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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Research article

Keywords: Tranexamic acid, Bleeding, Intertrochanteric fracture, Proximal femoral nail anti-rotation

Posted Date: January 23rd, 2020

DOI: <https://doi.org/10.21203/rs.2.21728/v1>

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Abstract

Background: The specific method and dose of tranexamic acid (TXA) topically applied in intertrochanteric fracture have not been well established. The aim of this study is to investigate the efficacy and safety of TXA topically treated by our protocol in perioperative bleeding management for elderly patients with intertrochanteric fracture treated undergoing proximal femoral nail anti-rotation (PFNA). **Methods:** A retrospective comparative analysis was performed. Group TXA was comprised of 82 patients with topical use of TXA and group control was comprised of 82 patients without TXA during the procedure of PFNA. Intraoperative, total and hidden blood loss, drainage volume, postoperative blood transfusion volume and complications were compared between the two groups. **Results:** Intraoperative, total and hidden blood loss, and drainage volume were significantly lower in the TXA group than those in the control group ($P=0.012$, $P<0.01$, $P<0.01$, $P=0.014$, respectively). The volume and rate of blood transfusion in TXA group were significantly lower than those in the control group ($P<0.01$). There were no significant differences in complications between two groups ($P>0.05$). **Conclusion:** Topical application of TXA offers an effective and safe option in reducing perioperative blood loss and transfusion for elderly patients with intertrochanteric fractures undergoing PFNA.

Background

With the speedy increase of the aged population, hip fractures increase rapidly in elderly people and cause serious public health and social problems[1]. Intertrochanteric fracture is one of the major types of hip fractures, and the 1-year mortality rate after intertrochanteric fractures is reported to be approximately 25%[2]. Proximate femoral nail annotation (PFNA) has become a routine fixation method for treating senile intertrochanteric fractures with the advantages of minimally invasive, simple operation and less intraoperative blood loss[3, 4]. Compared to femoral neck fractures, patients with intertrochanteric fracture incur hidden blood loss and thus more often require blood transfusion[5]. Excessive postoperative bleeding would cause needs of blood transfusion, which is accompanied by risks of hypersensitivity, haemolytic reaction, cardiovascular dysfunction, infectious diseases and rejection[6, 7].

Tranexamic acid (TXA), an antifibrinolytic agent, which 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[8, 9]. In consideration of serious systemic side effects following intravenous TXA exposure are quite rare but do exist[10], topical application of TXA was attracted more and more attention and confirmed to reduce postoperative blood loss and blood transfusion requirements safely in patients receiving hip arthroplasty[11, 12].

For patients with intertrochanteric fractures who have a higher risk of bleeding, especially in 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 retrospective study was conducted to evaluate the efficacy and safety of topical application of TXA in elderly patients with intertrochanteric fractures undergoing PFNA.

Methods

Population

From August 2015 to August 2019, patients with intertrochanteric fractures undergoing PFNA were retrospectively enrolled in this study. Inclusive criteria were (1) age ≥ 70 years at the time of injury; (2) a confirmed diagnosis of intertrochanteric fractures classified according to AO type by X-ray or CT; (3) eligibility for intertrochanteric fracture surgery using the PFNA system, as determined by the senior orthopaedic surgeon. Exclusive criteria were (1) allergy to TXA or low-molecular weight heparin; (2) old, multiple or pathological fractures; (3) severe dysfunction of heart, lung, liver, kidney or coagulation; (4) anticoagulant therapy such as antiplatelet drugs or warfarin before operation; (5) recent or ongoing thromboembolic events include deep venous thrombosis, pulmonary embolism, arterial thrombosis, cerebral thrombosis, or stroke; (6) follow-up less than 1 month. 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.

