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Original Article

Timing of tranexamic acid administration in elderly patients with intertrochanteric fracture

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Abstract: This study aimed to explore the safety and effects of tranexamic acid administration at different time points, in elderly patients with intertrochanteric fracture treated by proximal femoral nail anti-rotation (PFNA) measured by the blood loss in perioperative. A total of 120 elderly patients with intertrochanteric fracture admitted to our hospital from January 2016 to April 2018 were divided into group A (GA, n=40), group B (GB, n=40) and the control group (CG, n=40) according to different administration of treatment. The operation time, length of hospital stay, blood loss, changes of coagulation function, incidence of postoperative complications, joint function scores before and after operation, overall response rate, as well as Hb and Hct levels of the three groups were compared. The total blood loss, dominant blood loss, intraoperative blood loss, postoperative drainage volume, recessive blood loss and blood transfusion rate in GA and GB were lower than those in CG ($P<0.05$), and GB expressed lower total blood loss, postoperative drainage volume, recessive blood loss and blood transfusion rates than GA ($P<0.05$). No significant difference was observed in prothrombin time, activated partial thromboplastin time, fibrinogen incidences of limb swelling, intramuscular vein thrombosis and incision fat liquefaction among the three groups ($P>0.05$). After operation, Harris scores increased in all three groups and were highest in GB ($P<0.05$). The overall response rate, Hb and Hct levels of GB were higher than GA and CG at 1 d and 5 d after operation ($P<0.05$). Compared with single administration before operation, intravenous drip of tranexamic acid before and at 7 h after operation can effectively and safely reduce the blood and hemoglobin loss in elderly patients with intertrochanteric fracture and thus it is beneficial to postoperative recovery of joint function with a high overall response rate.

Keywords: Tranexamic acid, intertrochanteric fracture, blood loss, safety

Introduction

Studies have shown that patients with intertrochanteric fracture generally have anemia after operation, and the severity of anemia is correlated with intraoperative blood loss, which may be related to recessive blood loss during perioperative period. PFNA is a commonly used operating method for the treatment of intertrochanteric fracture [1-3]. Although the amount of dominant blood loss is small, the recessive blood loss is significant and accounts for about 84.5% of the total blood loss [4-6]. If not treated in time, it will aggregate and affect incision healing and chronic diseases [7-9], inducing severe anemia, or even shock and perioperative death. Therefore, it is very important to reduce the amount of recessive blood loss after PFNA treatment in elderly patients with intertrochanteric fracture [10-12].

Tranexamic acid can competitively inhibit the binding of profibrolysin and fibrin, prevent the activation of profibrolysin, and achieve the purpose of hemostasis [13-15]. Preoperative application of tranexamic acid along with PFNA treatment in patients with intertrochanteric fracture could effectively reduce total blood loss, recessive blood loss and blood transfusion rates [16]. However, the most optimal timing of tranexamic acid administration has not been determined. The purpose of this study was to explore the safety and effects of tranexamic acid administration at different time points on the blood loss in the perioperative period of elderly patients with intertrochanteric fracture treated with PFNA.

Materials and methods

General materials

A total of 120 elderly patients with intertrochanteric fracture admitted to our hospital from January 2016 to April 2018 were included according to the following criteria: (1) With surgical indications for treatment with PFNA; (2) Aged >60 years; (3) With normal coagulation function before operation; (4) Informed consent was provided by patients and their family members. Exclusion criteria: (1) Complications of malignant tumors, fractures at other sites, severe hemorrhagic diseases, liver and kidney insufficiency, pathologic fracture and old fractures; (2) Allergic to tranexamic acid; (3) Previous history of thrombogenesis. Patients were divided into group A (GA, n=40), group B (GB, n=40) and control group (CG, n=40) according to the mode of administration. The study has been approved by the Ethics Committee of our hospital.

Methods

Preoperative preparation: After admission, anti-hypertension and anti-hyperglycaemia treatments were provided to patients based on their underlying diseases. Imaging means such as hip X-ray and B-ultrasound of veins of the lower extremity were adopted to evaluate patients' conditions and the specific conditions of fracture. Routine blood tests and tests of liver, kidney and coagulation functions were conducted. Cefmetazole was administered by intravenous drip in case of infection.

