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ORIGINAL RESEARCH

Impact of tranexamic acid on intraoperative fluid intake in patients undergoing posterior spine fixation: a retrospective cohort study

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Abstract

Background: Significant intraoperative bleeding is followed by infusion of a large amount of fluid. However, massive fluid intake itself, even when not necessarily associated with a largely positive input-output balance, is associated with poor functional outcomes and in-hospital complications. Tranexamic acid (TXA) attenuates intraoperative bleeding in various studies. This study compared the total intraoperative crystalloid intake in patients undergoing posterior spine fixation in those who were administered TXA versus those who were not. **Methods**: This retrospective cohort study included adult patients who underwent posterior spinal fixation at the Department of Neurosurgery. The primary outcome was the adjusted fluid infusion rate, which was calculated as the total volume of crystalloid fluid administered divided by (total anesthetic time $\times$ body weight). The secondary outcomes were intraoperative transfusion and 30-day postoperative complications. A propensity score matching adjusting age, sex, anesthesia time, and physical status was done. **Results**: A total of 302 patients met eligibility criteria, and 94 patients were included in each group after the propensity score matching. The adjusted fluid infusion rate was less in the TXA group than the control group (8.7 ± 3.6 *vs.* 6.4 ± 1.7 mL/kg/h, mean difference 2.3 mL/kg/h (95% confidence interval 1.5–3.1); $p < 0.001$). Intraoperative transfusions were less frequent in the TXA group than in the control group. Postoperative complications including thromboembolism were comparable between the two groups. **Conclusions**: TXA administration in spine fixation resulted in less intraoperative crystalloid input and transfusion, presumably owing to attenuated intraoperative bleeding. TXA could be beneficial in patients at risk of major bleeding and fluid overload.

Keywords

Tranexamic acid; Posterior spine fixation; Intraoperative bleeding; Crystalloid infusion rate; Blood transfusion; Postoperative complications

1. Introduction

The number of patients undergoing spine surgery is increasing due to the aging population in various high-income countries, including the Republic of Korea [1, 2]. Spinal surgery is often accompanied by significant hemorrhage. Bleeding occurs during the dissection of muscle and soft tissue, as in other types of surgery, and is further complicated by bleeding from tissues where hemostasis can be difficult, such as the dura and bone. Cases of massive hemorrhage have occasionally been reported in patients undergoing spine surgery [3].

Administration of a large amount of fluid is inevitable when a patient experiences significant bleeding [4]. This fluid overload increases the perioperative risk of cardiovascular, pulmonary, and infectious complications [5]. Anesthesia providers try to avoid overload and deficits in the circulatory volume to minimize perioperative complications. It is worth knowing that massive fluid intake itself can be risky, even where it has not resulted in positive fluid balance. Rass *et al.* [6] reported that massive fluid intake itself is associated with poor functional outcomes and in-hospital complications.

Tranexamic acid (TXA), a cost-effective antifibrinolytic agent, has been frequently reported to attenuate intraoperative bleeding in various studies conducted on cardiac, obstetric, traumatic, and orthopedic surgical cases [7–10]. The authors planned a retrospective cohort study to compare the total intraoperative crystalloid intake in patients undergoing posterior spine fixation who received TXA versus those who did not. The hypothesis was patients administered tranexamic acid would require less intraoperative crystalloid due to diminished surgical blood loss.

2. Materials and methods

This retrospective cohort study included adults who underwent posterior spine fixation at the Department of Neurosurgery, Wonju Severance Christian Hospital, Republic of Korea, between February 2021 and January 2024. Exclusion criteria were as follows: those whose fluid intake or output was not completely recorded or who had combined surgery involving sites other than the spine. This study was reviewed and approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR324035, approval date: 04 June 2024).

