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Comparison of hemocoagulase atrox versus tranexamic acid used in primary total knee arthroplasty: A randomized controlled trial

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ABSTRACT

Background: Total knee arthroplasty (TKA) has been considered as an effective choice for end-stage osteoarthritis or rheumatic arthritis. Tranexamic acid (TXA) has been widely used to prevent excessive blood loss perioperatively. Similarly, hemocoagulase atrox can significantly diminish blood loss and transfusion requirements in surgeries, however, it was rarely used in TKA. The purpose of this study is to identify whether hemocoagulase atrox is equal to TXA in reducing blood loss and transfusion rates following TKA, and compare clinical outcomes and complications between the two groups.

Methods: 74 patients were randomized to receive TXA (1.5 g intra-articular combined with 1.5 g intravenous), or hemocoagulase atrox (1 U intra-articular combined with 1 U intravenous). The primary outcome was total blood loss. The secondary outcomes included reduction of hemoglobin concentration, clinical outcomes, blood coagulation values, thromboembolic complications, and transfusion rates.

Results: The mean total blood loss was 431.7 mL in the TXA group compared with 644.6 mL in the hemocoagulase atrox group, with statistical significance ($P < 0.05$). There were significant differences in reduction of hemoglobin level ($P < 0.05$). The rate of deep vein thrombosis (DVT) in patients given TXA was higher than those given hemocoagulase atrox, however, there were no significant differences. No transfusions were required in either group, and no significant differences were found in the length of hospital stay and clinical outcomes.

Conclusions: Although the blood loss was significantly greater in the hemocoagulase atrox group, no transfusions were required and no significant differences were observed for any other outcomes measured. Meanwhile, the rate of DVT in the hemocoagulase atrox group tends to be lower than those in TXA group. We concluded that hemocoagulase atrox was not superior to TXA in reducing perioperative blood loss. Further studies are warranted to evaluate if hemocoagulase atrox use could improve perioperative blood loss in patients with high thrombotic risk undergoing TKA.

1. Introduction

Total knee arthroplasty (TKA) is regarded as one of the most successful orthopedic surgeries that relieves pain and improves function but is associated with excessive perioperative blood loss that might lead to anemia and blood transfusions [1–4]. Allogeneic transfusion may result in several undesirable adverse events, such as infection, heart failure, immunologic reaction, and myocardial infarction, and as a consequence involve increased morbidity and mortality and additional health care costs [5–7]. The use of pharmacologic antifibrinolytics such as tranexamic acid (TXA) has been employed as a blood-saving strategy in many institutions to reduce surgery-related blood loss and minimize the risk of post-operative transfusions [8–11].

Tranexamic acid, an antifibrinolytic medication, can prevent plasminogen activation by blocking the lysine binding site of plasminogen and inhibiting the formation of plasmin, and thereby promote coagulation process [12,13]. TXA can be administered either intravenously (IV), intra-articularly (IA), or orally in the setting of TKA. Oral administration of TXA had beneficial blood and cost-saving effect, as confirmed in some randomized controlled trials (RCT), and also reduced transfusions without increased risk of thromboembolic complications compared with placebo [14,15]. Compared with oral or IV TXA, the IA TXA can provide a maximum concentration of TXA in surgical site and thereby a prolonged effect to reduce postoperative blood loss, but is associated with minimal levels of systemic absorption, which may increase safety. Numerous RCTs [16,17] and meta-analyses [18]

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showed valid evidence favoring the effectiveness of various dosages and routes of IA TXA in reducing blood loss and allogeneic transfusion requirements in TKA.

Hemocoagulase atrox, a serine protease that clots fibrinogen, can significantly diminish blood loss and transfusion requirements in surgeries [19]. Accumulating data have demonstrated that hemocoagulase atrox has the ability to reduce local bleeding, but is not associated with any increase in the prothrombin level and consequently constitutes no danger of thrombosis [20].

Thus, the objective of our prospective, randomized trial was to assess the efficacy and safety of hemocoagulase atrox compared with TXA in the setting of primary unilateral TKA. We hypothesized that hemocoagulase atrox would be equivalent to TXA in reduction of blood loss and transfusion rates without increasing thromboembolic complications.

2. Methods

2.1. Participant recruitment

This prospective, randomized, controlled trial was conducted at the Department of Joint Surgery in Zhongshan Hospital, Fujian University. Approval was obtained from the Institutional Review Board, and written informed consent and research authorizations were obtained from all participants. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR1800017563).

