

# Effect and safety of topical application of tranexamic acid to reduce perioperative blood loss in elderly patients with intertrochanteric fracture undergoing PFNA

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## Abstract

The specific method and dose of tranexamic acid (TXA) topically applied for intertrochanteric fractures have not been well established. The aim of this study is to investigate the efficacy and safety of TXA topically administered via our protocol for perioperative bleeding management in elderly patients with intertrochanteric fractures who underwent proximal femoral nail anti-rotation (PFNA).

A retrospective comparative analysis was performed. The TXA group was composed of 82 patients with topical use of TXA, and the control group was composed of 82 patients without TXA use during the PFNA procedure. Intraoperative, total and hidden amounts of blood loss, drainage volumes, postoperative blood transfusion volumes and complications were compared between the 2 groups.

The intraoperative, total and hidden amounts of blood loss and the drainage volumes were significantly lower in the TXA group than in the control group ( $P = .012$ ,  $P < .01$ ,  $P < .01$ ,  $P = .014$ , respectively). The volume and rate of blood transfusion in the TXA group were significantly lower than those in the control group ( $P < .01$ ). There were no significant differences in complications between the 2 groups ( $P > .05$ ).

Topical application of TXA offers an effective and safe option for reducing perioperative blood loss and transfusion in elderly patients with intertrochanteric fractures undergoing PFNA.

**Abbreviations:** APTT = activated partial thromboplastin time, Hb = haemoglobin, Hct = haematocrit, IBL = intraoperative blood loss, INR = international normalized ratio, PBL = postoperative blood loss, PFNA = proximal femoral nail anti-rotation, PT = prothrombin time, TBL = total blood loss, TXA = tranexamic acid.

**Keywords:** bleeding, intertrochanteric fracture, proximal femoral nail anti-rotation, tranexamic acid

## 1. Introduction

With the rapid increase in the aged population, hip fractures increase rapidly in elderly people and cause a significant social

and economic problem.<sup>[1]</sup> Intertrochanteric fractures represent one of the common types of hip fractures, and the 1-year mortality rate after intertrochanteric fractures is reported to be approximately 25%.<sup>[2]</sup> Proximal femoral nail anti-rotation (PFNA) has become a routine fixation method for treating senile intertrochanteric fractures with the advantages of being minimally invasive, being a simple operation and having limited intraoperative blood loss.<sup>[3,4]</sup> Compared to those with femoral neck fractures, patients with intertrochanteric fractures incur hidden blood loss and thus more often require blood transfusion.<sup>[5]</sup> Excessive postoperative bleeding causes the need for blood transfusion, which is accompanied by risks of hypersensitivity, haemolytic reactions, cardiovascular dysfunction, infectious diseases and rejection.<sup>[6,7]</sup>

Tranexamic acid (TXA), an antifibrinolytic agent that can help improve coagulation function by inhibiting the degradation of fibrin, has been confirmed to reduce blood loss and transfusion requirements in hip and knee arthroplasty.<sup>[8,9]</sup> Considering that serious systemic side effects following intravenous TXA exposure are quite rare but do exist,<sup>[10]</sup> topical application of TXA has attracted increasing attention and has been confirmed to reduce postoperative blood loss and blood transfusion requirements safely in patients undergoing hip arthroplasty.<sup>[11,12]</sup>

For patients with intertrochanteric fractures who have a high risk of bleeding, especially elderly patients, the current literature contains little information about the effects of topical application of TXA on surgical outcomes after PFNA in this population. This

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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retrospective study was conducted to evaluate the efficacy and safety of the topical application of TXA in elderly patients with intertrochanteric fractures undergoing PFNA.

## 2. Materials and methods

This retrospective study was approved by the Ethics Committee of Nanchuan People's Hospital of Chongqing Medical University (YLJS-202025) and performed in line with the Declaration of Helsinki international ethical guidelines for studies involving human subjects. Written informed consent was obtained prospectively from all patients prior to surgery. From August 2015 to August 2019, patients with intertrochanteric fractures undergoing PFNA (short) were retrospectively enrolled in this study. Before February 2018, patients with PFNA were not treated with TXA. After February 2018, all the patients with PFNA were treated with topical TXA.

### 2.1. Inclusion criteria

The inclusion criteria were

1. age  $\geq 70$  years at the time of injury;
2. a confirmed diagnosis of intertrochanteric fractures classified according to AO type by X-ray or CT; and
3. eligibility for intertrochanteric fracture surgery using the PFNA procedure, as determined by the senior orthopaedic surgeon.