Surgical patients receive goal-directed fluid therapy by monitoring pulse pressure variation (PPV) in real-time [11]. Hypotensive patients with PPV >13% were treated first with 100 mL of intravenous crystalloid fluid [12]. All patients underwent cannulation of the radial artery. The dorsalis pedis was cannulated where radial artery cannulation could not be accomplished. The femoral artery was cannulated when both arteries were inaccessible. Estimated blood loss was calculated through inspection of blood aspirates in suction bottles and hemostatic gauzes. Tranexamic acid administration was determined at the discretion of an attending anesthesiologist. Tranexamic acid was administered as a prophylactic measure in high risk cases, meanwhile the drug was utilized to attenuate bleeding in some cases. The tranexamic acid administration protocol of our medical center consisted of loading dose of 1 g, followed by 125 mg/h infusion until conclusion of surgery [7, 13].

Surgical patients were listed retrospectively, and eligible cases were selected using the electronic health record system at the medical center. Group identification of patients administered TXA versus those who were not blinded by the author who conducted the statistical analyses. Propensity score matching was performed by the nearest neighbor method with a caliper width of 0.4, adjusting for age, sex, anesthesia time, and physical status to enhance comparability between groups.

The primary outcome was the total volume of crystalloid fluid administered divided by (total anesthetic time × body weight). The amount of transfusion and basic demographic data, such as age, sex, height, and body weight, were recorded. The following 30-day postoperative complications were documented: pneumonia, respiratory failure, acute kidney injury, wound infection, wound dehiscence, readmission, and in-hospital mortality.

Descriptive analysis was performed by comparing both groups, and the chi-square test (or Fisher's exact test where appropriate) was used to compare categorical variables. The *T*-test was used to compare continuous variables with a normal distribution, and the Wilcoxon rank-sum test was used to compare continuous variables with a non-normal distribution. The R statistics program version 4.3.1 was used for statistical analysis, and the "ggplot2" package of the program was used for visualization.

Binomial logistic regression analysis for 30-day postoperative complications was performed to determine the risk of large crystalloid input (defined more than one standard deviation from the mean intraoperative crystalloid input of the matched sample) adjusted for the effects of covariates. The covariates included in the analysis were age, sex, total anesthetic time, and preoperative anemia of Hemoglobin less than 10 g/dL.

3. Results

A total of 302 patients were in the entire cohort (Fig. 1). No significant differences were noted in the baseline demographics between the groups, except for the duration of anesthesia, which was longer in the TXA group (Table 1). More than half of the patients (62.2% of the entire cohort) had an American Society of Anesthesiologists (ASA) physical status classification of III or IV, which was similar in both groups.

After propensity score matching, 94 patients remained in each group, and 114 unmatched patients were excluded from the final analysis. Duration of anesthesia was comparable following the matching, and there was no statistical difference of baseline characteristics (Table 2).

The crystalloids administered to the cohort were of two types: normal saline and plasmalyte. The total crystalloid input was greater in the control group, and this trend was the same for crystalloid input adjusted for body weight and anesthesia duration (Table 3). The effect size of TXA on intraoperative fluid intake was greater than 0.7, which can be translated to large effect. The difference is illustrated in Fig. 2.

Colloid fluids were used in a limited manner in the entire cohort, administered to 8.5% of the matched sample, which was similar in both groups. Estimated blood loss was greater in the control group. Meanwhile, urine output adjusted for anesthesia time was comparable between the two groups. In addition, the postoperative decrease in hemoglobin concentration on postoperative days 1 and 2 was comparable between the groups.

Relative risk for transfusion was 0.21 (95% confidence interval 0.09–0.49) in the TXA group compared to the control group (Table 4). No difference was noted in 30-day complications, in-hospital mortality, and re-admission between the two groups (Table 5). One patient in control group experienced thromboembolic event on the POD #13; pulmonary thromboembolism. The patient expired on the POD #18. There was no thromboembolism in TXA group.

4. Discussion

TXA administration in patients undergoing posterior spinal fixation was associated with a reduced intraoperative crystalloid requirement in this study. This association may be mediated by attenuated blood loss with TXA, a well-established benefit of the drug. A previous meta-analysis by Heyns *et al.* [14] reported that blood loss was reduced to 153 mL in patients. The loading dose of TXA widely varies from 0.5 g to 10 g, and the most common dose was 15 mg/kg in the meta-analysis. This was also comparable to 1 g of TXA used in the current study, which was converted to 15.6 mg/kg in each patient.

