ORIGINAL STUDY

acta orthopaedica belgica, 2023, 89, 645-650

doi.org/10.52628/89.4.11959

Effectiveness and safeties of hemocoagulase and tranexamic acid to reduce perioperative blood loss in intertrochanteric fracture PFNA fixation

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This study evaluated the efficacy of hemocoagulase and tranexamic acid (TXA) in minimizing perioperative blood loss in perioperative period of proximal femoral nail antirotation (PFNA) repair. 99 patients having intertrochanteric fracture PFNA fixation were randomly assigned to the hemocoagulase, TXA, and control groups (n=33 per group). In the hemocoagulase group, 1 KU of hemocoagulase was injected preoperatively and postoperatively local sprayed, respectively; in the TXA group, 0.5g TXA was injected preoperatively and postoperatively local sprayed, respectively; and in the control group, 100 mL of physiological saline was injected before surgery and was used by postoperative local spraying, respectively. The hemocoagulase and TXA groups exhibited significant differences in preoperative hemoglobin (HB) and hematocrit (HCT) levels on postoperative days 1 and 3, intraoperative bleeding, 24-hour postoperative drainage, total perioperative bleeding, transfusion rate, and postoperative hospitalization duration compared to the control group. Furthermore, the hemocoagulase and TXA groups showed significant differences in postoperative day 3 HB and HCT levels and postoperative hospitalization duration compared to each other. In conclusions, the combined use of systemic preoperative and local postoperative hemocoagulase and TXA spraying is found to significantly decrease perioperative blood loss in intertrochanteric fracture patients undergoing PFNA. Hemocoagulase is observed to have a superior effect compared to TXA.

Keywords: Hemocoagulase, tranexamic acid, intertrochanteric fractures, blood loss, postoperative hemorrhage.

INTRODUCTION

Intertrochanteric femoral fractures are predominantly caused by senile osteoporosis and their incidence is rising with the ageing of the population, resulting in an estimated 6.3 million cases of femoral fractures worldwide by 2050[1]. Surgical treatment is currently the most effective approach for treating intertrochanteric femoral fractures in the elderly population[2]. However, surgical procedures often result in significant overt and hidden bleeding, which may even require blood transfusions[1]. Massive blood loss can have negative impacts on patient health and increase the burden on multiple organs, and clinical transfusions carry potential risks[3].

Anemia is common after surgery, with rates of 87-10%[4]. Intertrochanteric fractures are cancellous bone fractures with excellent blood circulation and sizable cavities, making bleeding difficult to stop. Closed fractures can cause persistent bleeding into adjacent soft tissue, leading to hematoma and limb enlargement[5]. Intramedullary needle insertion can cause more bleeding in the marrow cavity, and tiny incision procedures cannot fully stop soft tissue hemorrhage[6]. Older patients with intertrochanteric fractures have poorer physical conditions, which can result in more hidden blood loss due to reduced red blood cells and coagulation factors[7]. Controlling bleeding and transfusion in older patients is important for orthopedic surgeons. Over 90% of patients with proximal femur fractures develop postoperative anemia, mainly elderly patients with comorbidities[1,8]. Surgeons must choose hemostatic drugs that reduce bleeding and transfusion rates while minimizing complications, in addition to selecting the best surgical approach and reducing tissue damage.

Snake venom thrombin preparation is a protease hemostatic drug with rapid onset, long-lasting effect, and low toxicity. Studies show it is more effective than other drugs for surgical hemostasis[9]. Recent studies have shown that intra-articular infusion of tranexamic acid (TXA) or hemocoagulase is more effective in reducing postoperative blood loss compared to direct intravenous administration[10-12]. Local administration of TXA also

has a higher safety profile with 70% lower plasma drug concentration than direct intravenous administration[13]. However, TXA may increase the risk of thrombosis due to its procoagulant and pro-fibrinogenic effects.

Comparing the effectiveness and safety of different hemostatic drugs is crucial for reducing bleeding and transfusion rates while minimizing associated complications. In this prospective study, we aim to compare the efficacy and safety of TXA and injectable hemocoagulase in reducing intraoperative and postoperative blood loss in intertrochanteric fracture-proximal femoral nail antirotation (PFNA) fixation.

MATERIALS AND METHODS

The study included patients who underwent PFNA fixation for intertrochanteric fracture between June 2015 and June 2017 at the Department of Orthopedics, West China Guang'an Hospital, Sichuan University. The study was approved by the ethical committee of West China Guang'an Hospital (No.2015133), and all patients provided informed consent.

