Original Article

Topical Tranexamic Acid Reduces Postoperative Blood Loss in Posterior Spinal Fusion with Instrumentation: A Retrospective Clinical Study of Patients with Thoracolumbar Spinal Injury

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Background: There is limited literature regarding the topical use of tranexamic acid [TXA] to control postoperative bleeding in posterior spinal fusion [PSF] procedures, operations which often required blood transfusions.

Objective: To evaluate the effect of topically applied TXA on postoperative blood loss in patients undergoing conventional open PSF surgeries.

Materials and Methods: A retrospective study was conducted on a total of 73 patients who had spinal injuries of the thoracolumbar vertebrae and who had undergone long-segment instrumented PSF without decompression between January 2011 and April 2015. Thirty-five patients were assigned to be given topical TXA (1 g/20 mL) and then their drain was clamped for 2 hours. Thirty-eight patients in the control group were treated using similar procedures but with continuous drainage and without antifibrinolytic agents.

Results: The rate of postoperative packed red cells [PRC] transfusion was significantly lower in the topical TXA group than in the control group (11.4% vs. 44.7%; $p = 0.002$; relative risk, 0.26; 95% confidence interval, 0.1 to 0.69). Median drainage blood loss, median days to drain removal and median postoperative hospitalization were significantly less in the topical TXA group ($p<0.05$). Multinomial logistic regression analysis indicated that the use of topical TXA was a significant factor in reducing the rate of postoperative PRC transfusion ($p = 0.004$).

Conclusion: The use of topically administered 1 g TXA in thoracolumbar spinal trauma cases undergoing PSF with long-segment instrumentation reduces postoperative transfusion requirements, decreases the total amount of drainage blood loss, lessen the time to drain removal and shortens the period of postoperative hospitalization.

Keywords: Tranexamic acid, Postoperative hemorrhage, Spinal fusion, Pedicle screws, Spinal injuries, Thoracic vertebrae, Lumbar vertebrae

J Med Assoc Thai 2018; 101 [Suppl. 3]: S15-S22
Full text. e-Journal: http://www.jmatonline.com

Spinal injuries constitute a significant proportion of skeletal injuries, and nearly 80% of spinal fractures occur in the thoracic or lumbar regions[1]. About half of these are unstable and can result in significant disability and deformity[2]. Current practice is that patients with a Thoracolumbar Injury Classification and Severity [TLICS] score of 5 or greater should be considered for operative management[3]. Conventional open surgical techniques are associated with higher rates of morbidity due to greater blood loss[4]. Acute excessive bleeding can lead to anemia which usually requires replacement by homologous blood transfusion. Additionally, research has shown that such transfusions are associated with a risk of

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How to cite this article: Sudprasert W, Tanaviriyachai T, Choovongkomol K, Jongkittanakul S, Piyapromdee U. Topical Tranexamic Acid Reduces Postoperative Blood Loss in Posterior Spinal Fusion with Instrumentation: A Retrospective Clinical Study of Patients with Thoracolumbar Spinal Injury. J Med Assoc Thai 2018;101;Suppl.3:

microbial infection, viral transmission and fluid overload[5]. Careful dissection with meticulous hemostasis is essential to reduce perioperative bleeding; the utilization of pharmaceutical agents which inhibit fibrinolytic system activation such as tranexamic acid [TXA] have been demonstrated to minimize blood loss in various types of surgery[6-9].

Although the incidence of venous thrombo-embolism [VTE] is low[10-13], surgeons should be aware to the fact that receiving systemic antifibrinolytic drugs to reduce bleeding may further increase the risk of thrombotic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism)[14]. Wong et al reported an asymptomatic non-Q myocardial infarct related to intravenous administration of TXA in adult patients having posterior thoracic/lumbar instrumented spinal fusion surgery[7]. Topically applied TXA would be an ideal route and a more safer way to locally inhibit fibrinolytic activity than the intravenous route[15]. Saline-based irrigation of topical TXA has been used to offers the same efficacy but with less systemic absorption, thus theoretical advantages include reducing the risk of VTE complications[16,17].

