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Original Research

The efficacy and safety of multiple doses of oral tranexamic acid on blood loss, inflammatory and fibrinolysis response following total knee arthroplasty: A randomized controlled trial

Yanfeng Tang[1], Yangyang Wen[1], Wuyin Li, Hongjun Li, Yuxia Yang, Youwen Liu*

Department of Orthopedics, Luoyang Zhenggu Hospital of Henan province(Henan Orthopedic Hospital), Luoyang, Henan Province, 471000, China

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ABSTRACT

Background: The aim of the study was to identify the efficacy and safety of multiple doses of oral tranexamic acid (TXA) on reducing blood loss and minimizing the postoperative inflammatory and fibrinolytic responses following primary total knee arthroplasty (TKA).

Materials and methods: In this prospective, double-blinded, randomized trial, we randomly assigned a total of 151 patients into three groups to receive 2 g of oral TXA 2 h preoperatively (group A); an additional dose of 2 g of oral TXA 4 h postoperatively (group B); or additional doses of 2 g of oral TXA at 4, 10, and 16 h postoperatively (group C). The primary outcome was total blood loss (TBL). The secondary outcomes were maximum drop in hemoglobin (Hb) and hematocrit (Hct), level of inflammatory and fibrinolytic parameters, transfusion rate, and the incidence of complications.

Results: The results were represented as mean ± standard deviation. The mean TBL was 607 ± 254 mL in group C, 743 ± 347 mL in group B ($p = 0.027$ vs group C), and 978 ± 335 mL in group A ($p < 0.001$ vs group C). The maximum Hb and Hct drop was 18.3 ± 7.7 g/L and 0.051 ± 0.025 in group C, 22.3 ± 9.7 g/L and 0.070 ± 0.028 in group B ($p = 0.022$ and $p = 0.001$ vs group C), 29.6 ± 11.7 g/L and 0.090 ± 0.034 in group A ($p < 0.001$ and $p < 0.001$ vs group C). In addition, C-reactive protein and interleukin-6 in group C were lower than in group A ($p < 0.001$ and $p = 0.003$) and in group B ($p = 0.031$ and $p < 0.001$) on postoperative day (POD) 3. Moreover, fibrin degradation products and D-dimer in group C were lower than in groups A and B on both POD 1 and POD 3. The incidence of complications did not differ significantly between the three groups ($p > 0.05$).

Conclusion: Multiple postoperative doses of oral TXA could further reduced blood loss and the drop in Hb and Hct, and diminished the postoperative inflammatory and fibrinolytic responses in primary TKA with no apparent increase in the incidence of complications.

Level of evidence: Level I, therapeutic study.

1. Introduction

Total knee arthroplasty (TKA) is effective in correcting deformity, ameliorating pain, and improving quality of life in patients with end-stage osteoarthritis of the knee [1]. The number of TKAs performed has increased annually in recent years [2]. However, the surgery is associated with substantial blood loss, contributing to a high risk of anemia and allogeneic blood transfusions, which increase the incidence of morbidity, immunologic reactions, transmission of disease, and infection [3–5]. Thus, various blood-conserving strategies have been used and the transfusion rate for primary TKA has decreased significantly [6].

Hyperfibrinolysis following surgery is a major contributor to perioperative blood loss in TKA [7]. Tranexamic acid (TXA), as an antifibrinolytic agent, has been shown to be effective and safe in reducing blood loss in primary TKA [1,8,9]. TXA could be administered intravenously, topically, orally, or via a combination of these routes. Oral TXA provides a considerable cost-saving benefit compared with the

* Corresponding author. Department of Orthopedics, Luoyang Zhenggu Hospital of Henan province(Henan Orthopedic Hospital), 82# QiMing Road, Luoyang, Henan Province, 471000, China.Tel number:

E-mail addresses: Yanfengt@163.com (Y. Tang), YYwen@163.com (Y. Wen), 15036707316@163.com (W. Li), 13721646820@163.com (H. Li), 531932508@qq.com (Y. Yang), 13688172272@163.com (Y. Liu).

[1] Yanfeng Tang and Yangyang Wen contributed equally to this work.

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intravenous or topical routes [10,11].