Operating method: All patients were treated with PFNA. They lied on their back and were locally anaesthetized at the femoral nerve and lateral femoral cutaneous nerve. Closed reduction was performed under the guidance of a C-arm machine, followed by disinfection and draping. The skin and subcutaneous tissue were cut open by a 5cm incision to expose the greater trochanter of femur, and a guide needle was inserted for aming. The fracture was fixed with appropriate bone nails. A guide needle was inserted into the femoral neck and then PFNA screw blades were driven in and locked. The distal end was drilled and locked with interlocking screws and caps. In these steps, bone nail position, effects of inserting a guide needle into the femoral neck and distal interlocking were affirmed by C-arm machine examinations. Afterwards, the incision was rinsed with normal saline, placed with an indwelling drainage tube and sutured to end the operation. All operations were performed by the same medical team.

Postoperative treatment: Pneumatic pumps for extremities were used and the anticoagulant Rivaroxaban was administered 1 d after operation. Fluid supplements were given within 24 h and the volume was less than 2,000 ml in case of short-term changes in blood volume affecting the calculating results. The affected limb was raised by 30° at 1 d after operation, and long muscles, such as the quadriceps femoris, was exercised by appropriate contraction; patients were guided to passively and persistently exercise the hip and knee joints on the affected side, 2 d after operation to appropriately promote the blood circulation in the veins of the lower extremities; 3 d after operation, hip joint flexion and extension exercise was under taken on the affected side; and 7 d after operation, the hip, knee and ankle joints were actively flexed and extended. Standing and walking exercises were arranged according to each patient's individual conditions.

Administration of tranexamic acid

Tranexamic acid was administered to patients in GA and GB at the dose of 15 mg/kg by intravenous drip 20 min before operation, and supplemented at a dose of 1 g additionally for patients in GB at 7 h after operation. For patients in CG, normal saline of equivalent volume was administered at 20 min before operation by intravenous drip.

Observation indicators

The primary observation indicators included blood loss, blood biochemical indicators, hemoglobin and Hct. The secondary observation indicators included perioperative indicators, complications, joint function score and overall response rate.

Perioperative indicators

The operation time and length of hospital stay were recorded for all patients. The operation time refers to the time from the start of anesthesia in the operating room to the complete end of the operation. The length of hospital stay refers to the time from the first day of admission until the patient is discharged from hospital.

Blood loss

Blood volume was calculated according to the formula proposed by Nadler and his colleagues [17] as follows: blood volume = k_1 × Height (m)^3 + k_2 × Weight (kg) + k_3, where constants k_1, k_2 and k_3 are 0.3561, 0.03308 and 0.1833 for female, 0.3669, 0.03219 and 0.6041 for male. Routine blood tests were performed at 1 d before operation and 1 d, 3 d and 5 d after operation to record Hct. Total blood loss was calculated according to the Gross linear formula [18]: total blood loss = blood volume × (preoperative Hct-postoperative Hct)/average Hct, where, preoperative Hct is measured at 1 d before operation, postoperative Hct takes the minimum of three measurements and average Hct takes the mean value of four measurements. Dominant blood loss was recorded for all patients, including intraoperative visible blood loss and postoperative drainage volume. Recessive blood loss was calculated by total blood loss minus dominant blood loss. The blood transfusion rate was recorded for the three groups.

Blood biochemical indicators

At 1 d before operation and 1 d and 5 d after operation, blood was collected from all patients to test PT, APTT and FIB with an automatic coagulometer (Sysmex, CA-500).

Complications

The incidences of postoperative incision infection, limb swelling, deep vein thrombosis, intramuscular vein thrombosis and incision fat liquefaction were recorded for all patients.

Joint function score and overall response rate

All patients were subject to an evaluation of joint function by the 100-score Harris scale before and after operation. A higher score indicates better joint function. According to the Harris score, overall response rate was scored as excellent: ≥90, good: 80-89, acceptable: 70-79, and poor: <70. Overall response rate = (Excellent case + Good case)/Total number of cases × 100% [19].