The present study was conducted as a contribution to the limited literature regarding the topical use of TXA in spine surgery and the lack of data on different application techniques. The primary objective of the study was to evaluate the efficacy of topically applied TXA via drain tube combined with subsequent clamping of the drain for 2 hours in patients with thoracolumbar spinal injuries undergoing posterior spinal fusion [PSF] with instrumentation.

Materials and Methods

All spinal trauma patients requiring operative intervention admitted to Maharat Nakhon Ratchasima Hospital from January 2011 through April 2015 were evaluated retrospectively after obtaining appropriate the approval of the hospital's institutional review board for the study. Patients were included if they were aged 18 to 70 years, were undergoing PSF with instrumentation of 4 to 6 segments for unstable thoracolumbar spinal injuries (TLICS score of 5 or greater), and had no neurological deficit. Exclusion criteria were a history of coagulopathy, American Society of Anesthesiologists Physical Status class IV to V, wedging of the edge of the displaced laminar fracture on computed tomography [CT] axial section that might be associated with higher rates of dural tears[18], and absence of evaluation criteria data.

In the operations, long-segment posterior stabilization was performed using a pedicle screw fixation (Global Standard Screw system, GS Medical Co., Ltd., Geumcheon-gu, Seoul, Korea) without decompression of neural elements. The injured spine was fused using autogenous local bone graft obtained from the spinous processes (Figure 1). The surgery was performed by the senior author (WS). The patients were classified into to 2 groups based on admission date. Thirty-eight patients in the control group had

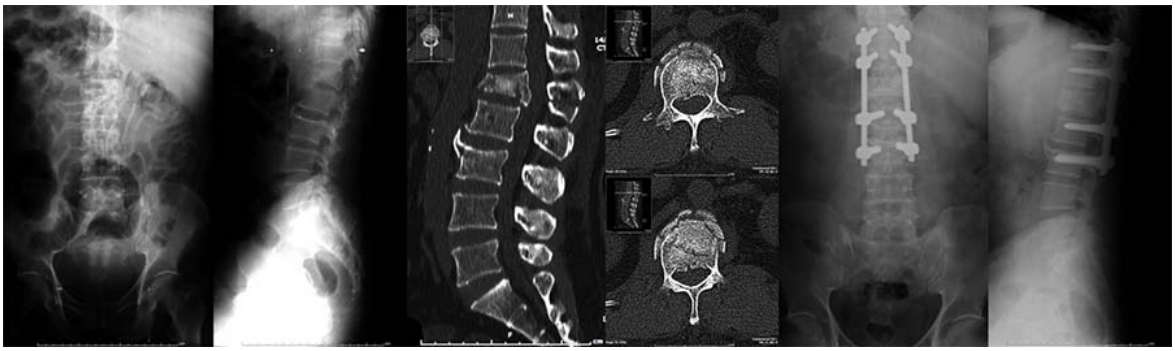

Figure 1. A 58-year-old male fell about 3 meters from a tree, complained of severe back pain at the thoracolumbar junction. On admission, the patient was neurologically intact. Standard anteroposterior and lateral radiographs showed a burst fracture of L1. Sagittal computed tomography [CT] reconstruction confirmed the diagnosis of a burst fracture with retropulsion fragment and posterior ligamentous complex involvement. The axial CT scan showed a minor displacement of the vertebral fragment without neural compromise and a non-displaced complete type lamina fracture. The spine was instrumented with pedicle screws at T11-L3. A posterior fusion was added with autologous bone graft from the spinous processes at T12-L2. The postoperative radiographs demonstrated a nearly anatomic reduction of the fracture.

undergone instrumented PSF without using antifibrinolytic agents between 2011 and 2013, the period before use of topical TXA in spinal surgery was implemented by the authors' department. The topical TXA group included 35 patients, operated on in 2014 or 2015, who had received TXA (TRANEX; WINDLAS Biotech Ltd, Dehradun, Uttarakhand, India) at the end of the same instrumented fusion operation. The solution contained 1 g of TXA (250 mg/5 mL, 20 mL total volume) and was injected into the posterior surface of the decorticated laminae via the drain tube (Redon-Drain; Pfm Medical Mepro GmbH, Am Soterberg, Nonnweiler-Otzenhausen, Germany) after closure of the watertight spinal fascia to prevent leakage. The drain bottle was then connected to the drain tube and clamped for 2 hours. The drain was removed not later than five days after the surgical procedure or when the drainage output had been less than 50 mL for the previous 24 hours. A record of adverse events related to the usage and any incidents of VTE that occurred during the first three months following surgery were identified from a chart review in the topical TXA group.

