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Tranexamic Acid and Intraoperative and Postoperative Accumulative Bleeding in Elective Degenerative Spine Surgery

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Purpose: Spinal surgeries are often associated with a high incidence of perioperative blood loss, which poses several complications. Much current research focuses on the importance of antifibrinolytic drugs during spinal surgeries to reduce blood loss, which can also reduce the risk of the need for blood transfusions. We evaluated the effects of prophylactic, low-dose tranexamic acid (TXA) in spinal fusion surgeries on blood loss, blood transfusions, and associated complications.

Materials and Methods: TXA was administered to 90 patients at a constant infusion rate of 10 mg/kg for 20 minutes after anesthesia induction, followed by a maintenance dose of 1 mg/kg/h until the end of the operation. An additional 91 patients were included as controls.

Results: There were no significant differences between the study groups in terms of intraoperative blood loss, which was 500 mL for both groups (p>0.999). Also, intraoperative blood transfusion requirements were similar between both groups (p=0.330). Mean blood transfusion amounts were 125±35 mL for patients in the TXA group and 85±25 mL in the control group. However, there was a significant reduction in postoperative blood transfusion (p=0.003) in the TXA group. Only three cases in the TXA group required blood transfusion, while 15 cases in the control group did.

Conclusion: We confirmed that low dose TXA has no effect on intraoperative blood loss volume or blood transfusion requirements and that it can significantly reduce the need for postoperative blood transfusions.

Key Words: Blood loss, blood transfusion, intraoperative, PLIF, postoperative, tranexamic acid

INTRODUCTION

Spinal surgeries are often associated with a high incidence of perioperative blood loss, which can lead to several complications, including anemia, organ failure, coagulopathy, and even death.[1-6] Perioperative blood loss increases the need for blood transfusion, which carries other possible complications, such as infection, kidney injury, immunomodulation, and lung injury.[1,4] Perioperative blood loss has also been shown to be associated with poor economic outcomes due to costs of intraoperative blood conservation technology, increased length of hospital stay, and management of potential complications.[2]

Many methods have been developed to decrease the risk of perioperative blood loss, such as improved surgical positioning to decrease intraabdominal pressure, controlled hypotensive anesthesia, intraoperative cell salvage, and the use of hemostatic agents that act locally and systemically [e.g., tranexamic acid (TXA)].[3,7] Antifibrinolytic agents, such as TXA and epsilon-aminocaproic acid (EACA), have gained popularity due to their ability to inhibit fibrinolysis, which can reduce perioperative blood loss during cerebral, lung, cardiac, and arthroplasty

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surgeries.[8] Specifically, TXA inhibits the fibrinolytic mechanism by blocking lysine-binding sites on plasminogen, which inhibits plasminogen activation to plasmin and prevents clot degradation.[9]

Much of the available research focuses on the importance of using antifibrinolytic drugs during spinal surgeries to decrease blood loss, which can decrease the risks of associated blood transfusions. However, optimal dosing and patient selection guidelines and drug safety profiles have not yet been fully established.[10] Therefore, in this study, we evaluated the effects of a prophylactic, low dose of TXA in spinal fusion surgeries on blood loss and the incidences of blood transfusions and associated complications.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea (IRB no. 4-2021-1702, on January 28, 2022). We conducted a retrospective cohort study utilizing available electronic medical records of 181 selected cases. Of these cases, 90 patients received TXA at a constant infusion of 10 mg/kg for 20 minutes after induction of anesthesia. This initial dose was followed by a maintenance dose of 1 mg/kg/h until the end of the operation. An additional 91 patients who did not receive TXA were included as controls. All selected cases were treated from August 2018 to December 2021 (Fig. 1).