Intraoperative bleeding necessitates fluid resuscitation, and crystalloid fluid administration is the treatment of choice. The resulting crystalloid volume-to-blood loss ratio ranges from 1:3 to 1:1, and this ratio was about 1:2 in the current study, considering comparison of estimated blood loss and intraoperative crystalloid infusion in both groups [15]. Postoperatively, crystalloid fluid overload during surgery is not readily excreted

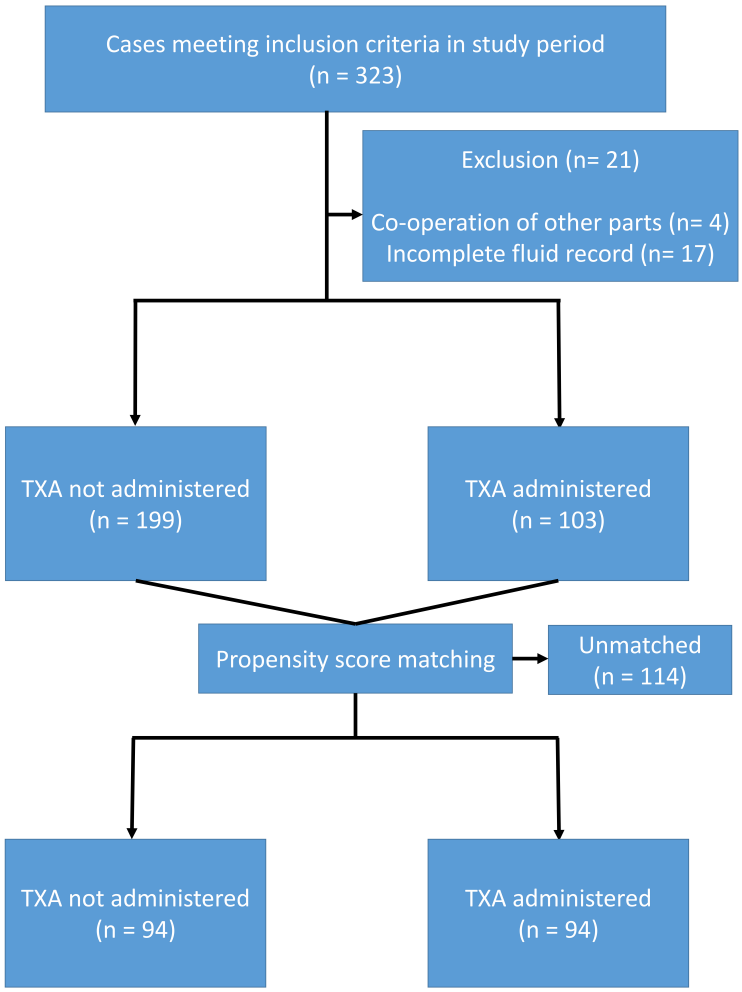

FIGURE 1. Study flow diagram of patient selection. TXA, Tranexamic acid.

TABLE 1. Baseline demographic and clinical characteristics of patients.

Characteristics	Control group (n = 199)	TXA group (n = 103)
Age, yr	65.2 ± 12.2	67.3 ± 12.0
Female, n (%)	83 (41.7)	43 (41.7)
Weight, kg	64.2 ± 12.0	64.1 ± 11.7
Height, cm	161.7 ± 10.3	160.7 ± 9.6
BMI, kg/m^2	24.5 ± 3.5	24.7 ± 3.4
Preoperative Hb, g/dL	12.8 ± 1.9	13.2 ± 1.8
Anesthesia duration, min***	305.1 ± 56.4	361.9 ± 60.0
ASA PS classification, n (%)		
I	4 (2.0)	0
II	76 (38.2)	34 (33.0)
III	112 (56.3)	61 (59.2)
IV	7 (3.5)	8 (7.8)
Extent of spine fixation, n (%)		
Short fusion (less than three levels)	69 (34.7)	36 (35.0)
Long fusion (three or more levels)	130 (65.3)	67 (65.0)

****$p < 0.001$. Otherwise no statistically significant differences between the two groups.*
ASA PS classification, American Society of Anesthesiologists physical status classification; BMI, body mass index; TXA, tranexamic acid; Hb, hemoglobin.