It was reported that hyperfibrinolysis continued for 18–24 h after surgery, and the duration of effective blood drug concentration for TXA was 6 h, which showed that a single dose of TXA could not meet the need for anti-fibrinolysis [12,13]. Some studies indicated that multiple dose of intravenous TXA could further reduce blood loss and restrain fibrinolysis compared with one or two doses of TXA following primary TKA [1,8,14]. In addition, a randomized trial performed by Cao et al. found that multiple boluses of oral TXA further reduced blood loss and the drop in hemoglobin (Hb) and hematocrit (Hct), and also decreased postoperative fibrinolysis in primary total hip arthroplasty (THA) without increasing the risk of complications [15]. However, little research has been performed on the efficacy and safety of multiple doses of oral TXA in the setting of primary TKA. Thus, little is known about the optimal timing and dosage of oral TXA.

This prospective, double-blinded, randomized trial was conducted in order to identify the clinical effect and safety of multiple doses of oral TXA in primary TKA. The hypothesis was that with multiple doses and proper timing, the oral TXA could further reduce blood loss, restrain postoperative inflammatory and fibrinolysis without increasing complications.

2. Materials and methods

2.1. Patients and design

This prospective, double-blinded, randomized trial was approved by the institutional review board of our center (201603137), registered at http://www.researchregistry.com (researchregistry4502). All patients gave their written informed consent for participation in the study before operation. The work had been reported in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines.

From June 2017 to July 2018, we consecutively screened patients aged 18 years or older who underwent primary unilateral TKA for osteoarthritis or rheumatoid arthritis. Exclusion criteria were as follows: presence of a congenital or acquired clotting disorder, anemia (< 120 g/L for women, < 130 g/L for men), a history of deep venous thrombosis (DVT) or pulmonary embolism (PE), cardiovascular problems, renal insufficiency, or a known allergy to TXA.

Enrolled patients were randomly assigned into three study groups using a computer-generated randomization protocol. Those in group A were given 2 g of oral TXA (four 500-mg tablets) 2 h preoperatively and four placebo tablets, identical in appearance but with no active ingredients, at 4, 10, and 16 h postoperatively. Those in group B were given 2 g of oral TXA 2 and 4 h postoperatively, along with four placebo tablets at 10 and 16 h postoperatively. Those in group C were given 2 g of oral TXA 2 h preoperatively, and additional identical doses at 4, 10, and 16 h postoperatively. A nurse not involved in the trial implemented the perioperative protocol. The patients, surgeons, and researchers were blinded to the group allocation. When patients took medicine at incorrect time or suffered from side effects because of oral TXA, they would be deleted from the study.

2.2. Surgery procedure

All of the surgeries were performed using a midline skin incision, medial parapatellar approach, and a measured resection technique. All patients received a surgeon-selected, cemented, posterior-stabilized prosthetic design with patellar resurfacing. The surgery was performed by a single joint surgeon using the same technique. All of the TKAs were conducted under general or lumbar anesthesia. The tourniquet was used with inflation to 100 mmHg above the systolic pressure before the incision and deflation after closure of the incision. Drains, nerve blocks, and blood salvage were not used in these patients. The patients were discharged when they met discharge criteria, which included no wound leakage, swelling, or infection, independent mobility, no pain or mild pain, and knee flexion ≥100° and extension ≥ −5° [16].

2.3. Perioperative care

All patients had the same perioperative protocols. The patients received physical prophylaxis and chemoprophylaxis for venous thromboembolism. Patients began to perform ankle pump and knee extension exercises when they returned to the ward from the operating room. A half-dose of low-molecular-weight heparin (2000 IU in 0.2 ml; Clexane, Sanofi-Aventis, France) was injected subcutaneously on operative day after the operation and repeated at 24-h intervals until discharge, and then 10 mg of Rivaroxaban (Xarelto, Bayer, Germany) was taken orally once a day for 10 days. Doppler ultrasound examinations were used on a routine basis preoperatively, at discharge, and on POD 15 to detect DVT. Clinical symptoms and computed tomography scans were used to detect PE. The patients after surgery received intravenous chalybeate 200 mg qd and erythropoietin 10 thousand IU qd subcutaneously when they were diagnosed as postoperative anemia (< 120 g/L for women, < 130 g/L for men). Transfusions were applied according to the guidelines of the Chinese Ministry of Health [17]. Transfusions were given when the Hb level was < 70 g/L or 70–100 g/L with symptoms of anemia, such as impaired mental status, palpitations, or shortness of breath not owing to other causes.

