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Application of Topical Tranexamic Acid Reduces Postoperative Blood Loss after Posterior Spinal Fusion with Instrumentation in Patients with Adolescent Idiopathic Scoliosis

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Purpose: There is limited literature regarding the topical use of tranexamic acid (TXA) to control postoperative bleeding during spinal deformity correction and fusion procedures, which often require blood transfusions. This study aimed to evaluate the effect of topical TXA on postoperative blood loss in patients undergoing deformity correction and posterior spinal fusion (PSF) surgeries.
Methods: A retrospective study was conducted between January 2011 and April 2017 in 51 patients with adolescent idiopathic scoliosis who underwent long-segment PSF with hybrid thoracic-hook pedicle screw instrumentation or pedicle-screw-alone constructs. Twenty-five patients were assigned to receive topical TXA (1 g/20 mL), and the drain was clamped for 2 h. Twenty-six patients in the control group were treated with antifibrinolytic agents.
Results: Median drainage blood loss, median day of drain removal, and median postoperative hospitalization were significantly lower in the topical TXA group (all p <0.05). The postoperative packed red cell transfusion rate was significantly lower in the topical TXA group than that in the control group (15 of 25, 60% vs. 23 of 26, 88.5%; p=0.02; risk ratio, 0.68; 95% confidence interval, 0.48–0.96).
Conclusions: The use of topically administered 1 g TXA in AIS patients undergoing instrumented PSF effectively reduced postoperative transfusion requirements, decreased the total amount of drainage blood loss, reduced the time till drain removal, and shortened the length of postoperative hospitalization.

Keywords: Tranexamic acid, postoperative hemorrhage, adolescent idiopathic scoliosis, spinal fusion, hybrid instrumentation, pedicle screw instrumentation

Surgery for scoliosis is often associated with substantial blood loss and potentially harmful adverse effects, especially in children and adolescents. Infusion of intravenous fluids for blood replacement due to massive bleeding can lead to hypothermia and hemodilution, diluting coagulation factors and ultimately exacerbating surgical bleeding[1]. Allogeneic blood transfusions are associated with the risk of infection from the donor and microbial components introduced during blood processing, allergic reactions, volume overload, and immunosuppression[2,3]. Careful dis-

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section with meticulous hemostasis is essential to reduce perioperative bleeding, and medical agents to inhibit the fibrinolytic system, such as tranexamic acid (TXA), have been proven to minimize blood loss in various types of surgeries[4-7].

Although the incidence of venous thromboembolism (VTE) is relatively low in spinal surgeries[8-11], surgeons should be concerned that the administration of intravenous antifibrinolytic drugs to reduce bleeding may further increase the risk of thrombotic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism)[5,12]. In addition, topically applied TXA would be an ideal and safe route to locally inhibit fibrinolytic activity compared with the intravenous route[13]. Saline-based irrigation with topical TXA has been used to offer the same efficacy and with less systemic absorption, thus theoretically lowering the risk of VTE complications[14,15]. However, these studies used small doses of topical TXA for one- or two-level lumbar procedures.

Clinical trials on the administration of TXA have evaluated its effect on decreasing perioperative blood loss and reducing transfusion rates in children undergoing surgical correction for scoliosis[1,16], which are used intravenously, and there is limited data regarding the safety of intravenous TXA. Moreover, there is limited literature regarding the topical use of TXA in scoliosis surgery, and a lack of data on the use of different application techniques. Therefore, this study aimed to evaluate the efficacy of the topical application of TXA via a drain tube in reducing blood loss and transfusion requirements in AIS patients undergoing deformity correction and posterior spinal fusion (PSF) surgery.

MATERIALS AND METHODS

All AIS patients who required operative intervention and were admitted from January 2011 to April 2017 were retrospectively evaluated after obtaining approval from the Institutional Review Board of our institution (certificate number 063/2017). AIS patients aged 11–20 years undergoing deformity correction and instrumented PSF and were followed up by a spine physician for at least three months were included in the study. Exclusion criteria were a history of thromboembolism, coagulopathy, TXA drug allergy, evidence of current use of aspirin or nonsteroidal anti-inflammatory drugs for any indication, American Society of Anesthesiologists Physical Status class IV–V, and absence of data on the evaluation criteria.