TABLE 2. Baseline demographic and clinical characteristics of patients after propensity score matching.

Characteristics	Control (n = 94)	TXA (n = 94)	SMD
Age, yr	66.8 ± 10.9	66.7 ± 12.2	0.001
Female, n (%)	37 (39.4)	39 (41.5)	NA
Weight, kg	64.8 ± 12.9	64.1 ± 11.7	0.054
Height, cm	161.9 ± 10.9	160.6 ± 9.7	0.121
BMI, kg/m^2	24.7 ± 3.8	24.8 ± 3.4	0.026
Preoperative Hb, g/dL	12.9 ± 1.8	13.2 ± 1.8	0.164
Anesthesia duration, min	344.6 ± 48.4	353.0 ± 52.5	0.165
ASA PS classification, n (%)			
I or II	31 (33.0)	33 (35.1)	0.045
III or IV	63 (67.0)	61 (64.9)	
Extent of spine fixation, n (%)			
Short fusion (less than three levels)	29 (30.9)	34 (36.2)	0.113
Long fusion (three or more levels)	65 (69.1)	60 (63.8)	

ASA PS classification, American Society of Anesthesiologists physical status classification; BMI, body mass index; TXA, tranexamic acid; Hb, hemoglobin; SMD, standardized mean difference; NA, not applicable.

TABLE 3. Perioperative crystalloid administration, including total intake, intake adjusted for body weight, and anesthesia duration in the matched sample.

Parameters	Control (n = 94)	TXA (n = 94)	Mean difference (95% CI)	Cohen's *d* (95% CI)	*p*-value
Crystalloid input, mL***	3082.3 ± 1240.6	2326.6 ± 571.6	755.7 (477.0–1034.5)	0.73 (0.46–1.00)	<0.001
Adjusted by anesthetic time, mL/h***	535.1 ± 190.4	397.4 ± 87.6	137.8 (95.0–180.6)	0.84 (0.58–1.11)	<0.001
Adjusted by body weight, mL/kg***	49.8 ± 22.0	37.1 ± 9.9	12.7 (7.7–17.7)	0.70 (0.43–0.98)	<0.001
Adjusted by (body weight × time)***	8.7 ± 3.6	6.4 ± 1.7	2.3 (1.5–3.1)	0.76 (0.49–1.03)	<0.001
Crystalloid type, mL					
Plasmalyte***	2486.4 ± 1078.4	2018.4 ± 638.4	468.0 (212.6–723.4)	0.51 (0.23–0.79)	<0.001
Normal saline***	596.0 ± 651.0	308.2 ± 370.2	287.8 (135.1–440.4)	0.53 (0.25–0.80)	<0.001
Colloid-administered patients, n (%)†	10 (10.6)	6 (6.4)			0.434
Estimated blood loss, mL***	931.1 ± 700.0	531.8 ± 376.4	399.3 (223.6–575.1)	0.66 (0.36–0.96)	<0.001
Urine output adjusted by anesthetic time, mL/h	115.2 ± 78.5	125.3 ± 63.9	10.1 (−30.7–10.5)		0.336
Hb POD #1, g/dL	9.91 ± 1.59	10.64 ± 1.84			
Hb change from baseline‡	2.97 ± 1.51	2.59 ± 1.42	0.38 (−0.05–0.81)		0.083
Hb POD #2, g/dL	9.62 ± 1.43	10.22 ± 1.72			
Hb change from baseline‡	3.26 ± 1.75	3.02 ± 1.57	0.24 (−0.24–0.73)		0.321

****$p < 0.001$. †Examined with Fisher's exact test. ‡Bonferroni correction was done. POD, postoperative day; Hb, hemoglobin; CI, confidence interval; TXA, Tranexamic acid.*