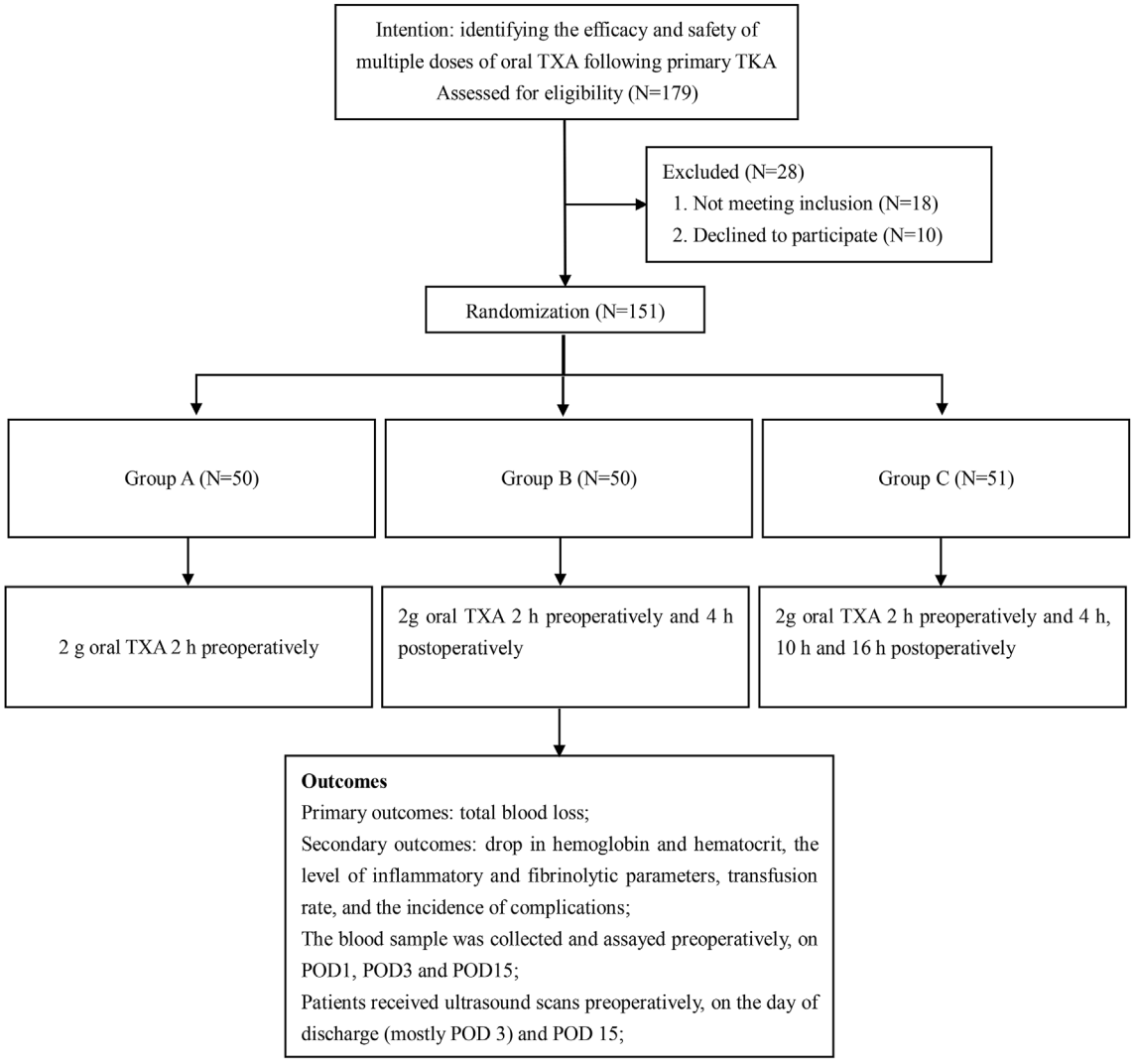
2.4. Outcome measurements

Demographic characteristics, medical history, and medications of the patients were collected preoperatively. Hb, Hct, inflammatory markers (C-reactive protein [CRP], interleukin 6 [IL-6]), and fibrinolysis markers (fibrin degradation products [FDP], D-dimer) were tested preoperatively, on PODs 1, 3, and 15. The primary outcome was total blood loss (TBL). TBL was calculated by the Gross and Nadler formula [18,19]. TBL = patient's blood volume (PBV) × (Hct_{pre}-Hct_{post})/Hct_{ave} (Hct_{pre} = the initial preoperative Hct level, Hct_{post} = the Hct on the morning of POD3. PBV = k_1 × height $(m)^3 + k_2$ × weight $(kg) + k_3$ (k_1 = 0.3669, k_2 = 0.03219, and k_3 = 0.6041 for men; and k_1 = 0.3561, k_2 = 0.03308, and k_3 = 0.1833 for women, Hct_{ave} = the average of the Hct_{pre} and Hct_{post}). If either reinfusion or allogeneic transfusion was performed, the TBL was equal to the loss calculated from the change in Hct plus the volume transfused [20]. The secondary outcomes were a maximum drop in Hb and Hct, the level of inflammatory and fibrinolytic parameters, transfusion rate, and the incidence of complications during the first month after surgery. The maximum Hb and Hct drop was defined as the difference between the preoperative Hb and Hct and the lowest postoperative Hb and Hct during the hospitalization.

2.5. Statistical analysis

All analyses were performed by using SPSS version 22.0 (SPSS Inc. USA) and a p-value < 0.05 was considered to be statistically significant. The continuous variables, such as demographic variables and blood loss, were compared among the three study groups using one-way ANOVA. For continuous variables measured in varied time points, such as CRP, IL-6, FDP, D-dimer, repeated measure ANOVA was made. The categorical variables were compared using Pearson chi-square test or Fisher exact test.

Sample size were calculated on the outcome of TBL and on our preliminary data using PASS 2011 (NCSS, LLC, Kaysville, UT, USA) software. To detect a difference of 100 mL, 42 patients were needed for per group with a power of 0.90 and an alpha of 0.05. With the consideration of the loss to follow-up, exclusion and declination, we decided to include 179 patients totally, about 60 patients in each group. Two statisticians had reviewed the manuscript.