Long-segment deformity correction and PSF with hybrid thoracic-hook pedicle screw or pedicle-screw-alone construct were performed with an interval pedicle screw placement technique using pedicle screw fixation (Global Standard Screw system; GS Medical Co., Ltd., Geumcheon-gu, Seoul, Korea). The corrected spine was fused using an autogenous local bone graft obtained from spinous processes. The surgery was performed by the first author (S.J.), primary surgeon, and assistant surgeon (W.S.). The patients were classified into two groups according to the date that topical use of TXA was implemented for spinal surgery in the author's department. The control group included 26 patients who underwent surgery with non-clamping drain and without antifibrinolytic agents between 2011 and 2013 before topical TXA was used in our institution. The topical TXA group included 25 patients who underwent surgery in 2014 and 2017 and received TXA (TRANEX; WINDLAS Biotech Ltd., Dehradun, Uttarakhand, India) at the end of the operation, which was performed in the same manner as previously. A solution containing 1 g of TXA (250 mg/5 mL, 20 mL total volume) was injected into the posterior surface of the decorticated laminae via the drain tube (Redon-Flasche, OP®; Pfm Medical Mepro GmbH, Am Söterberg, Nonnweiler-Otzenhausen, Germany) after watertight closure of the spinal sheath to prevent leakage. The drain bottle was then connected to the drain tube and clamped for 2 h. The drain was removed four days after surgery or when the drainage output was ≤ 50 mL over 24 h. In the hospital, patients in the topical TXA group were examined daily for VTE symptoms and signs. If any patient had clinical VTE, diagnostic Doppler ultrasound examination of both legs and computed tomographic pulmonary angiography were performed to detect deep vein thrombosis and acute pulmonary embolism. Adverse events related to

usage and any VTE three months after surgery were recorded at every clinic visit. Baseline levels of hemoglobin, hematocrit, platelet count, prothrombin time, and active partial thromboplastin time were measured at the initial assessment or at least a week before the procedure and 2 h after the procedure. Postoperatively, the patients were evaluated for blood loss by the drainage volume collected and hemoglobin and hematocrit values at 24, 48, and 72 h. The transfusion guidelines were based on the recommendation of the Thai Society of Hematology and were consistent with the author's institutional protocol[17]. The criteria for blood transfusion were hemoglobin less than 8 g/dL or if the patient developed symptoms of anemia with hemoglobin less than 10 g/dL.

Statistical analysis

The sample size calculation for this study was based on a pilot study in our institution, where the mean drainage blood loss for AIS patients with deformity correction and PSF was 880 mL (standard deviation [SD] = 333 mL). Hence, the total sample size required to demonstrate a 30% reduction in perioperative blood loss in the treatment group was 25 patients, assuming a type I error of 0.05 and a statistical power of 0.8.

Continuous variables with normally distributed data were reported as mean ± standard deviations, and the independent samples t-test was used to compare differences between the mean values. Other continuous data were summarized as medians and interquartile range (IQR) for variables with a non-normal distribution and compared using the nonparametric Mann-Whitney U test. Categorical data are presented as percentages. Statistical analysis was performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, USA). Statistical significance was set <0.05.

RESULTS

The 51 patients with AIS included 13 (25.5%) males and 38 (74.5%) females with a median age of 16 (IQR 14–18) years. The baseline characteristics did not differ significantly between the two treatment groups (Table 1).

A comparison analysis of perioperative parameters between the topical TXA group and the control group demonstrated no significant difference in the level of spinal fusion, operative time, intraoperative fluid volume, intraoperative blood loss, and visual analog scale (VAS) pain scores as measured preoperatively, 24 h after surgery, 48 h after surgery, and at the time of hospital discharge (Table 2).

The median total drainage volume was significantly lower in the topical TXA group than that in the control group (540 mL, IQR 395–820 vs. 880 mL, IQR 730–1160; p=0.001). The median day of drain removal in the topical TXA group was 2.7 days (IQR 2.3–3) compared to 3.3 days (IQR 2.7–3.7) in the control group. The difference between the two groups was statistically significant (p=0.001).

The transfusion rates among the topical TXA and control groups did not show statistical differences intraoperatively (44% vs. 61.5%; p=0.21). Postoperatively, the percentage of patients who received a packed red cell (PRC) transfusion in the topical TXA group was significantly lower than that in the control group (60% vs. 88.5%; p=0.02; relative risk 0.68; 95% confidence interval 0.48–0.96). A comparison between the two groups regarding the percentage of patients who received PRC transfusions during the perioperative period is shown in (Fig. 1).

The hemoglobin level demonstrated no significant difference between the preoperative and postoperative values at 2 h. However, the hemoglobin levels at 24 and 28 h postoperatively were significantly higher in the topical TXA group (p=0.03) (Fig. 2). A significant difference in the median postoperative hospitalization was observed between the two operative groups (6 days, IQR 5.5–8 vs. 8 days, IQR 7–12.3; p=0.003). During the 12-week follow-up period, none of the patients experienced any complications related to topical TXA. The clinical outcomes observed in both groups are shown in Table 2.

