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ORIGINAL PAPER

# The efficacy and safety of multiple-dose oral tranexamic acid on blood loss following total hip arthroplasty: a randomized controlled trial

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## Abstract

**Purposes** To explore the efficacy and safety of multiple-dose oral tranexamic acid (TXA) on blood loss following primary total hip arthroplasty (THA).

**Methods** A total of 152 patients were randomized into three groups to receive 2 g of oral TXA two hours pre-operatively (group A), or another bolus of 2 g of oral TXA four hours post-operatively (group B), or another three boluses of 2 g of oral TXA four, ten, and 16 hours post-operatively (group C). The primary outcomes were total blood loss (TBL), hidden blood loss (HBL), and transfusion rate. The secondary outcomes were haemoglobin (Hb) and haematocrit (Hct) drop, the level of fibrinolysis parameters (fibrin degradation products, D-dimer), and complications (thrombotic diseases, stroke, cardiac infarction, and infection).

**Results** The mean TBL and HBL in group C were lower than those in group A ($p < 0.001$ and $p < 0.001$) and group B ($p = 0.012$ and $p = 0.029$). The Hb drop on post-operative day one (POD1) and POD3 in group C was lower than those in group A ($p < 0.001$ and $p = 0.029$) and group B ($p < 0.001$ and $p = 0.004$). The difference was similar regarding Hct drop on POD3 ($p < 0.001$ and $p = 0.014$). Moreover, fibrin degradation products and D-dimer in group C were lower than in groups A and B on POD1 and POD3 ($p < 0.001$ and $p < 0.001$). The incidence of complications such as venous thromboembolism did not differ significantly among the three groups ($p > 0.05$).

**Conclusions** Multiple boluses of oral TXA could further reduce blood loss, Hb and Hct drop, and restrain post-operative fibrinolysis in primary THA without increasing the risk of complications.

**Level of Evidence I** Therapeutic study.

**Keywords** Total hip arthroplasty · Tranexamic acid · Oral · Blood loss

## Introduction

Total hip arthroplasty (THA) is one of the most common surgeries used for the treatment of end-stage degenerative hip disease, which is almost always accompanied by joint pain, deformity, and dysfunction. However, the procedure is associated with substantial blood loss, often leading to acute anaemia and blood transfusion. This increases the risk of post-operative

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infection, delayed functional recovery, prolonged hospital stay, and even mortality [1–3]. Consequently, it is crucial to find effective methods to minimize peri-operative blood loss and reduce the rate of blood transfusion.

It has been reported that surgical trauma and hyperfibrinolysis lead to peri-operative blood loss in THA and hyperfibrinolysis occurred as a result of the systemic inflammatory effect of surgery [4]. Therefore, tranexamic acid (TXA), an antifibrinolytic agent that can be administered intravenously, topically, orally, or by multiple routes, has been used extensively to decrease blood loss. Previous studies found that TXA was effective and safe at reducing blood loss in patients undergoing THA through those routes of administration [5–9]. Because of the cost-benefit advantage of oral TXA, research related to oral TXA administration has attracted much attention [10, 11]. However, the optimal dosage and timing of oral TXA are still controversial, and the majority of the regimens have involved a single dose given either intravenously or topically [6, 8, 9].

Studies reported that fibrinolysis peaked six hours after THA and was maintained for about 18 hours post-operatively [12, 13]. Recent research showed that multiple boluses of intravenous TXA further reduced blood loss, inflammation, and fibrinolysis without increasing the risk of complications following THA and total knee arthroplasty (TKA) [4, 14–16]. However, the evidence supporting multiple boluses of oral TXA has been limited. Moreover, the optimal timing and dosage of oral TXA remain unclear. Hence, we conducted this randomized, controlled, double-blinded trial to examine the efficacy and safety of multiple boluses of oral TXA in decreasing blood loss and fibrinolysis after primary THA.

## Materials and methods

### Study design and patients

This prospective, double-blinded, randomized trial was approved by the institutional review board of our center and registered at www.chictr.org.cn (ChiCTR-IPR-17012266). All patients gave their written informed consent for participation in the study before operation. All patients undergoing primary unilateral THA for osteoarthritis, osteonecrosis of the femoral head, and developmental dysplasia of hip (Crowe I/II) were considered eligible for enrollment from June 2017 to November 2017. Exclusion criteria included patients with anemia (< 120 g/L for female, < 130 g/L for male), history of deep venous thrombosis (DVT) or pulmonary embolism (PE), cardiovascular problems, congenital or acquired clotting disorders, known allergy to TXA and renal insufficiency.