TXA = Tranexamic acid, TKA = Total knee arthroplasty, POD = Postoperative day.

Fig. 1. Flow of patients through the study. TXA = Tranexamic acid, TKA = Total knee arthroplasty, POD = Postoperative day.

3. Results

3.1. Patients' demographics

A total of 179 patients recruited for primary unilateral TKA were screened for eligibility in our center from January 2017 to July 2018. Eighteen patients were excluded and 10 patients declined to participate. The remaining 151 patients (50 in Group A, 50 in Group B, and 51 in Group C) were observed and studied (Fig. 1). The baseline characteristics of the patients in the three groups were comparable (Table 1).

3.2. Blood loss

The mean TBL in group C (607 ± 254 mL) was lower than in group A (978 ± 335 mL, $p < 0.001$) and in group B (743 ± 347 mL, $p = 0.027$). In addition, no patient received an allogeneic blood transfusion in any group. The maximum decreases in Hb and Hct in group C (19.3 ± 7.7 g/L; 0.051 ± 0.025) were lower than in group A (29.6 ± 11.7 g/L, $p < 0.001$; 0.090 ± 0.034, $p < 0.001$) and in group B (22.3 ± 9.6 g/L, $p = 0.022$; 0.070 ± 0.028, $p = 0.001$). Differences were similarly detected between group A and B ($p = 0.001$ and $p = 0.002$). The outcome of blood loss is summarized in Table 2.

3.3. Inflammatory parameters

The interaction between the study groups and time points for the variables were significant through repeated ANOVA and we are interested in the comparison of the three study groups within the same time point. The mean CRP level peaked on POD 3 and the mean IL-6 level peaked on POD 1. Significant differences among the three groups were present on POD 3 (Fig. 2). The levels of CRP and IL-6 (58.96 ± 33.74 pg/mL; 23.13 ± 20.16 pg/mL) in group C were lower than in group A (90.92 ± 49.68 pg/mL, $p < 0.001$; 57.53 ± 49.53 pg/mL, $p = 0.003$) and in group B (77.69 ± 48.51 pg/mL, $p = 0.031$; 35.56 ± 20.12 pg/mL, $p < 0.001$) on POD 3. Patients in group A had a lower level of IL-6 compared with those in group B ($p = 0.007$). However, there was no difference in the level of CRP between the two groups ($p = 0.193$) on POD3.

Table 1
Baseline characteristics.