Table 1 Baseline characteristics of the 51 patients.

Variable	Topical TXA group (n = 25)	Control group (n = 26)	p-value
Age (years)	16 (14.5-17.5)	15 (12.8-18)	0.38
Sex			0.38
Male	5 (20%)	8 (30.8%)	
Female	20 (80%)	18 (69.2%)	
Bodyweight (kg)	42 (36.5-46)	44.5 (34.5-50.7)	0.43
Height (cm)	155 (148.5-164.5)	158.5 (149.3-164.3)	0.79
BMI (kg/m^2)	17 ± 1.9	18.3 ± 3.9	0.14
Lenke classification			0.33
1	8 (32%)	10 (38.5%)	
2	11 (44%)	7 (26.9%)	
3	0 (0%)	3 (11.5%)	
4	4 (16%)	2 (7.7%)	
5	1 (4%)	1 (3.9%)	
6	1 (4%)	3 (11.5%)	
No. of structural curve			0.64
1	9 (36%)	11 (42.3%)	
2	12 (48%)	13 (50%)	
3	4 (16%)	2 (7.7%)	
Preoperative curve (degree)			
Proximal thoracic	26.7 ± 13.1	25.7 ± 9.2	0.76
Main thoracic	62.9 ± 15.6	58.9 ± 12.1	0.32
Thoracolumbar/lumbar	43.2 ± 19.8	39 ± 13	0.38
Major curve Cobb angle	65 ± 15.2	61.2 ± 11	0.30
Bending (degree)			
Proximal thoracic	20 ± 10.4	18.7 ± 7.7	0.59
Main thoracic	35.6 ± 10.7	32.5 ± 6.8	0.23
Thoracolumbar/lumbar	18.2 ± 10.5	17 ± 9.4	0.67
Major curve Cobb angle	35.2 ± 10.5	32.7 ± 6.7	0.31
Flexibility rate (%) (major curve)	45.9 ± 8.2	46.5 ± 5.8	0.78
Risser	4 (2-4.5)	3.5 (2-4)	0.49
Lumbar lordosis (degree)	38.8 ± 9.8	40.6 ± 8.1	0.47
Thoracic kyphosis (degree)	22.8 ± 12.2	21.3 ± 7.9	0.59
Hemoglobin (g/dL)			
Preoperative	11.8 (11.4-12.7)	12 (11.7-13)	0.36

Values are presented as median (interquartile range), number (%), or mean ± standard deviation

Table 2 Patient outcomes.

Variable	Topical TXA group (n = 25)	Control group (n = 26)	p-value
Level of spinal fusion	13 (9.5-13.5)	12 (9-13)	0.43
No. of anchor (screw and/or hook)	15 (13.5-18)	14 (12-16)	0.10
Screw density	0.7 ± 0.1	0.6 ± 0.1	0.19
Type			0.000*
Interval+Apex	23 (92%)	3 (11.5%)	
Interval	0 (0%)	15 (57.7%)	
Hybrid	2 (8%)	8 (30.8%)	
Postoperative curve (degree)			
Proximal thoracic	11.3 ± 7.5	13.7 ± 6.5	0.23
Main thoracic	22.9 ± 12.8	26 ± 8	0.31
Thoracolumbar/lumbar	14 ± 8.7	16.1 ± 6.7	0.33
Major curve Cobb angle	22.5 ± 13.2	26.2 ± 8	0.23
Correction rate (%) (major curve)	67.1 ± 13.8	57.7 ± 8.3	0.005*
Correction index (major curve)	1.5 ± 0.2	1.3 ± 0.2	0.001*
Lumbar lordosis (degree)	33.5 ± 4.9	36.5 ± 6.8	0.07
Thoracic kyphosis (degree)	18.4 ± 8.2	20 ± 5.7	0.42
Operative time (min)	220.2 ± 67.7	212.7 ± 56.6	0.67
Intraoperative fluid volume (mL)	3052.8 ± 666.5	3346.2 ± 1102.2	0.26
Intraoperative blood loss (mL)	500 (350-850)	500 (400-1000)	0.64
Drainage blood loss (mL)	540 (395-820)	880 (730-1160)	0.001*
24 h drainage blood loss	450 (300-585)	585 (485-830)	0.009*
24-48 h drainage blood loss	110 (60-185)	150 (117.5-255)	0.013*
>48 h drainage blood loss	20 (0-65)	65 (30-185)	0.003*
Time of drain removal (days)	2.7 (2.3-3)	3.3 (2.7-3.7)	0.001*
Postoperative hospitalization (days)	6 (5.5-8)	8 (7-12.3)	0.003*
Length of stay in the hospital (days)	10 (8-12)	12 (9-19.3)	0.04*
VAS			
VAS at 24 h preoperatively	1 (0-2)	1 (0-1.3)	0.51
VAS at 24 h postoperatively	8 (6-10)	9 (6.8-10)	0.29
VAS at 48 h postoperatively	7 (5-8)	6 (4.8-7.3)	0.23
VAS at hospital discharge	2 (1-2)	2 (1-2)	0.51
Packed red cells transfusion			
Intraoperatively (No/Yes)	14/11	10/16	0.21
Postoperatively (No/Yes)	10/15	3/23	0.02*
Hemoglobin (g/dL)			
2 h postoperatively	11 (10-11.8)	11.5 (10.8-12)	0.13
24 h postoperatively	11 (9.8-11.5)	9.8 (9.3-11)	0.03*
48 h postoperatively	9.8 (9.5-11.4)	9.2 (8.6-9.6)	0.03*