Hemoglobin and Hct

Blood samples were collected from all patients 1 d before operation, and 1 d and 5 d after operation and analyzed to obtain the Hb and Hct.

Statistical analysis

Statistical analysis was performed with SPSS 19.0. All numerical data were normally distributed, expressed as mean ± standard deviation (mean ± SD), and subject to t test; in the case of nominal data it was expressed as [n (%)], comparison studies were carried out through chi-squared test for intergroup comparison. For all statistical comparisons, significance was defined as $P<0.05$.

Results

Intergroup comparison of general materials

There was no significant differences in general data of the three groups including; gender, age, fracture site and AO type, complications and time from being injured to operation, BMI, platelet and Hct ($P>0.05$), which were comparable between the groups (**Table 1**).

Intergroup comparison of perioperative indicators

The three groups expressed no significant difference in operation time and length of hospital stay ($P>0.05$), suggesting that compared to single dose of tranexamic acid before operation, intravenous drip before operation and at 7 h after operation will not prolong the operation time and length of hospital stay (**Figure 1**).

Intergroup comparison of blood loss

The three groups expressed significant difference in total blood loss, dominant blood loss, intraoperative blood loss, postoperative drainage volume, recessive blood loss and blood transfusion rates ($P<0.05$). The total blood loss, dominant blood loss, intraoperative blood loss, postoperative drainage volume, recessive blood loss and blood transfusion rate in GA and GB were lower than those in CG ($P<0.05$), and the total blood loss, postoperative drainage vol-

Table 1. Intergroup comparison of general materials

Group	n	Gender		Age (year)	Affected side (n)		AO type (n)			Complication (n)		
		Male	Female		Left	Right	A1	A2	A3	Hypertension	Diabetes	Hyperlipemia
GA	40	21	19	68.24±7.25	18	22	7	24	9	12	10	7
GB	40	24	16	67.43±5.21	20	20	8	25	7	10	9	9
CG	40	22	18	66.94±5.79	17	23	9	22	9	11	8	8
F/X^2		0.473		0.456	0.470		0.767			0.251	0.287	0.313
P		0.789		0.635	0.791		0.943			0.882	0.866	0.855

Group	n	Time from being injured to operation(d)	BMI (kg/m^2)	Platelet (×10^9/L)	Hct (%)
GA	40	2.84±0.56	21.48±1.35	204.64±28.57	40.71±1.78
GB	40	2.93±0.72	21.58±1.46	201.46±30.27	41.04±1.80
CG	40	2.79±0.68	21.12±1.42	208.15±27.59	40.65±1.65
F		0.467	1.388	0.593	0.580
P		0.628	0.254	0.555	0.562

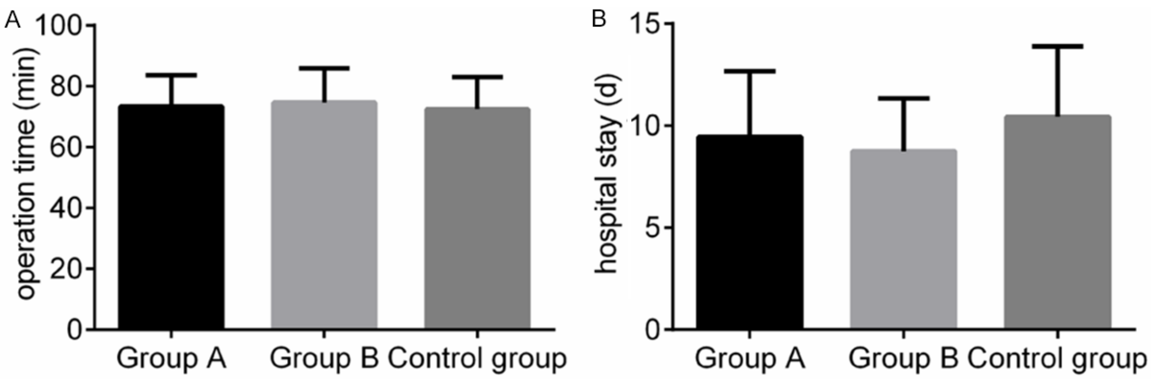

Figure 1. Intergroup comparison of perioperative indicators. Note: $^*P$<0.05 vs CG; $^\#P$<0.05 vs GA.

ume, recessive blood loss and blood transfusion rate in GB were lower than those in GA (P<0.05). Nevertheless, the two groups were not statistically different in terms of dominant blood loss and intraoperative blood loss (P>0.05), suggesting that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation can effectively reduce the total blood loss, postoperative drainage volume and recessive blood loss (**Figure 2**).