Baseline Characteristic	Group A (n = 50)	Group B (n = 50)	Group C (n = 51)
Demographic characteristics			
Age (y)	65.5 ± 7.4	63.2.6 ± 7.7	66.2 ± 7.8
Gender (M/F)	7/43	12/38	9/42
Height (cm)	155.9 ± 5.9	158.2 ± 6.6	157.5 ± 6.3
Weight (kg)	62.0 ± 8.8	63.1 ± 11.1	64.2 ± 11.1
BMI (kg/m^2)	25.5 ± 3.4	25.2 ± 3.9	25.8 ± 3.9
Diagnose: OA/RA	1/49	2/48	2/49
Comorbidities (N, %)			
Hypertension	21 (42.0%)	29 (58.0%)	28 (54.9%)
Diabetes	7 (14.0%)	6 (12.0%)	7 (13.7%)
Preoperative laboratories			
Platelet count (*1000/mm^3)	185.9 ± 54.5	183.0 ± 62.2	202.4 ± 68.3
PT (secs)	11.29 ± 0.72	11.55 ± 0.88	11.39 ± 0.51
APTT (secs)	27.0 ± 2.9	27.8 ± 3.9	27.0 ± 3.0
INR	1.02 ± 0.15	1.11 ± 0.13	0.99 ± 0.13
Hb (g/L)	130.2 ± 10.3	130.7 ± 12.8	132.8 ± 9.5
Hct	49.8 ± 2.9	39.7 ± 3.5	40.1 ± 2.9
PBV (mL)	3868.6 ± 500.3	3774.7 ± 474.2	3843.5 ± 676.3
Operative variables			
Anesthesia method			
General	17 (34.0%)	12 (24.0%)	20 (39.2%)
Regional	33 (66.0%)	38 (76.0%)	31 (60.8%)
ASA class			
< 3	44 (88.0%)	45 (90.0%)	42 (82.5%)
≥3	6 (12.0%)	5 (10.0%)	9 (17.5%)
Postoperative length of stay (days)	3.4 ± 0.7	3.4 ± 0.8	3.2 ± 0.7
Operating time (min)	73.0 ± 10.7	72.3 ± 8.4	73.2 ± 13.5

BMI: Body mass index = Weight/$Height^2$; OA: Osteoarthritis; RA: Rheumatoid arthritis; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; Hb: Hemoglobin; Hct: Hematocrit; PBV: patient blood volume; ASA: American Society of Anesthesiologists.
The results of continuous variables were represented as means and SD, and categorical variables as percentages.

3.4. Fibrinolysis parameters

FDP and D-dimer increased after surgery in all patients. The mean serum levels of FDP and D-dimer in group C (9.54 ± 6.52 mg/L, 3.65 ± 2.80 mg/L FEU) were lower than in group A (38.13 ± 22.16 mg/L, $p < 0.001$; 13.18 ± 5.25 mg/L FEU, $p < 0.001$) and in group B (18.65 ± 14.16 mg/L, p = 005; 7.19 ± 5.26, mg/L FEU, p = 0.007) on POD 1. In addition, the mean serum levels of FDP and D-dimer in group B (7.74 ± 3.53 mg/L, 2.41 ± 1.09 mg/L FEU) were lower than in group A (10.51 ± 3.00 mg/L, p < 0.001; 4.25 ± 1.67 mg/L FEU, p < 0.001). However, the differences in the levels of FDP and D-dimer between groups B and C on POD 3 did not reach statistical significance (Fig. 3).