Postoperative blood loss was quantified by measuring the volume of blood in the dressing gauze pack; blood in the pack usually appeared only on the first and second day. Blood volume was assessed using a modified visual estimation method. The categories were faintly, slightly, partially, mostly and completely soaked dressing gauze pack based on amounts of 10, 25, 50, 75 and 100 mL, respectively[19]. In addition, the patients were evaluated by observing drainage volume collected and recording changes in hemoglobin values at intervals of 24, 48 and 72 hours. The criteria for blood transfusion were either hemoglobin less than 8 g/dL or the patient developing symptoms of anemia with hemoglobin less than 10 g/dL. These transfusion guidelines were based on the recommendations of the Thai Society of Hematology and were consistent with authors' institutional protocol[20].

Continuous variables with normally distributed data are reported as mean ± standard deviation, and the independent samples t-test was used to compare differences between mean values. Other continuous data are summarized as medians and interquartile range [IQR] for variables with a non-normal distribution and were compared with the nonparametric Mann-Whitney U test. Categorical data are presented as frequency (percentage); Fisher's exact test was used if at least 25% of the cells had expected values less than five; otherwise, Chi-square tests were used to compare proportions of categorical variables. The postoperative blood transfusion requirements and other clinical parameters were compared between the two groups. Additionally, the association between clinical factors and the need for postoperative blood transfusion were analyzed using multinomial logistic regression models. Statistical analysis was performed using the software program SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

Results

The seventy-three patients with a normal neurological function but with unstable spinal injuries of the thoracic and lumbar vertebrae included 51 males (69.9%) and 22 females (30.1%). Mean age was 40.2±16.8 years. A preoperative CT study was not available for review for 4 patients, all in the control group. Baseline characteristics did not differ significantly between the two treatment groups (Table 1).

Comparative analysis between the topical TXA group and the control group demonstrated no significant difference in the level of instrumentation. There were no statistically significant differences in parameters between the two groups for operative time, intraoperative fluid volume, or intraoperative blood loss. Similarly, there were no statistically significant differences between the groups in postoperative visual analog scale [VAS] pain scores as measured preoperatively, at 24 and 48 hours after surgery, and at time of discharge from the hospital. The median blood loss in dressing gauze was 25 mL (IQR, 10 to 50 mL) in the topical TXA group and 37.5 mL (IQR,10 to 56.3 mL) in the control group, with no significant difference between the groups ($p = 0.13$). However, the median total drainage volume and the total volume of blood loss were significantly lower in the topical TXA group compared to the control group (300, IQR 180 to 390 vs. 490, IQR 327.5 to 715 mL, 320, IQR 190 to 460 vs. 542.5, IQR 345 to 746.3 mL, respectively, both $p<0.001$). The median time of drain removal in the topical TXA group was 2 days after surgery (IQR, 1.7 to 2.7 days) compared to 2.8 days (IQR, 2.3 to 3 days) in the control group; the difference between the two groups was statistically significant ($p = 0.002$). There was no significant difference in time to surgery ($p = 0.19$) between the two groups, while a significant difference in the median postoperative hospitalization was observed between the operative groups (7, IQR 5 to 11 vs. 9.5, IQR 7 to 17.3 days, $p = 0.02$). During the 12-week follow-up period, none of the patients had complications, related either to surgery or to topical TXA therapy.