From May 2018 to September 2018, all patients (40 years or older) with primary osteoarthritis scheduled for undergoing primary unilateral TKA were screened for enrollment. All perioperative managements of TKA were conducted based on a well-established multimodal enhanced-recovery strategy, including pain control [21–23], blood-saving management [24], and early ambulation [25,26]. The exclusion criteria were secondary osteoarthritis (rheumatoid arthritis, post-septic arthritis, or post-traumatic arthritis), a history of arterial or venous thromboembolic disease, a history of major comorbidities (severe pulmonary disease, severe renal insufficiency, hepatic failure, or severe stroke), a history of hematopoietic or hemophilia disease or active cancer, participation in another clinical trial during the last year, pregnancy, and alcohol abuse. These patients were also excluded if they declined to participate or refused to receive blood products.

2.2. Randomization

Patients were randomized to 1 of 2 groups: TXA (1.5 g intra-articular combined with 1.5 g intravenous), or hemocoagulase atrox (1 U intra-articular combined with 1 U intravenous). The randomization schedule was generated prior to the initiation of enrollment for the study. The randomization schedule was generated using blocks, with stratification for clinical site and surgeon to ensure an equivalent number of patients in each group over the course of the study in case early termination was required. The randomization schedule was generated by the HSS Epidemiology and Biostatistics Core, with the randomization list provided to the investigators prior to the initiation of patient recruitment, with only the patient being blinded to his or her randomization assignment.

2.3. Surgical procedure and postoperative management

At our institution, the TKA was conducted by the same senior orthopedic surgeon (C. X) under general anesthesia with a standard medial para-patellar approach. All prostheses were fixed with cement, and patella resurface technique was used in all patients. All patients received general anesthesia and standard analgesia perioperatively. Antibiotic prophylaxis in all patients was administered intravenously with 2.0 g of Cefazolin sodium half an hour before surgery. No intraarticular drainage tube was applied in all patients in our center.

2.4. Blood transfusion protocol

Participants were also received the standard practice of blood-transfusion protocol at our institution, which was consistent with the perioperative transfusion guidelines of Chinese Ministry of Health. Blood products were transfused if the hemoglobin (Hb) level < 7 g/dL in patients who were asymptomatic or if Hb level between 7 and 10 g/dL in patients who developed concomitant clinical symptoms (anemia or myocardial ischemia) or if a patient with any anemia-related organ dysfunction regardless of Hb level.

2.5. Thromboembolism prophylaxis protocol

Patients received standard venous thromboembolism prophylaxis based on individualized protocol at our institution, including mechanical and chemical thromboprophylaxis. Lower-extremity strength training and passive and active physiotherapy were performed under the supervision of a professional physiotherapist. As for chemical prophylaxis, rivaroxaban (10 mg, Xarelto, Bayer, Germany) was administered orally once a day for 30 days postoperatively if no bleeding events occurred.

2.6. Outcome assessment

The primary outcome was total blood loss. The estimated blood loss was calculated applying the Gross formula [27], which is total blood loss (TBL) = patient's blood volume (PBV) $\times$ ($Hct_{pre} - Hct_{post}$) / Hct_{ave} (Hct = hematocrit, Hct_{pre} = the initial preoperative Hct level, Hct_{post} = the Hct on the morning of postoperative day 3. PBV = k1 $\times$ height $(m)^3$ + k2 $\times$ weight (kg) + k3 (k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men; and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women, Hct_{ave} = the average of the Hct_{pre} and Hct_{post}). If a reinfusion or an allogenic transfusion was performed, the volume transfused should be added when calculating total blood loss.

The secondary outcomes included Hb, reduction of Hb concentration, platelet concentration, hematocrit level, coagulation indicators (prothrombin time, thrombin time, activated partial thromboplastin time and plasma fibrinogen) on 24 h postoperative. Other secondary outcomes included postoperative knee function (the range of motion and knee society score), pain score, surgical site infection, transfusion rates, and number of blood units transfused.

All patients were examined daily for clinical symptoms of DVT during hospitalization, including pain, swelling, tenderness, superficial venous engorgement, and Homan's sign in the thigh or calf. Diagnostic Doppler ultrasound was applied for all patients to exam both lower limbs by senior ultrasound physicians on postoperative day 3. The computed tomography (CT) was used to diagnose pulmonary embolism (PE) on postoperative day 3. All patients stayed in the hospital for a minimum of 7 days.

