Safety and efficacy of tranexamic acid with epinephrine for prevention of blood loss following surgery for trochanteric femoral fractures

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Abstract

**Objective:** This study aimed to determine whether the local administration of tranexamic acid (TXA) combined with diluted epinephrine (DEP) reduces blood loss and the need for transfusions compared with the administration of TXA alone following surgery for trochanteric femoral fractures.

**Methods:** Hundred patients were enrolled in this study. In the target group (TXA/DEP group: n=50; 19 men and 31 women, mean age 72.5±11.1 years), the surgical sites were injected with 35 mL normal saline mixed with 3 g of TXA with 0.2 mg of DEP at a 1:200,000 dilution (TXA/DEP) immediately after musculoaponeurotic closure. In the control group (TXA group: n=50; 22 men and 28 women; mean age: 70.5±12.2 years), the surgical site was injected with 35 mL normal saline containing 3 g of TXA alone. The main outcome measures were postoperative hemoglobin (Hb) levels, hematocrit, drainage volume, and total blood loss (TBL); the secondary measures included transfusion requirements and perioperative complications.

**Results:** The mean Hb levels among patients in theTXA/DEP group were significantly lower than among those in the TXA group, measured on postoperative day 1 at 101.0±14.1 g/L vs. 106.9±10.5 g/L and day 3 as 104.2±8.2 g/L vs. 108.5±9.1 g/L, respectively (p<0.05). Drainage volume from the surgical site and TBL measured on postoperative day 2 were also significantly reduced in the TXA/DEP group vs. the TXA group, measured at 71.4±26.0 mL vs. 82.5±24.6 mL and 343.6±148.0 mL vs. 419.6±165.4 mL, respectively (p<0.05). Furthermore, 11 patients (22%) from the TXA group and 15 (30%) from the TXA/DEP group received blood transfusions; the mean number of transfusion events (1.2±0.4 vs. 1.9±0.7) and the amount of blood transfused (1.7±0.5 Units vs. 2.9±1.0 Units) was also markedly reduced in the TXA/DEP group (p<0.05). Two cases in the TXA/DEP group and three in the TXA group were diagnosed with deep vein thrombosis, a difference that did not reach statistical significance (p>0.05).

**Conclusion:** Local administration of TXA with DEP reduced blood loss and limited the need for blood transfusions after surgery for trochanteric femoral fracture without increasing the risk of perioperative complications. Our study indicates that the local administration of TXA/DEP is safe and more effective than the administration of TXA alone in treating trochanteric femoral fractures.

Level of Evidence: Level III, Therapeutic study

**Introduction**

Trochanteric femoral fracture is one of the most common injuries to the lower extremity. The incidence of trochanteric fractures has significantly increased during the recent decades and is expected to double in the next 25 years, thereby presenting a tremendous global economic burden (1, 2). Surgical treatment of this fracture is often associated with massive perioperative blood loss, resulting in postoperative anemia that requires allogeneic blood transfusions (3, 4). Accordingly, safe and effective means to prevent postoperative blood loss are necessary.

Recent reports have revealed that the administration of tranexamic acid (TXA) reduces surgery-associated blood loss and the need for postoperative blood transfusions (5, 6). Current evidence indicates that the local administration of TXA during the surgery for trochanteric femoral fracture is safe and does not increase the rate of postoperative venous thromboembolism (7). Epinephrine is widely used in orthopedic surgery to reduce blood loss (8-11). There is growing evidence that diluted epinephrine (DEP) can act as a procoagulant by promoting platelet production and aggregation, decreasing platelet transit time, stimulating the release of coagulation factors, and promoting the contraction of peripheral blood vessels; one or
more of these factors may limit blood loss during surgery (12). In theory, the combination of TXA and DEP might be more effective in reducing blood loss than the administration of either agent alone. Advances in the understanding of the basic mechanisms have revealed that the hemostatic impact of TXA could be synergistic with the vasoconstrictive effects of epinephrine. Several studies have revealed that the combination of TXA and DEP was effective in limiting blood loss and decreasing transfusion requirements without raising the incidence of perioperative complications, particularly in the cases of total hip arthroplasty (THA) (8, 13). To date, only a few reports have documented the use of this protocol following surgery for trochanteric femoral fracture.

