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Preoperative dose of intravenous tranexamic acid safely reduces blood loss and transfusion in patients undergoing hip hemiarthroplasty for femoral neck fracture. A randomized controlled trial

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The objectives were to evaluate the effectiveness and safety of a single preoperative dose of intravenous tranexamic acid (TXA) in reducing perioperative blood loss and requirement for transfusion in patients undergoing hip hemiarthroplasty for femoral neck fracture. A double-blind randomized controlled trial was conducted in 140 patients with hip fracture. After randomization, 68 patients received a single dose of 1 gr of intravenous TXA at the start of the surgery (TXA group), and 72 received a placebo treatment (placebo group). TXA group had a significant decrease in blood loss ($p < 0.001$) and requirement for transfusion ($p < 0.001$) compared with the placebo group. There were seven thromboembolic events, all in the placebo group ($p = 0.014$). Mortality within 1-year postoperatively was not significantly different between groups ($p = 0.297$).The use of a single dose of intravenous TXA at the start of the surgery significantly reduces blood loss and requirement for transfusion without increasing the risk of thromboembolic events in patients with femoral neck fracture undergoing hip hemiarthroplasty.

Keywords: hip fracture, tranexamic acid, blood loss, transfusion, hemiarthroplasty.
Level of evidence: I

INTRODUCTION

Femoral neck fracture is a devastating injury in older patients, representing a meaningful cost to the public health system. Hip hemiarthroplasty is currently a recognized method for the treatment of displaced femoral neck fractures in older adults, with satisfactory functional outcomes. However, this surgical procedure may be associated with significant blood loss during the perioperative period[1], and this anemia could contribute to the high morbidity and mortality rates after hip surgery[2]. Furthermore, this blood loss may require allogeneic blood transfusions[1,3], with a potentially higher incidence of complications[2].

Several randomized studies[4-8] have reported the efficacy and safety of tranexamic acid (TXA) in reducing blood loss in patients with hip fractures, but there is a paucity of studies focused exclusively on patients with femoral neck fracture undergoing hip hemiarthroplasty[9-12], and only Narkbunnam et al.[12] designed a prospective study, comparing different groups depending on dose and time of TXA administration.

The purpose of this study was to evaluate the effectiveness and safety of a single preoperative dose of intravenous TXA in reducing perioperative blood loss and transfusion requirements in older patients with displaced femoral neck fractures undergoing hip hemiarthroplasty, within the first postoperative year. The hypothesis was that administering a single dose of intravenous TXA would decrease the perioperative bleeding and reduce the need for transfusion without increased thrombotic risk and mortality within one postoperative year.

MATERIALS AND METHODS

This single-centre, randomized, placebo controlled, double blinded trial was approved by the institutional review board (PI2018-142) and included in a public registry (ClinicalTrials.gov NCT03211286). Informed consent was obtained prior to randomization. This research was performed under the Declaration of Helsinki International Ethical Guidelines, and the protocol was conducted and reported according

to the Consolidated Standards of Reporting Trials (CONSORT).

Consecutive patients with displaced femoral neck fracture admitted to our institution from January 2018 to September 2021 were eligible for the study. The inclusion criteria were age over 75, a femoral neck fracture that occurred within 24 hours prior to admission, and implantation of cemented hip hemiarthroplasty within 48 hours of admission. The exclusion criteria were: 1) ASA group IV-V; 2) tumoral pathologic fracture; 3) other concomitant fracture; 4) refusal to receive blood products; 5) anticoagulant or antiplatelet treatment in the three days prior to surgery; and 6) described contraindications for TXA[13]. During the pandemic by the SARS-CoV-2 virus, positive patients were excluded because venous thrombosis was a potential complication in those patients[14].

Randomization was based on a computer-generated number list using the block method by an independent assistant. Each assignment was sealed in a consecutively numbered opaque envelope opened by the nurse who prepared the intravenous solutions in the operating room. Patients were allocated (ratio 1:1) into one of two groups: 1) TXA group, whose patients received 1 gr of intravenous TXA (Amchafibrin, Rottapharm Madaus, Germany) diluted in 100 ml of saline solution; 2) Placebo group, whose patients received an equivalent volume of intravenous saline solution. Masking was ensured by preparing the same volume of solution with an identical appearance. Just before the surgical incision, both treatments were performed. The surgeons, anesthetists, and patients were blinded to the assignment until the completion of the study. The dose of intravenous TXA chosen for this study was based on previous reports[15,16].

All surgical procedures were performed under spinal anesthesia. In our institution, intracapsular hip fractures in patients over 75 years were treated with a cemented bipolar hemiarthroplasty. Experienced hip surgeons performed all the operations using a Hardinge approach with the same surgical technique among all patients. Diathermy was routinely used. At the end of the operation, a deep vacuum drain was placed for 24 hours.