2.7. Statistical analysis

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL) software. A two-sided P value of < 0.05 was generally considered statistically significant for all comparisons. Distributions of demographic data, preoperative laboratory values, surgical data, knee function, and primary and secondary outcomes were assessed with summary statistics, including measures of central tendency (means and standard deviations) for quantitative data and numbers and percentages for qualitative data. Independent t-test was used to compare the normal distributed continuous variables, and Wilcoxon Mann-Whitney U test was applied to analyze non-normal distribution or unequal variables. Pearson chi-square test or Fisher exact test was used for categorical variables. Before breaking the randomization code, statistical analyses were conducted blinded.

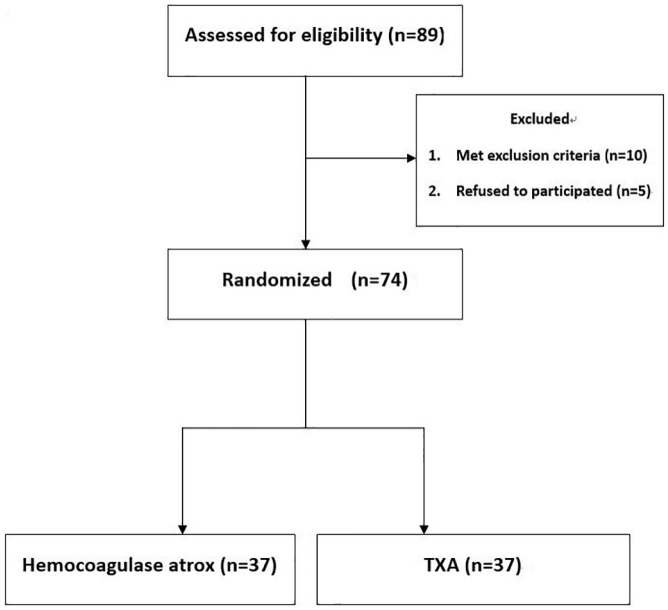

Fig. 1. Patient distribution of the total cohort.

3. Results

89 patients scheduled for primary unilateral total knee arthroplasty were screened for participation in this trial. Twelve patients were excluded for the following reasons: 10 were ineligible based on our exclusion criteria, 5 declined to participate (Fig. 1). The remaining 74 patients underwent randomization to receive study medication. Thus, a total of 74 eligible participants were randomized to receive TXA ($n = 37$) or hemocoagulase atrox ($n = 37$) (Fig. 1).

No significant differences between the allocation groups were identified with respect to demographic data, perioperative surgical characteristics, knee function, and preoperative laboratory values (Table 1).

The calculated blood loss (primary outcome) was 431.7 ± 288.4 mL in the TXA group and 644.6 ± 237.5 mL in the hemocoagulase atrox group ($P < 0.05$), with significant difference between two groups. Regarding secondary outcomes, there were significant differences in post-operative drop in hemoglobin (TXA: 1.21 ± 0.85 vs. hemocoagulase atrox: 2.08 ± 0.77) ($P < 0.05$), and significant differences were identified in hematocrit level postoperative (TXA: 36.4 ± 3.6 vs. hemocoagulase atrox: 34.4 ± 3.2) ($P < 0.05$). Meanwhile, the hemoglobin levels were higher than 8 g/dL in all patients postoperatively, none of the patients received allogeneic blood transfusion in this study.

Doppler ultrasonography was used to diagnose DVT. The rate of DVT did not differ significantly between the groups, with 3 cases in the TXA group compared with 1 in the hemocoagulase atrox group, all DVT are peripheral thrombosis. Among these patients, 2 patients showed no DVT-related clinical symptoms, and all 4 DVT patients were discharged and treated with outpatient thromboembolism prophylaxis protocol.

Post-operative VAS score was not significantly different between two groups at postoperative day 7. Moreover, knee range of motion and knee society score were similar among the groups at postoperative day 7.

Table 1
Baseline demographic and clinical characteristics.

Variable	TXA Group ($n = 37$)	Hemocoagulase atrox Group ($n = 37$)	*P* value
Patient characteristics			
Age (yr)	67.5 ± 6.7	64.2 ± 7.6	0.06
Gender (female/male)	26/11	28/9	0.60
BMI (kg/m^2)	26.1 ± 3.9	26.4 ± 3.6	0.74
Preop. laboratory values			
Hemoglobin (g/dL)	13.3 ± 1.2	13.5 ± 1.3	0.35
Hematocrit (L/L)	40.4 ± 3.3	41.0 ± 3.5	0.44
Platelet count ($\times 10^9$/L)	233.7 ± 56.6	237.4 ± 65.2	0.81
Prothrombin time (s)	11.1 ± 0.8	10.9 ± 0.8	0.35
APTT (s)	28.1 ± 2.5	27.9 ± 3.0	0.80
Fibrinogen (g/L)	3.0 ± 0.5	2.9 ± 0.4	0.16
Thrombin time (s)	17.5 ± 0.6	17.8 ± 1.4	0.21
Preop. knee function			
Pain VAS score	5.8 ± 0.9	5.5 ± 0.9	0.24
Knee society score (KSS)	49.5 ± 5.3	48.2 ± 5.9	0.36
Range of motion (ROM)	88.7 ± 12.4	89.4 ± 11.0	0.78