We postulated that the administration of TXA with DEP (TXA/DEP) considerably reduces blood loss and transfusion requirements in the setting of trochanteric femoral fracture surgery compared with the administration of TXA alone. To explore this hypothesis, we performed a clinical study aimed at assessing the relative efficacies of TXA/DEP or TXA alone. We evaluated multiple indicators such as mean hemoglobin (Hb) levels, hematocrit (Hct), total blood loss (TBL), the need for blood transfusion and amount of blood required, as well as perioperative complications.

Materials and Methods

From October 2014 to June 2017, hundred patients with a primary diagnosis of trochanteric femoral fracture were included in this retrospective study. The combination of TXA/DEP was administered to 50 consecutive patients undergoing surgery (TXA/DEP group) from October 2014 to February 2016. Furthermore, TXA alone was administered to 50 additional consecutive patients (TXA group) from March 2016 to June 2017. This protocol was approved by the local Institutional Review Board and was performed in accordance with the principles of the Declaration of Helsinki. Exclusion criteria included a history of bleeding diathesis, any previous thromboembolic episodes, neurological disorders, hepatic, or renal insufficiency, serious cardiac disorders, and/or allergy to TXA. Cases with bilateral hip fractures, pathological fractures, or multiple fractures needing open reduction were excluded. All hip fractures were stabilized with the TRIGEN INTERTAN nail (Smith & Nephew, USA) in procedures performed by one of the two experienced surgeons. The procedures were performed according to the standard technique specified by Smith & Nephew (14). Further, 35 mL normal saline with 3 g of TXA and 0.2 mg of DEP (1:200,000 dilution) or an equal volume of normal saline were injected after musculoaponeurotic closure of the surgical site. The targets for injection were located with monitoring from a C-arm X-ray machine and an 18-gage needle (Figure 1). The end cap of the nail was identified as the first target; the needle was introduced at an oblique angle from the incision and 20 mL of solution with TXA/DEP or TXA alone was administered. The needle was withdrawn and repositioned if blood or a bubble was observed in the syringe prior to injection. The remaining 15 mL was injected into two additional sites, including 10 mL targeting the head of the integrated interlocking screw and 5 mL targeting the head of the distal interlocking screw. Negative pressure drainage was placed and clamped within the first postoperative six hours and was withdrawn on postoperative day 2.

We recorded the type of anesthesia, intravenous fluid administration, the time required for surgery, and the total blood loss. Intraoperative blood loss including the blood in the suction bottle (minus the lavage fluid) and blood loss onto gauzes and sponges were precisely calculated. All patients received one dose of cefazolin (2 g) within 30 minutes of the first sur-

### MAIN POINTS

- Local administration of tranexamic acid with diluted epinephrine can reduce blood loss and limit the need for blood transfusions after trochanteric femoral fracture surgery.
- This technique is safe and easy to operate.
- Combined administration of tranexamic acid and diluted epinephrine is more effective than tranexamic acid alone in treating trochanteric femoral fractures.
gical incision and subsequent 2 g doses at 12-hour intervals for 2 days postoperatively. Postoperative thromboprophylaxis included lower molecular weight heparin (one dose of 40 mg per day administered subcutaneously) administered 12 hours postoperatively and every 12 hours for 4 weeks thereafter. Patients received blood transfusions if Hb levels dropped below 80 g/L or the Hct dropped below 25%; those with symptomatic anemia (Hb level<90 g/L associated with hypotension, hypovolemia, or heart failure) were also provided with blood transfusions. Transfusions of allogeneic leukocyte-depleted packed red blood cells were administered to reach Hb levels above 80 g/L. Subcutaneous low molecular heparin was started from 12 hours postoperatively and stopped at the sixth postoperative week. Radiographic views were obtained on postoperative day 1. All patients were permitted full weight bearing on postoperative day 2 if no abnormal conditions (severe osteoporosis, failure to achieve or maintain reduction of the fracture) were observed on imaging.

