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Effects of aminocaproic acid on perioperative hidden blood loss in elderly patients with femoral intertrochanteric fracture treated with proximal femoral nail anti-rotation

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Abstract

Objective: To determine the efficacy of aminocaproic acid on perioperative hidden blood loss (HBL) in elderly patients with femoral intertrochanteric fracture treated with proximal femoral nail anti-rotation (PFNA).

Methods: Seventy consecutively admitted elderly patients with femoral intertrochanteric fracture treated with PFNA between 1 May 2017 and 1 May 2018 were recruited. The patients were randomised into the experimental and control groups receiving 1 g aminocaproic acid in 200 mL saline and only 200 mL normal saline intravenously, respectively. The following factors were recorded: demographic characteristics, haemoglobin and haematocrit levels on preoperative day 1 and postoperative days 1 and 3, surgical blood loss, postoperative drainage, the rate and volume of transfusion, and complications.

Results: No significant differences were seen in surgical blood loss and postoperative drainage between the experimental and control groups, though total blood loss was greater in the control group. Visible blood loss and HBL were significantly lower in the experimental group than in the control group, and a lower rate and volume of transfusion were also recorded in the experimental group.

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Conclusion: Aminocaproic acid significantly reduced perioperative HBL and volume and rate of transfusion in elderly patients with femoral intertrochanteric fracture receiving PFNA.

Keywords
Blood loss, femoral fracture, aminocaproic acid, intramedullary nail, hidden blood loss, elderly patients

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Introduction

Femoral intertrochanteric fracture is one of the most common types of hip fracture seen in the elderly population. Epidemiological studies estimate that >3 million cases of femoral intertrochanteric fractures are likely to occur across the globe by 2050.[1,2] Fractures in the elderly are often associated with underlying diseases, such as hypertension and diabetes. The estimated 1-year mortality rate among elderly patients with femoral intertrochanteric fracture is 27% to 30%, and it increases to 36.2% to 50% among those receiving conservative treatment,[3] thereby making its clinical management challenging and difficult for orthopaedic surgeons.

The surgical fixation approaches for fractures are classified as intramedullary or extramedullary. The extramedullary approach exposes the fracture and facilitates intraoperative reduction and fixation but requires more extensive dissection of soft tissues, which can lead to greater surgical trauma and slower postoperative recovery. However, intramedullary implantation, an example of which is proximal femoral nail anti-rotation (PFNA), is minimally invasive and results in less trauma, less intraoperative blood loss, fewer complications, a higher fracture healing rate, and a lower internal fixation failure rate.[4]

In recent years, intramedullary fixation has become commonplace in the treatment of elderly patients with a femoral intertrochanteric fracture. On the basis of its minimal invasiveness, patients can be rehabilitated early, thereby reducing the risk of hypostatic pneumonia, bedsores, lower extremity deep vein thrombosis (DVT), and other complications resulting from being bed-ridden. However, although the operative time and intraoperative blood loss are greatly reduced by PFNA, a perioperative reduction in haemoglobin level has been observed.[5] Postoperative anaemia in elderly patients often causes related complications, thereby extending hospitalization and increasing the physiological, psychological, and economic burden on the patients. The concept of hidden blood loss (HBL) was introduced by Sehat et al.[6] in a study evaluating the total blood loss after total knee arthroplasty. HBL is a key issue in elderly patients with femoral intertrochanteric fracture receiving PFNA.

The measures to reduce perioperative blood loss include preoperative and postoperative supplementation with iron and erythropoietin (EPO),[7] intraoperative hypertension control,[8] autologous blood doping,[9] and anti-fibrinolytic drugs, such as tranexamic acid (TXA).[10] Studies have shown that TXA considerably reduces perioperative HBL in joint replacement surgery, spinal surgery, and intertrochanteric femur fracture surgery. Aminocaproic acid, a derivative of the amino acid

lysine,[11] competitively inhibits the enzymes that bind to the lysine binding sites, for example, that of the fibrinolytic enzyme, plasmin. By inhibiting these enzymes, aminocaproic acid can reduce acute blood loss due to excessive fibrinolytic activity. Several clinical studies have shown that aminocaproic acid effectively reduces HBL during the perioperative period following total knee and total hip arthroplasty.[12,13] To the best of our knowledge, only a few studies so far have examined the role of aminocaproic acid in reducing perioperative HBL in femoral intertrochanteric fractures. Therefore, we conducted a prospective randomised controlled trial to determine the efficacy of aminocaproic acid in decreasing HBL in elderly patients with femoral intertrochanteric fractures undergoing the PFNA procedure.