### 2.2. Exclusion criteria

The exclusion criteria were

1. allergy to TXA or low-molecular-weight heparin;
2. old, multiple or pathological fractures;
3. severe dysfunction of the heart, lung, liver, or kidney or coagulation dysfunction;
4. anticoagulant therapy such as antiplatelet drugs or warfarin before the operation;
5. recent or ongoing thromboembolic events including deep venous thrombosis, pulmonary embolism, arterial thrombosis, cerebral thrombosis, or stroke; and
6. follow-up of less than 1 month.

### 2.3. Treatment

All the patients underwent a standard surgical procedure by a single senior surgeon who specialized in hip and trauma surgery and had 8 years of experience. All patients received spinal or general anesthesia. In the study group, the wound was bathed in 3 g/100 mL TXA solution for 5 minutes after greater trochanter exposure and before wound closure. For all patients, one drain was placed in the wound. The drain was clamped for 6 hours and then released. The limb pneumatic pump was used for all patients on the first day after the operation (pneumatic pump treatment should be stopped if lower extremity deep vein thrombosis occurs after surgery). All patients received standard thromboprophylaxis with low-molecular-weight heparin from the second day after admission to 24 hours prior to the operation and for 12 hours after the operation. The drain was removed when the drainage volume was  $< 20$  mL. When patients' haemoglobin (Hb) concentration was  $< 70$  g/L, allogeneic blood transfusion was

administered. Routine follow-up visits were scheduled at 1, 3, 6, and 12 months postoperatively.

### 2.4. Data collection

Data were collected from medical records. Demographic and clinical characteristic data included age, sex, height, weight, and time from injury to surgery; AO type of fracture, American Society of Anesthesiologists score and anesthesia method; and preoperative Hb and haematocrit (Hct) levels. The intraoperative and postoperative clinical data included the operation time and intraoperative blood loss (IBL); postoperative Hb and Hct levels; postoperative coagulation indicators including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT) and D-dimer; postoperative blood loss (PBL), which was evaluated by the drainage volume; and transfusion volume. Postoperative complications included deep venous thrombosis and pulmonary embolism; wound haematoma and deep or superficial infection; myocardial infarction; and cerebrovascular accidents. Mortality and readmission rates 1 month after discharge were also collected.

Blood loss was determined on the basis of millilitres. Intraoperative blood loss (IBL) was recorded using a suction apparatus and gauze, measured during the procedure. PBL was evaluated by wound drainage. The Hb levels in the blood were measured preoperatively and on postoperative day 1 (POD1) and 3 (POD3). Total blood loss (TBL) = patient's blood volume (PBV)  $\times ((\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}) / (\text{Hct}_{\text{pre}} + \text{Hct}_{\text{post}}) / 2)$ .<sup>[13]</sup>  $\text{PBV} = k_1 \times \text{height (m)}^3 + k_2 \times \text{weight (kg)} + k_3$  ( $k_1 = 0.3669$ ,  $k_2 = 0.03219$ , and  $k_3 = 0.6041$  for men;  $k_1 = 0.3561$ ,  $k_2 = 0.03308$ , and  $k_3 = 0.1833$  for women);<sup>[14]</sup>  $\text{Hct}_{\text{pre}}$  means the preoperative Hct level;  $\text{Hct}_{\text{post}}$  means the Hct level on postoperative day 3. Hidden blood loss (HBL) = TBL - IBL - PBL + transfusion.

### 2.5. Statistical methods

A total of 218 patients were enrolled, 82 patients were administered topical TXA (study group), and 136 patients were not administered topical TXA during PFNA. To minimize selection bias, propensity score matching was performed prior to analysis. All patients in the study group ( $n = 82$ ) were included in the final analysis and matched with patients who did not receive topical TXA (control group,  $n = 82$ ), as shown in Figure 1. Due to the propensity matching process, the groups did not differ significantly in terms of age, sex, height, weight, time from injury to surgery, AO type of fracture, American Society of Anesthesiologists score, anesthesia method, or preoperative Hb and Hct level (Table 1). Once the 2 groups of patients were matched, further statistical analyzes were conducted. Numerical data are presented as the mean  $\pm$  standard deviation (mean  $\pm$  SD). At baseline, group differences in clinical measures between the 2 groups were tested via an analysis of variance (ANOVA) and Kruskal-Wallis tests. Categorical data were compared with Chi-Squared and Fisher exact tests. A repeated-measures ANOVA was used to analyze the effects of TXA on Hb POD1, Hb POD3, Hct POD1, and Hct POD3.  $P < .05$  was considered statistically significant. SPSS 23.0 statistical software (Chicago, IL) was used to analyze the data in this study.