The clinical outcomes observed in both

Table 1. Baseline characteristics (73 patients)

Variable	Topical TXA group (n = 35)	Control group (n = 38)	*p*-value
Age (years)	40.5±18.1	39.9±15.8	0.87
Sex			0.21
Male	22 (62.9%)	29 (76.3%)	
Female	13 (37.1%)	9 (23.7%)	
Bodyweight (kg)	58 (48 to 64)	60 (54 to 66)	0.09
Height (cm)	160 (155 to 170)	161 (160 to 170)	0.10
BMI (kg/m^2)	21.8±3.7	22.8±2.9	0.24
TLICS score			0.26
5	31 (88.6%)	28 (73.7%)	
6	2 (5.7%)	4 (10.5%)	
7	2 (5.7%)	6 (15.8%)	
Mechanism of injury			0.43
Fall from height	17 (48.6%)	13 (34.2%)	
Motorcycle accident	11 (31.4%)	12 (31.6%)	
Motor vehicle accident	5 (14.3%)	6 (15.8%)	
Stuck by a heavy object	2 (5.7%)	5 (13.2%)	
Pedestrian struck by a car	0 (0%)	2 (5.2%)	
Hemoglobin (g/dL)			
At admission	12.3 (11.1 to 13.4)	12.5 (12 to 13.2)	0.84
Before operation	11.8 (11 to 12.9)	12.1 (11.6 to 12.6)	0.53

Values are presented as mean ± standard deviation, number (%) or median (interquartile range)
BMI = body mass index; TLICS = Thoracolumbar Injury Classification and Severity

groups are shown in Table 2.

The transfusion rates among the topical TXA group and the control group did not show statistically significant differences during the preoperative and intraoperative periods (22.9% vs. 39.5%, $p = 0.13$, 17.1% vs. 7.9%, $p = 0.3$, respectively). In the postoperative period, however, the percentage of patients that received a packed red cells [PRC] transfusion was 11.4% for the topical TXA group, significantly lower than that the 44.7% for the control group ($p = 0.002$; relative risk, 0.26; 95% confidence interval, 0.1 to 0.69).

Factors potentially affecting outcomes were analyzed using the Chi-square test or Fisher's exact test as appropriate. Intraoperative blood loss lower than 300 mL and topical TXA use were associated with reduced postoperative PRC transfusion ($p = 0.01$, $p = 0.002$, respectively). There were no differences in the rate of postoperative PRC transfusions among age groups, sex, levels instrumented, operative time, or intraoperative volume replacement. The association between the reduced of PRC transfusion requirement and the topical use of TXA was analyzed after controlling for age, sex, number of instrumented levels, operative time, intraoperative fluid volume replacement, and estimated blood loss. The results of multinomial logistic regression analysis showed that a significant factor for reduced postoperative PRC transfusion was the use of topical TXA ($p = 0.004$; odds ratio, 0.12; 95% confidence interval, 0.03 to 0.5) (Table 3).

Discussion

The purpose of surgical treatment of thoracic and lumbar vertebral fractures without a neurological deficit is to realign misaligned vertebrae, stabilize the spine with instrumentation, prevent further kyphotic deformity, permit safe mobility, and allow early discharge from hospital[2,3,21]. Pedicle screw fixation using a conventional posterior approach has been shown to be effective in both reduction and stabilization of fractures with a high risk of instability[4]. However conventional open PSF with instrumentation can cause substantial blood loss which may require transfusion[21,22]. Furthermore, correcting postoperative anemia with blood product replacement can lead to increased morbidity and prolonged hospitalization[5]. Adequate hemostasis is essential to minimize significant

Table 2. Outcomes (73 patients)