Demographic information was collected for each patient: age, sex, type of fracture sustained, and morbidity-associated factors; preoperative laboratory values included prothrombin time (PT) and activated partial thromboplastin time (APTT). The primary outcomes evaluated were Hb levels, Hct, drainage volume, and TBL. The Hb levels and Hct were recorded at 0 hour preoperatively and on postoperative days 1 and 3. Secondary outcomes included transfusion requirements and perioperative complications. The potential for deep vein thrombosis (DVT) was assessed using Doppler ultrasound examination within six hours prior to the procedure and on postoperative day 3. Patients were not routinely monitored for pulmonary embolism (PE) as in our experience, they are not typically clinically significant unless symptoms appear. TBL was calculated using the modified Gross formula (15).

$$TBL (L) = 2 \times \text{Blood Volume} \times \frac{(Hct \text{-pre} - Hct \text{-post})}{(Hct \text{-pre} + Hct \text{-post})}$$

Male Blood Volume (L) = 0.3669 x Height (m) + 0.03219 x Weight (Kg) + 0.6041

Female Blood Volume (L) = 0.3561 x Height (m) + 0.03308 x Weight (Kg) + 0.1833

**Statistical analysis**

Using the Statistical Package for the Social Sciences version 19.0 software (IBM Corp.; Armonk, NY, USA), all data were analyzed by the research team of our department in conjunction with a medical statistician blinded of the study design. Continuous data were presented as means±standard deviation and were analyzed using paired or unpaired Student’s t-test. Categorical data were presented using proportions and were analyzed using the chi-square test with Fisher’s exact test. Odds ratios with 95% confidence intervals were calculated to compare the complication rates between the two groups. Values of p<0.05 were considered to be significant.

**Results**

Table 1 presents the baseline demographic characteristics and preoperative clinical and laboratory data. The two groups were well-matched; no significant differences were observed in age, gender, morbidity factors, PT, APTT, or fracture classification preoperatively (p>0.05). The type of anesthesia used was similar in each group (Table 2). Total intraoperative intravenous fluid administration was 557.0±135.2 mL in the TXA group, which did not significantly differ from that administered to the TXA/DEP group (540.0±130.9 mL; p>0.05). The intraoperative blood loss was 127.4±51.1 mL in the TXA group, which did not significantly differ from that sustained by the TXA/DEP group (133.6±53.9 mL; p>0.05). The mean preoperative Hb levels in the TXA and TXA/DEP groups were 117.0±13.9 g/L and 114.5±11.8 g/L (no significant difference; p>0.05). Interestingly, Hb levels in the TXA group were significantly lower than those in the TXA/DEP group, measured at 101.0±14.1 g/L vs. 106.9±10.5 g/L on postoperative day 1 and 104.2±8.2 g/L vs. 108.5±9.1 g/L on postoperative day 3 (p<0.05). Preoperative Hcts did not significantly differ from one another, at 36.4±3.2% and 36.9±3.6% in the TXA and TXA/DEP groups, respectively (p>0.05). Interestingly, Hb levels in the TXA group were significantly lower than those in the TXA/DEP group, measured at 101.0±14.1 g/L vs. 106.9±10.5 g/L on postoperative day 1 and 104.2±8.2 g/L vs. 108.5±9.1 g/L on postoperative day 3 (p<0.05). Preoperative Hcts did not significantly differ from one another, at 36.4±3.2% and 36.9±3.6% in the TXA and TXA/DEP groups, respectively (p>0.05). No significant differences were identified on postoperative days 1 and 3 and included 34.2±4.7% in the TXA group vs. 35.2±5.0% in the TXA/DEP group and 33.2±4.2% in the TXA group vs. 34.3±4.5% in the

### Table 1. Demographic characteristics and preoperative clinical data

|                  | TXA Group (n=50) | TXA/DEP Group (n=50) | p    |
|------------------|------------------|----------------------|------|
| Age (yr)         | 70.5±12.2        | 72.5±11.1            | 0.403|
| Gender           |                  |                      | 0.542|
| Male             | 22               | 19                   |      |
| Female           | 28               | 31                   |      |
| Morbidity factors|                  |                      | 0.756|
| Falling accidents | 15               | 19                   |      |
| Accidental falls | 26               | 23                   |      |
| Traffic accidents | 7                | 5                    |      |
| Assault injuries | 2                | 3                    |      |
| Preoperative PT (s) | 37.6±2.8        | 36.8±3.2             | 0.199|
| Preoperative APTT (s) | 12.8±2.2        | 12.5±2.8             | 0.548|
| Fracture classification | 0.357   |                      |      |
| A1               | 17               | 24                   |      |
| A2               | 26               | 21                   |      |
| A3               | 7                | 5                    |      |
TXA/DEP group, respectively (p>0.05). We noted significantly less drainage and TBL in the TXA/DEP group vs. the TXA group on postoperative day 2; these values included 71.4±26.0 mL vs. 82.5±24.6 mL of drainage and 343.6±148.0 mL vs. 419.6±165.4 mL of TBL; p<0.05). Furthermore, 11 patients (22%) in the TXA group and 15 (30%) patients in the TXA/DEP group required blood transfusions. The mean number of transfusion events was 1.2±0.4 in the TXA/DEP group, which was significantly less than that received by patients in the TXA group (1.9±0.7; p<0.05). The mean transfusion volumes were (2.9±1.0 Units) and (1.7±0.5 Units), respectively, which also differed significantly (p<0.05). The TXA/DEP group had overall shorter postoperative hospital stays compared with the TXA group (5.2±2.5 days vs. 5.7±2.4 days, although this difference did not reach statistical significance (p>0.05).