Methods

Patients

A prospective randomised controlled clinical trial was conducted in elderly patients with stable and unstable femoral intertrochanteric fractures who were admitted in our department between 1 May 2017 and 1 May 2018. The inclusion criteria were: (1) $\geq$60 years old with no severe systemic disease, (2) normal platelet count, prothrombin time, partial thromboplastin time, and international normalised ratio, (3) low-energy trauma, and (4) availability of complete medical records in the perioperative period. The exclusion criteria were: (1) allergy to aminocaproic acid, (2) history of recent or ongoing thromboembolic event (pulmonary embolism or DVT), (3) history of recent anticoagulation therapy, (4) history of subarachnoid bleeding, malignancy, pathological fracture, or prior surgery on the injured hip, (5) disseminated intravascular coagulation or hepatic/renal diseases with impaired coagulation function, and (6) American Society of Anesthesiologists (ASA) classification level IV. The study was approved by the ethics committee of our hospital (reference number: ZYSY-16-24), and signed informed consent was obtained from each patient before surgery.

Intervention

The patients were randomised (using computer-generated random numbers) into the experimental and control groups, and were administered 1 g aminocaproic acid in 200 mL saline or only 200 mL normal saline (NS) intravenously, respectively, after anaesthesia but before surgery. All patients underwent PFNA (Dabo Medical Corporation, Xiamen, China) performed by the same orthopaedic surgeon. Anaemia was defined as a haemoglobin level of $<$90 g/L, and anaemic patients were infused with red blood cells (RBCs).

Outcome measurement

The demographic details, such as age, gender, body mass index (BMI), side of injury (right/left), AO fracture classification, and ASA classification were obtained. The haemoglobin level and haematocrit (Hct) on preoperative day 1, and postoperative days 1 and 3 were recorded from the hospital information system. The anaesthesiologist estimated perioperative blood loss. Postoperative drainage, and RBC transfusion rate and volume were also recorded. Complications, including surgical site infection, DVT, pulmonary embolism, haematoma, pneumonia, and renal failure, were noted.

Nadler's formulae were used to calculate blood volume, visible blood loss, and HBL[14–16] as follows:

$$\text{Blood volume (L)} = K1 \times \text{height (m3)} + K2 \times \text{weight (kg)} + K3$$

For males, K1 = 0.3669, K2 = 0.03219, and K3 = 0.6041; for females, K1 = 0.3561, K2 = 0.03308, and K3 = 0.1833.

Total blood loss (L) = Blood volume × (Hctpreop − Hctpostop)

Hctpreop was defined as Hct on preoperative Day 1; and Hctpostop as Hct on postoperative Day 3.

Visible blood loss (L) = (Surgical blood loss + postoperative drainage) × [(Hctpreop − Hctpostop)/2]

Hidden blood loss (L) = Total blood loss − visible blood loss + transfused blood.

Statistical analysis

The data were analysed using SPSS v22.0 for Mac (IBM Corp., Armonk, NY, USA). Continuous data are presented as mean±standard deviation (mean ± SD), categorical data are presented as percentages and frequency counts. The chi-squared test or Student's t-test was used to compare the demographic and clinical characteristics. In addition, a non-parametric test was used to evaluate the ASA classification. A P-value < 0.05 was considered statistically significant.

Results

A total of 121 elderly patients with a femoral intertrochanteric fracture were treated in our hospital between 1 May 2017 and 1 May 2018, of which 72 were enrolled in our study according to the inclusion and exclusion criteria. After randomization, 36 patients were administered aminocaproic acid and 36 were given normal saline. One patient died in each group, leaving 35 patients for the analysis (Figure 1). We found no significant differences between the two groups in terms of the demographic characteristics (Table 1).

Surgical blood loss (135.40 ± 23.10 mL vs. 138.50 ± 22.48 mL; P = 0.46) and postoperative drainage (90.12 ± 33.45 mL vs. 91.20 ± 34.05 mL; P = 0.93) were similar between the experimental and control groups. However, the total blood loss was higher in the control group compared with that in the experimental group (725.35 ± 106.85 mL vs. 612.75 ± 104.25 mL; P = 0.004), while transfusion volume and rate were lower in the experimental group than in the control group (155.15 ± 35.50 mL vs. 260.45 ± 34.28 mL; P = 0.019, and 35.16% vs. 62.71%; P = 0.01, respectively). Visible blood loss and the HBL were also significantly lower in the experimental group as compared with that in the control group (224.71 ± 45.16 mL vs. 271.25 ± 44.67 mL; P = 0.025 and 501.28 ± 35.17 mL vs. 664.37 ± 38.29 mL, respectively; P = 0.005) (Table 2).