Enrolled patients were randomly assigned into three study groups. Randomization was blind and performed with the use of sealed envelopes opened just prior to surgery. Group A: patients received 2 g of oral TXA using four tablets of 500 mg two hours pre-operatively and four placebo tablets, identical in appearance with no active ingredient, four, ten, and 16 hours post-operatively. Group B: patients received 2 g of oral TXA two hours pre-operatively and four hours post-operatively along with four placebo tablets ten and 16 hours post-operatively. Group C: patients received 2 g of oral TXA two hours pre-operatively and then three more doses four, ten, and 16 hours post-operatively. A nurse not involved in the trial implemented peri-operative protocol. The patients, surgeons, data collector, and analyst were blinded.

### Surgery procedure

All the operations were performed by a senior surgeon through the posterolateral approach. All the THAs were conducted under general anesthesia with blood pressure controlled within 90–110 mmHg/60–70 mmHg throughout the procedure. All patients received cementless prosthesis. Wound drainage and blood salvage was not used in these patients. The intra-operative blood loss was calculated and recorded carefully.

### Post-operative care

Physical prophylaxis and chemoprophylaxis for venous thromboembolism were applied for all patients. Patients began to do ankle pump and knee extension exercises when they recovered from anesthetic. The intermittent pneumatic compression device (Daesung Maref Co. Ltd., Gunpo, Korea) was applied for every patient on the day of surgery. A half-dose of low-molecular-weight heparin (LMWH; 2000 IU in 0.2 mL; Clexane, Sanofi-Aventis, France) was injected percutaneously six hours post-operatively and repeated at 24 hours intervals until discharge, and then 10 mg Rivaroxaban (Xarelto, Bayer, Germany) was taken orally once a day for ten days. Doppler ultrasound examinations were used routinely pre-operatively, at discharge, two weeks, and three months after surgery to detect DVT. Clinical symptoms and CT scans were used to detect PE.

Transfusions were applied if the Hb level was < 70 or 70–100 g/L with symptoms of anaemia (defined as bad mental status, palpitation, or shortness of breath not due to other causes) according to the guidelines by the National Ministry of Health.

### Outcome measurements

Demographic characteristics, medical history, and medications of the patients were collected pre-operatively. Complete blood count and coagulation function were tested pre-operatively, on post-operative day 1 (POD1), and POD3. In addition, intra-operative blood loss, allogenic transfusion units and rate, and complications were carefully recorded. The primary outcomes were total blood loss (TBL), hidden blood loss (HBL), and transfusion rate. The secondary outcomes were haemoglobin (Hb) and haematocrit (Hct) drop, the level of fibrinolysis parameters (fibrin degradation products, D-dimer), and complications.

TBL was calculated by the Gross and Nadler formula according to our previous study [9]. TBL = patient's blood volume (PBV) × ($Hct_{pre} - Hct_{post}$)/$Hct_{ave}$ ($Hct_{pre}$ = the initial pre-operative 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 [17]. Intra-operative blood loss was calculated using the difference between the weights of used gauze and the original unused gauze, in addition to the blood volume accumulated in suction bottles. HBL was defined as TBL minus intra-operative blood loss.

### Statistical analysis

Sample size calculations were performed using PASS 2011 (NCSS, LLC, Kaysville, UT, USA) software. Sample size was calculated on the outcome of HBL and on our preliminary data. 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. The continuous variables were compared using the one-way analysis of variance, Wilcoxon Mann-Whitney *U* test, or independent *t* test. The categorical variables were compared using Pearson chi-square test or Fisher exact test. All analyses were compared by using SPSS version 22.0 (SPSS Inc. USA), and a $p$ value $< 0.05$ was considered to be statistically significant.

## Results

### Patients' demographics

Totally, 183 patients recruited from June 2017 to November 2017 were scheduled to receive a primary unilateral THA in our center. However, 21 patients were ineligible, and ten patients declined to participate in the study. All 152 patients (51 group A, 51 group B, and 50 group C) were observed and studied (Fig 1). There was no demographic difference among the three groups (Table 1).

