Randomised Controlled Trial

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Effect of oral tranexamic acid on postoperative bleeding in spinal surgery: a randomized controlled trial

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Background and objective: This study aimed to investigate the effect of oral administration of tranexamic acid (TXA) on reducing intraoperative bleeding during spinal surgeries.

Method: The study was a single-center, double-blind, randomized, placebo-controlled clinical trial. Participants were individuals over 20 years old who underwent spinal surgery. Patients received 1.5 g of TXA orally, 2 h before surgery. Intraoperative bleeding volume, blood volume in the drain after surgery, length of hospital stays after surgery, incidence of nausea or vomiting, decrease in hemoglobin (Hb) level, and postoperative coagulation test results were evaluated in each group.

Results: In this study, patients were assigned to each study group based on inclusion and exclusion criteria. The mean age of patients was 69.6 ± 6.47 years, and 65% were male. There was no significant difference in age, sex, pre and postoperative Hb levels, prothrombin time (PT), or international normalized ratio (INR) between the study groups. Intraoperative bleeding volume and blood volume in the drain after surgery were significantly lower in the TXA group. Additionally, the length of hospital stay after surgery was significantly shorter in the TXA group. The incidence of nausea or vomiting was significantly higher in the TXA group. Furthermore, postoperative partial thromboplastin time (PTT) was significantly higher in the TXA group compared to the placebo group.

Conclusion: Oral administration of TXA before spinal surgery leads to a significant reduction in intraoperative and postoperative bleeding without significant adverse effects and also reduces the length of hospital stay.

Keywords: postoperative bleeding, spine surgery, tranexamic acid

Introduction

Over the past few decades, the number of spinal surgeries performed in the United States has significantly increased, with growth reaching over 200% from 1990 to the present[1–4]. As the volume and complexity of spinal procedures have increased, the management of intraoperative blood loss has become a central research topic in this field[5–7]. Many spinal surgeries are associated with significant blood loss, particularly in revision surgeries for deformities. Moreover, the highest incidence of postoperative blood transfusion ranges from 8 to 30%, depending on patient characteristics such as advanced age, higher BMI, greater surgical complexity, and longer fusion constructs[8–10].

HIGHLIGHTS

- Partial thromboplastin time (PTT) was significantly higher in the tranexamic acid (TXA) group after surgery compared to the control group.
- TXA is one of the main antifibrinolytic agents used in clinical practice.
- Administration of TXA before spinal surgery leads to a significant reduction in intraoperative and postoperative bleeding.

Transfusion, a common approach to significant blood loss, is associated with numerous adverse effects such as infection transmission through blood, immunological cross-reactivity, thromboembolic events, and immune system suppression[11–13]. These complications can lead to longer hospital stays, increased direct costs, and higher mortality rates among hospitalized patients[5,14,15]. Several past studies have shown increased postoperative mortality rates, complication rates, and overall care costs related to blood transfusion in both spinal and non-spinal surgery populations[11,16–20]. Among the most concerning complications are significant fluid shifts that can damage the heart, lungs, and kidneys, as well as acute lung injury related to transfusion and acute kidney injury.

One of the biggest advances in minimizing blood loss during spinal surgery has been the introduction of antifibrinolytic agents, which have been shown in select studies to reduce blood loss by up to 50%[21]. With the exit of aprotinin from the US market in 2008, the two main antifibrinolytic agents used in clinical practice

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are tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). Both are lysine analogs that bind to plasminogen, preventing its activation and thus inhibiting fibrinolysis and promoting clot stabilization. Despite concerns that such a preemptive anticoagulation mechanism may increase the risk of postoperative venous thromboembolism (VTE), this concern has not been substantiated in studies[22,23]. The few FDA-defined contraindications for using these agents include active bleeding (such as epidural hematoma or subdural hemorrhage), acquired defective color vision (TXA only), active intravascular clotting, and severe known hypersensitivity to antifibrinolytic agents. This study aims to evaluate the effect of oral TXA on reducing blood loss during spinal surgeries.

Method

Study design

The present study was conducted as a single-center, double-blind randomized placebo clinical trial. The Ethics Committee of the University of Medical Sciences and the National Ethics Committee approved this study, and it was carried out following the principles of the Helsinki Declaration. The current study has been reported in line with the CONSORT criteria[24].