Inclusion criteria were: (i) age > 55 years; (ii) normal platelets and coagulation function before surgery; (iii) no abnormalities in venous ultrasound of both lower limbs; (iv) hemoglobin (HB) > 100 g/L; (v) no previous deep vein thrombosis. The exclusion criteria were patients with one or more of the following: (1) contraindications to the use of TXA or injectable hemocoagulase: including patients with a tendency to thrombosis (malignant tumor, neurovascular disease, or history of thromboembolism, etc., and patients after stent implantation); (2) severe hepatic and renal insufficiency; (3) patients with a clear allergy to TXA or injectable hemocoagulase. The included cases were randomly assigned to one of the three groups: hemocoagulase, TXA, and control groups.

The patients underwent PFNA fixation using a lateral incision with the patient in the supine position, utilizing the PFNA system (http://www.wegortho.com). Twenty min before surgery, the hemocoagulase group received an intravenous infusion of 1 KU hemocoagulase (1 KU hemocoagulase added to 100 mL saline, Heamocogulase Agkistrodon, Penglai Nokang Pharmaceutical Co., Ltd. China); the TXA group received an intravenous infusion of 0.5g TXA (0.5 g TXA added to 100 mL saline, Ruiyang Pharmaceutical Co., Ltd. China)[14,15]; the control group received an intravenous infusion of 100 mLsaline. After the incision, at the end of layer-by-layer suturing, the TXA group sprayed 0.5g TXA /50 mL saline on the surgical wound; the hemocoagulase group sprayed 1 KU hemocoagulase/50 mL saline on the surgical wound; the control group only sprayed 50 mL saline. Drains were closed for six hours, and two experienced orthopedic surgeons (Wang and Zhang) with proficiency in intertrochanteric fracture PFNA fixation performed the procedures with meticulous hemostasis.

Upon admission, patients and their family members were given detailed information on the importance of preventing deep vein thrombosis and the methods to prevent it. Specialized nurses instructed the patients on performing Ankle pump exercises and encouraged them to move their lower limbs frequently to promote blood circulation and enhance muscle strength. All patients were treated with comprehensive anticoagulation therapy according to the Chinese Guidelines for the Prevention of Deep Vein Thrombosis in Major Orthopedic Surgery. Enoxaparin sodium injection (Kesse, Aventis, France) was administered based on body weight, with a subcutaneous injection of 3000 IU given eight hours after surgery, a second injection of 3000 IU given 24 hours later, and a subcutaneous injection of 6000 IU every 24 hours until discharge. To prevent thrombosis after joint surgery, all patients took rivaroxaban 10 mg/day for 14 days after discharged[16]. Patients performed Ankle pump exercises immediately after waking up from anesthesia and completed flexion, extension, and abduction training of both lower limbs on the hospital bed 20 times/hour. If the postoperative X-ray was normal, patients could get out of bed with a walker more than 3 times a day and continued to strengthen the flexion, extension, and abduction training of their lower limbs on the bed. Routine blood, liver and kidney function, coagulation function, and D-dimer tests were conducted on day 3 of anticoagulation therapy, and routine ultrasound examination of veins of both lower limbs was performed on day 7 after surgery. Blood transfusions were given on the morning of the first postoperative day if HB was less than 80g/L.

On postoperative day 1 and day 3, venous blood was collected from all patients for routine blood and coagulation tests, including measurements of hemoglobin (HB), hematocrit (HCT), blood platelet count (BPC), plasma prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin clotting time (TPT), and thromboplastin time (TPT). These measurements were compared to preoperative values. In addition, intraoperative changes in PT, APTT, thrombin time (TT), and fibrinogen (Fbg) were assessed, as well as intraoperative bleeding, 24-hour postoperative drainage, total perioperative blood loss, transfusion rate, number of postoperative hospital days, and incidence of incisional infections and venous thrombosis (including deep vein thrombosis, isolated intramuscular vein thrombosis, and pulmonary embolism).

STATISTICAL ANALYSIS

Data were analyzed using SPSS 20.0. Mean and SD were used for normally distributed data and compared using ANOVA-Bonferroni test. Count data were expressed as rates and analyzed with chi-square/exact fisher's test. Statistical significance was set at $P < 0.05$. In determining the required sample size to achieve $1-\beta = 0.80$ and $\alpha = 0.05$, an ANOVA test was conducted and the statistical power results indicated that a minimum of 31 subjects were required in each group.