Intergroup comparison of coagulation function indicators

The three groups showed no significant difference in PT, APTT and FIB (P>0.05), suggesting that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation didn't change the coagulation function (**Table 2**).

Intergroup comparison of postoperative complications

No incision infection or deep vein thrombosis was reported in any of the three groups, and the three groups had no significant difference in the incidences of complications such as limb swelling, intramuscular vein thrombosis and incision fat liquefaction (P>0.05). Suggesting that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation will not result in postoperative complications (**Table 3**).

Intergroup comparison of preoperative and postoperative Harris scores

There was no significant difference in Harris scores amongst the three groups before operation (P>0.05). After operation, Harris scores were increased, and the score in GB was higher than that in GA and CG (P<0.05), suggesting

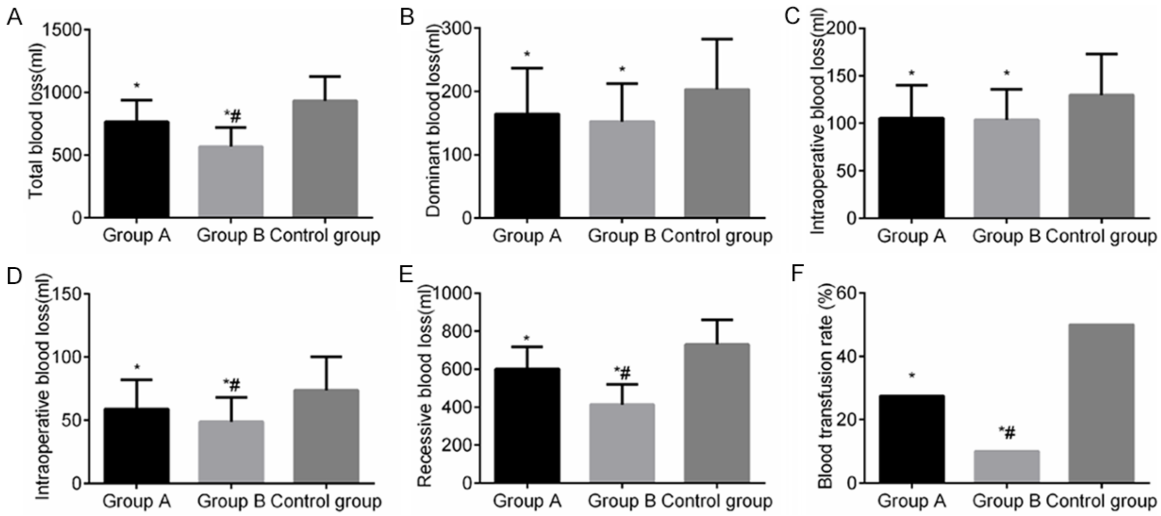

Figure 2. Intergroup comparison of blood loss.

Table 2. Intergroup comparison of coagulation function indicators

Group	n	Time	PT (s)	APTT (s)	FIB (g/L)
GA	40	1 d before operation	12.48±1.56	32.21±5.11	3.65±0.36
		1 d after operation	11.48±1.45	32.03±4.56	3.73±0.45
		5 d after operation	11.44±1.17	31.87±4.87	3.74±0.46
GB	40	1 d before operation	12.43±1.07	32.16±5.05	3.71±0.42
		1 d after operation	11.26±1.32	31.83±4.98	3.56±0.53
		5 d after operation	11.31±1.46	31.72±4.57	3.76±0.48
CG	40	1 d before operation	12.40±1.65	32.14±4.25	3.67±0.45
		1 d after operation	12.01±1.31	33.21±4.24	3.59±0.52
		5 d after operation	12.26±1.42	32.67±4.58	3.63±0.60