## 3. Results

Because there were 2 five-minute wait times for the topical use of TXA in the study group. Finally, the operation time except TXA

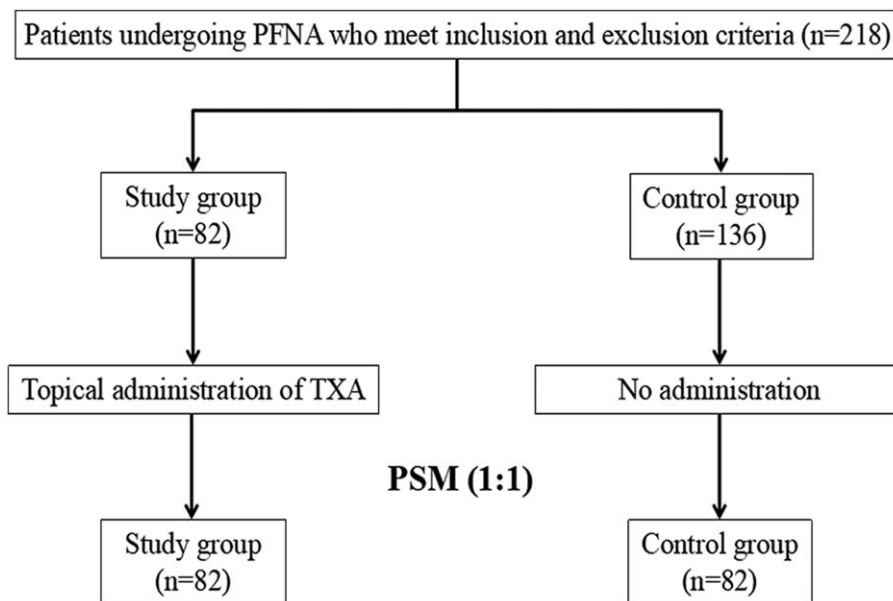


Figure 1. Flowchart demonstrating patient selection.

application in the TXA group (10 minutes) was no significant differences compared with control group. (Table 2).

The study group had significantly less IBL ( $121.58 \pm 71.86$  vs  $168.29 \pm 98.16$  mL,  $P = .012$ ), TBL ( $566.87 \pm 186.23$  vs  $813.65 \pm 293.36$  mL,  $P < .01$ ), drainage ( $112.32 \pm 57.86$  vs  $202.38 \pm 76.61$  mL,  $P = .014$ ), and HBL ( $447.16 \pm 187.39$  vs  $652.65 \pm 271.43$  mL,  $P < .01$ ) than the control group. The levels of Hb and Hct on postoperative day 1 were apparently higher in the study group than in the control group ( $99.23 \pm 22.31$  vs  $86.76 \pm 17.88$  g/L,  $P = .039$ ;  $29.15 \pm 3.16$  vs  $27.42 \pm 3.84\%$ ,  $P = .027$ ). However, on postoperative day 3, no significant intergroup differences were observed in the Hb or Hct levels. During the hospital stay, the study group had a significantly lower transfusion volume ( $103.64 \pm 72.35$  vs  $213.48 \pm 88.41$  mL,  $P < .01$ ) and transfusion rate ( $14.63$  vs  $25.61\%$ ,  $P < .01$ ) than the control group (Table 2).

To assess the effect of TXA on the perioperative coagulation function, the data regarding the perioperative PT, INR, APTT and D-dimer level were analyzed, and there were no statistically significant differences between the 2 groups (Fig. 2).

There were no significant differences in deep venous thrombosis, pulmonary embolism, wound haematoma, deep or superficial infection, myocardial infarction, cerebrovascular accident, mortality or readmission 1 month after discharge in the 2 groups (Table 3).