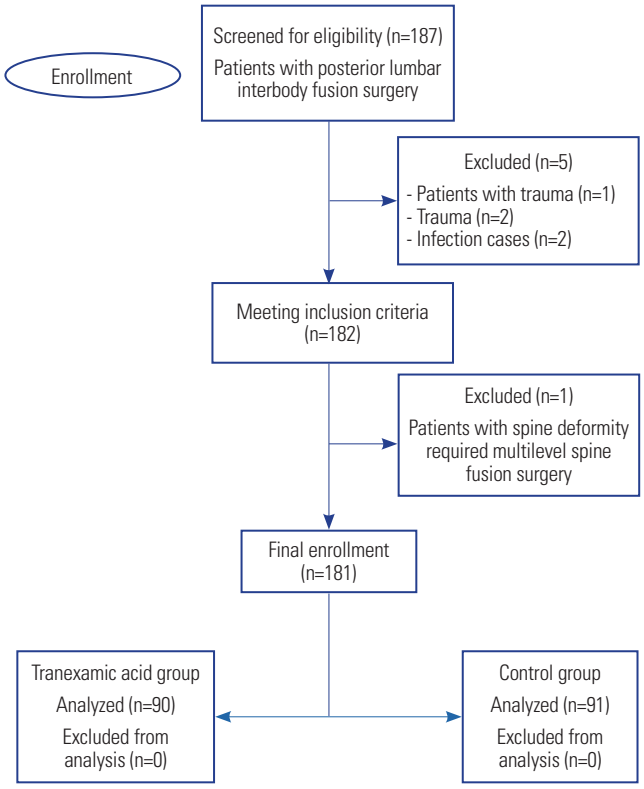

Fig. 1. Flow chart of the patient enrollment.

To be considered for inclusion, patients had to have a degenerative spine disorder diagnosis (spinal canal stenosis, foraminal stenosis, or degenerative spondylolisthesis) and be indicated for fusion surgery [posterior lumbar interbody fusion (PLIF)] after failed attempts at more conservative management practices. The following conditions are contraindicated for TXA use, and patients who met any of these criteria were excluded from this study: a history of thromboembolic events [deep vein thrombosis (DVT), myocardial infarction (MI), stroke, or pulmonary embolism (PE)], renal impairment, pregnancy, lactation, or current use of specific medications, such as oral contraceptive pills or anticoagulant drugs. Additionally, any cases related to trauma, tumor growth, or infection were excluded from our study.

The mean arterial blood pressure (MAP) was maintained at approximately 70–80 mm Hg for all patients during all surgeries. Additionally, local hemostatic agents, such as microfibrillar collagen hemostats (Avitene™) and gelatin-thrombin matrix hemostatic sealants (Floseal), were used, in conjunction with bipolar electrocautery, in instances of uncontrollable epidural bleeding.

The perioperative parameters examined in this study included the following: intraoperative blood loss, need for allogenic packed red blood cell (pRBC) transfusion, volume of fluid transfusion, and urine output. The postoperative parameters examined were postoperative blood loss, time until drain removal, the need for blood transfusions during postoperative recovery, and any other postoperative complications.

All statistical analyses were performed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

No significant differences in demographics, diagnoses, comorbidities, or surgical interventions were noted across the 181 patients included in this study (Table 1). The TXA treatment group (n=90) comprised 54 male and 36 female, aged 44 to 84 years, with a mean age of 66.1 years. Similarly, the control group (n=91) comprised 56 male and 35 female, aged 47 to 84 years, with a mean age of 68.4 years. Patients in both groups had similar spinal fusion levels (two levels) (Table 2).

In the TXA group, 50 cases presented with spinal canal stenosis, 25 cases presented with degenerative spondylolisthesis, and 15 cases presented with foraminal stenosis. Comparatively, in the control group, 37 cases presented with spinal canal stenosis, 30 cases presented with degenerative spondylolisthesis, and 24 cases presented with foraminal stenosis (Table 2).

The median blood loss volume among patients in both groups was 500 mL (p>0.999) (Table 3). The mean volume of intraoperative administration of pRBCs was 125±35 mL for patients in the TXA group and 85±25 mL for patients in the control group.

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Table 1. Sociodemographic Characteristics of the Study Groups (n=181)

Variable	TXA (n=90)	Control (n=91)	*p* value
Age (yr)	66.1±10.4	68.4±10.2	0.150*
Sex			0.832†
Female	36 (40.0)	35 (38.5)	
Male	54 (60.0)	56 (61.5)	
Height (cm)	157.8±5.9	160.5±6.3	0.267*
Weight (kg)	58.2±6.7	60.5±8.2	0.366*
Diabetes mellitus	19 (21.3)	17 (18.7)	0.655*
Hypertension	34 (38.2)	32 (35.2)	0.672*
Smoker	26 (29.5)	34 (37.8)	0.245†
Alcohol use	45 (50.6)	54 (59.3)	0.237†

TXA, tranexamic acid.
p≤0.05 (statistically significant). Data are presented as mean±standard deviation or n (%).
*Independent sample t-test was used to compare means between groups; †Chi-square test was used to compare frequencies between groups.