RESULTS

A total of 99 cases were included in the study and were randomly assigned to one of three groups: hemocoagulase (n=33), TXA (n=33), and control (n=33). The hemocoagulase group included 12 males and 21 females with a mean age of 62.9 ± 5.7 years, the TXA group included 14 males and 19 females with a mean age of 64.1± 8.3 years, and the control group included 11 males and 22 females with a mean age of 65.1 ± 7.4 years.

In the three groups, age, sex, body mass index (BMI), and classification were compared, and the differences were not statistically significant ($P > 0.05$, Table 1).

Comparison of the changes of coagulation indexes between the three groups of patients before and after surgery

HB, HCT, BPC, PT, APTT, TT, and Fbg levels were comparable among the three groups pre-surgery ($P>0.05$). However, post-surgery, HB and HCT levels in the hemocoagulase group were significantly higher than those in the TXA group ($P < 0.05$), and both hemocoagulase and TXA groups had significantly higher HB and HCT levels compared to the control group ($P < 0.05$).On postoperative day 3, both hemocoagulase and TXA groups showed significantly higher HB and HCT levels compared to the control group ($P < 0.05$), while no significant differences were observed between hemocoagulase and TXA groups in terms of HB and HCT levels ($P > 0.05$). (Table 2).

Comparison of other clinical data among the three groups of patients

Postoperative 24-hour drainage, overall perioperative blood loss, and transfusion rate were significantly different between the hemocoagulase and TXA groups ($P < 0.05$). However, there was no significant difference in intraoperative bleeding ($P > 0.05$). Compared to the control group, both the hemocoagulase and TXA groups showed significant differences in intraoperative bleeding, 24-hour postoperative drainage, total perioperative blood loss, and transfusion rate ($P < 0.05$, Table 3).

Comparison of postoperative hospitalization days, incisional infections and venous thrombosis within 3 months after surgery in the three groups

No significant difference was found between the hemocoagulase and TXA groups in terms of postoperative hospital stay and the incidence of incisional infection and venous thrombosis at 3 months ($P > 0.05$). However, when compared with the control group, there was a significant difference in the number of postoperative hospital days between the hemocoagulase and TXA groups ($P < 0.05$), while no

Table 1. — Comparison of baseline information of patients in 3 groups (x±s)

Indexes	HCA group	TXA group	Control group	F	P
Sex (M/F	12/21	14/19	11/22		
Age (years)	62.9±5.7	64.1±8.3	65.1±7.4	0.208	>0.05
BMI (kg/m^2)	20.9±3.41	21.1±4.09	19.8±2.68	0.115	>0.05
Evans classification II	9	12	13	0.952	>0.05
Modified Evans classification III	24	21	20	1.536	>0.05
APTT(s)	28.19±3.57	27.43±1.77	29.01±6.21	2.337	<0.05
PLT(*10^9/L)	132±20	133±21	135±23	1.579	>0.05
D-Dimer	0.37±0.06	0.42±0.04	0.43±0.04	1.443	>0.05
ASA Classification	2.1±0.6	2.1±0.5	2.1±0.4	0.982	>0.05
Surgery time (min)	55±13	40±18	40±21	1.136	>0.05

HCA group: hemocoagulase group; Control group: normal saline group; TXA group: tranexamic acid group; BMI: body mass index; APTT: active partial thromboplastin time; PLT: platelet count; ASA: anesthesia classification; Modified Evans: modified intertrochanteric fracture; ASA: anesthesia classification; Modified Evans: modified intertrochanteric fracture.

Table 2. — Comparison of preoperative and postoperative HB, HCT, BPC, PT, APTT, TT and Fbg in the three groups (x±s)