The incidence of postoperative complications between groups was not significantly different, as summarized in Table 3. Three patients in the TXA group and two patients in the TXA/DEP group were diagnosed with DVT of the lower extremities. No serious adverse events such as clinically significant PE or acute limb ischemia emerged during the two-week follow-up period. These patients were advised to seek further evaluation and follow-up for this condition when discharged to outpatient care.

**Discussion**

Our main finding is that combined intraoperative administration of TXA and DEP significantly reduces blood loss, drainage volume, and conditions requiring blood transfusions compared with the administration of TXA alone for trochanteric femoral fracture surgery. In addition, combined treatment of TXA and DEP did not impact the rate or nature of perioperative complications.

TXA is a simple and an inexpensive hemostatic agent and has been approved for various clinical applications (16). It is widely used in orthopedic surgery as it is easy to administer and can be provided at high concentrations directly on the site of potential bleeding (17). Recent studies have revealed that the local administration of TXA to the surgical site was as effective as an agent delivered via the intravenous route following total joint arthroplasty or spine surgery while the serum level remains

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### Table 2. Perioperative clinical data

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| Type of anesthesia   |                  |                      | 0.181 |
| General anesthesia   | 17               | 11                   |       |
| Spinal anesthesia    | 33               | 39                   |       |
| Intravenous fluid administration (mL) | 557.0±135.2 | 540.0±130.9 | 0.693 |

### Hb levels (g/L)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| Preoperatively       | 117.0±13.9       | 114.5±11.8           | 0.337 |
| 1 day postoperatively| 101.0±14.1       | 106.9±10.5           | 0.018 |
| 3 days postoperatively| 104.2±8.2       | 108.5±9.1            | 0.015 |

### Hct levels (%)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| Preoperatively       | 36.4±3.2         | 36.9±3.6             | 0.420 |
| 1 day postoperatively| 34.2±4.7         | 35.2±5.0             | 0.343 |
| 3 days postoperatively| 33.2±4.2        | 34.3±4.5             | 0.229 |

### Intraoperative total blood loss (mL)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 127.4±51.1           | 133.6±53.9       | 0.556                |       |

### Postoperative day 2 drainage (mL)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 82.5±24.6            | 71.4±26.0        | 0.031                |       |

### Total blood loss (mL)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 419.6±165.4          | 343.6±148.0      | 0.017                |       |

### Transfusion rate

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 11/50                | 6/50             | 0.183                |       |

### Mean number of transfusion events

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 1.9±0.7              | 1.2±0.4          | 0.032                |       |

### Mean transfusion amount (Unit)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 2.9±1.0              | 1.7±0.5          | 0.014                |       |

### Length of postoperative hospital stay (days)

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | p     |
|----------------------|------------------|----------------------|-------|
| 5.2±2.3              | 5.7±2.4          | 0.627                |       |

### Table 3. Perioperative complications

|                      | TXA Group (n=50) | TXA/DEP Group (n=50) | OR (95% CI) | p     |
|----------------------|------------------|----------------------|-------------|-------|
| Respiratory infection| 6                | 8                    | 0.716 (0.229-2.238) | 0.564 |
| Respiratory distress | 3                | 1                    | 3.128 (0.314-31.142) | 0.610 |
| Urinary tract infection| 1            | 2                    | 0.490 (0.043-5.582) | 1.000 |
| Urinary retention    | 3                | 5                    | 0.574 (0.130-2.545) | 0.712 |
| Superficial wound infection| 1          | 2                    | 0.490 (0.043-5.582) | 1.000 |
| Deep vein thrombosis | 3                | 2                    | 1.532 (0.245-9.587) | 1.000 |
substantially lower (18-20). This is especially critical for patients with conditions that may not tolerate high serum levels of TXA, including chronic renal dysfunction, history of previous DVT or/ and PE, and cerebrovascular and cardiovascular disease (18). Drakos et al. reported the results of a randomized trial on 200 patients with intertrochanteric fractures stabilized with intramedullary nails. In this study, TXA or placebo was administered at the fracture site just prior to completion of the procedure; administration of TXA significantly reduced blood loss and transfusion rate, which are effective measures to reduce healthcare costs (19).