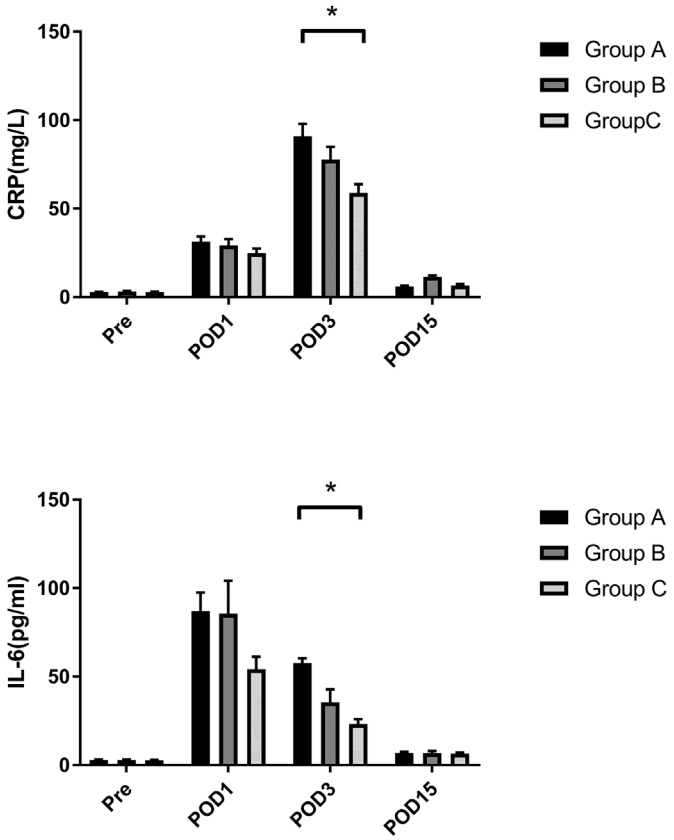


Fig. 2. The perioperative levels of CRP and IL-6 in serum. CRP = C-reactive protein, IL-6 = interleukin 6, Pre = preoperative, POD1 = postoperative days 1, POD3 = postoperative days 3, POD15 = postoperative days 15. The results were represented as mean and SE. Error bars expressed SE and * expressed significant difference among the three groups.

3.5. Complications

The period of observation was one month in this study and no data was lost. Only one patient in group A developed DVT. No patients developed DVT in groups B and C. Five patients in group A, three in group B, and seven in group C developed calf muscular vein thromboses. The incidence of complications was similar among the groups (Table 3). All patients were discharged uneventfully after symptomatic treatment.

4. Discussion

Perioperative blood loss in TKA has been a crucial issue despite advances in blood management strategies [6]. Searching appropriate blood-conserving strategies was important for joint surgeons. The Cochrane review performed by Henry et al. showed that lysine analogues, such as TXA, were effective in reducing blood loss during and after orthopaedic surgery, and appeared to be free of serious adverse effects

Table 2
Comparison of blood loss.

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 51)	P
TBL (mL)	978.2 ± 335.2	742.5 ± 346.8	606.5 ± 254.0	< 0.001*
Transfusion rate (%)	0	0	0	–
Maximum Hb drop	29.6 ± 11.7	22.3 ± 9.6	19.3 ± 7.7	< 0.001*
Maximum Hct drop	0.090 ± 0.034	0.070 ± 0.028	0.051 ± 0.025	< 0.001*

TBL: Total blood loss; HBL: Hidden blood loss; P represents P value of group A vs B vs C.
The results of continuous variables were represented as means and SD, and categorical variables as percentages.
*Significant difference.

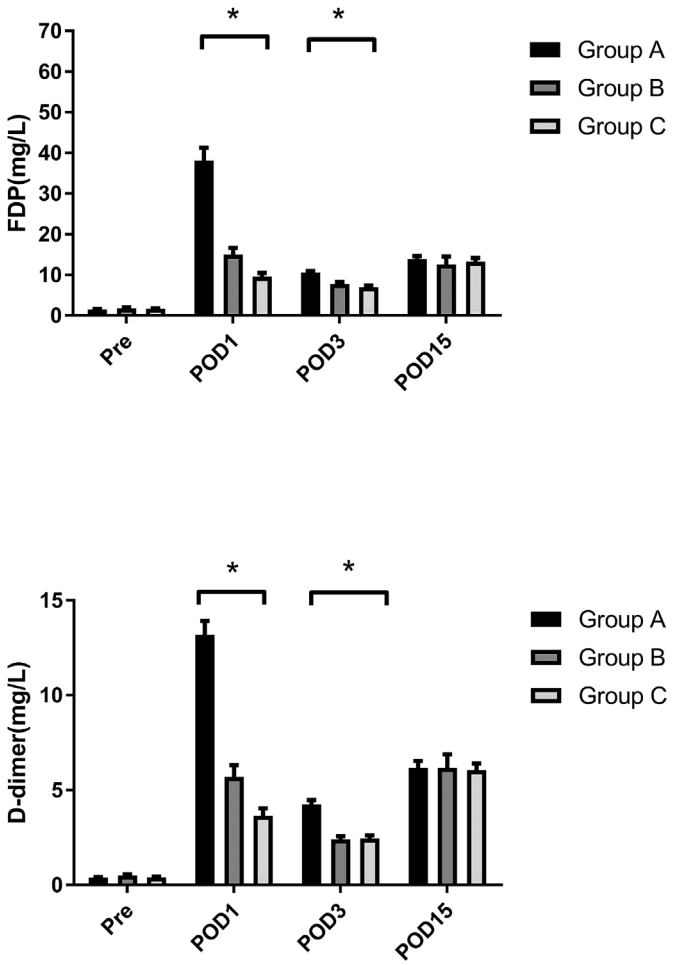


Fig. 3. The perioperative levels of FDP and D-dimer in serum. FDP = fibrin degradation products, Pre = preoperative, POD1 = postoperative day 1, POD3 = postoperative day 3, POD15 = postoperative days 15. The results were represented as mean and SE. Error bars expressed SE and * expressed significant difference among the three groups.