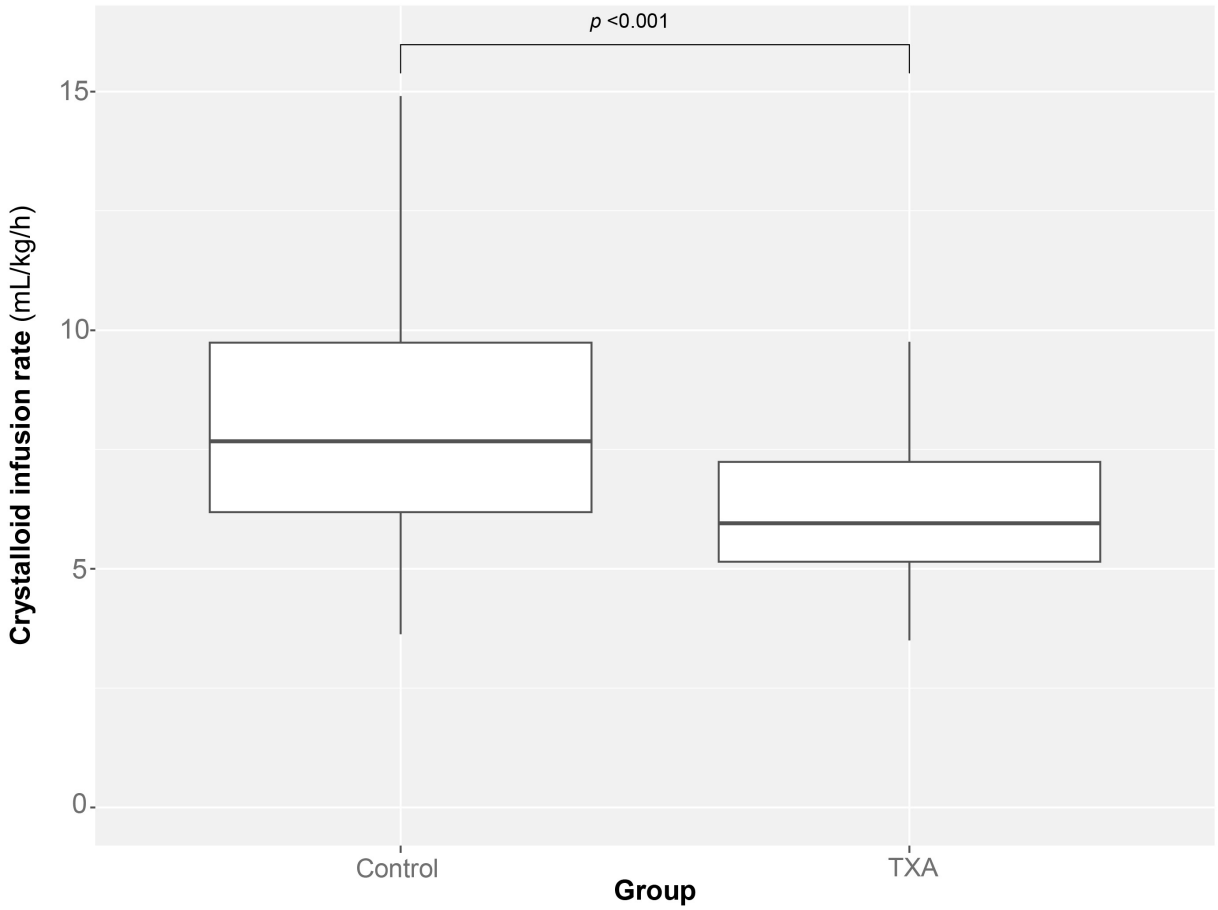

FIGURE 2. Crystalloid infusion rate adjusted by body weight and anesthetic time for each group. *T*-test was used in statistical comparison. TXA, Tranexamic acid.

TABLE 4. Secondary outcomes by matched group.