Variable	Topical TXA group (n = 35)	Control group (n = 38)	*p*-value
Level of instrumentation			0.48
4-level instrumentation	31 (88.6%)	36 (94.7%)	
5-level instrumentation	1 (2.8%)	0 (0%)	
6-level instrumentation	3 (8.6%)	2 (5.3%)	
Operative time (minutes)	100 (85 to 110)	95 (90 to 110)	0.73
Intraoperative fluid volume (mL)	2,118±745.1	2,088.7±883.2	0.88
Intraoperative blood loss (mL)	300 (200 to 400)	300 (250 to 500)	0.06
Intraoperative blood loss			0.14
<300 mL	16 (45.7%)	11 (28.9%)	
≥300 mL	19 (54.3%)	27 (71.1%)	
Postoperative blood loss (mL)			
Dressing gauze blood loss	25 (10 to 50)	37.5 (10 to 56.3)	0.13
Drainage blood loss	300 (180 to 390)	490 (327.5 to 715)	0.00*
Total blood loss	320 (190 to 460)	542.5 (345 to 746.3)	0.00*
Time to drain removal (days)	2 (1.7 to 2.7)	2.8 (2.3 to 3)	0.00*
Time from injury to surgery (days)	5 (3 to 8)	6 (4.8 to 8.5)	0.19
Postoperative hospitalization (days)	7 (5 to 11)	9.5 (7 to 17.3)	0.02
Length of stay in the hospital (days)	13 (9 to 19)	16 (13 to 27.5)	0.01
VAS			
VAS at 24 hours before operation	5 (4 to 7)	4 (3 to 5)	0.18
VAS at 24 hours after operation	8 (7 to 9)	8 (6 to 9)	0.12
VAS at 48 hours after operation	6 (5 to 8)	6 (5 to 7.3)	0.50
VAS at discharge from hospital	2 (1 to 5)	3 (1.8 to 4.3)	0.32

Values are presented as number (%), median (interquartile range) or mean ± standard deviation
VAS = visual analogue scales
* Statistically significant ($p<0.01$)

blood loss perioperatively and additional use of antifibrinolytic medication is an effective systemic therapy to minimize postoperative bleeding[23]. Numerous studies of spinal surgery have shown that the use of intravenous antifibrinolytic agents including TXA significantly decrease perioperative blood loss and reduce transfusion rates[6-8,14,15,23]. Available data were insufficient regarding either the safety of systemic antifibrinolytics or the incidence of myocardial infractions and systemic VTE of intravenous use of TXA. Those complications are rare but they are potentially life-threatening events in surgical patients[7,14,15].

A systematic review of topical TXA use in arthroplasty and cardiac surgery showed encouraging results. Topical application to bleeding surfaces during surgery may be a more targeted and safer drug delivery strategy. Topical TXA appears to have fewer systemic adverse effects and at least equal benefit in minimizing blood loss as compared with the intravenous route of administration[24,25]. Few studies have been published reporting on the effectiveness of topical TXA for reducing bleeding and transfusions in spinal surgery. In the two studies available for review by the authors, only saline-based irrigation with relatively small doses of topical TXA had been used to reduce postoperative bleeding in one- and two-level lumbar procedures[16,17]. Locally applied TXA has dose-response properties comparable to those of systemic TXA, but a high dose of 3 to 5 g has been associated with a considerable increase in the incidence of VTE, convulsive seizures, and refractory ventricular fibrillation[26,27]. Concern about safety led to the authors to undertake research using a moderate dose of topical TXA. The present study demonstrated that the use of a 1 g dose was sufficient to control bleeding in four- to six-level spinal instrumentation procedures.

Postsurgical transfusion may not be necessary for patients treated using a conventional posterior approach with intermediate screws in combination with

Table 3. Comparison of categorized affecting factors and postoperative packed red cells transfusion

Variable	Analysis of individual clinical factors			Analysis of all associated clinical factors*		
	Postoperative PRC transfusion		*p*-value	Odds ratio		*p*-value
	Yes (n = 21) Cases (%)	No (n = 52) Cases (%)		Value	95% confidence interval	
Age			1.00**	1.488	(0.10 to 21.39)	0.77
<65 years	20 (95.2)	48 (92.3)				
≥65 years	1 (4.8)	4 (7.7)				
Sex			0.71***	2.225	(0.58 to 8.58)	0.25
Male	14 (66.7)	37 (71.2)				
Female	7 (33.3)	15 (28.8)				
Level of instrumentation			0.67**	1.744	(0.12 to 25.47)	0.68
≤4 levels	20 (95.2)	47 (90.4)				
>4 levels	1 (4.8)	5 (9.6)				
Operative time			1.00**	1.785	(0.38 to 8.49)	0.47
<120 minutes	17 (81)	42 (80.8)				
≥120 minutes	4 (19)	10 (19.2)				
Intraoperative fluid volume			0.17***	0.432	(0.11 to 1.68)	0.23
<2,000 mL	8 (38.1)	29 (55.8)				
≥2,000 mL	13 (61.9)	23 (44.2)				
Intraoperative blood loss			0.01***	0.258	(0.06 to 1.20)	0.08
<300 mL	3 (14.3)	24 (46.2)				
≥300 mL	18 (85.7)	28 (53.8)				
Group			0.00***,****	0.122	(0.03 to 0.50)	0.00****
Topical TXA group	4 (19)	31 (59.6)				
Control group	17 (81)	21 (40.4)				