Values are presented as median (interquartile range), mean ± standard deviation, or number (%)

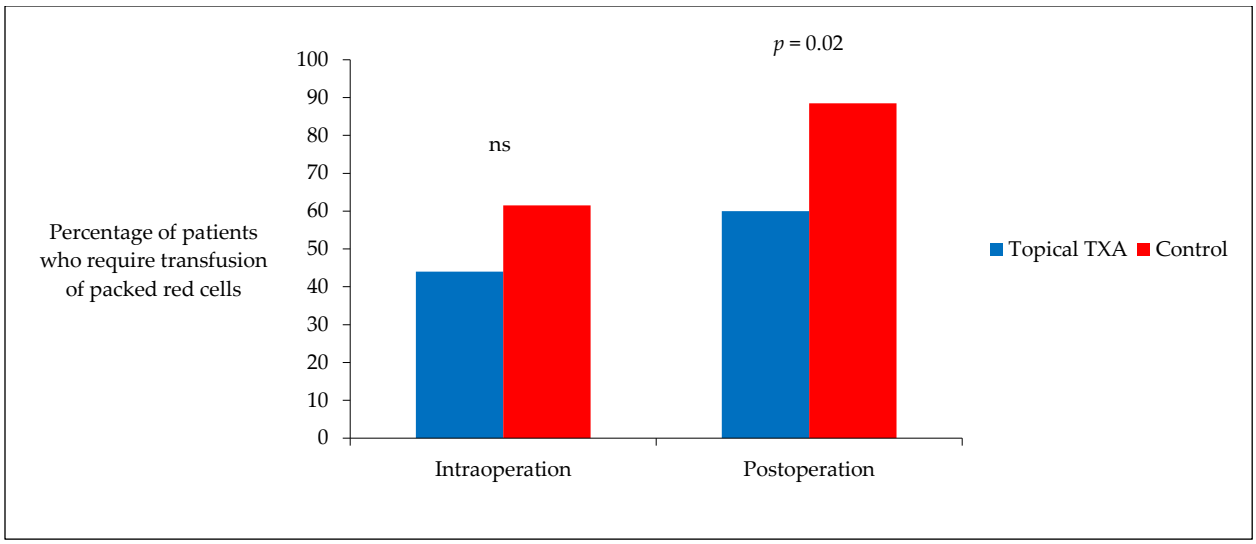

Fig. 1. Comparison of the two groups regarding the rates of packed red cells transfusion.

