. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database Syst Rev*. 2013;(7):CD010562. doi: 10.1002/14651858.CD010562.pub2. [PubMed: 23881695].
4. Luo W, Sun RX, Jiang H, Ma XL. The efficacy and safety of topical administration of tranexamic acid in spine surgery: A meta-analysis. *J Orthop Surg Res*. 2018;13(1):96. doi: 10.1186/s13018-018-0815-0. [PubMed: 29690892]. [PubMed Central: PMC5937828].
5. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2011;(3):CD001886. doi: 10.1002/14651858.CD001886.pub4. [PubMed: 21412876]. [PubMed Central: PMC4234031].
6. Elwatidy S, Jamjoom Z, Elgamal E, Zakaria A, Turkistani A, El-Dawlatly A. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: A prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)*. 2008;33(24):2577-80. doi: 10.1097/BRS.0b013e318188b9c5. [PubMed: 19011538].
7. Sabzi F, Teimouri H, Zokai A. Myoclonus, seizure, and ventricular fibrillation after intrathecal injection of tranexamic acid. *J Tehran Heart Cent*. 2009;4(4):253-5. [In Persian].
8. Damji KF, Noel LP, Peterson RG, Ma PE, Clarke WN, Gilberg S, et al. Topical versus intravenous administration of tranexamic acid: A comparison of intraocular and serum concentrations in the rabbit. *Can J Ophthalmol*. 1998;33(6):308-13. [PubMed: 9818127].
9. Puigdellivol E, Carral ME, Moreno J, Pla-Delfina JM, Jane F. Pharmacokinetics and absolute bioavailability of intramuscular tranexamic acid in man. *Int J Clin Pharmacol Ther Toxicol*. 1985;23(6):298-301. [PubMed: 4018929].
10. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One*. 2013;8(2):e55436. doi: 10.1371/journal.pone.0055436. [PubMed: 23424632]. [PubMed Central: PMC3570541].
11. Morgan A, Jeffrey-Smith A. BET 1: Should tranexamic acid be given to patients who are having an upper gastrointestinal bleed? *Emerg Med J*. 2012;29(9):773-7. doi: 10.1136/emermed-2012-201686.2. [PubMed: 22903425].
12. Molloy DO, Archbold HA, Ogonda L, McConway J, Wilson RK, Beverland DE. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: A prospective, randomised controlled trial. *J Bone Joint Surg Br*. 2007;89(3):306-9. doi: 10.1302/0301-620X.89B3.17565. [PubMed: 17356139].
13. Shakeri M, Salehpour F, Shokouhi G, Aeinfar K, Aghazadeh J, Mirzaei F, et al. Minimal dose of tranexamic acid is effective in reducing blood loss in complex spine surgeries: A randomized double-blind placebo controlled study. *Asian Spine J*. 2018;12(3):484-9. doi: 10.4184/asj.2018.12.3.484. [PubMed: 29879776]. [PubMed Central: PMC6002182].
14. Xu D, Zhuang Q, Li Z, Ren Z, Chen X, Li S. A randomized controlled trial on the effects of collagen sponge and topical tranexamic acid in posterior spinal fusion surgeries. *J Orthop Surg Res*. 2017;12(1):166. doi: 10.1186/s13018-017-0672-2. [PubMed: 29110696]. [PubMed Central: PMC5674845].
15. 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):284-95. doi: 10.1055/s-0035-1563609. [PubMed: 27099820]. [PubMed Central: PMC4836933].
16. Cheriyan T, Maier SP, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: A meta-analysis. *Spine J*. 2015;15(4):752-61. doi: 10.1016/j.spinee.2015.01.013. [PubMed: 25617507].
17. Neilipovitz DT. Tranexamic acid for major spinal surgery. *Eur Spine J*. 2004;13(Suppl 1):S62-S65. doi: 10.1007/s00586-004-0716-2. [PubMed: 15127250]. [PubMed Central: PMC3592185].
18. Alvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. *Transfusion*. 2008;48(3):519-25. doi: 10.1111/j.1537-2995.2007.01564.x. [PubMed: 18067499].
19. Shi H, Ou Y, Jiang D, Quan Z, Zhao Z, Zhu Y. Tranexamic acid reduces perioperative blood loss of posterior lumbar surgery for stenosis or spondylolisthesis: A randomized trial. *Medicine (Baltimore)*. 2017;96(1):e5718. doi: 10.1097/MD.0000000000005718. [PubMed: 28072709]. [PubMed Central: PMC5228669].