Indexes	Days	HCA group	TXA group	Control group	F	P
HB (g/L)	Pre-operative	134.42±20.19	137.69±15.37	132.16±15.42	1.224	**>0.05**
	Post-operative day 1	124.11±10.26#	110.31±9.25	91.18±5.27*	8.472	**<0.01**
	Postoperative day 3	122.35±7.17	109.78±5.73	90.34±2.38*	10.52	**<0.01**
HCT (%)	Pre-operative	44.11±1.68	42.03±3.07	43.97±2.15	0.875	**>0.05**
	Postoperative day 1	41.92±1.39#	36.74±3.08	30.24±3.47*	7.885	**<0.01**
	Postoperative day 3	39.19±1.04	34.91±1.53	27.33±2.82*	6.167	**<0.01**
BPC (X10^9/L)	Pre-operative	202.24±24.38	199.47±19.51	202.32±17.33	1.023	**>0.05**
	Postoperative day 1	212.19±17.47	220.36±18.41	229.33±16.73	0.783	**>0.05**
	Postoperative day 3	224.85±19.25	227.18±20.39	228.43±13.47	0.925	**>0.05**
PT (s)	Pre-operative	12.27±1.39	11.98±0.79	12.16±0.79	0.604	**>0.05**
	Postoperative day 1	13.19±2.44	12.17±1.05	12.71±0.96	0.900	**>0.05**
	Postoperative day 3	12.87±1.36	13.01±2.57	12.65±1.02	1.052	**>0.05**
APTT (s)	Pre-operative	28.19±3.57	27.43±1.77	29.01±6.21	2.337	**>0.05**
	Postoperative day 1	29.13±5.42	27.39±2.15	28.35±4.03	1.589	**>0.05**
	Postoperative day 3	27.63±3.09	26.92±2.69	27.53±2.53	2.045	**>0.05**
TT (s)	Pre-operative	15.91±3.19	17.13±2.47	16.06±3.27	2.643	**>0.05**
	Postoperative day 1	16.37±4.09	16.72±3.41	16.67±4.31	0.679	**>0.05**
	Postoperative day 3	16.09±2.78	16.05±4.01	17.13±2.47	0.781	**>0.05**
Fbg (g/L)	Pre-operative	2.97±0.43	3.01±0.57	3.14±0.93	1.247	**>0.05**
	Postoperative day 1	2.13±0.81	3.48±0.63	2.93±1.12	**0.812**	**>0.05**
	Postoperative day 3	2.65±0.47	2.97±1.01	3.02±0.77	**0.900**	**>0.05**

HCA group: hemocoagulase group; Control group: normal saline group; TXA group: tranexamic acid group; HB: hemoglobin; HCT: hematocrit; BCP-blood platelet count; PT: prothrombin time; APTT: active partial thromboplastin time; TT: thrombin time; Fbg: fibrinogen. *: P<0.05 as the control group compared to the HCA and TXA groups; #: P<0.05 as the HCA group compared to the TXA group.

Table 3. — Comparison of intraoperative bleeding, postoperative 24h drainage, total perioperative blood loss and transfusion rate among the three groups of patients

Indexes	HCA group	TXA group	Control group	F	P
Intraoperative bleeding	394.31±47.92	413.36±39.15	538.87±40.72*	7.863	<0.05
Postoperative 24h drainage	192.17±6.52#	277.29±9.34	363.27±8.76*	6.946	<0.05
Total blood loss (mL)	#502.76±67.45	664.27±90.23	959.34±69.54	10.561	<0.05
Blood transfusion rate (%)	12.12, 4/33#	27.27, 9/33	42.42, 14 /33*	6.667	<0.05

HCA group: hemocoagulase group; Control group: normal saline group; TXA group: tranexamic acid group. *: P<0.05 as the control group compared to the HCA and TXA groups; #: P<0.05 as the HCA group compared to the TXA group.

Table 4. — Comparison of postoperative incisional infections, postoperative hospital days, and venous thrombosis in the three groups

Indexes	HCA group	TXA group	Control group	F	P
Postoperative incision infection (cases)	0	0	1	0	>0.05
Post-operative hospital days	15.27±3.14	12.49±4.57	22.78±3.96*	0.036	<0.05
Venous thrombosis	2 cases of isolated intramuscular vein thrombosis	1 case of isolated intramuscular vein thrombosis	2 cases of isolated intramuscular vein thrombosis	0.216	>0.05

HCA group: hemocoagulase group; Control group: normal saline group; TXA group: tranexamic acid group. *: P<0.05 as the control group compared to the HCA and TXA groups.

significant difference was observed in the incidence of incisional infection and venous thrombosis at 3 months (P > 0.05, Table 4).

DISCUSSION

TXA and hemocoagulase have been widely used for surgical hemostasis due to their established efficacy

and safety[12,17], which is also demonstrated in our study. Hemocoagulase, derived from snake venom, has also been used to prevent and treat surgical bleeding, with significant improvements in postoperative coagulation parameters and hospitalization length compared to control patients[18,19]. However, it does not significantly affect intraoperative bleeding[20].

The study used a combination of preoperative systemic and postoperative local spraying hemostatic drugs to reduce perioperative bleeding. The results showed a significant difference in intraoperative bleeding between the hemocoagulase and TXA groups compared to the control group, consistent with a previous study by Feng[21]. Results showed that both the hemocoagulase and TXA groups exhibited lower total blood loss and transfusion rates than the control group, indicating the efficacy of the treatment method in reducing perioperative blood loss in patients undergoing extracapsular surgery. These findings suggest that the drug administration approach employed in this study could be useful in minimizing perioperative blood loss in patients undergoing traumatic orthopedic procedures.