Table 3
Complications.

Complications	Group A (n = 50)	Group B (n = 50)	Group C (n = 51)
PE	0	0	0
DVT	1 (2%)	0	0
CMVT	5 (10%)	3 (6%)	7 (13.7%)
Cardiac infarction	0	0	0
Acute renal failure	0	0	0
Wound secretion	3 (6%)	2 (4%)	3 (5.9%)
Superficial infection	1 (2%)	0	0
Deep infection	0	0	0

PE: pulmonary embolism; DVT: deep venous thrombosis; CMVT: calf muscular vein thrombosis.
The results of continuous variables were represented as means and SD, and categorical variables as percentages.

[21]. Because of great cost-efficient benefits, the benefit of oral TXA to reduce blood loss has been well established recently. However, the total blood loss was 1281 ± 265 ml when TXA was only used once [10] and the 48 h Hb drop was 2.90 ± 0.43 g/L, transfusion rate was 10.7% when TXA was used twice [22], and the blood loss was still high [10,22]. Moreover, the efficacy and safety of multiple intravenous TXA doses in primary THA and TKA, and oral TXA in primary THA, has been confirmed by some authors [8,15,23]. However, there has been a paucity of large studies on protocols for multiple doses of oral TXA in the setting of TKA. In this study, we found that a single preoperative dose and three postoperative doses of oral TXA could further decrease blood loss, the drop in Hb and Hct, and the postoperative inflammatory and fibrinolytic responses following primary TKA.

It was reported that TXA maintained levels above the therapeutic threshold for about 6 h, which was less than the duration of hyperfibrinolysis (18–24 h) [15]. Thus, it was necessary and beneficial to repeat the administration of TXA. Irwin et al. found that the appropriate dose of oral TXA was 2 g, and oral TXA should be administered 2 h in advance [13]. Therefore, we gave 2 g of oral TXA 2 h preoperatively and at 4, 10, and 16 h postoperatively. Medication interval was 6 h, which was consistent to the therapeutic threshold. The usage was similar to the study performed by Cao et al. [24]. In this way, oral TXA reached the therapeutic threshold preoperatively and at 6, 12, and 18 h postoperatively, which covered the whole process of hyperfibrinolysis. Moreover, previous studies indicated that multiple doses of intravenous or oral TXA could further reduce the blood loss and minimize inflammation and fibrinolysis without increasing the risk of complications, and oral and intravenous TXA had equivalent efficacy and safety in primary THA [8,15,24]. This study provided strong evidence concerning the efficacy and safety of multiple doses of oral TXA in primary TKA.

Owing to the cost-effectiveness and greater ease of administration of oral TXA, it has been the focus of many researchers in recent years [9,22,25,26]. A retrospective cohort study performed by Perreault et al. found that oral TXA reduced transfusions and the Hb drop in primary TKA, while there was no difference in transfusion rates between the single and two-dose groups [9]. The reason may be that the interval of drug administration (2 h preceding surgery and an optional additional dose 2 h after surgery) was less than the duration that oral TXA could maintain levels above the therapeutic threshold (6 h) for [13,27]. The first dose could offset the effect of the second dose. Keerati and colleagues showed that repeated application of oral TXA (0.5 mg; three times daily) for 5 days was superior to a single bolus in primary TKA [25]. In addition, Wang et al. found that the addition of two or three postoperative doses of TXA to a preoperative dose produced a significant reduction in blood loss and a two-dose postoperative regimen was the least necessary regimen for clinical efficacy in TKA [26]. The dose after surgery was 1 g each time. However, we thought that the oral dose (1 g) was likely too low to obtain a therapeutic plasma concentration because the proper dosage of oral TXA was about 2 g each time, based on previous studies [13,27]. Yuan et al. enrolled 560 patients undergoing primary TKA and randomized them to an intravenous group (two doses of 20 mg/kg intravenous TXA), a topical group (3.0 g topical TXA), an oral group (two doses of 20 mg/kg oral TXA), and a control group. The results indicated that the three modes of TXA administration significantly reduced the postoperative Hb drop and transfusion rate. However, the TXA was used only twice, and the 48-h Hb (2.9 g/L) drop and transfusion rate (10.7%) remained high [22]. Maximum Hb drop was the minus of preoperative Hb and the lowest postoperative Hb (mainly POD3) during the hospitalization. So the maximum Hb drop could be regarded as the Hb drop on POD3, namely, 72 h postoperatively. The maximum Hb drop (at 72 h postoperatively) was 19.3 g/L, and no patient required a blood transfusion in this study, which showed that multiple doses of oral TXA could further reduce blood loss after primary TKA.