Values are presented as number (%)
PRC = packed red cells
* Result of multinomial logistic regression analysis; ** Result of Fisher's exact test; *** Result of Chi-square test; **** Statistically significant ($p<0.01$)

short segmental fixation (3 levels) for thoracolumbar fracture because it results in less tissue damage and a smaller volume of postoperative drainage[4]. Patients with severe thoracolumbar injuries involving the posterior ligamentous complex are candidates for extensive procedures. Traditionally, at least 2 levels above and 2 levels below the injured level (4 to 6 levels total) have been used for fixation of severely unstable 3-column lesions. The posterior open approach with long-segment instrumentation techniques, however, requires longer operative time and more soft tissue dissection resulting in a possibility of greater perioperative blood loss. Grossbach et al suggested that minimally invasive percutaneous pedicle screw fixation might be considered an option in selected patient groups[22]. Minimally invasive surgery, however, is technically challenging and further studies are needed to assess the long-term outcome of non-fusion spinal procedures.

The authors decided to exclude the patients who showed a neurological deficit which required decompressive surgery and neurologically intact patients who were suspected of having dural laceration based on the preoperative CT scans in order to avoid accidental intrathecal spread of topical TXA. Because experimental investigations had shown that topically applied TXA with surgery within or close to the central nervous system causes epileptic seizures in a rat model, caution needs to be taken to prevent direct contact between TXA and neural tissues[28]. Also, theoretically

there might be an additional risk of spinal cord or nerve root compression after decompressive laminectomy due to epidural hematomas (blood clots) resulting from topical treatment with TXA combined with intermittent clamping of the drainage tube.

The application of topical TXA in orthopedic surgery has been investigated using various techniques, including direct wash and injection into the field both with and without drain clamping[6,9,15,24]. According to the pharmacodynamics and pharmacokinetic properties of TXA, administration results in maximum plasma concentrations occurs after 30 minutes and the terminal elimination half-life is about 2 hours. Thus a drain clamping interval of 2 hours is equal to the TXA half-life value[29]. Furthermore, a two-hour period of clamping is not sufficiently long to result in massive clot formation that could cause severe postoperative pain and wound complications.

The main limitations of this study were the retrospective nature of the analysis, the risk of bias, the small sample size, and the short follow-up period. Another limitation was the lack of a placebo-control group with identical drainage clamping procedures. Despite these limitations, the topical route of TXA administration successfully achieved the objectives of reducing the drainage volume and decreasing the rate of postoperative PRC transfusion.

Conclusion

The use of topically administered 1 g TXA can significantly reduce the postoperative rate of PRC transfusion in the PSF surgery with long-segment instrumentation for thoracolumbar spinal trauma cases. Furthermore, topical application of TXA directly to the surgical site produces a decrease in postoperative bleeding as determined by examining total amount of drainage volume, which can effectively reduce the time before drain removal and shorten the length of postoperative hospital stay.

What is already known on this topic?

Results of trials on the efficacy of topical TXA on postoperative bleeding and blood transfusion in spinal surgery continue to be implemented and published in the literature[15-17].

What this study adds?

This study provides additional documentation indicating that topical TXA significantly reduces PRC transfusion in PSF with long-segment instrumentation for thoracolumbar spinal trauma. The results of this study, combined with future randomized trials of the use of topically applied TXA on postoperative bleeding and related biochemical variables, are likely to add new information and improve the outcome of the spinal fusion procedure.

Potential conflicts of interest

The authors declare no conflict of interest.

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