### Blood loss

The mean TBL and HBL in group C (744.0 ± 287.8; 631.3 ± 266.1) were lower than those in group A (1102.2 ± 412.2, $p < 0.001$; 988.2 ± 410.8, $p < 0.001$) and group B (903.2 ± 370.2, $p = 0.012$; 789.7 ± 286.6, $p = 0.029$). The mean TBL and HBL in group B were lower than those in group A ($p = 0.023$ and $p = 0.036$). What was more, no patient received allogeneic blood transfusion in any group (Table 2).

### Hb and Hct drop

The Hb drop on POD1 and POD3 in group C (13.7 ± 8.2; 25.2 ± 9.2) was lower than those in group A (21.6 ± 12.4, $p < 0.001$; 37.4 ± 13.4, $p = 0.029$) and group B (18.0 ± 10.5, $p < 0.001$; 31.8 ± 11.1, $p = 0.004$). The Hct drop of group C on POD3 was lower that of group A and group B ($p < 0.001$ and $p = 0.014$). Nevertheless, there was no difference between groups A and B. In addition, the Hct drop on POD1 in group B ($p = 0.025$) and group C ($p < 0.001$) was lower than that in group A.

### Fibrinolysis parameters

The mean serum level of fibrin degradation products (FDP) and D-dimer in group C (6.54 ± 4.97, 3.02 ± 2.45) were lower than in group A (18.86 ± 14.88, $p < 0.001$; 7.35 ± 5.21, $p < 0.001$) and group B (18.65 ± 14.16, $p < 0.001$; 7.19 ± 5.26, $p < 0.001$) on POD1. Similar difference was detected on POD3. The differences of the level of FDP and D-dimer in groups A and B did not reach statistical significance (Figs 2 and 3).

### Complications

Four patients in group A, five in group B, and six in group C developed calf muscular vein thrombosis. One patient developed posterior tibial vein thrombosis in group A, and one patient developed peroneal vein thrombosis in group C. The differences were not statistically significant ($p = 0.782$ and $p = 0.991$, respectively). All patients were discharged from hospital uneventfully after symptomatic treatment. No PE, stroke, cardiac infarction, and superficial or deep infection were observed in any group during the three month follow-up period (Table 3).

## Discussion

TXA has been widely used to reduce blood loss and transfusion following THA. This benefit has been established with the intravenous, topical, and oral dosage form [5–9]. Some studies demonstrated that the blood-sparing efficacy of intravenous, topical, and oral forms of TXA was equivalent in the setting of primary THA. However, the TXA was administered only once and the blood loss was still high (more than 1000 mL) [10, 11]. In this research, four doses of oral TXA could further decrease blood loss, Hb and Hct drop, and