Intraoperative and postoperative procedures

All the patients accepted standard surgical procedure by a single senior surgeon who specialized in hip and trauma surgery with 8 years of experience. All patients received spinal or general anaesthesia. In the study group, the wound was bathed in 3 g/100 ml TXA solution for 5 min after greater trochanter exposure and before wound closure, respectively. For all patients, one drainage was placed in the wound. The drainage was clamped for 6 h and then released. The limb pneumatic pump was used for all patients on the first day after operation (pneumatic pump treatment should be stopped if the 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 h prior to operation, and for 12 h after operation. The drainage was removed when volume of drainage < 20 ml. When patients' hemoglobin (Hb) concentration < 70 g/L, allogeneic blood transfusion should be given. Routine follow-up visits were scheduled at 1, 3, 6 and 12 months postoperatively.

Data collections

Data were collected from medical records. Demographic and clinical characteristics data included age, sex, height, weight, time from injury to surgery; AO type of fracture, American society of anesthesiologists (ASA) score and anesthesia method; preoperative Hb and hematocrit (Hct). Intraoperative and postoperative clinical data include operation time and intraoperative blood loss (IBL); postoperative Hb and Hct; postoperative coagulation indicators include prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT) and D-dimer; postoperative blood loss (PBL) which is evaluated by volume of drainage; volume of transfusion. Postoperative complications include deep venous thrombosis and pulmonary embolism; wound haematoma and deep or superficial infection; myocardial infarction and cerebrovascular accident. Mortality and readmission in one month after discharge were also collected.

Calculation methods

The blood loss was determined on the basis of milliliters. IBL = weight of surgical sponges + volume of blood in suction canisters-the volume of irrigation fluids. PBL was evaluated by wound drainage. The Hb levels of blood were measured preoperatively, postoperative days 1 (POD1) and 3 (POD3). Total blood loss (TBL) = patient's blood volume (PBV) × (Hct_{pre} - Hct_{pod3}) / Hct_{ave} [13]. 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) [14]; Hct_{pre} = the preoperative Hct level; Hct_{pod3} = the Hct of day 3 postoperation; Hct_{ave} = the average of the Hct_{pre} and Hct_{pod3}. Hidden blood loss (HBL) = TBL - IBL - PBL + transfusion.

Statistical methods

In order 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 those did not receive topical TXA (control group, n = 82), as showed in Fig. 1. Due to the propensity matching process, the groups did not differ significantly in terms of age, sex, height, weight, the time from injury to surgery, AO type of fracture, ASA score and anesthesia method; preoperative Hb and Hct (Table 1). Once the two groups of patients were matched, further statistical analyses were conducted. Numerical data were represented in mean ± standard deviation (mean ± SD) and compared with independent t-tests. categorical data were compared with chi-square and Fisher's exact tests. P < 0.05 was considered statistically significant. SPSS 23.0 statistical software (Chicago, IL) was used for analyzing data in this study.

Table 1
Demographic and preoperative data in both groups.

	Control group (n = 82)	Study group (n = 82)	P
Age(year)	79.81(6.12)	80.53(5.84)	0.288
Gender(Male/Female)	27/55	26/56	0.836
Height(m)	1.63(0.12)	1.62(0.09)	0.174
Weight(kg)	59.11(11.65)	61.82(12.14)	0.136
BMI(kg/m ²)	22.56(4.03)	22.72(3.63)	0.328
Time from injury to surgery(day)	3.84(1.91)	4.12(2.12)	0.131
AO type of fracture(31 A1/31 A2/31 A3)	40/27/15	37/29/16	0.211
ASA score(II/III/IV)	3/76/3	2/75/5	0.266
Anesthesia(Spina/General)	37/45	36/46	0.714
Preoperative Hb(g/L)	108.34(13.45)	111.28(14.21)	0.082
Preoperative Hct(%)	33.32(4.48)	33.96(3.98)	0.344
BMI: body mass index; AO: ASA: American society of anesthesiologists;			
Hb: hemoglobin; Hct: hematocrit			

Results

The operation time in study group = recorded time minus 10 min because there are two five-minute wait time for topical use of TXA in the study group. Finally, no significant intergroup differences were observed in the operation time (Table 2).