#### 4. Discussion

Intertrochanteric fractures represent a common type of hip fracture that incurs substantial blood loss because there is a large amount of muscle insertion involved around this region, and a large bone surface area is available for blood loss in extracapsular fractures.<sup>[15]</sup> Particularly for elderly and frail patients who receive surgical treatment (most of these patients have anemia), massive blood loss usually results in blood transfusion and a high risk of perioperative morbidity and mortality.<sup>[16,17]</sup> TXA has been reported to reduce surgical blood loss effectively and safely<sup>[18]</sup> and improve perioperative care in patients undergoing hip arthroplasty.<sup>[11]</sup> However, the data regarding its use in

Table 1

Demographic and preoperative data in both groups.

	Control group (n = 82)	Study group (n = 82)	P value
Age (yr)	79.81 (6.12)	80.53 (5.84)	.288
Gender (Male/Female)	27/55	26/56	.836
Height (m)	1.63 (0.12)	1.62 (0.09)	.174
Weight (kg)	59.11 (11.65)	61.82 (12.14)	.136
BMI (kg/m <sup>2</sup> )	22.56 (4.03)	22.72 (3.63)	.328
Time from injury to surgery (d)	3.84 (1.91)	4.12 (2.12)	.131
AO type of fracture (31 A1/31 A2/31 A3)	40/27/15	37/29/16	.211
ASA score (I/II/III/IV)	3/76/3	2/75/5	.266
Anesthesia (Spina/General)	37/45	36/46	.714
Preoperative Hb (g/L)	108.34 (13.45)	111.28 (14.21)	.082
Preoperative Hct (%)	33.32 (4.48)	33.96 (3.98)	.344

ASA = American society of anesthesiologists, BMI = body mass index, Hb = hemoglobin, Hct = hematocrit.

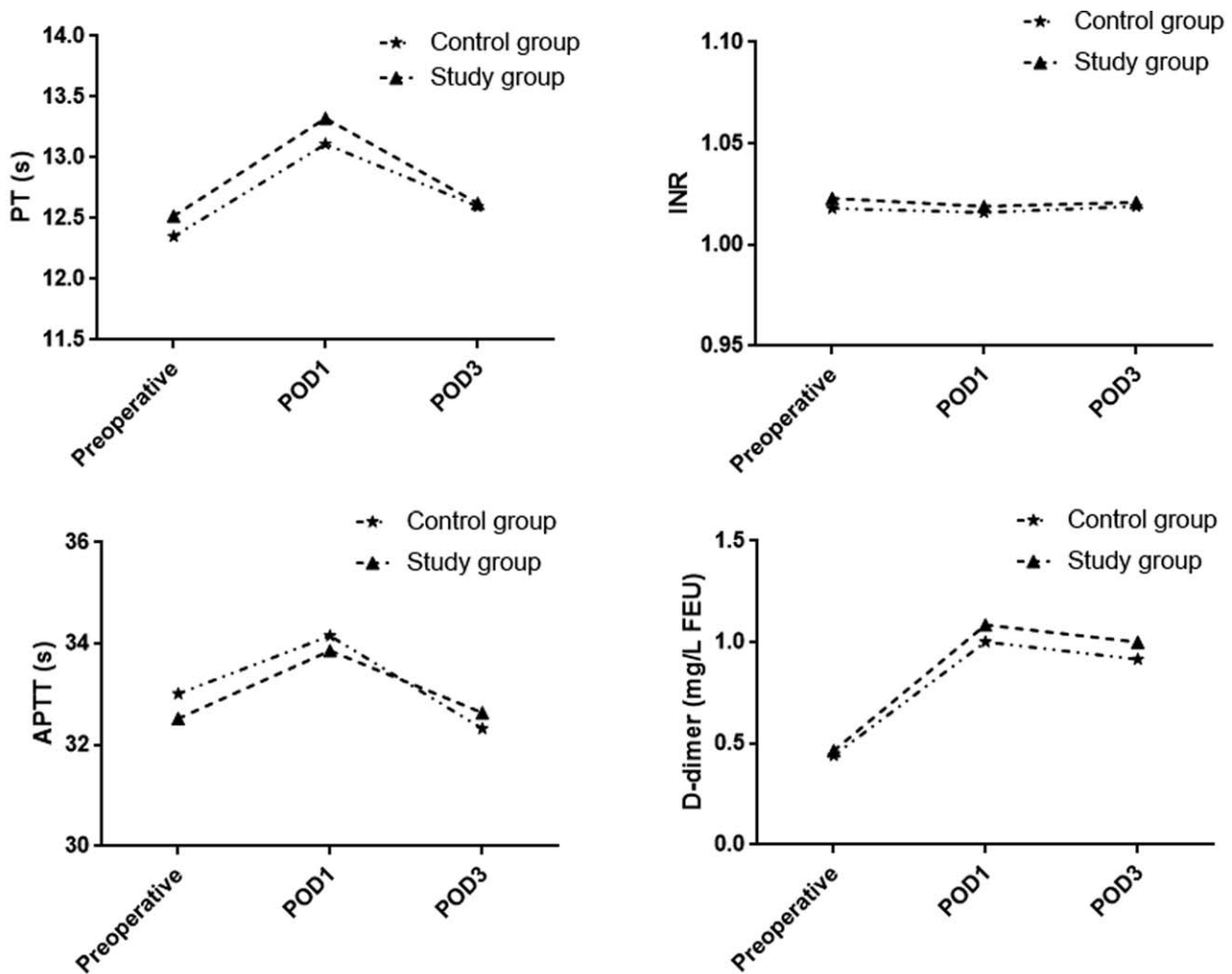
**Table 2**  
Comparison of perioperative data between the 2 groups.