Participant

In this study, individuals who were referred to the Educational and Therapeutic Hospital, for spinal surgery from 2020 to 2023 were enrolled as participants. Written informed consent was obtained from all the patients before enrolling in this study.

Inclusion criteria

Patients meeting the following conditions will be included in this study: (1) aged 20–75 years, (2) undergoing spinal surgery for conditions such as discopathy, spinal canal stenosis, and listhesis with bilateral fusion at two or more levels, and (3) providing informed consent to participate in the study.

Exclusion criteria

Patients will be excluded from the study if they have: (1) lack of consent to participate, (2) cardiovascular disease, (3) abnormal bleeding, (4) platelet count less than 150 000/μl, (5) history of thrombosis or embolism, (6) severe allergy, (7) use of drugs that interfere with blood hemostasis, (8) uncontrolled high blood pressure (systolic BP > 160/90 mmHg), (9) BMI > 30 kg/m^2, (10) chronic kidney disease, or (11) history of open heart surgery or presence of a cardiac stent.

Blinding and randomization

Random allocation will be performed using the SNOSE method to maintain blinding. This method is a common approach to random allocation concealment. First, a random sequence will be generated using the software specified, and then several aluminum-wrapped envelopes (to prevent content visibility) will be prepared based on the sample size. Each of the generated random sequences will be recorded on a registration card and placed inside an envelope. To maintain the random sequence, each envelope will be numbered on the outer surface. Finally, the sealed envelopes will be placed in a box in order. When participants register for the study, one of the envelopes will be opened in order of entry, and the assigned group for that participant will be revealed.

Intervention

After obtaining written informed consent, patients undergoing spinal fusion surgery for two or more levels will be enrolled in the study. Patients in the intervention group will receive three 500 mg capsules of TXA (totaling 1.5 g) orally, 2 h before surgical incision. According to pharmacokinetic findings, oral TXA reaches therapeutic levels after 2 h and is maintained above the treatment threshold for up to 6 h after administration. All patients will receive general anesthesia and prophylactic IV antibiotics for 48 h after surgery. Systolic blood pressure during surgery will be maintained between 100 and 120 mmHg. All surgeries will be performed by one neurosurgeon using a midline incision in the lumbar region, and patients will undergo laminectomy, foraminotomy, and fusion at two or three levels. The duration of surgery and the amount of blood loss will be recorded at the end of the procedure. Blood loss will be calculated during surgery based on blood-contaminated sponge counts and suction contents, and blood products will be administered if necessary. Patients' coagulation levels will also be checked during the procedure and 24 h after surgery, and coagulation products will be prescribed if needed.

Statistical analysis

First, the distribution of quantitative variables will be assessed using the Shapiro–Wilk test. For normally distributed variables, mean and standard deviation will be used to describe them, while for non-normally distributed variables, median, minimum, and maximum values will be used. Qualitative variables will be described using frequency (percentage). Independent samples *t*-test or Mann–Whitney U test will be used for comparative analyses of normally or non-normally distributed data between two independent groups, respectively. χ^2 or Fisher's exact tests will be used to analyze qualitative variables. In all cases, a two-tailed *P* value less than 0.05 will be considered statistically significant. SPSS version 26 software will be used for statistical analyses.

Results

Demographic characteristics

Based on the inclusion and exclusion criteria, a total of 120 patients were enrolled in this study, with 60 patients in each group. Eighty-six patients had discopathy, 22 patients had spinal canal stenosis, and 12 patients had listhesis, among whom a total of 30 patients underwent fusion surgery, including 18 patients with discopathy, 8 patients with spinal canal stenosis, and all 12 patients with listhesis. The mean age was 47.27 ± 9.70 years in the TXA group and 48.0 ± 9.72 years in the control group. There was no statistically significant difference in age between the study groups ($P = 0.771$). Additionally, 60% of patients in the TXA group and 70% in the control group were male. There was no statistically significant difference in gender between the study groups ($P = 0.417$). (Table 1).

Table 1

Demographic and clinical characteristics of the study participants.