The study group suffered significantly less IBL (121.58 ± 71.86 vs 168.29 ± 98.16 mL, $P = 0.012$), TBL (566.87 ± 186.23 vs 813.65 ± 293.36 mL, $P < 0.01$), Drainage (112.32 ± 57.86 vs 202.38 ± 76.61 mL, $P = 0.014$), HBL (447.16 ± 187.39 vs 652.65 ± 271.43 mL, $P < 0.01$) than the control group. The levels of Hb and Hct on postoperative day 1 were apparently higher in study group than those in control group (99.23 ± 22.31 vs 86.76 ± 17.88 g/L, $P = 0.039$; 29.15 ± 3.16 vs $27.42 \pm 3.84\%$, $P = 0.027$). However, on postoperative day 3, there were no significant intergroup differences were observed in the Hb and Hct. Duration of hospital stay, the study group suffered significantly less transfusion volume (103.64 ± 72.35 vs 103.64 ± 72.35 mL, $P < 0.01$) and transfusion rate (14.63 vs 25.61% , $P < 0.01$) than the control group (Table 2).

In order to assess the effect of TXA on perioperative coagulation function, the data of perioperative PT, INR, APTT and D-dimer were analyzed and there were not statistical significant in two groups (Fig. 2).

Table 2
Comparison of perioperative data between the two groups.

	Control group	Study group	P
Operation time(min)	76.54(19.23)	74.87(22.72)	0.589
IBL(mL)	168.29(98.16)	121.58(71.86)	0.012
Hb POD1(g/L)	86.76(17.88)	99.23(22.31)	0.039
Hb POD3(g/L)	85.14(19.21)	92.58(24.45)	0.281
Hct POD1(%)	27.42(3.84)	29.15(3.16)	0.027
Hct POD3(%)	26.98(4.12)	28.41(3.66)	0.082
Transfusion rate(n, %)	21(25.61%)	12(14.63%)	< 0.01
Transfusion volume(mL)	213.48(88.41)	103.64(72.35)	< 0.01
TBL(mL)	813.65(293.36)	566.87(186.23)	< 0.01
Drainage(mL)	202.38(76.61)	112.32(57.86)	0.014
HBL(mL)	652.65(271.43)	447.16(187.39)	< 0.01
IBL: intraoperative blood loss; Hb: hemoglobin; Hct: hematocrit;			
POD1/3: postoperative days 1/3; TBL: total blood loss; HBL: hidden blood loss			

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

Table 3
Postoperative complications in both groups.

	Control group	Study group	P
Deep venous thrombosis (n, %)	18(21.95%)	16(19.51%)	0.521
Pulmonary embolism(n, %)	1(1.22%)	2(2.44%)	0.753
Wound haematoma(n, %)	3(3.66%)	3(3.66%)	0.851
Wound infection(n, %)	3(3.66%)	2(2.44%)	0.662
Myocardial infarction(n, %)	0	0	–
Cerebrovascular accident(n, %)	1(1.22%)	0	0.412
Mortality(n, %)	0	0	–
Readmission(n, %)	1(1.22%)	1(1.22%)	0.996

Discussion

Intertrochanteric fracture is a major type of hip fracture which incurs substantial blood loss because much muscles insertion involved around this region, great bone surface area is available for blood loss in the extracapsular fractures[15]. Especially for elderly and frail patients who receive surgical treatment (most of these patients associated with anemia), massive blood loss usually result in blood transfusion and a high risk of perioperative morbidity and mortality[16, 17]. TXA has been reported to reduce surgical blood loss effectively and safely[18], improve perioperative care for patients undergoing hip arthroplasty[11]. However, the data regarding its use in intertrochanteric fracture with PFNA, especially topical applications, is limited. Therefore, in the present study, we sought to determine whether topical application of TXA would reduce perioperative blood loss effectively and safely.