Table 2. Diagnoses and Intervention Strategies according to Treatment Group

Parameter	TXA (n=90)	Control (n=91)	*p* value
Diagnosis, n (%)			0.107*
Spinal canal stenosis	50 (55.6)	37 (40.7)	
Degenerative spondylolisthesis	25 (27.8)	30 (33.0)	
Foraminal stenosis	15 (16.7)	24 (26.4)	
Fused spine level (PLIF)			
Median (IQR)	2 (2)	2 (2)	>0.999†

PLIF, posterior lumbar interbody fusion; TXA. tranexamic acid.
*Chi-square test was used to compare frequencies between groups; †Mann Whitney U-test was used to compare medians between groups.

There was no significant difference in the mean volumes administered between the two groups (p=0.330).

The median postoperative blood loss volume was 789 mL for patients in the TXA group and 890 mL for patients in the control group, which was not significantly different (p=0.096) (Table 3). However, the need for postoperative blood transfusion was significantly lower among patients in the TXA group than those in the control group (p=0.003) (Table 3). Three patients only in the TXA group required postoperative blood transfusions, compared with 15 patients in the control group (Table 3).

Finally, no significant differences between groups were identified for any of the other examined parameters, including anesthesia time, surgical procedure time, MAP, urine output volume, intraoperative fluid transfusion volume, time until drain removal, and incidences of postoperative complications (Table 3).

Table 3. Surgical Procedural Data according to Treatment Group

Variable	TXA (n=90)	Control (n=91)	*p* value
Anesthesia time (min.)	240 (81)	240 (110)	0.849*
Operation time (min.)	181 (85)	180 (96)	0.814*
Mean arterial blood pressure (mm Hg)	73.6±4.6	3.8±5.3	0.927†
Intraoperative fluid transfusion	1575 (1300)	1600 (1250)	0.861†
pRBCs (mL)	125±35	85±25	0.330†
Blood loss (mL)	500 (500)	500 (500)	>0.999*
Urine output (mL)	335 (313)	305 (301)	0.666*
Postoperative blood loss (mL)	789 (519)	890 (522)	0.096*
Time until drain removal (days)	3.50±0.7	3.39±0.9	0.399†
Post-operative blood transfusion required (mL)	0 (0)	0 (0)	>0.999*
Number of cases that needed blood transfusion, n (%)	3 (3.3)	15 (16.5)	0.003‡

IQR, interquartile range; pRBC, packed red blood cell; TXA, tranexamic acid.
p≤0.05 (statistically significant). Data are presented as mean±standard deviation or median (IQR).
*Mann Whitney U-test was used to compare medians between groups; †Independent Sample t-test was used to compare means between groups; ‡Chi-square test was used to compare frequencies between groups.

DISCUSSION

Spinal surgery is often associated with a high incidence of blood loss,[4,11] making it imperative to continue searching for effective tools to prevent and control blood loss.[12] Surgical positioning, blood pressure control, cell salvage, autologous blood transfusions, preoperative angiography and embolization, and erythropoietin are current strategies used to mitigate spinal surgery blood loss.[3,7,13] Antifibrinolytic drugs, such as TXA and EACA, are also used to decrease intraoperative blood loss.[14] TXA has been proven effective during orthopedic surgeries, especially in arthroplasty procedures, but remains inconsistently used during spinal surgeries.[15] Therefore, we investigated TXA's effects on mitigating perioperative blood loss during corrective procedures for degenerative lumbar conditions,[16] one of the most frequent spinal conditions indicated for surgical intervention. Our goal was to determine whether TXA should be recommended for routine use in spinal surgeries to reduce blood loss volume, as well as transfusion requirements. However, no significant reductions in intraoperative blood loss or blood transfusion requirements were observed for patients that received TXA, compared with patients in the control group, in our study.