4. Discussion

Perioperative bleeding and postoperative wound bleeding are very important issues for surgeons. An inappropriate hemostasis intervention will cause hematoma in surgical site, delay wound healing, increase the chance of infection, reduce the patient's quality of life and even endanger the lives of patients [28].

TXA exerts its antifibrinolytic effects by inhibiting plasminogen, which prevents plasminogen activation and the binding of plasmin to fibrin, which leads to clot stabilization and decreases blood loss in surgical patients. The hemocoagulase atrox is obtained from Brazil spearhead Agkistrodon after segregation and purification. It can turn fibrinogen into fibrin monosomic I, which further turned into fibrin multimer I, leading to blood clot formation. The phospholipid-dependent factor X (FX) activator of hemocoagulase atrox can also make blood coagulation FX changed and turned thrombinogen into thrombin, fibrinogen into fibrin and decreased bleeding in result.

TKA has good outcomes for the treatment of end-stage knee arthritis, however, blood loss may vary from 800 mL to 1800 mL [29–31], and the incidence of transfusion may range from 11 to 67% [1,32]. Allogeneic blood transfusions are an economic burden and may result in the transmission of bloodborne pathogens, an immunomodulatory response, and periprosthetic joint infection [33]. Control of perioperative blood loss is associated with lower transfusion rates and shorter length of hospital stay [34,35].

In our study, there was no significant differences between the two groups regarding range of motion, knee society score, VAS score, and length of hospital stay. Both TXA and hemocoagulase atrox reduced postoperative bleeding in TKA patients receiving rivaroxaban for thromboprophylaxis. The hemoglobin levels were higher than 8 g/dL in all patients postoperatively, therefore none received allogeneic blood transfusion in this study. The calculated blood loss was 431.7 ± 288.4 mL in the TXA group and 644.6 ± 237.5 mL in the hemocoagulase atrox group, with significant difference between two groups, which indicated that hemocoagulase atrox was inferior to TXA in terms of blood loss prevention, and these results didn't agree with the expectation of hemocoagulase atrox would be equivalent to TXA in reduction of blood loss, it could be more precise when adding placebo group at this circumstance, which is a limitation for our study. And we reviewed previous placebo-controlled trials, we found that the total blood loss was from 400 mL to 1000 mL in TXA groups and from 1000 mL to 1800 mL in placebo groups [36]. Evidently, the total blood loss in placebo groups were significantly higher than that in the hemocoagulase atrox group (644.6 mL) in our study, and hemocoagulase atrox can significantly diminish blood loss and transfusion requirements in other surgery [19,37–40], therefore, it is reasonable to believe the effect of hemocoagulase atrox in reducing total blood loss is greater

Table 2
Primary and secondary outcomes.

Variable	TXA group (n = 37)	Hemocoagulase atrox group (n = 37)	P value
Primary outcome			
Total blood loss (mL)	431.7 ± 288.4	644.6 ± 237.5	< 0.001
Blood transfusion (U)	0	0	–
Hemoglobin (g/dL)	12.4 ± 1.2	11.5 ± 1.3	0.06
Hemoglobin Change (g/dL)	1.2 ± 0.8	2.1 ± 0.8	< 0.001
Hematocrit (L/L)	36.4 ± 3.6	34.4 ± 3.2	< 0.05
Platelet count ($\times 10^9$/L)	208.6 ± 54.7	194.2 ± 59.9	0.3
Prothrombin time (s)	12.1 ± 0.9	12.1 ± 0.9	0.95
APTT (s)	33.3 ± 4.4	33.0 ± 5.1	0.76
Fibrinogen (g/L)	3.3 ± 1.0	2.5 ± 0.7	< 0.001
Thrombin time (s)	16.9 ± 1.1	17.4 ± 1.5	0.11
Length of hospital stay	10.2 ± 1.6	10.2 ± 1.8	0.98
Postop. complications			
Deep vein thrombosis (DVT)	3	1	0.31
Pulmonary embolism (PE)	0	0	–
Superficial infection	0	0	–
Postop. knee function (day 7)			
Pain VAS score	6.9 ± 0.8	6.7 ± 0.9	0.23
Knee society score (KSS)	55.3 ± 4.5	54.6 ± 4.8	0.53
Range of motion (ROM)	92.2 ± 7.8	94.1 ± 5.5	0.61

than the placebo in TKA (see Table 2).