TXA, a synthetic amino acid analogue that can reduce the need for blood loss and transfusion for its characteristic of plasminogen inhibition[11, 12]. In selective knee and hip arthroplasty, the efficacy of TXA in reducing blood loss is generally accepted[19]. Some study has focused on intravenous TXA for bleeding management in intertrochanteric fracture patients with PFNA. It indicated that intravenous use of TXA perioperatively can reduce total and hidden blood loss[20]. We first reported the effects of topical application of TXA in intertrochanteric fracture patients with PFNA. Our data showed that the TBL reduce 30% (from 813 reduce to 566 mL) and the HBL reduce 31% (from 652 reduce to 447 mL) after treated with TXA topically during operation. Moreover, we also confirmed a obvious reduction in IBL (28%, from 168 reduce to 121 mL) and drainage (45%, from 202 reduce to 112 mL) in the study group. Our data indicated that topical application of TXA has equivalent or even better effects of controlling perioperative bleeding than intravenous TXA in intertrochanteric fracture patients with PFNA.

Only two literatures reported the effects of topical application of TXA in intertrochanteric fracture patients with short cephalomedullary nail, dynamic hip screw and barrel plate, but not PFNA. Drakos et al reported a randomized prospective trial in 200 intertrochanteric fractures treated with a short cephalomedullary nail[21]. The patients received 3 g of 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 SR et al reported a randomized prospective trial in 137 intertrochanteric fractures treated with dynamic hip screw and barrel plate[22]. The patients received subfascial and intramuscular infiltration of 2 g TXA before wound closure. However, they found no significant differences of transfusion between the TXA and control group. These differences could be due to the different internal fixation methods, mode of application and the dosage of TXA. Our results is similar to Drakos et al report[21] and showed a 42.6% reduction in transfusion requirements in the study group. In consideration of administration before wound closure does not reduce intraoperative bleeding, we soaked TXA in the wound for 5 min after greater trochanter exposure and before wound closure. We confirmed a obvious reduction in IBL (28%, from 168 reduce to 121 mL). We found the similar approach was used recently in bleeding control of acetabular fractures and it was confirmed to reduce IBL effectively[23].

The potential increased risk of thromboembolic events was the primary concern when administering TXA because TXA promotes thrombosis by inhibiting fibrinolysis and increases thrombus mass[24]. 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 and cerebrovascular accident. These results were consistent with recent studies on the topical application of TXA in hip fractures[21, 22, 25]. Coagulation function was also evaluated and perioperative PT, INR, APTT and D-dimer were no significant difference between two groups in this study. There was one patient in each group was readmitted in one 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 and mortality.

To our knowledge, this is the first study of topical application of TXA in intertrochanteric fracture patients with PFNA and propensity score matching was used to minimize selection bias. However, this was a retrospective study with a small number of patients. In addition, the optimal dosing and timing of TXA administration

is still controversial. Therefore, further prospective randomized controlled trial including larger sample sizes and different dosing and timing of TXA administration are warranted to confirm our findings.

Conclusions

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

Abbreviations

PFNA: Proximate femoral nail annotation; TXA: Tranexamic acid; Hb: Hemoglobin; ASA: American society of anesthesiologists; Hct: Hematocrit; IBL: Intraoperative blood loss; PT: Prothrombin time; INR: International normalized ratio; APTT: Activated partial thromboplastin time; PBL: Postoperative blood loss; POD: Postoperative days; TBL: Total blood loss; PBV: Patient's blood volume; HBL: Hidden blood loss

Declarations

Acknowledgements

We would like to thank Dr. Gang Luo from Department of Orthopaedics, The first affiliated hospital of Chongqing medical university for providing guidance for this study.

Authors' contributions

HPW Data collection, Data analysis, Writing the paper. TJH Data collection, Data analysis, Writing the paper. JFH Performed the experiments. MHX conception and Design of study, Principal Investigators. And all authors have read and approved the manuscript.

Funding

Not applicable.

Availability of data and materials

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

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Nanchuan People's Hospital of Chongqing Medical University 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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flowchart demonstrating patient selection.

Figure 2

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