The procedures included in our study were short fusion surgeries (two–three PLIF levels), which used a low-dose TXA regimen consisting of a 10 mg/kg preoperative loading dose, followed by a 1 mg/kg/h infusion until the end of the surgical procedure. This dosage was determined based on previous studies documenting TXA's efficacy in blood loss mitigation and reducing blood transfusion requirements.[3,17-19] However, other studies have shown that the use of low-dose TXA is ineffective for blood loss control.[20,21] We were also concerned about the potential increased risk of thromboembolism that has been shown to be associated with high TXA doses.[9,22] Although systematic reviews of TXA use have reported no significant increases in thromboembolism events or renal impairment,[4,20] concerns remain regarding the increased incidence of thrombo-

embolic complications,[23] and patients with histories of thromboembolic events or renal impairment have been excluded from most studies.[24]

Our results were consistent with previous studies, such as the study by Farrokhi, et al.,[20] who found that low-dose TXA administration during spinal fixation surgery has no significant effect on total blood loss volume. Additionally, our results were consistent with the findings of Wong, et al.[18] who showed that although low-dose TXA decreased perioperative blood loss, it did not necessarily decrease the requirement for blood transfusions. Other studies, including the study by Elmose, et al., support the conclusion that routine use of TXA during minor lumbar surgeries, such as short-segment spinal fusion surgeries, has no significant effects on intraoperative blood loss[7,21] or hemoglobin levels.[25]

However, Elmose, et al.[21] found a significant reduction in postoperative draining volume. Interestingly, our results also showed a reduction in postoperative blood loss volume, although this change was not significant. Regardless, these findings are consistent with those reported by Wong, et al.[18] and Kim, et al.[26] who reported that low-dose TXA significantly decreased postoperative blood loss, and this effect was larger than the effect on intraoperative blood loss. These findings may be related to TXA's effect on slowing the discharge of blood from tissues during the postoperative period.[27] Additionally, we hypothesized that this discrepancy between intraoperative and postoperative blood loss control might be related to the effects of blood pressure control in our study. The maintenance of MAP between 70 and 80 mm Hg in all patients might have been sufficient to control blood loss during the intraoperative period, resulting in increased blood loss when MAP normalized during the postoperative period.

Increased postoperative blood loss might have affected the need for postoperative blood transfusions.[18,26] Blood transfusion was indicated in our study when hemoglobin levels fell below 8 mg/dL. However, hemoglobin levels can be affected by other patient conditions and comorbidities, and other indications were considered, such as the presence of oxygen deficiency symptoms (orthostatic hypotension, chest pain of cardiac origin, or tachycardia unresponsive to fluid resuscitation) when determining whether a blood transfusion was necessary. Therefore, despite the significant reduction in the need for blood transfusions during the postoperative period, we cannot recommend routine TXA use solely based on this finding.

Additionally, when low-dose TXA has been compared with other antifibrinolytic agents, other agents have been shown to be more effective at controlling blood loss. In a study from Peters, et al.[28] comparing EACA, low-dose TXA, and a placebo, significant reductions in blood loss volume and the need for blood transfusions were observed among patients in the EACA group, compared with patients in the placebo group; however, patients in the low-dose TXA group showed no significant reduction in blood loss, compared with patients in the placebo group. Similarly, during three lumbar column osteotomies to correct adult spine deformities, aprotinin, another medication indicated for reducing perioperative blood loss, significantly reduced blood loss volume and the need for transfusions. However, no significant reduction in either parameter was observed for patients treated with TXA, compared with a control group.[29] Other studies, such as those by Choi, et al.,[3] have documented the efficacy of low-dose TXA for reducing blood loss and transfusion requirements during complex spinal surgeries.

Few studies have investigated other aspects of TXA use, including the optimal prophylactic dose, the route of administration, which types of surgeries should include TXA, or which patients should receive the drug.[2,15] A few studies comparing low- and high-dose TXA have found that high-dose TXA is superior for controlling blood loss and reducing blood transfusion requirements, compared to low-dose TXA. These studies, reported by Johnson, et al.[30] and Kim, et al.,[26] focused on adolescent idiopathic scoliosis and degenerative lumbar diseases, respectively. However, the procedure used by Kim, et al.[26] was brief (single-level PLIF), and cost-benefit analysis may not favor the use of high-dose TXA due to potential risks associated with a higher-dose TXA use for overall patient health.

The meta-analysis by Zufferey, et al.[31] revealed that the efficacy of TXA is dose-related.[26,30] Moreover, a randomized control trial from Colomina, et al.[32] indicated that increased levels in a fusion operation were associated with increased total procedure times, which resulted in better control of blood loss by TXA. Notably, many studies reporting TXA efficacy have used higher doses during particularly complex spinal surgeries. Therefore, we concluded that high doses of TXA should be reserved for complex spinal surgeries, such as deformity and revision surgeries, during which a patient could lose up to 55% of their total blood volume.[33] Indeed, in adult deformity surgeries, Lin, et al.[23] determined that high-dose TXA resulted in significantly decreased blood loss volume. Additionally, in pediatric scoliosis surgeries, Grant, et al.[14] and Sethna, et al.[34] confirmed that administering high-dose TXA decreased blood loss significantly, even when vertebral column resection was necessary.[35] This finding was also reported for patients with Duchenne muscular dystrophy (DMD): Shapiro, et al.[36] found that high-dose TXA was effective in decreasing intraoperative blood loss by 58% during scoliosis fusion procedures for patients with DMD, resulting in a subsequent decrease in transfusion requirements.