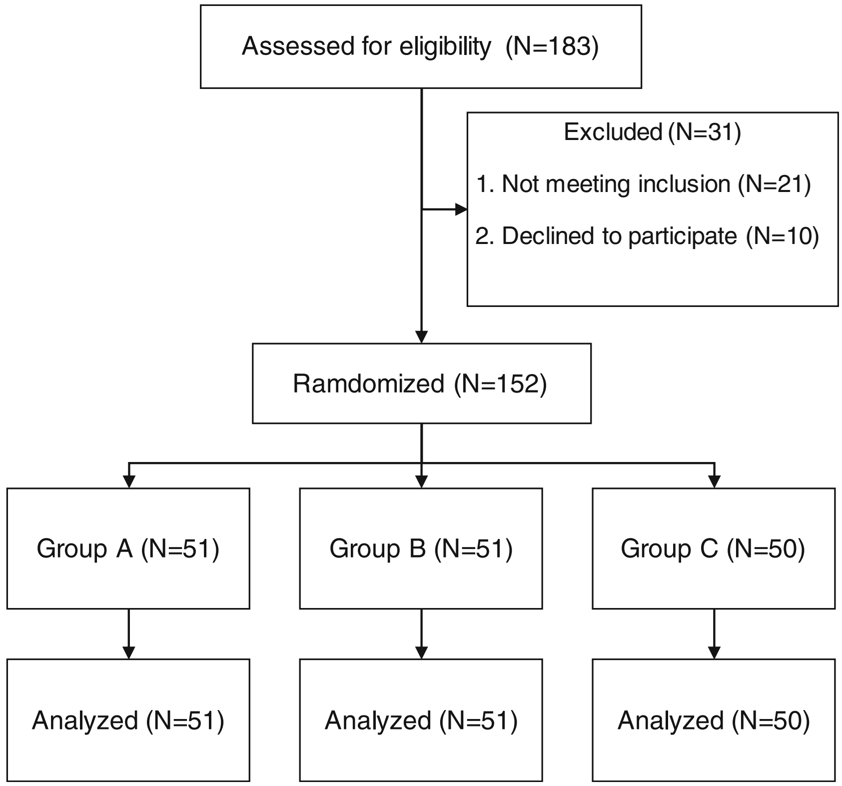


**Fig. 1** Flowchart of the inclusion and exclusion of the patients

post-operative fibrinolysis response following primary THA. The result was similar to the study of multiple boluses of intravenous TXA [4].

Peri-operative blood loss of THA has been a major problem despite advances in blood management strategies [18, 19]. The peri-operative blood loss is constituted by overt blood loss (intra-operative bleeding and volume of drainage) and HBL, resulting from hyperfibrinolysis, which contributes 60% of TBL [17]. So, the main purpose of repeating application of TXA is to inhibit the fibrinolysis to reduce HBL. According to literatures, 2 g dose of oral TXA could reach effective blood concentration after approximately two hours and maintain levels

**Table 1** Baseline characteristics

| Demographic | Group A ($n = 51$) | Group B ($n = 51$) | Group C ($n = 50$) | $p$ |
|---|---|---|---|---|
| Age (year) | 64.6 ± 12.8 | 64.2.6 ± 10.1 | 64.9 ± 11.9 | 0.538 |
| Gender(M/F) | 27/24 | 20/31 | 22/28 | 0.369 |
| Height (cm) | 159.6 ± 7.1 | 157.7 ± 6.0 | 160.8 ± 8.1 | 0.110 |
| Weight (kg) | 60.8 ± 8.4 | 61.4 ± 10.1 | 60.2 ± 10.4 | 0.823 |
| BMI(kg/m$^2$) | 23.8 ± 3.0 | 24.7 ± 3.7 | 23.2 ± 2.8 | 0.075 |
| OA/ONFH | 38/13 | 39/12 | 31/19 | 0.221 |
| Operative site (L/R) | 26/25 | 24/27 | 24/26 | 0.918 |
| ASA class | | | | |
| 1–2 | 46 | 43 | 44 | 0.662 |
| ≥3 | 5 | 8 | 6 | |
| Pre-operative Hb (g/L) | 137.8 ± 9.5 | 136.7 ± 9.2 | 134.3 ± 11.3 | 0.201 |
| Pre-operative Hct | 0.412 ± 0.030 | 0.410 ± 0.030 | 0.405 ± 0.031 | 0.486 |
| Pre-operative FDP (mg/L) | 2.35 ± 0.91 | 2.35 ± 0.71 | 2.25 ± 0.98 | 0.818 |
| Pre-operative D-dimer (mg/L) | 0.89 ± 0.55 | 0.87 ± 0.59 | 0.85 ± 0.54 | 0.942 |
| PBV (mL) | 3868.6 ± 500.3 | 3774.7 ± 474.2 | 3843.5 ± 676.3 | 0.679 |

*BMI* body mass index = weight/height$^2$ ; *OA* osteoarthritis, including primary osteoarthritis and secondary osteoarthritis caused by developmental dysplasia of hip (types I and II); *ONFH* osteonecrosis of the femoral head; *ASA* American Society of Anesthesiologists; *Hb* hemoglobin; *Hct* hematocrit; *FDP* fibrin degradation products; *PBV* patient blood volume