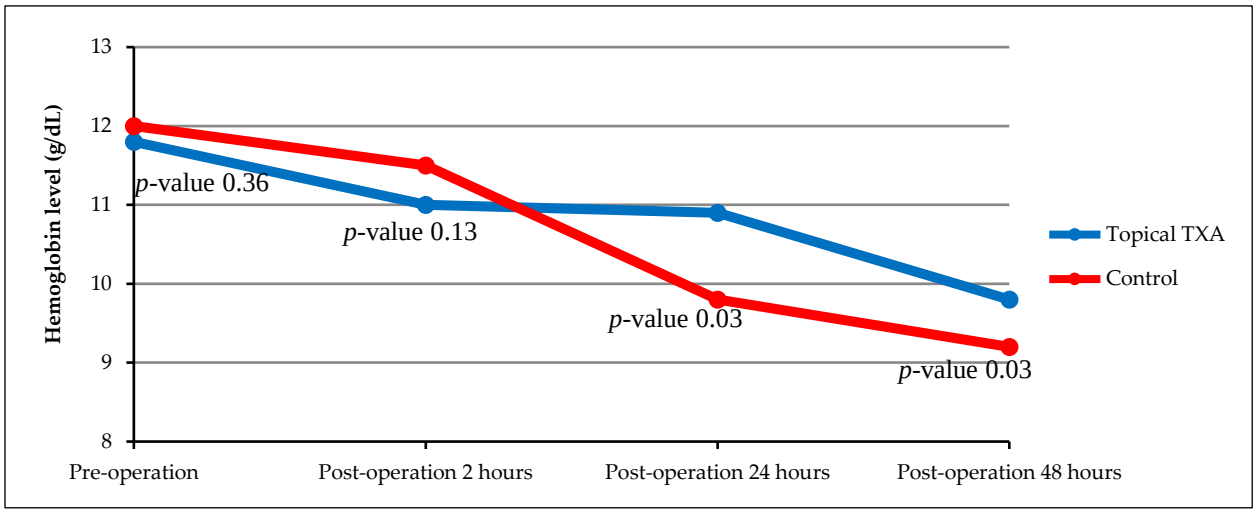

Fig. 2. Comparison of the hemoglobin levels between the two groups.

DISCUSSION

Substantial bleeding during the surgical correction of scoliosis can lead to severe complications. There are many methods for decreasing and controlling blood loss, including drugs that modify the coagulation cascade, such as TXA, an effective systemic therapy to prevent postoperative bleeding [15]. In addition, numerous spinal surgery studies have shown that intravenous TXA significantly decreases perioperative blood loss and transfusion rates[1,4-6,12,13,16,18]. However, the available data were too limited to reach reliable conclusions regarding the safety of the intravenous use of TXA. Myocardial infarction and systemic VTE complications are rare but potentially life-threatening events in surgical patients[5,12,13].

Topical application to bleeding surfaces during surgery may be a safer and more targeted drug delivery strategy at the site of action. Topical TXA appears to have fewer systemic adverse effects and at least equal benefits in minimizing blood loss compared to the intravenous route of administration[19,20]. Few studies have been published regarding the efficacy of topical TXA in reducing bleeding

and transfusions in spinal surgery. Of the two studies contributing data to the author's review, only saline-based irrigation with relatively small doses of topical TXA have been used to reduce postoperative bleeding in one- or two-level lumbar procedures[14,15]. Locally applied TXA has dose-response properties comparable to those of systemic TXA, but a high dose of 3–5 g is associated with a considerable increase in the risk of VTE incidence, convulsive seizures, and refractory ventricular fibrillation[21,22]. Concerns regarding safety led to research using a moderate dose of topical TXA. However, the use of a 1 g dose was proven to be sufficient for long-segment PSF in patients with thoracolumbar fracture[23] and long-segment deformity correction and PSF procedures, as demonstrated by the results of this study.

The application of topical TXA in orthopedic surgery has been investigated using various techniques, including direct washing or injection into the surgical field with or without drain clamping[4,7,13,19,23,24]. According to the pharmacodynamic and pharmacokinetic properties of TXA, administration with maximum plasma concentrations was obtained at 30 min, and the half-life was approximately 2 h. Therefore, an interval of 2 h for drain clamping in the authors' protocol was equal to the TXA half-life value[25]. Furthermore, the clamping period was not long enough to harm patients with massive clot formation, which may cause severe postoperative pain and wound complications.

There were several limitations to this study, including its retrospective nature, small sample size, and short follow-up period. Asymptomatic VTE may not have been detected because the institution had limited resources. For example, lower-extremity Doppler ultrasound or pulmonary angiography was not routinely performed to detect occult VTE complications in all patients. Another limitation was the lack of a placebo-control group with drainage clamping procedures to support the effect of topical TXA, and this application technique may reduce only postoperative blood loss, and not intraoperative blood loss. Despite these limitations, the topical route of TXA administration successfully achieved short-term outcomes, reducing the drainage volume and decreasing the rate of postoperative PRC transfusion.

CONCLUSIONS

Topically administered 1 g TXA can significantly reduce the postoperative rate of PRC transfusion in deformity correction and PSF surgery in patients with AIS. Furthermore, the topical application of TXA directly to the surgical site decreases postoperative bleeding, as determined by examining the total drainage volume, which can effectively reduce the time for drain removal and shorten the length of postoperative hospital stay with fewer complications.

ETHICAL CONSIDERATIONS

Ethics approval was obtained from the relevant Institutional Review Board: IRB No. 063/2017.

CONFLICTS OF INTEREST

The authors (s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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