

Original Research Article

Efficacy of erythropoietin combined with tranexamic acid in reducing perioperative blood loss and blood transfusion rate in elderly patients with femoral intertrochanteric fractures

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Abstract

Purpose: To investigate the efficacy of exogenous recombinant human erythropoietin (rhEPO), combined with tranexamic acid (TXA) and administered by different routes, in the treatment of elderly patients with femoral intertrochanteric fractures.

Methods: 252 elderly patients in Suzhou Xiangcheng People's Hospital were randomly divided into groups (A, B and C), with 84 patients in each group. All the patients were given rhEPO and iron sucrose, followed by TXA which was administered via topical injection at the fracture site in Group A, via intravenous infusion in Group B, and via topical injection combined with intravenous infusion in Group C. The perioperative actual total blood loss, occult blood loss, hematocrit (HCT), platelet count (PLT), hemoglobin (Hb), and activated partial thromboplastin time (APTT) were assessed. Also evaluated were prothrombin time (PT), fibrinogen (FIB), blood transfusion rate and incidence of deep venous thrombosis (DVT) of the lower limbs. The results were then compared among the three groups.

Results: Perioperative total blood loss and occult blood loss as well as the blood transfusion rate were lowest in Group C, followed by Group B and then Group A. The differences were statistically significant ($p < 0.05$). The HCT and Hb levels were highest in Group C, followed by Group B and then Group A ($p < 0.05$).

Conclusion: Multi-modal administration of drugs (rhEPO combined with topical injection and intravenous infusion of TXA) is effective in treating elderly patients with femoral intertrochanteric fractures. The strategy efficiently reduces perioperative blood loss and blood transfusion rate, and also improves relevant blood biochemical indicators.

Keywords: Femoral intertrochanteric fracture, Elderly, Erythropoietin, Tranexamic acid, Blood loss, Blood transfusion rate

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INTRODUCTION

Femoral intertrochanteric fracture, a common type of hip fractures, is one of the leading causes

of hospitalization in elderly patients. Its attack increases fracture-related mortality and reduces the activity and quality of life of patients. Increasing cases with unstable femoral intertrochanteric fractures are mainly treated by

surgery [1,2]. Great attention should be paid to blood management in the clinic, since massive perioperative blood loss may cause death.

Exogenous recombine human erythropoietin (rhEPO) aids improvement in the hemoglobin (Hb) levels, as well as the reduction of the blood transfusion rate in fracture patients [3]. Tranexamic acid (TXA) is an artificial synthetic antifibrinolytic agent able to reduce the perioperative blood loss and transfusion of patients undergoing proximal femoral nail antirotation (PFNA) for fractures [4]. In contrast to topical administration of TXA alone, intravenous combined with topical administration of TXA shows a lower blood transfusion rate and more beneficial biochemical indicator (e.g., Hb) level [5].

However, there are currently few reports on the application of different administration routes of TXA combined with EPO in patients with femoral intertrochanteric fractures, whose effects still need to be demonstrated by more studies.

In this study therefore, the effects of rhEPO combined with TXA administered by different routes in the treatment of elderly patients with femoral intertrochanteric fractures were investigated, in order to further optimize blood management protocols for elderly patients with femoral intertrochanteric fractures.

METHODS

General patient profile

Following approval from the Ethics Committee of the Suzhou Xiangcheng People's Hospital, China, 252 elderly patients with femoral intertrochanteric fractures who underwent elective surgery in Suzhou Xiangcheng People's Hospital from January 2019 to January 2022 were included in the study and randomly assigned to three groups (A, B and C), with 84 patients in each group. Group A was comprised 27 males and 57 females, aged 62 - 87 years (mean, 75.44 ± 6.83 years), and in terms of Evans-Jensen classification, there were 21 cases of type II and 63 cases of type III. Group B included 29 males and 55 females aged 61 - 85 years (mean, 74.39 ± 6.95 years), and in terms of Evans-Jensen classification, there were 20 cases of type II and 64 cases of type III. Group C consisted of 28 males and 56 females aged 64 - 88 years (mean, 75.63 ± 6.77 years), and in terms of Evans-Jensen classification, there were 23 cases of type II and 61 cases of type III. No statistically significant differences were observed

in the general profile of the patients among the three groups ($p > 0.05$).

Inclusion criteria

(1) Patients who presented with hip joint pain and met the diagnostic criteria for femoral intertrochanteric fractures [6], and was confirmed by x-ray examination; (2) patients aged ≥ 60 years; (3) patients who met the indications for reduction and internal fixation with PFNA; and (4) patients who were informed of the treatment risks and benefits, and signed informed consent.

Exclusion criteria

Patients with the following conditions were excluded: (1) hematological diseases, bleeding tendency or blood coagulation dysfunction; (2) deep venous thrombosis (DVT) of lower limbs or severe cardiovascular or cerebrovascular diseases before surgery; (3) allergy to drugs in this study or who took anticoagulants, thrombolytic or hemostatic agents in the past 7 days; (4) multiple fractures or pathological fractures.