**Table 2** Comparison of blood loss and LOH

| Variable | Group A ($n$ = 51) | Group B ($n$ = 51) | Group C ($n$ = 50) | P | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|
| TBL (mL) | 1102.2 ± 412.2 | 903.2 ± 370.2 | 744.0 ± 287.8 | < 0.001* | 0.023* | < 0.001* | 0.012* |
| HBL (mL) | 988.2 ± 410.8 | 789.7 ± 286.6 | 631.3 ± 266.1 | < 0.001* | 0.036* | < 0.001* | 0.029* |
| Transfusion rate (%) | 0 | 0 | 0 | – | – | – | – |
| Hb drop on POD1 | 21.6 ± 12.4 | 18.0 ± 10.5 | 13.7 ± 8.2 | 0.001* | 0.150 | < 0.001* | 0.029* |
| Hb drop on POD3 | 37.4 ± 13.4 | 31.8 ± 11.1 | 25.2 ± 9.2 | < 0.001* | 0.054 | < 0.001* | 0.004* |
| Hct drop on POD1 | 0.064 ± 0.033 | 0.048 ± 0.035 | 0.039 ± 0.027 | 0.001* | 0.025* | < 0.001* | 0.206 |
| Hct drop on POD3 | 0.104 ± 0.036 | 0.089 ± 0.036 | 0.072 ± 0.027 | < 0.001* | 0.102 | < 0.001* | 0.014* |

*TBL* total blood loss, *HBL* hidden blood loss, *LOH* length of hospital stay, *POD* postoperative day, *P p* value of group A vs B vs C, *P1 p* value of group A vs B, *P2 p* value of group A vs C, *P3 p* value of group B vs C

*Significant difference

above the therapeutic threshold for six hours after administration [20, 21]. To our best knowledge, there was only one study designed to compare the effect and safety of multiple boluses of oral TXA in primary THA. Qunn et al. enrolled 108 patients undergoing primary THA and randomized them to trial group with 1 g of oral TXA two hours preoperatively, and six and 12 hours post-operatively while control group without drug [7]. The results indicated that three doses regime of oral TXA was effective in blood sparing in terms of reduction in Hb drop, HBL, and TBL. However, the dosage of 1 g of oral TXA was not enough to provide plasma concentration of therapeutic levels [20, 21]. The minimal concentration of TXA required to maintain a hemostatic effect in vivo was 10 mg/L. It was reported that 2 g of oral TXA could maintain haemostatic threshold about six hours after administration [20]. In addition, the comparison and difference between one and several boluses of oral TXA were absent. Thus, one or two additional doses of oral TXA had been administered in our study, and we made efforts to search the answer which regimen was ideal.

Although we knew that TXA enjoyed a strong evidence in reducing blood loss and pre-operative oral TXA provided equivalent effect with the intravenous and topical formulation [10, 11, 22], the optimum dose and time of oral TXA were still unclear. What was more, whether it should be administered as one or several boluses had not been systematically studied. Roger and his colleagues found that there was no statistical difference on blood loss between single-dose (1.95 g, 2 hours preceding surgery) and two doses (1.95 g, 2 hours preceding surgery and an optional additional dose 2 hours after surgery) of oral TXA in primary THA. But, the results showed a downward tendency on transfusion rate and Hb drop [23]. Another study showed that multiple doses of oral TXA were superior to placebo in primary THA [7]. Moreover, a prospective trial conducted by Keerati et al. indicated that an oral form of the TXA (0.5 mg; three times daily) for five days was superior to a single bolus in primary TKA [24]. Our research provided evidence of the advantage of multiple-dose oral TXA, inspiring further studies examining systematically the effects and safety of different doses of oral TXA in primary THA.

Hyperfibrinolysis was the main reason of blood loss [16]. The level of FDP and D-dimer in group A and B showed no difference in this study. Thus, it could be seen that two boluses oral TXA failed to effectively restrain post-operative fibrinolysis and more boluses were necessary in primary THA. Lei et al. reported that five doses of intravenous TXA could conduce to better fibrinolysis inhibition following primary TKA, particularly on POD1 [15]. Similarly, one important finding in

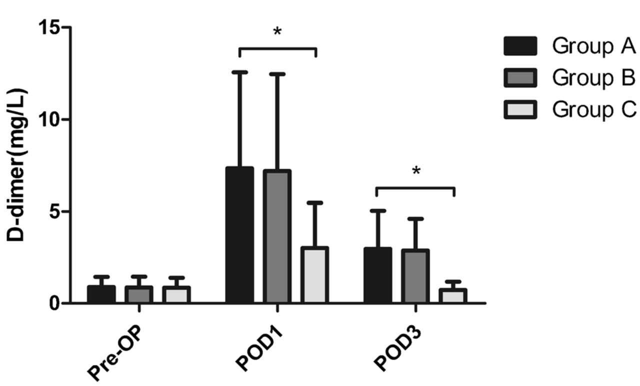


**Fig. 2** The level of FDP in serum. FDP fibrin degradation products, Pre-OP pre-operative, POD1 post-operative day 1, POD3 post-operative day 3. *Significant difference