All patients were followed up for 1 month after surgery, and no significant difference was seen between the two groups in terms of complications (Table 3). Patients with surgical site infection, pulmonary embolism, haematoma, pneumonia, and renal failure were cured successfully with conservative treatment. Two of the three patients with DVT were treated with an inferior vena cava filter.

Discussion

Femoral intertrochanteric fracture in elderly patients is a surgical challenge due to substantial perioperative blood loss that can affect postoperative recovery and mortality. The intramedullary nail is superior to extramedullary devices for reducing surgical trauma, blood loss, and other complications.[17,18] TXA is also widely used to reduce HBL during the perioperative period and is associated with good clinical outcomes.

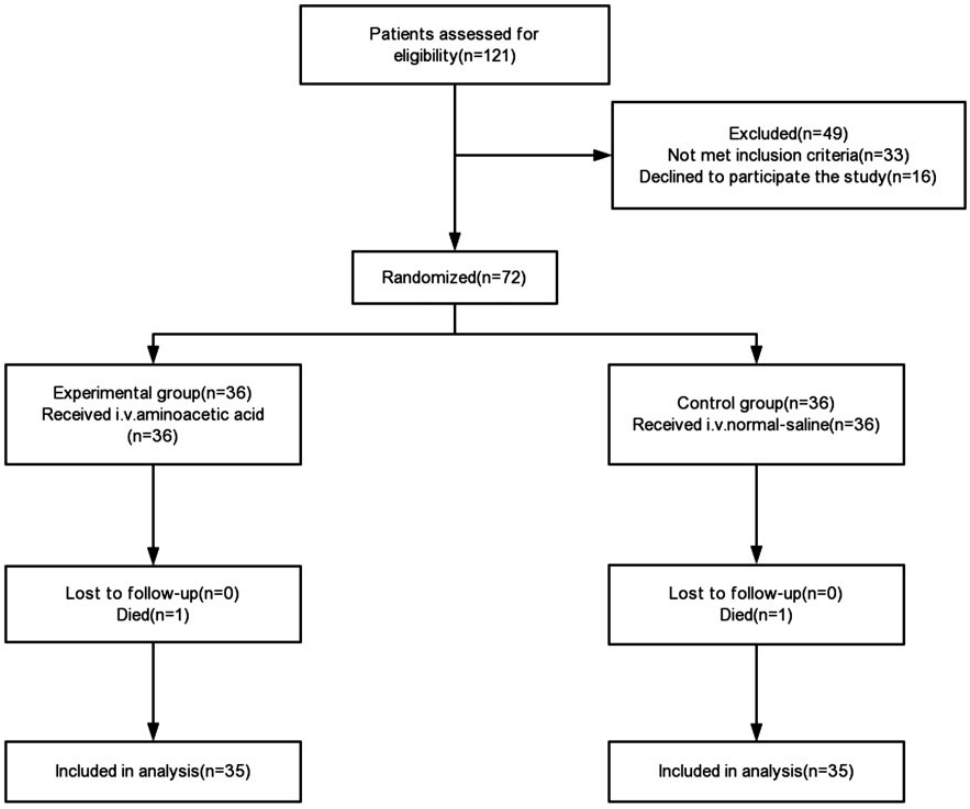

Figure 1. Study flow-chart.

Table 1. Demographic information of the enrolled patients.

Variables	Experimental group (n = 35)	Control group (n = 35)	P value
Female (%)	31 (88.57)	30 (85.71)	0.82#
Age (years)	78.50 ± 9.15	79.10 ± 8.95	0.58^
BMI	23.14 ± 2.15	23.26 ± 2.27	0.62^
Injured side (Left/Right)	17/18	19/16	0.69#
AO classification			
31 A1	13	14	0.72#
31 A2	11	12	
31 A3	11	9	
ASA classification			
I	6	7	0.81*
II	17	17	
III	10	11	

#Chi-squared test; ^two-sided Student's t test; *non-parametric test; BMI, body mass index;
ASA (American Society of Anesthesiologists) classification level IV removed owing to exclusion criteria.

Table 2. Comparison of perioperative clinical outcome between the experimental group and control group.