Treatments

The therapeutic agent (rhEPO; Shenyang Sunshine Pharmaceutical Co. Ltd, NMPA: S20010001, strength: 10000 IU) and iron sucrose (Nanjing Hencer Pharmaceutical Co. Ltd, NMPA: H20113004, strength: 200 mg/10 mL) were routinely given to all the patients for blood management. Specifically, the patients were treated with intravenous infusion of 100 mg of iron sucrose, 3 times/week, and subcutaneous infusion of rhEPO 150 IU/kg once daily, until 7 days after surgery. In addition, in Group A, 2 g of TXA (Shanxi Pude Pharmaceutical Co. Ltd, NMPA: H14020887, strength: 5 mL, i.e., 0.25 g, was administered *via* topical injection at the fracture site after the deep fascia was sutured, and then the incision was closed. In Group B, 1 g of TXA was mixed with 100 mL of 0.9 % sodium chloride injection, and the mixture was given *via* intravenous drip infusion 10 - 15 min before the skin incision was made. In Group C, TXA was administered *via* topical injection combined with intravenous infusion, with the same procedures as those in Groups A and B.

Evaluation of parameters/indices

Total blood loss and occult blood loss

The perioperative actual total blood loss and occult blood loss were calculated as in the

following equations and then compared among the three groups.

1) Actual total blood loss = theoretical value of total blood loss + allogeneic red blood cell transfusion volume during and after surgery.

2) Theoretical value of total blood loss = total blood volume \times difference of hematocrit (HCT) before and after surgery.

3) Total blood volume = k_1 (male: 0.3669, and female: 0.3561) \times height³ + k_2 (male: 0.03219, and female: 0.03308) \times body mass (kg) + k_3 (male: 0.6041, and female: 0.1833)

4) Occult blood loss = actual total blood loss - dominant blood loss (where dominant blood loss represented the volume of red blood cell loss that was visible in medical materials) (including gauze and rinse fluid increments) during the perioperative period.

Blood biochemical indicators

Fasting venous blood was drawn from each patient before and 3 days after surgery. The blood biochemical indicator levels including HCT, platelet count (PLT) and Hb were measured using the XY-9021 whole-blood cell analyzer (Roche), and then compared among the three groups.

Fasting venous blood was collected from each patient before and 3 days after surgery. The blood coagulation indicator levels including activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen (FIB) were detected using the CA1500 automatic blood coagulator (Sysmex Corporation, Japan), and then compared among the three groups.

Blood transfusion rate

The number of patients with blood transfusion was counted and the blood transfusion rate was calculated.

DVT incidence

Both lower limbs were examined by color Doppler ultrasound 7 d after surgery, to observe the presence or absence of DVT events. Then the DVT incidence was compared among the three groups.

Statistical analysis

Statistical Package for Social Sciences (SPSS) 23.0 software (IBM, Armonk, NY, USA) was adopted for statistical analysis. Measurement

data (including perioperative actual total blood loss and occult blood loss, and the blood biochemical and blood coagulation indicator levels) were compared by the *F* test and expressed as mean \pm standard deviation (SD). Enumeration data (including blood transfusion rate and DVT incidence) were analyzed by χ^2 test and expressed as percentage (%). *P* < 0.05 was considered statistically significant.

RESULTS

Perioperative total blood loss and occult blood loss

The perioperative total blood loss and occult blood loss were lowest in Group C, followed by Groups B and A, respectively (*p* < 0.05; Table 1).

Table 1: Comparisons of perioperative total blood loss and occult blood loss among the three groups (mean \pm SD, mL, n = 84)

Group	Total blood loss	Occult blood loss
A	425.34 \pm 53.12	285.67 \pm 23.19
B	364.77 \pm 45.68	241.34 \pm 20.15
C	278.45 \pm 40.29	192.18 \pm 20.26
<i>F</i>	210.250	406.960
<i>P</i> -value	< 0.001	< 0.001

Blood biochemical indicators

After surgery, the difference in PLT showed no statistical significance among the three groups (*p* > 0.05), while HCT and Hb levels were highest in Group C, followed by Groups B and A respectively (*p* < 0.05; Table 2).

Blood coagulation indicators

After surgery, the APTT, PT and FIB did not exhibit statistically significant difference among the three groups (*p* > 0.05; Table 3).

Blood transfusion rate and incidence of DVT

Blood transfusion rate was lowest in Group C, followed by Groups B and A, respectively (*p* < 0.05); however, there was no significant difference in DVT incidence among the three groups (*p* > 0.05; Table 4).