Table 3. Intergroup comparison of postoperative complications

Group	n	Limb swelling	Intramuscular vein thrombosis	Incision fat liquefaction
GA	40	3 (7.50)	2 (5.00)	2 (5.00)
GB	40	1 (2.50)	2 (5.00)	1 (2.50)
CG	40	3 (7.50)	1 (2.50)	1 (2.50)
X^2		1.214	0.417	0.517
P		0.545	0.812	0.772

that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation could markedly increase the postoperative Harris scores (**Figure 3**).

Intergroup comparison of overall response rate

The overall response rate in GB was higher than that in GA and CG, showing statistical difference ($P<0.05$) (**Table 4**). This indicated that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation could significantly improve the overall response rate of the elderly patients with intertrochanteric fracture.

Intergroup comparison of preoperative and postoperative Hb and Hct

At 1 d before operation, the Hb and Hct levels had no significance difference amongst the three groups ($P>0.05$). At 1 d and 5 d after

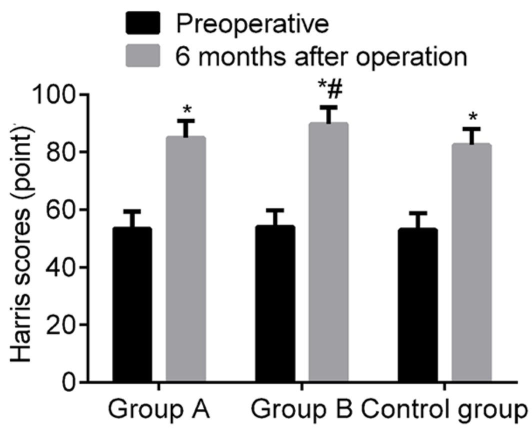

Figure 3. Intergroup comparison of Harris scores ($\bar{x}\pm s$, Score). Note: $^{*}P<0.05$ vs CG; $^{\#}P<0.05$ vs GA.

operation, the Hb and Hct levels in GB were higher than those in GA and CG ($P<0.05$) (**Table 5**). This indicated that compared to single dose before operation, intravenous drip of tranexamic acid before operation and at 7 h after operation could significantly improve the blood loss of elderly patients with intertrochanteric fracture.

Discussion

Intertrochanteric fracture is common in the elderly and involves fracture from the base of the femoral neck to the lesser trochanter [20-22]. Intramedullary fixations performed by PFNA have demonstrated good biomechanical properties and capacity to bear great torque forces that re-fracture of internal fixation or dislocation of fracture end are seldom reported [23, 24] Besides, it is minimally invasive [6, 25]. Nevertheless, PFNA is associated with high recessive blood loss in the perioperative period. The recessive blood loss in the PFNA group was higher than that in dynamic hip screw (DHS) group in the case of elderly patients with intertrochanteric fracture according to Zeng and his colleagues [26], and is also reported similarly in the case of elderly patients with intertrochanter fracture of the femur according to Wang and his colleagues [27]. This may be due to the severe intramedullary vascular destruction caused by intramedullary reaming and other operations during intramedullary fixation, resulting in more blood loss. Recessive blood loss often leads to postoperative anemia where some patients require a blood transfusion, which may increase the burden on the heart and the incidence of postoperative infection, and compromise postoperative incision healing and functional recovery [28]. Therefore, how to reduce perioperative recessive blood loss has become a key point of clinical study.