	Intervention group	Control group	P
Age (year)	70.9 ± 27.47	72.9 ± 0.48	0.771
Sex, *n* (%)			0.417
Male	36 (60)	42 (70)	
Female	24 (40)	18 (30)	

Blood loss

The intraoperative blood loss volume was 1341.67 ± 167.27 ml in the TXA group and 1490.33 ± 162.40 ml in the control group. Intraoperative blood loss was significantly less in the TXA group compared to the control group ($P = 0.001$). Additionally, the postoperative blood loss volume was 176.33 ± 29.18 ml in the TXA group and 202.33 ± 28.48 ml in the control group. In fact, Postoperative blood loss was significantly less in the TXA group compared to the control group ($P = 0.001$). (Table 2).

Effect of TXA on length of hospitalization

The median length of hospital stay after surgery was 2 days in the TXA group and 3 days in the control group. In fact, The length of hospital stay after surgery was significantly shorter in the TXA group. (Table 2).

Effect of TXA on postoperative complications

43.3% of patients in the TXA group and 13.3% in the control group experienced nausea or vomiting after surgery. The incidence of nausea or vomiting after surgery was significantly higher in the TXA group compared to the control group ($P = 0.01$). (Table 3).

Effect of TXA on hematological and coagulation factors

In this study, the mean postoperative hemoglobin levels were 6.30 ± 1.11 and 6.60 ± 0.910 gr/dl in the TXA and control groups, respectively. This difference was not statistically significant ($P = 0.130$). Additionally, the median preoperative hemoglobin levels were 12.1 gr/dl in both the TXA and control groups. There was no statistically significant difference in preoperative hemoglobin levels between the study groups. The evaluation of coagulation factors showed that the median postoperative PT was 2.12 and 5.12 seconds in the TXA and control groups, respectively. This difference was not statistically significant ($P = 0.193$). The median postoperative INR was 0.9 in both the TXA and control groups, and there was no statistically significant difference in INR between the study groups ($P = 0.446$). The median postoperative PTT was 33.4 and 31.7 sec in the TXA and control groups, respectively. PTT was significantly higher in the TXA group after surgery ($P = 0.002$). (Table 3).

Table 2

Effect of Tranexamic Acid on Hemodynamic.

	Intervention group	Control group	P
Blood lost during surgery	1341.67 ± 167.27	1490.33 ± 162.40	0.001
Postoperative blood volume in surgery drain	176.33 ± 29.18	202.33 ± 28.48	0.001
Length of hospitalization			0.029
Min	1	1	
Median	2	3	
Max	4	4	
Nausea or vomiting			0.01
Yes	26 (43.3)	8 (13.3)	
No	34 (56.7)	52 (86.7)	

Table 3

Postoperative Complications.

	Intervention group	Control group	P
Postoperative HGB	11.1 ± 0.63	10.9 ± 0.66	0.130
Preoperative HGB			
Min	11.1	13.7	0.473
Median	12.1	12.6	
Max	13.8	11.2	
Length of hospitalization			0.029
Min	1	1	
Median	2	3	
Max	4	4	
PT			0.193
Min	11.1	11.1	
Median	12.2	12.5	
Max	13.4	13.5	
PTT			0.002
Min	30.2	29.8	
Median	33.4	31.7	
Max	35.2	35.6	
INR			0.446
Min	0.8	0.8	
Median	0.9	0.9	
Max	1	1	

HGB Hemoglobin; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Discussion

TXA has been widely used in spinal and other orthopedic surgeries. Multiple studies have reported its safety and efficacy in reducing postoperative blood loss. Clinical guidelines for the common use of TXA in general surgery have been expanded, but there are few guidelines for spinal surgery. A systematic review by Yerneni *et al.*[25] demonstrated that local use of TXA is effective in reducing average blood loss after surgery. Xiong and colleagues concluded that both high and low doses of IV TXA during surgery for adolescent spinal deformity are effective and safe. However, there is insufficient clinical evidence for comprehensive decision-making due to a lack of comparison between dosage regimens and drug administration methods (oral, IV, and local)[26].