Variables	Experimental group (n = 35)	Control group (n = 35)	P value
Surgical blood loss (mL)	135.40 ± 23.10	138.50 ± 22.48	0.46^
Postoperative drainage (mL)	90.12 ± 33.45	91.20 ± 34.05	0.93^
Total blood loss (mL)	612.75 ± 104.25	725.35 ± 106.85	0.004^
Transfusion rate (%)	35.16	62.71	0.01#
Transfusion (mL)	155.15 ± 35.50	260.45 ± 34.28	0.019^
Visible blood loss (mL)	224.71 ± 45.16	271.25 ± 44.67	0.025^
Hidden blood loss (mL)	501.28 ± 35.17	664.37 ± 38.29	0.005^

^Two-sided Student's t test; #chi-squared test.

Table 3. Comparison of the postoperative complications between the two groups.

Complications	Experimental group (n = 35)	Control group (n = 35)	P value#
Surgical site infection	1	2	0.60
Deep vein thrombosis	1	2	0.60
Pulmonary embolism	0	1	1.00
Haematoma	1	3	0.34
Pneumonia	2	3	0.91
Renal failure	1	0	1.00

#Chi-squared test.

Aminocaproic acid is a novel antifibrinolytic drug that has recently been used in total hip and knee arthroplasty to reduce blood loss.[19,20] Our prospective randomised controlled clinical trial aimed to examine the efficacy of aminocaproic acid to treat perioperative HBL following femoral intertrochanteric fracture in elderly patients.

We found no significant differences in terms of surgical blood loss and drainage in the experimental and control groups, which is probably explained by the same surgical method being used in both groups. However, the total blood loss in the control group was higher than in the experimental group. Because the demographic characteristics of the patients were similar between the groups, we surmised that an aminocaproic acid-mediated reduction in the perioperative Hct (Hctpreop – Hctpostop) was responsible for a similar visible blood loss observed in the groups. Previous studies have estimated a 19% to 60% perioperative blood transfusion rate in patients with hip fracture.[21,22] A higher volume of transfused blood adds to the cardiac load, and thus increases the risk of heart failure. The experimental group showed a lower transfusion rate and volume compared with those in the control group. This is in accordance with the findings of Hobbs et al.[20] who showed that aminocaproic acid reduced blood loss and transfusion rate during primary arthroplasty.

The potential mechanism and advantage of the application of aminocaproic acid in reducing hidden blood loss are to directly target the site of bleeding just before wound closure after surgical haemostasis has been achieved. The inhibited local fibrinolytic activity helps to prevent fibrin clot dissolution and increases its volume and strength at the raw surgical surfaces, thus enhancing microvascular haemostasis.

The patients receiving aminocaproic acid also had lower HBL as compared with that in the control patients. Liu et al.[23] found that a BMI < 25 kg/m2, intramedullary nail surgery, and a haemoglobin level at admission <30 g/L were associated with a higher risk of HBL in elderly patients with a femoral intertrochanteric fracture. Lei et al.[24] found that TXA reduced HBL in patients with intertrochanteric fracture undergoing PFNA. Several factors can affect the HBL, such as preoperative blood loss, which is not reflected in the primary haemoglobin and haematocrit levels, postoperative anti-coagulant treatment,[21] and different intramedullary fixation methods.[25]

We treated patients with a low dose of aminocaproic acid (1 g) to avoid the possible risk of thrombosis. However, recent studies and meta-analyses have not unequivocally shown that anti-fibrinolytic drugs TXA or aminocaproic acid increase the risk of thrombosis.[12,26,27] Finally, the incidence of complications, such as surgical site infection, haematoma, DVT, and pulmonary embolism was also similar between the groups. In our study, we used TXA 1 g in 200 mL normal saline as recommended by Wingerter et al.[26] To avoid bias from using different doses of different drugs, we also used 1 g of aminocaproic acid in 200 mL normal saline. We considered that different doses of aminocaproic acid may affect the perioperative HBL in elderly patients with femoral intertrochanteric fracture treated with PFNA.

Our study had two major limitations that should be considered. First, the sample size was small, which might have influenced the statistical significance, and second, we evaluated the complications only during the first month after surgery and did not determine the long-term effects. A multi-centre, randomised controlled clinical trial with a larger sample size should be performed in the future. The effects of different doses of aminocaproic acid should also be investigated.

Conclusion

Aminocaproic acid significantly reduced perioperative HBL and transfusion rate in elderly femoral patients with intertrochanteric fracture treated with PFNA. Our findings need to be validated in a larger cohort study and should be compared with those seen with other fibrinolytic drugs, such as TXA.

Declaration of conflicting interest

The authors declare that they have no conflicts of interest.

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