Tranexamic acid may reduce blood loss in orthopedic operations related to intertrochanteric fracture, *etc*., but no final conclusion has been made regarding its administration mode. So far, the recommendation for clinical practice is a single dose 20 min before operation. However, based on the half-life of approximately 7 h, the concentration of tranexamic acid in the blood gradually reduces 7 d after administration [29]. Zhang and his colleagues [30] found that intravenous drip of tranexamic acid 10 min before operation and 7 h after operation can significantly reduce the postoperative blood loss in patients after total hip replacement compared to a single dose before operation. According to the findings in this study, the blood loss and blood transfusion rates were higher than those in GA and GB, and the Hb and Hct levels in GB were higher than those in GA and CG at different postoperative periods, indicating that tranexamic acid can effectively reduce blood loss in elderly patients with intertrochanteric fracture. Moreover, GB had lower total blood loss, postoperative drainage volume, recessive blood loss and blood transfusion rate and higher postoperative hemoglobin level than GA, suggesting that intravenous drip of tranexamic acid before and at 7 h after operation can maximally reduce the total blood loss, in particular, recessive blood loss. It is possible that two doses of tranexamic acid by intravenous drip can maintain the drug concentration in the blood for a longer period of time to achieve better efficacy and hemostasis effects. Tranexamic acid is a synthetic derivative of lysine. Its high affinity to the binding site of lysine and can competitively inhibit the activity of fibrinoclase to reduce fibrin decomposition and hemostasis. At the same time, tranexamic acid at a high concentration can certainly non-competitively inhibit the effects of plasmin by blocking its binding with the fibrin containing lysine residues so as to avoid fibrin from decomposition and reduce postoperative blood loss. Preoperative intravenous drip of tranexamic acid can prevent the increase of anti-fibrinolytic protective proteins during the operation, reduce the incidence of fibrinolysis caused by trauma

Table 4. Intergroup comparison of overall response rate [n (%)]

Group	n	Excellent	Good	Acceptable	Poor	Overall response rate
GA	40	18 (45.00)	13 (32.50)	9 (22.50)	0 (0.00)	31 (77.50)
GB	40	23 (57.50)	15 (37.50)	2 (5.00)	0 (0.00)	38 (95.00)
CG	40	16 (40.00)	14 (35.00)	9 (22.50)	1 (2.50)	30 (75.00)
χ^2						6.580
P						0.037

Table 5. Intergroup comparison of Hb and Hct before and after operation ($\bar{x}\pm s$)

Time	Group	n	Hb (g/L)	Hct (%)
1 d before operation	GA	40	136.14±12.42	40.71±1.78
	GB	40	135.22±10.92	41.04±1.80
	CG	40	135.97±11.89	40.65±1.65
	F		0.069	0.580
	P		0.933	0.562
1 d after operation	GA	40	113.35±9.09	29.91±1.51
	GB	40	121.45±9.55	32.31±1.71
	CG	40	110.25±8.31	28.28±1.37
	F		16.523	69.644
	P		0.000	0.000
5 d after operation	GA	40	125.13±9.78	36.04±1.60
	GB	40	133.55±10.47	40.28±1.88
	CG	40	120.02±10.46	34.73±1.42
	F		17.800	124.516
	P		0.000	0.000

and produce persistent after effects. In the meantime, postoperative injection of tranexamic acid can maximize the drug concentration in the tissues without raising the total blood concentration. Based on its inhibitory effects on the fibrinolytic system, tranexamic acid has the theoretical potential to increase the risk of thrombosis. Though a large number of studies have proved that the use of tranexamic acid will not increase the incidence of venous thrombus [28, 31], they are based on a single dose before operation. The safety after increasing the administration frequency shall be emphasized. The results of this study showed that the three groups expressed no statistical difference in terms of PT, APTT and FIB at each time point, indicating that intravenous drip of tranexamic acid would not significantly affect the patients' coagulation function and lead to a hypercoagulative state. No incision infection and deep vein thrombosis were reported and no significant difference was found in the incidences of limb swelling, intramuscular vein thrombosis and incision fat liquefaction, suggesting that intravenous drip of tranexamic acid before and 7 h after operation is very safe and will not increase the risk of thrombosis, the incidence of limb swelling nor incision fat liquefaction. It was further found in this study that the postoperative Harris score and overall response rate in GB were higher than those in GA and CG, indicating that intravenous drip of tranexamic acid before and at 7 h after operation provides good postoperative joint recovery and improves the overall response rate.

In conclusion, when PFNA is adopted in the treatment of elderly patients with intertrochanteric fracture, intravenous drip of tranexamic acid before and 7 h after operation can effectively reduce the recessive blood loss with higher safety compared to single dose before operation. However, this is a single-center study with limited samples. The findings shall be verified in larger multi-center studies.