A meta-analysis by Cao *et al.*[27] examined all relevant and high-quality RCTs for a comprehensive comparison of the efficacy and safety of different TXA administration methods during spinal surgery. According to the SUCRA ranking, IV TXA administration may have a better effect on reducing intraoperative bleeding compared to local, oral, or local infiltration. Although no significant difference was observed between IV and other strategies. Another study by Zakariaei and colleagues showed that even local use of TXA is effective in reducing local bleeding during n inguinal hernia surgery[28]. SUCRA ranking in this study showed that local TXA use is more effective in reducing postoperative bleeding compared to IV infusion, although there

was no significant difference between local administration and IV infusion. Local infiltration of TXA had the worst performance, only accompanied by a small or insignificant decrease in intraoperative bleeding, postoperative bleeding, changes in hemoglobin within 24 h after surgery, and transfusion rates compared to placebo. All TXA administration methods were well tolerated and safe compared to placebo. Network meta-regression showed that BMI may have an impact on postoperative blood transfusion, and the nature of the surgical procedure may affect intraoperative bleeding[27]. This result is consistent with the findings of Jiang *et al.*[29] that obesity is associated with more blood loss during spinal surgery. The present study, which only examined oral TXA administration and compared it to the placebo group, also showed that intraoperative bleeding and postoperative drainage in the TXA group were significantly lower than in the placebo group. No significant changes in Hb were observed between the two study groups. However, the length of hospital stay after surgery was shorter in the TXA group, and PTT was significantly higher in the TXA group than in the placebo group.

The results of the study by Paul and colleagues demonstrated that patients receiving TXA had significantly less intraoperative bleeding and shorter hospital stays compared to the placebo group, which is consistent with the findings of the present study[30]. One of the factors that can lead to a shorter hospital stay in patients undergoing TXA treatment is that these patients have less blood loss during surgery and are less likely to experience postoperative anemia. Another possible reason is that there is less postoperative bleeding, which is associated with less drainage volume and fewer postoperative complications, allowing for earlier discharge from the hospital[31].

Cheryian *et al.*[31] investigated the effect of TXA on intraoperative bleeding during spinal surgery and found that oral TXA is associated with a reduction in intraoperative bleeding compared to placebo, which is also consistent with the present study. Cordoba *et al.*[32] examined the effect of TXA on reducing postoperative bleeding volume in patients and found a significant difference between the TXA and placebo groups, which is consistent with the present study. Deylamani and colleagues investigated the effect of TXA on reducing intraoperative bleeding in patients undergoing endoscopic sinus surgery and found a significant difference between the TXA and placebo groups in terms of intraoperative bleeding and mean arterial pressure[33]. Aghadavoudi *et al.*[34] evaluated the effect of TXA on intraoperative bleeding and surgeon satisfaction in patients undergoing mastoidectomy and found that TXA is effective in reducing intraoperative bleeding, which is consistent with the present study.

In surgery, IV, oral, and local administration of TXA are commonly used. IV administration has been the most common route in previous studies. A meta-analysis by Brown *et al.*[35] showed that the most common method of administration in laminectomy and fusion surgeries is an IV injection of 15 mg/kg of TXA before surgery, which significantly reduces blood loss in patients who had previously received TXA. In addition, loading doses up to 50 mg/kg be safe in spinal and knee surgeries. In this study, only the effect of administering a total of 5.1 g of TXA was investigated[25,36,37].

Although TXA is safe and effective in reducing blood loss in spinal surgery, there is still no optimal practical recommendation for its use. The heterogeneity in defining high and low doses in previous studies has also reduced the credibility of the results. Furthermore, there have been many complex administration strategies for TXA, and their definitions have sometimes been unclear in studies. Therefore, the results of investigations and meta-analyses on the use of TXA in spinal surgery should be interpreted carefully, especially when recommendations for high-dose TXA are based on meta-analysis results[25,38]. It is important to understand that the optimal dosing regimen for one route of administration, such as oral, may not be desirable for IV administration.

Limitations

The main weakness of this single-center study is its lack of generalizability. However, despite being conducted in a single center, it includes an acceptable sample size in both groups.

Ethics approval and consent to participate

The Ethics Committee of the University of Medical Sciences approved this study and Informed consent was obtained from all patients and their legal guardians for participate in this study.

Consent for publication

Not applicable.

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Author contribution

S.K. and A.K. involved in interpretation and collecting of data, and editing the manuscript. F.G. and S.N. involved in writing, editing and preparing the final version of manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest for authors in this study.

Research registration unique identifying number (UIN)

1. Name of the registry: researchregistry Unique identifying number or registration ID: : researchregistry9680
2. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://researchregistry.knack.com/researchregistry#home/registrationdetails/654d1fb0c0390e002939260a/

Guarantor

Dr Sajjad Najafi.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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