	Control group (n=82)	Study group (n=82)	P value
Operation time (min)	76.54 (19.23)	74.87 (22.72)	.589
IBL (mL)	168.29 (98.16)	121.58 (71.86)	.012
Hb POD1 (g/L)	86.76 (17.88)	99.23 (22.31)	.039
Hb POD3 (g/L)	85.14 (19.21)	92.58 (24.45)	.281
Hct POD1 (%)	27.42 (3.84)	29.15 (3.16)	.027
Hct POD3 (%)	26.98 (4.12)	28.41 (3.66)	.082
Transfusion rate (n, %)	21 (25.61%)	12 (14.63%)	<.01
Transfusion volume (mL)	213.48 (88.41)	103.64 (72.35)	<.01
TBL (mL)	813.65 (293.36)	566.87 (186.23)	<.01
Drainage (mL)	202.38 (76.61)	112.32 (57.86)	.014
HBL (mL)	652.65 (271.43)	447.16 (187.39)	<.01

Hb = hemoglobin, HBL = hidden blood loss, Hct = hematocrit, IBL = intraoperative blood loss, POD1/3 = postoperative days 1/3, TBL = total blood loss.  
Statistical analysis for comparison between groups:  $P < .05$ , statistical significance.

intertrochanteric fractures with PFNA, especially topical applications, are limited. Therefore, in the present study, we sought to determine whether topical application of TXA would reduce perioperative blood loss effectively and safely.

TXA is a synthetic amino acid analogue that can reduce the need for blood loss and transfusion due to its characteristic of plasminogen inhibition.<sup>[11,12]</sup> In selective knee and hip arthroplasty, the efficacy of TXA in reducing blood loss is generally



**Figure 2.** Comparison of perioperative coagulation function between 2 groups. There were not statistical significant in PT, INR, APTT, and D-dimer between 2 groups.

**Table 3**  
**Postoperative complications in both groups.**

	Control group (n = 82)	Study group (n = 82)	P value
Deep venous thrombosis (n, %)	18 (21.95%)	16 (19.51%)	.521
Pulmonary embolism (n, %)	1 (1.22%)	2 (2.44%)	.753
Wound haematoma (n, %)	3 (3.66%)	3 (3.66%)	.851
Wound infection (n, %)	3 (3.66%)	2 (2.44%)	.662
Myocardial infarction (n, %)	0	0	–
Cerebrovascular accident (n, %)	1 (1.22%)	0	.412
Mortality (n, %)	0	0	–
Readmission (n, %)	1 (1.22%)	1 (1.22%)	.996

accepted.<sup>[19]</sup> Some studies have focused on intravenous TXA for bleeding management in intertrochanteric fracture patients with PFNA. The results have indicated that intravenous use of TXA perioperatively can reduce total and hidden blood loss.<sup>[20]</sup> Recently, Vasileios et al also confirmed that elderly patients who undergo intramedullary nailing for an intertrochanteric fracture can benefit from a single dose of 15 mg/kg TXA before the onset of surgery. A similar tendency was identified in patients undergoing hemiarthroplasty for a subcapital fracture but not to a statistically significant level.<sup>[21]</sup> We first reported the effects of topical application of TXA in intertrochanteric fracture patients with PFNA. Our data showed that the TBL was reduced by 30% (from 813–566 mL) and the HBL was reduced by 31% (from 652–447 mL) after topical treatment with TXA during surgery. Moreover, we also confirmed an obvious reduction in IBL (28%, from 168–121 mL) and drainage (45%, from 202–112 mL) in the study group. Our data indicate that topical application of TXA has equivalent or even better effects for controlling perioperative bleeding than intravenous TXA in intertrochanteric fracture patients with PFNA.