Postoperative complications	Control (n = 94)	TXA (n = 94)	*p* value
Intraoperative transfusion, n (%)***	28 (29.7)	6 (6.8)	<0.001
30-day complication, n (%)†	17 (18.1)	21 (22.3)	NS
Thromboembolic event	1 (1.1)	0	NS
Pneumonia	3 (3.2)	2 (2.1)	NS
AKI	1 (1.1)	2 (2.1)	NS
Readmission, n (%)	5 (5.3)	6 (6.4)	NS
In-hospital mortality, n (%)	2 (2.1)	0	NS

****p < 0.001. †Examined with χ^2 test. The other complications were compared with Fisher's exact test. AKI, acute kidney injury; NS, not significant; TXA, Tranexamic acid.*

TABLE 5. Result of multivariate logistic regression analysis for postoperative complications.

Variable	Odds ratio (95% CI)	*p* value	VIF
Intraoperative crystalloid input ≥3739 mL*	3.37 (1.07–10.65)	0.039	1.102
Age, yr*	1.05 (1.01–1.09)	0.015	1.010
Anesthesia time, min	1.00 (0.99–1.00)	0.465	1.082
Preoperative anemia of Hb <10g/dL	2.69 (0.59–12.39)	0.203	1.033
Female (versus male)	0.87 (0.40–1.88)	0.717	1.073

**p < 0.05. Hb, hemoglobin; CI, confidence interval; VIF, variance inflation factor.*

[16]. This delay in fluid excretion is more severe with rapid crystalloid infusions. Hahn *et al.* [17] conducted a kinetic analysis in which less edema was followed by a slower infusion of crystalloid fluid. When rapidly infused, crystalloid fluid is distributed into the perivascular tissue and interstitial space. Circulatory volume is expected to be replaced most efficiently when crystalloid fluids are infused slowly and steadily.

Excessive crystalloids lead to delayed postoperative recovery in surgical patients due to gastrointestinal edema. Shim *et al.* [18] reported that an increased volume of crystalloid fluid was associated with postoperative ileus. A large amount of intraoperative fluid, >6000 mL, has been reported to be associated with a higher incidence of infectious complications and postoperative intervention in patients undergoing pancreaticoduodenectomy [19]. This threshold of a large intraoperative fluid could be 3800 mL or less, considering the result of the current study and other study [20]. Selection of intravenous crystalloid fluid is also important since excessive normal saline could be associated with higher mortality and kidney injury [21]. Increase renal complication risk with normal saline appears to be higher chloride concentration, followed by reduced renal perfusion and glomerular filtration [22].

TXA administration can be considered in various surgical populations because of its low-risk profile. Prophylactic administration of the antifibrinolytic agent is not associated with thromboembolic risk and is safe for the surgical population. Physicians could be reluctant to administrate TXA due to thromboembolic risk. However, recent well-designed trials and meta-analysis report no increased risk of thromboembolic events with TXA [13, 23]. This was similar to our study result and authors suggest TXA could be a safe pharmacologic measure to reduce crystalloid administration in surgical patients at risk of fluid overload.

Intravenous crystalloid infusion avoiding fluid overload could also be beneficial for postoperative recovery. A meta-analysis including major gastrointestinal surgery reported lower complication and shorter length of stay with restrictive fluid therapy [24]. Voldby and colleagues reported that fluid balance less than 2 L was associated with decreased risk of cardiovascular complication and ERAS society recommend the same fluid balance [20].

The findings of this study are limited by its retrospective design; a causal relationship cannot be established because patients were not randomized and PPV data were not consistently available. However, it is noteworthy that the difference in intraoperative crystalloid administration between the two groups was substantial. The sample size was too small to compare the incidence of overall 30-day complications and mortality between the two groups and adequately powered studies are required to elucidate the benefits and risks of TXA and the associated reduction in intravenous fluid administration during spine surgery.

5. Conclusions

TXA administration in patients undergoing posterior spine fixation was associated with a reduced intraoperative crystalloid requirement. Further adequately powered randomized studies are warranted to determine whether this reduction in crystalloid administration translates into improved clinical outcomes, such as lower mortality or enhanced recovery.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

GP and SWS—designed the research study. GP, BK and SWS—performed the research; wrote the manuscript. BK, SAS and SWS—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR324035, approval date: 04 June 2024). The requirement for informed consent was waived by Institutional Review Board of Wonju Severance Christian Hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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