DISCUSSION

Femoral intertrochanteric fractures will become an increasingly serious socio-economic problem with the onset of an aging population. It is mainly treated with surgeries, and clinical consensus has been reached regarding active preoperative preparation to ensure the safety of fracture

Table 2: Comparison of blood biochemical indicators among the three groups (mean \pm SD, n =84)

Group	HCT (%)		PLT ($\times 10^{11}$)		Hb (g/L)	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
A	40.78 \pm 5.31	28.53 \pm 2.16*	184.26 \pm 59.43	219.39 \pm 25.45*	114.36 \pm 23.15	71.69 \pm 14.29*
B	40.77 \pm 5.29	31.47 \pm 2.35*	187.67 \pm 54.32	221.58 \pm 28.77*	115.37 \pm 23.56	89.45 \pm 15.37*
C	40.69 \pm 5.23	35.37 \pm 2.59*	185.49 \pm 55.68	225.67 \pm 29.41*	114.29 \pm 23.44	106.32 \pm 20.56*
F	0.010	175.590	0.080	1.090	0.060	87.550
P-value	0.993	< 0.001	0.925	0.337	0.946	< 0.001

*P < 0.05 vs. before surgery

Table 3: Comparison of blood coagulation indicators among the three groups (mean \pm SD, n =84)

Group	APTT (s)		PT (s)		FIB (g/L)	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
A	30.54 \pm 2.47	35.67 \pm 3.25*	12.37 \pm 2.31	13.67 \pm 2.17*	3.87 \pm 0.35	4.59 \pm 0.84*
B	30.16 \pm 2.43	35.44 \pm 3.17*	12.19 \pm 2.15	13.26 \pm 2.11	3.93 \pm 0.31	4.48 \pm 0.89*
C	30.19 \pm 2.58	36.18 \pm 3.22*	12.23 \pm 2.26	13.71 \pm 2.14	3.91 \pm 0.27	4.76 \pm 0.92
t	0.600	2.670	0.150	1.140	0.810	2.140
P-value	0.548	0.071	0.861	0.322	0.447	0.120

*P < 0.05 vs. before surgery

Table 4: Comparison of blood transfusion rate and incidence of DVT among the three groups (n, (%), N = 84)

Group	Blood transfusion rate	DVT incidence
A	29 (34.52)	5 (5.95)
B	20 (23.81)	1 (1.19)
C	13 (15.48)	7 ()
χ^2	8.257	
P-value	0.016	

treatment. Blood transfusion preparation is vital for surgical treatment, but there is a social problem which is that the demand for blood supply has increased, and blood transfusion itself has certain potential risks. Therefore, great attention should be paid to blood management. Based on multivariate logistic regression analysis, advanced age, fracture type and Hb at admission are considered as independent risk factors for postoperative blood transfusion [7]. For fracture patients with the above high-risk factors, it is clinically believed that monitoring perioperative Hb level is crucial for the timely correction of severe anemia and the prevention of anemia. EPO is a peptide hormone and hematopoietic growth factor that not only stimulates the formation of bone marrow erythrocytes through the dimer erythropoietin receptor, but also participate in bone remodeling and angiogenesis induction through signal pathways. In the hypoxic environment of bone marrow hypoxia, there is an irrevocable link between bone homeostasis and hematopoiesis,

and the fine balance activity of osteoblasts in bone synthesis and osteoclasts in bone absorption contributes to the continuous bone remodeling [8]. Long *et al* [9] reported that the blood transfusion volume (1.96 \pm 0.85 units) and blood transfusion rate (25.8 vs. 55.0 %) were significantly lower, though postoperative Hb level was significantly higher and the length of hospital stay was significantly shorter in the trial group (combined with EPO) than those in control group (iron). The pharmacological mechanism of TXA is the suppression of the activation of plasminogen to plasmin and the degradation of fibrin, and then the stabilization of the clotting plaque, thus exerting a hemostatic effect [10].

The results of the present study showed that perioperative total blood loss and occult blood loss were the lowest, while blood transfusion rate was lowest in Group C, followed by Groups B and A respectively. The HCT and Hb levels were highest in Group C, followed by Groups B and A respectively, while APTT, PT, FIB and DVT incidence did not differ significantly among the three groups. These findings indicate that the multi-modal administration of drugs (rhEPO combined with systemic and topical application of TXA) throughout the whole treatment process reduced blood loss and transfusion, and improved indicators related to blood biochemistry and blood coagulation, consistent with reports by Li *et al* [11].

Relative to dominant blood loss, occult blood loss is concealed, with relatively complex

mechanisms, mainly involving hematopoiesis function decline in the elderly population, red blood cell loss due to the use of anticoagulant agents and surgical trauma, and hemolysis resulting from the increase in red blood cell permeability and cell fragility caused by fractures. In the multi-mode application of TXA, topical injection targets drug delivery, thus directly increasing local drug concentration and reducing systemic side effects. While systemic administration *via* intravenous drip infusion expanded the scope of efficacy and effectively suppressed the fibrinolysis activated by surgery, thus reducing the bleeding volume. By and large, the individual advantages of each of the methods can be derived through their combined administration, as this enhances the hemostatic effect and improves blood biochemical indicators. Moreover, a rapid and effective hemostasis is able to diminish blood loss and reduce blood transfusion rate, as the hypercoagulable state of blood would not easily occur.

CONCLUSION

Multi-modal administration of drugs (rhEPO combined with topical injection and intravenous infusion of TXA) is effective in treating elderly patients with femoral intertrochanteric fractures. This strategy efficiently reduces perioperative blood loss and blood transfusion rate, as well as improves the relevant blood biochemical indicators.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of the Suzhou Xiangcheng People's Hospital, China.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Dongyang Zhao and Jin Chen contributed equally to this work.

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