Overall, we conclude that the potential benefits of using high-dose TXA for short fusion procedures are far outweighed by the potential risks. In the study from Lin, et al.[23] assessing high-dose TXA in adult deformity cases, two DVT cases and one PE were documented, though all were fortunately treated with no major sequelae. Similarly, in the study by Colomina, et al.,[32] two cases of mildly impaired renal function were reported for patients in the TXA group. The risks of high-dose TXA administration include not only DVT but also PE, MI, stroke, renal function impairment, and even death, indicating that high-dose TXA

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use should be considered carefully and not be taken lightly. The lack of these potential complications occurring during our study does not alter our conclusion. Based on these findings, we strongly recommend against the routine use of TXA in all spinal surgeries[37] and instead recommend reserving TXA use for cases in which the procedure carries a high incidence of major bleeding.[38]

In our study, we also used other methods to minimize blood loss in both groups, which appears to have been effective and may have masked TXA's role in controlling blood loss. First, normotensive or controlled hypotensive anesthesia was used during all procedures. According to Verma, et al.,[39] an MAP of 65 mm Hg reduced blood loss by 33% in adolescent idiopathic scoliosis fusion surgery. Although some concern has been raised regarding controlled hypotension, we posit that an expert anesthesiologist can easily maintain the balance between vital organ perfusion demands and a low MAP to minimize blood loss.[40] However, based on our procedures, we suggest that MAP values of 70–80 mm Hg are sufficient to reduce intraoperative blood loss while maintaining a high safety profile. As reflected in our findings, maintaining a low MAP may have a superior effect on reducing blood loss, compared with some antifibrinolytic drugs. Previous high-dose TXA studies that have described TXA efficacy in complex spinal deformity surgeries also utilized controlled hypotension during the procedures (MAP= 60–70 mm Hg).[34,36,41] Therefore, controlled hypotension may have a synergistic effect with high-dose TXA. Second, we used local hemostatic agents, such as Floseal and Avitene, during all procedures. Both of these have mechanical effects and activate clotting mechanisms with similarly effective results.[42,43]

A major strength of this study was the homogeneous population. All patients in the study were operated on by a single senior author, with the same surgical procedure, under the same anesthesia protocol. The limitations of this study are related to the sample size and outside confounding factors unrelated to TXA. This retrospective study included a relatively small number of participants (only 181 patients). To more accurately assess the role of TXA, future studies should be performed in the absence of other confounding factors, such as blood pressure control or other local hemostatic agents. Finally, additional randomized trials with larger sample sizes remain necessary to analyze ideal TXA dosing and the complication rate associated with its use.

In conclusion, we confirmed that low dose TXA plays no role in reducing intraoperative blood loss volume or blood transfusion requirements; however, it could significantly decrease the need for post-operative blood transfusion requirements.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: Mahmoud Abdou. Formal analysis: Mahmoud Abdou. Funding acquisition: Byung Ho Lee. Investigation: Mahmoud Abdou and Byung Ho Lee. Methodology: Mahmoud Abdou and Byung Ho Lee. Project administration: Byung Ho Lee. Resources: Hye Jin Kim, Bora Lee, and Yong Seon Choi. Software: Mahmoud Abdou. Supervision: Ji-Won Kwon, Hye Jin Kim, Bora Lee, Yong Seon Choi, Seong-Hwan Moon, and Byung Ho Lee. Validation: Ji-Won Kwon, Hye Jin Kim, Bora Lee, Yong Seon Choi, Seong-Hwan Moon, and Byung Ho Lee. Visualization: Ji-Won Kwon, Hye Jin Kim, Bora Lee, Yong Seon Choi, Seong-Hwan Moon, and Byung Ho Lee. Writing— original draft: Mahmoud Abdou. Writing—review & editing: Mahmoud Abdou and Byung Ho Lee. Approval of final manuscript: all authors.

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