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Disclosure of conflict of interest

None.

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References

[1] Sun FG, Wang DX, Hu YT and Xu RM. Clinical observation of proximal femoral anti-rotation nail for the treatment of femoral intertrochanteric fracture. Zhongguo Gu Shang 2017; 30: 915-919.

[2] Sun QZ, Ruan CQ, Li GM, Chen WL, Ding Q and Zhang CJ. Comparison of clinical effect betweem reconstructing femoral calcar and proximal femoral antirotation nail for the treatment of unstable femoral intertrochanteric fracture in elderly patients. Zhongguo Gu Shang 2016; 29: 684-688.

[3] Wu B, Dai M, Zou F, Zhang B, Li B, Luo S and Qiu P. Effectivenes of anterolateral C-shaped approach in treatment of intertrochanteric fracture of femur in elderly patient. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2013; 27: 985-989.

[4] Guo Q, Shen Y, Zong Z, Zhao Y, Liu H, Hua X and Chen H. Percutaneous compression plate versus proximal femoral nail anti-rotation in treating elderly patients with intertrochanteric fractures: a prospective randomized study. J Orthop Sci 2013; 18: 977-986.

[5] Li DP, Y H and Shen TC. Analysis of peroperative blood loss in elderly patients treated by internal fixation with proximal femoral nail antirotation. Chinese Journal of Postgraduates of Medicine 2014; 37: 41-43.

[6] Zhang H, Zeng X, Zhang N, Zeng D, Xu P, Zhang L, Chen D, Yu W and Zhang X. InterTan nail versus proximal femoral nail antirotation-Asia for intertrochanteric femur fractures in elderly patients with primary osteoporosis. J Int Med Res 2017; 45: 1297-1309.

[7] Nasab SAM and Khorramdin E. The assessment of mortality and quality of life after intertrochanteric fracture of femur in patients older than 60 at Emam Khomeini Hospital of Ahvaz. Pak J Med Sci 2017; 33: 895-898.

[8] Turgut A, Kalenderer Ö, Günaydın B, Önvural B, Karapınar L and Ağuş H. Fixation of intertrochanteric femur fractures using Proximal Femoral Nail Antirotation (PFNA) in the lateral decubitus position without a traction table. Acta Orthop Traumatol Turc 2014; 48: 513-520.

[9] Xie H, Wang Z, Zhang J, Xu L and Chen B. Clinical outcome of dynamic hip locking plates and proximal femoral nails anti-rotation-Asia for treating intertrochanteric femur fracture with lateral wall fractures in the elder patients. Oncotarget 2017; 8: 82700-82704.

[10] Hou G, Zhou F, Tian Y, Ji H, Zhang Z, Guo Y and Lv Y. Predicting the need for blood transfusions in elderly patients with pertrochanteric femoral fractures. Injury 2014; 45: 1932-1937.

[11] Tian S, Shen Z, Liu Y, Zhang Y and Peng A. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. Injury 2018; 49: 680-684.

[12] Xie B, Tian J, Yang C, Zhou DP and Xiang LB. Case-control study on the efficacy of preoperative recombinant human erythropoietin administration for reducing transfusion requirements in elderly patients undergoing elective surgery for femoral intertrochanteric fractures. Zhongguo Gu Shang 2015; 28: 633-637.

[13] Huang F, Wu D, Ma G, Yin Z and Wang Q. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. J Surg Res 2014; 186: 318-327.

[14] Mase N and Horibe T. Organocatalytic Knoevenagel condensations by means of carbamic acid ammonium salts. Org Lett 2013; 15: 1854-1857.

[15] Nuzzi A, Fiasella A, Ortega JA, Pagliuca C, Ponzano S, Pizzirani D, Bertozzi SM, Ottonello G, Tarozzo G, Reggiani A, Bandiera T, Bertozzi F and Piomelli D. Potent α-amino-β-lactam carbamic acid ester as NAAA inhibitors. Synthesis and structure-activity relationship (SAR) studies. Eur J Med Chem 2016; 111: 138-159.