The anti-inflammatory effects of TXA have been confirmed by some authors [1,8,28]. It was reported that plasminogen plays a central role in the inflammatory response to biomaterials, which could be inhibited by TXA [29]. This may be a reason why multiple oral TXA doses could further block the inflammatory response. In addition, the mean level of CRP peaked on POD 3, while the level of IL-6 peaked on POD 1, indicating that IL-6 was more sensitive than CRP in predicting inflammation [30].

The levels of FDP and D-dimer in group C were lower than in groups A and B on POD 1 in our study, showing that multiple doses of oral TXA

could minimize fibrinolysis. Similarly, Lei at al found that multiple doses of intravenous TXA could further inhibit fibrinolysis following primary TKA, particularly on POD 1 [8]. Because hyperfibrinolysis was the primary reason for blood loss [7], more effective inhibition of fibrinolysis may contribute to less perioperative blood loss.

Whether TXA can increase the risk of thrombotic diseases and other related complications has been an important issue for clinicians [31]. The safety of multiple doses of TXA has been confirmed by previous studies, but mechanical and chemical thromboprophylaxis was necessary [1,8,26]. Only one patient developed DVT in the study and no patients developed PE, illustrating that there was no evidence for an increase in the risk of complications with the application of multiple doses of oral TXA in primary TKA. Further, larger studies are required.

There were several limitations of this study despite a careful design. First of all, the laboratory results were solely measured preoperatively, on POD 1, POD 3 and POD15, and the TBL was calculated based on the minus of preoperative Hct and Hct on POD 3. The Hct may continue to decline after POD3 [32]. However, we believe that the potential inaccuracy due to Hct did not influence the results because the method of calculation was the same in the three groups. Second, the sample size was calculated according to TBL, which would not be enough to detect a significant difference in other outcomes, such as maximum Hb and Hct drop, and complications. Third, patients received ultrasound scans only preoperatively, at the time of discharge and on POD 15. The patients suffering from thrombotic diseases (PE and DVT) before surgery were excluded. The patients who were found to be with thrombotic diseases after surgery received anticoagulant therapy. Moreover, considering the much blood loss without using TXA and ethics, we did not select the blank control in which patients did not receive oral TXA. This was a huge limitation. Finally, the follow-up time was only 1 month, which may be inadequate to sufficiently evaluate the risk of DVT and other complications. Therefore, additional studies with a long-term follow-up are required.

5. Conclusion

Multiple doses of oral TXA could further reduce blood loss, Hb and Hct drop and restrain postoperative inflammation and fibrinolysis in primary TKA with no apparent increase in the incidence of complications.

Ethical approval

This study was approved by Institutional Review Board of Luoyang Orthopaedic Hospital of Henan Province.

Sources of funding

None.

Author contribution

Drs. Yanfeng Tang and Youwen Liu take the responsibility for the integrity of the work as a whole. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Conception and design: Yanfeng Tang, Yangyang Wen and Youwen Liu.

Surgical Team: Yangyang Wen, Wuyin Li, Hongjun Li and Youwen Liu.

Collection and assembly of data: Hongjun Li and Yuxia Yang.

Drafting and critical revision of the article: Hongjun Li and Yuxia Yang.

Final approval of the version to be submitted: Yanfeng Tang, Yangyang Wen, Wuyin Li, Hongjun Li, Yuxia Yang and Youwen Liu.

Conflicts of interest

Each author certifies that neither he or she, nor any member of his or her immediate family, have funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Trial registry number

researchregistry4502.

Guarantor

Youwen Liu.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

All the data is true and valid in the study. A nurse not involved in the trial implemented perioperative protocol and collect data.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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