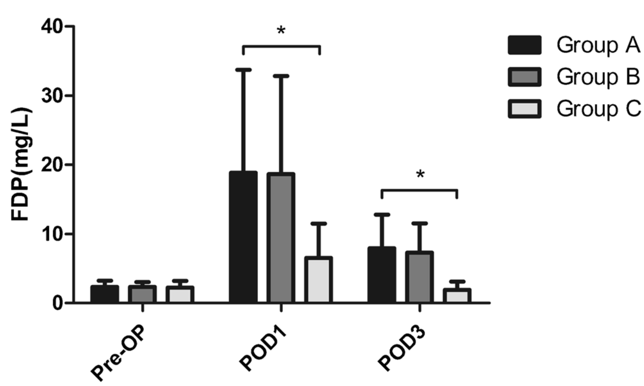


**Fig. 3** The level of D-dimer in serum. Pre-OP pre-operative, POD1 post-operative day 1, POD3 post-operative day 3. *Significant difference

**Table 3** Complications

| Complications | Group A ($n = 51$) | Group B ($n = 51$) | Group C ($n = 50$) | $p$ |
|---|---|---|---|---|
| DVT | 1 | 0 | 1 | 0.991 |
| PE | 0 | 0 | 0 | – |
| CMVT | 4 | 5 | 6 | 0.782 |
| Stroke | 0 | 0 | 0 | – |
| Cardiac infarction | 0 | 0 | 0 | – |
| Superficial infection | 0 | 0 | 0 | 0.546 |
| Deep infection | 0 | 0 | 0 | – |

*DVT* deep venous thrombosis, *PE* pulmonary embolism, *CMVT* calf muscular vein thrombosis

this study was that four doses of oral TXA could further inhibit post-operative fibrinolysis comparing to one dose and two doses, as evidenced by the level of FDP and D-dimer post-operatively. In addition, the TBL was more than 1000 mL in primary THA when one dose TXA was used in previous studies [10, 11], which was consistent with the result of group A in this study. However, the TBL dropped to 744 mL with the administration of four doses of oral TXA, which adequately covered the duration of post-operative hyperfibrinolysis.

Although TXA could reduce blood loss and was valuable for clinical application, whether TXA could increase the risk of VTE and other treatment-related complications was the principal concern for clinicians [25]. Considering the perspective of balancing risks and benefits, Lee thought that the four doses oral regime seemed too long in view of the theoretical risk of DVT, but further study was lacking [7]. The randomized controlled trials performed by Lei and Xie found that multiple boluses of intravenous TXA was effective to reduce blood loss without increasing the risk of complications including VTE through the combination of mechanical and chemical thromboprophylaxis [4, 15]. Similar result was observed in this study. Two patients suffered DVT in total 152 patients, and the incidence was very low, which could provide related evidence to evaluate the safety of multiple-dose oral TXA.

Although this study was carefully designed, there were still several limitations. First, the sample size was calculated based on HBL, which would be not enough to detect a significant difference in complications. Second, we calculated the TBL according to the level of Hct on POD3, which was influenced by liquid intake and output volume. However, the same method of calculation was applied to three study groups. We did not take it as a factor. Third, the comparison of different application routes of multiple-dose TXA was absent in our study. Last but not the least, the laboratory results were only measured on POD1 and POD3. We could not obtain the variation trend. Therefore, further studies with long-term follow-up are requisite and future researches about TXA should compare the efficacy and safety of different routes of multiple-dose TXA.

In conclusion, multiple boluses of oral TXA could further reduce blood loss, Hb, and Hct drop and restrain post-operative fibrinolysis in primary THA without increasing the risk of complications.

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## Compliance with ethical standards

**Conflict of interest** All authors declare no conflict of interest.

**Ethical approval** The trial was approved by the institutional review board and registered at the International Clinical Trial Registry (ChiCTR-IPR-17012266).

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

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