There are very few studies reported the effects of topical application of TXA in intertrochanteric fracture patients with short cephalomedullary nails, dynamic hip screws, barrel plates and Gamma-3 intramedullary nail but not with PFNA. Drakos et al reported a randomized prospective trial in 200 intertrochanteric fracture patients treated with short cephalomedullary nails.<sup>[22]</sup> The patients received 3 g TXA in the subfascial plane and around the fracture site before wound closure. Their data showed a 43% reduction in transfusion requirements in the TXA group. Virani et al reported a randomized prospective trial in 137 intertrochanteric fracture patients treated with dynamic hip screws and barrel plates.<sup>[23]</sup> The patients received subfascial and intramuscular infiltration of 2 g TXA before wound closure. However, they found no significant differences in transfusion between the TXA and control groups. These differences could be due to the different internal fixation methods, mode of application and dosage of TXA. Our results are similar to those of Drakos et al<sup>[22]</sup> who showed a 42.6% reduction in transfusion requirements in the study group. Considering that administration before wound closure does not reduce intraoperative bleeding, we soaked the wound with TXA for 5 minutes after greater trochanter exposure and before wound closure. We confirmed an obvious reduction in IBL (28%, from 168–121 mL). We found that a similar approach was used recently for bleeding control in acetabular fractures, and the approach was confirmed to effectively reduce IBL.<sup>[24]</sup> Recently, Li et al compared the efficacy and safety of intravenous combined with topical administration of TXA in reducing blood loss after Gamma-3 intramedullary

nail of intertrochanteric fractures.<sup>[25]</sup> They found intravenous combined with topical administration of TXA has better results than intravenous or topical alone. They reported  $584.53 \pm 226.62$  mL TBL in group intravenous combined with topical administration of TXA. However, there is only  $566.87 \pm 186.23$  mL in our study with topical administration of TXA. We considered that the different internal fixation and tranexamic acid treatment time points are the reasons for these differences. Further, whether our topical regimen in combination with preoperative intravenous TXA have better effects of reducing blood should be attempted in the future.

The potential increased risk of thromboembolic events is the primary concern when administering TXA because TXA promotes thrombosis by inhibiting fibrinolysis and increases thrombus mass.<sup>[26]</sup> Topical application has little or no systemic exposure of TXA, and it can potentially avoid the complications of intravenous TXA. Our data showed that there were no significant differences in deep venous thrombosis, pulmonary embolism, myocardial infarction or cerebrovascular accidents. These results were consistent with recent studies on the topical application of TXA in hip fractures.<sup>[22,23,27]</sup> Coagulation function was also evaluated, and perioperative PT, INR, APTT and D-dimer levels were not significantly different between the 2 groups in this study. One patient in each group was readmitted 1 month after discharge for wound infection and cured with antibiotics and dressing changes. We also found that topical use of TXA did not increase the risk of wound complications or mortality.

To the best of our knowledge, this is the first study on the topical application of TXA in intertrochanteric fracture patients with PFNA, and propensity score matching was used to minimize selection bias. However, some limitations remain in this study. First, this was a retrospective study with a small number of patients. Second, in the control group, the wound was not bathed in the same amount of saline as a comparison. In addition, only 1 combination of time and dosage was investigated in this study, the optimal dosing and timing of TXA administration are still controversial. Therefore, further prospective randomized controlled trials with larger sample sizes and different doses and times of TXA administration are warranted to confirm our findings.

## 5. Conclusion

This study demonstrated that topical application of TXA could effectively and safely reduce postoperative blood loss and decrease transfusion in senile intertrochanteric fracture patients undergoing PFNA.

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## Author contributions

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**Methodology:** Qiuping Xiao, Jianfeng He.

**Project administration:** Siping Xian, Menghong Xia.

**Software:** Jianfeng He.

**Supervision:** Siping Xian, Menghong Xia.

**Writing – original draft:** Huiping Wei.

**Writing – review & editing:** Tianji Huang.

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