The current study utilized a combination of intravenous systemic and local spray administration of TXA and hemocoagulase to control bleeding, which is consistent with the approach employed by Zhang et al.[20]. During the 3-month follow-up period, no increase in the incidence of venous thrombosis was observed with this treatment regimen. Qin et al. reported a higher incidence of deep vein thrombosis in patients receiving TXA compared to hemocoagulase, although the difference was not statistically significant [22]. In patients receiving intravenous TXA, the overall incidence of venous thromboembolism was 2.1%, which was not significantly different from the control group's incidence of 2.0%, according to a meta-analysis (risk difference: 0.01%, 95% CI: -0.05%, 0.07%; risk ratio: 1.067, 95% CI: 0.760-1.496). Serious drug-related side effects were infrequent (0.1%) in this study.

On the first postoperative day, the hemocoagulase and TXA groups showed a significant difference in HB and HCT, but not on the third day. Studies by Zhang et al.[23] indicate that intravenous administration of TXA can effectively reduce hemorrhage and transfusion requirements. The present study showed that the test groups had a total blood loss of 664.27 ± 90.23 mL, intraoperative blood loss of 413.36 ± 39.15 mL, and 24-hour flow rate of 277.29 ± 9.34 mL. In contrast, the control group had a total blood loss of 959.34 ± 69.54 mL, intraoperative blood loss of 538.87 ± 40.72 mL, and 24-hour flow rate of 277.29 ± 9.34 mL. There were significant differences in total blood loss, intraoperative blood loss, and postoperative drainage (363.27 ± 8.76 mL) between the two groups ($P < 0.01$). Wang et al.[24] also reported that intravenous administration of 1 g TXA significantly reduced total blood loss and was more effective than a single preoperative dose.

In this study, there was no significant difference in HB and HCT between the two groups on postoperative day 3, possibly due to transfusions occurring on day 1 and patients starting to eat on their own on day 1. No significant differences were found between the two groups in terms of postoperative hospitalization days, incisional infection rate, and venous thrombosis within 3 months after surgery. Therefore, the study concluded that intravenous + topical hemocoagulase spray was not only more effective than the TXA group, but also did not increase the risk of venous thrombosis.

Limitations of this study include: 1) focus on perioperative blood loss without examining long-term effects on postoperative function and quality of life; 2) small sample size for confirming efficacy and safety of intravenous injection + local spray hemocoagulase and TXA for extracapsular surgery; 3) lack of comparative analysis of postoperative D-dimer and the effects of hemocoagulase and TXA on D-dimer; and 4) this article did not compare the effects of different doses of TXA on reducing perioperative blood loss. The optimal administration of TXA in the context of total joint replacement surgery involves intravenous boluses ranging from 10 to 15 mg/kg[25]. An extensive and well-executed randomized controlled trial (RCT) put forth the notion that a high TXA dosage (> 80 mg/kg total) exhibited superior efficacy in mitigating bleeding in comparison to a lower dosage (< 50 mg/kg total)[26]. Consequently, future investigations should incorporate diverse TXA dosages (> 1 g), while amplifying sample sizes and embracing more comprehensive data gathering methodologies. Such efforts hold the potential to effectively address safety apprehensions and furnish more robust and substantiated insights pertaining to this subject matter.

CONCLUSION

Using both hemocoagulase and TXA in a combined approach of preoperative and postoperative topical applications can effectively reduce perioperative blood loss in patients undergoing PFNA for intertrochanteric fracture. The combination of intravenous systemic and postoperative local spraying of both agents in extracapsular surgery can enhance their synergistic effects, resulting in better efficacy.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by the Project Fund for Promoting High Quality Development of Hospitals in Guang'an People's Hospital in 2021 < Research on Diagnosis and Treatment System of Osteoarthritis Chronic Disease Based on Big Image Data > (Proclamation number: 21FZ014).

Ethical approval: Ethical approval for the conduct of the study was obtained from the Guang'an People's Hospital, approval number (No.2015133).

Authors' contribution: Leidi Wang: study idea, study design, data analyses, interpretation and reflection, writing the manuscript; Chao Wang: study design, data analyses, interpretation and reflection, reviewing the manuscript; Dagang Zhang: data collection, data interpretation and reflection, reviewing the manuscript; Weilin Wang: data collection, data interpretation and reflection, reviewing the manuscript; Fang Wang: study design, data analyses, interpretation and reflection, reviewing the manuscript

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