The combination of TXA and DEP has been applied in various surgical settings to reduce blood loss. Substantial drops in the transfusion rate have been reported since the introduction of this formulation into the protocol for perioperative management of total joint arthroplasty. Gao et al. randomized 107 patients undergoing THA into two groups, with 53 patients receiving intra-articular TXA (3 g) plus DEP at a 1:200,000 dilution (0.25 mg) and 54 patients receiving TXA (3 g) alone. Patients in the TXA/DEP group sustained significantly less dramatic drops in Hb levels and Hct, experienced less TBL, and required fewer transfusions (8). Similar results were obtained in another study on TXA/DEP vs. TXA in a randomized trial of 100 patients undergoing total knee arthroplasty (21). Additionally, conclusions from the most recent meta-analysis focused on total joint arthroplasty suggest that this protocol could decrease perioperative blood loss without increasing the incidence of DVT or PE compared with the administration of TXA alone (22). Our study has provided similar positive clinical outcomes. To the best of our knowledge, this is first study to report a successful outcome from perioperative administration of TXA and DEP for trochanteric femoral fracture surgery. Although optimal routes of administration and doses are still to be defined, combined administration of TXA and DEP is widely used and is well-tolerated (9, 22). Our dosing strategy and outcomes are similar to those reported in the study by Drakos et al., in which 3 g of TXA administered directly on the surgical site was shown to be safe and effective (19).

Analysis of the postoperative data including Hb levels, Hct, and TBL revealed that the addition of DEP is primarily effective at controlling blood loss, thereby reducing the requirement for transfusions and the incidence of complications such as bloodstream infections, febrile, and acute immune reactions to blood products. The application of DEP is highly cost-effective compared with blood transfusion, thus relieving some from the burden of healthcare systems, especially in developing countries (23). Moreover, the length of postoperative hospital stay was shorter in the TXA/DEP group, suggesting that these patients underwent more rapid recovery. However, the differences identified in this trial were not clinically relevant.

Finally, no significant differences were noted in the incidence of postoperative complications. Current evidence regarding the safety of DEP is limited and highly dependent on the administration protocol. Some studies have reported that local application increased the risk of skin lesions (9, 24). Our surgical protocol uses a minimum number of incisions; no skin necrosis or loss was observed. DEP also introduces the theoretical risk of DVT due to platelet aggregation; its vasoconstrictive effects generated some initial resistance to the use of DEP in orthopedic surgery. Nonetheless, a body of literature has indicated that no increased risk of clinically significant vasoconstriction exists when DEP is highly diluted and administered topically (8, 21). In this study, two cases in the TXA/DEP group and three cases in the TXA group were diagnosed with DVT at postoperative day 3; this difference does not reach statistical significance, and no evidence suggests that the development of DVT was related to the use of DEP.

Some limitations should be mentioned. The most important drawback of this study was its retrospective nature and that relatively few cases were examined. Similarly, the measurement of venous thromboembolic events included only cases of asymptomatic DVT in lower extremity. Furthermore, we were limited to hospitalized cases and had no long-term follow-up. Nonetheless, this study provides evidence that the combined administration of TXA and DEP was more effective for trochanteric femoral fracture surgery than the administration of TXA alone and thus is a vital reference for future research.

In conclusion, our study revealed that the direct administration of TXA with DEP at the surgical site could limit blood loss, prevent large drops in Hb, and reduce transfusion rates with no increased risk of perioperative complications compared with the administration of TXA alone for trochanteric femoral fracture surgery. Therefore, our findings suggest that the local administration of TXA and DEP is safe and more effective than the administration of TXA alone in treating trochanteric femoral fractures.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (L-2014-37).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept - X.X., Y.H.; Design - Y.H.; Supervision - L.X.; Resources - X.X.; Materials - L.X., H.Y.; Data Collection and/or Processing - H.Y.; Analysis and/or Interpretation - L.X.; Literature Search - X.X. H.Y.; Writing Manuscript - X.X. L.X.; Critical Review - X.X., Y.H.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.
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