[16] Lei J, Cong Y, Zhuang Y, Zhang B, Wei X, Wei W, Fu Y, Wang P, Wen S and Wang H. Effects of preoperative tranexamic acid administration on the recessive blood loss in treating intertrochanteric fracture by PFNA. Chinese Journal of Orthopaedic Trauma 2017; 19: 103-108.

[17] Nadler SB, Hidalgo JH and Bloch T. Prediction of blood volume in normal human adults. Surgery 1962; 51: 224-232.

[18] Miao K, Ni S, Zhou X, Xu N, Sun R, Zhuang C and Wang Y. Hidden blood loss and its influential factors after total hip arthroplasty. J Orthop Surg Res 2015; 10: 36.

[19] Cai BT, Xu CY and Cao J. Comparison of the efficacies of treating elderly intertrochanteric fracture patients by three internal fixation methods. Chinese Journal of Orthopaedic Trauma 2016; 18: 564-568.

[20] Knobe M, Nagel P, Maier KJ, Gradl G, Buecking B, Sönmez TT, Modabber A, Prescher A and Pape HC. Rotationally stable screw-anchor with locked trochanteric stabilizing plate versus proximal femoral nail antirotation in the treatment of AO/OTA 31A2.2 fracture: a biomechanical evaluation. J Orthop Trauma 2016; 30: e12-18.

[21] Zeng X, Zhang N, Zeng D, Zhang L, Xu P, Cao L, Yu W, Zhan K and Zhang X. Proximal femoral nail antirotation versus dynamic hip screw fixation for treatment of osteoporotic type 31-A1 intertrochanteric femoral fractures in elderly patients. J Int Med Res 2017; 45: 1109-1123.

[22] Zhang S, Zhang K, Jia Y, Yu B and Feng W. InterTan nail versus proximal femoral nail antirotation-asia in the treatment of unstable trochanteric fractures. Orthopedics 2013; 36: e288-294.
[23] Jonnes C, Sm S and Najimudeen S. Type II intertrochanteric fractures: Proximal Femoral nailing (PFN) Versus Dynamic Hip Screw (DHS). Arch Bone Jt Surg 2016; 4: 23-28.
[24] Shen NJ, Lin JP and Wang GJ. A comparative study of different operating methods to treat elderly intertrochanteric fracture patients. Journal of Practical Orthopaedics 2016; 22: 6-10.
[25] Jia L, Zhang K, Wang ZG, Wang L, Yang SY and Zheng YP. Proximal femoral nail antirotation internal fixation in treating intertrochanteric femoral fractures of elderly subjects. J Biol Regul Homeost Agents 2017; 31: 329-334.
[26] Zeng JS, Cai XH and Li W. Correlation analysis between the peroperative recessive blood loss in elderly patients with intertrochanteric fracture and gender and internal fixation methods. Chinese Journal of Orthopaedic Trauma 2015; 17: 134-137.
[27] Wang F, Mao WL and Li LY. Blood loss and factor analysis for medullary and extramedullary fixations treating elderly patients with intertrochanter fracture of femur. Chinese Journal of Bone and Joint Injury 2016; 31: 1023-1026.
[28] Cheng HG, Duan N and Ma T. Efficacy and safety of tranexamic acid in elderly patients with unstable intertrochanteric fracture. Journal of Practical Orthopaedics 2017; 23: 1138-1140.
[29] Zhang LF, Zhu F and Zhou J. Tranexamic acid reducing perioperative blood loss when treating intertrochanter fracture of femur by PFNA. Orthopedic Journal of China 2017; 25: 2248-2250.
[30] Zhang P, Chen YZ and Yang LS. Effects of tranexamic acid administration at different time points on reducing the intraoperative and postoperative blood loss in total hip replacement. Journal of Clinical Orthopaedics 2014; 17: 396-400.
[31] Jin ZC, Zheng XH and Yu X. Efficacy and safety of tranexamic acid reducing perioperative blood loss of intertrochanteric fracture. Zhongguo Zu Zhi Gong Cheng Yan Jiu 2018; 22: 2361-2366.