The using of TXA tends to have higher efficacy for reducing postoperative blood loss in TKA. However, the rate of DVT in hemocoagulase atrox group tends to be lower than those using TXA, with 3 cases in the TXA group compared with 1 in the hemocoagulase atrox group. DVT is one of the common complications of orthopedic surgery. The incidence of DVT is up to 50–60% in patients after arthroplasty [1], and PE which is one of its lethiferous complications can lead to severe mortality. According to the report from American Heart Association, approximately 2,000,000 people suffered from DVT per year and 10% of these died from PE, in the United States alone [2]. In our study, All DVT cases were diagnosed as peripheral DVT. However, the clinical relevance of peripheral DVT in patients is disputed. We believe that patients with peripheral DVT also need active treatment, patients with peripheral DVT subsequently developed central DVT without early accurate diagnosis and relevant treatment.

TXA has been widely used to reduce blood loss and transfusion following TKA, especially in enhanced recovery after surgery (ERAS). Increasing numbers of studies have supported this fact, and most of these studies focused on the routes of administration [41–47]. In China, more than two hundred thousand primary TKAs are conducted each year. Considering the aging population and longer life expectancy, this number of TKAs will increase dramatically over time, and the use of TXA will be more extensive for reducing swelling and inflammatory reactions after total joint arthroplasty.

Since TXA acts by affecting the fibrinolytic system, there has been concern about a potential increase in clotting events. However, high-quality studies and meta-analyses have not shown TXA to be associated with an increased risk of thromboembolic events [48,49]. And the rate of DVT in hemocoagulase atrox group tends to be lower than those using TXA. Therefore, hemocoagulase atrox may be an acceptable alternative to TXA for blood conservation for those with significant risk factors of thrombotic events. Further studies are warranted to evaluate if hemocoagulase atrox use could improve perioperative blood loss in patients with high thrombotic risk undergoing TKA.

4.1. Limitations

The present study had several limitations. First, the sample size of enrolled patients was not large enough, and it is a single center study. In addition, for some variables, small sample size may be underpowered to show significant differences. A multi-center large sample study would be required to validate our findings. Second, the comparison between TXA and hemocoagulase atrox is based upon the assumption that TXA was previously proven to significantly reduce intra-operative blood losses in other studies compared with placebo. However, our study found that hemocoagulase atrox was inferior to TXA in terms of blood loss prevention, and these results didn't agree with the expectation of hemocoagulase atrox would be equivalent to TXA in reduction of blood loss, it could be more precise when adding placebo group at this circumstance. Third, all DVT patients were diagnosed using ultrasonography, which may have a lower accuracy than venography. Fourth, we only obtained short-term follow-up data, further investigation is needed to determine longer-term clinical results.

4.2. Future directions

The rate of DVT in the hemocoagulase atrox group tend to be lower than those in TXA group, which suggested that hemocoagulase atrox may be an acceptable alternative to TXA for blood conservation for those with risk factors of thrombotic events. Further studies are warranted to evaluate if hemocoagulase atrox use could improve perioperative blood loss in patients with high thrombotic risk undergoing TKA.

5. Conclusions

Although the blood loss was significantly greater in the hemocoagulase atrox group, no transfusions were required and no significant differences were observed for any other outcomes measured, meanwhile, the rate of DVT trend to be lower than those using TXA. We concluded that hemocoagulase atrox was not superior to TXA in reducing perioperative blood loss, hemocoagulase atrox may be an acceptable alternative to TXA for blood conservation for those with risk factors of thrombotic events. Further studies are warranted to evaluate if hemocoagulase atrox use could improve perioperative blood loss in patients with high thrombotic risk undergoing TKA.

Author contributions

JZ.Q. SJ.W. and C.X. conceived and designed the experiments. JZ.Q., SJ.W., XP.Z., HH.Z., Y.L., L.S., and C.X. performed these experiments. JZ.Q., SJ.W., XP.Z., HH.Z., Y.L., L.S., and C.X. analyzed the data. JZ.Q., SJ.W. and C.X. prepared all the figures. JZ.Q. and SJ.W.

wrote the paper. All authors reviewed the manuscript.

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Declaration of competing interest

The authors declare that they have no competing interests.

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