1) Patient blood volume (PBV):

PBV(l) **= [height**(m)^3 **× k1] + [weight**(kg) **× k2] + k3**

where for women, k1=0.356, k2=0.033, k3=0.183

and for men, k1=0.367, k2=0.032, k3=0.604

2) Total Hb loos (Hbloss):

Hbloss(g) **= PBV**(l) **x [Hbadm**(g/dl) **- Hbfinal**(g/dl)**] + Hbtransf**(g)

where HBadm (Hb on admission), Hbfinal (final Hb), Hbtransf (Hb transfused)

3) Total blood loss (BL):

BL(ml) **= [Hbloss**(g) **/ Hbadm**(g/dl)**] × 1000**

Figure 1 — Mathematical formulas for calculating patient blood volume and perioperative blood loss.

With the proposal of minimizing the effect of isovolumetric hemodilution, postoperative fluid therapy was standardized for the first 24 hours with 1500 ml of saline solution. All patients received standardized antibiotics and thromboembolic prohylaxis with first-generation cephalosporin for 24 hours and low-molecular-weight heparin for 30 days. All patients were postoperatively mobilized under the assistance of a physiotherapist on the first postoperative day.

A standardized protocol for co-management between orthopaedic surgeons and geriatricians was used from admission to discharge. Comorbidity patient was categorized using the American Society of Anesthesiologists (ASA) scale[17] and Charlson comorbidity index[18]. Patient evaluation was made preoperatively and at one, three, six, and 12 post-operative months. Two independent surgeons who were blinded to the study groups evaluated all outcomes.

The primary effectiveness outcomes were the total blood loss and transfusion rate. Patients were monitored with serial haemoglobin (Hb) determinations during their stay and received a transfusion of packed red blood cells if their Hb dropped below 8 g/dL, or less than 9 g/dL if they had symptomatic anemia or heart disease.

The total blood loss was calculated according to widely accepted mathematical formulas[19,20] based on the Hb levels and the estimated blood volume (Fig. 1). For this purpose, the final Hb was determined according to the lowest level within four days after the operation[20]. Based on measurements at our hospital, a unit of packed red blood cells was considered to have a mean volume of 250 ml and to contain 52 g of Hb.

The primary safety outcome was the rate of thromboembolic event. Patients were clinically monitored for these events until one postoperative year. If there was suspicion of any event, the diagnosis was confirmed by doppler ultrasonography for deep venous thrombosis (DVT), computed tomography scan for pulmonary thromboembolism, magnetic resonance imaging for cerebral stroke, and electrocardiogram (ECG) and troponin level for myocardial infarction. Data on surgical or medical infection, readmission and death were also collected. The infection was diagnosed with positive cultures of drainage from the surgical wound.

According to a previous study[4] on TXA for hip fracture surgery, a reduction in blood loss of 500 ml

was considered clinically relevant. For a power of 80% and a two-sided type I error of 5%, 60 patients per group were needed. Assuming a drop-out rate of 5%, at least 63 patients per group were required.

Statistical analysis was performed using SPSS software v. 25 (SPSS Inc, Chicago, USA). Kolmogorov-Smirnov test was used to examine normal distribution of continuous data. Analyses between groups was performed with the chi-square or Fisher's exact test for categorical variables, and t-Student test or non-parametric Mann Whitney U-test for continuous variables. The paired t-Student test or Wilcoxon signed-rank test was used to compare preoperative and postoperative data. Multivariate logistic regression analyses were planned to identify independent risk factors for main outcome variables, including in the model only the variables with a univariate p-value <0.1. Data were shown as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was considered for p values less than 0.05 in all tests.

RESULTS

A total of 210 eligible patients were enrolled in the study at our hospital between January 2018 and September 2021. Sixty-four patients were excluded for various reasons, including failure to meet inclusion criteria (60 patients), decline to participate (three), or language barrier (one). The remaining 146 patients were randomized into the TXA group (73 patients) or placebo group (73 patients). Five patients from the TXA group and one from the placebo group were excluded due to loss of follow-up and failure to respond to telephone appointments. Therefore, there were 68 patients in the TXA group and 72 patients in the placebo group for the final analysis (Fig. 2). There were no significant differences in the baseline characteristics between the two groups (Table I). Postoperative follow-up was one year in all patients.

The mean total blood loss during the entire admission (Table II) was significantly lower in the TXA group (699.7 ml, SD 229.3) compared with the placebo group (1233.8 ml, SD 578.2) ($p < 0.001$). One patient required blood transfusion in the TXA group, while 20 patients received transfusion in the placebo group ($p < 0.001$) (Table II). In 18 cases, 1 unit of packed red blood cells was transfused, while 2 units were required in three patients. For the risk of blood transfusion, multivariate analysis adjusted for potential factors (Table III) revealed that only the TXA treatment (OR, 0.03; 95% CI, 0.004-0.2; $p = 0.001$) and Hb level on admission (OR, 0.61; 95% CI, 0.3-0.9; $p = 0.034$) were significant predictors.

There were seven thromboembolic events within one year postoperatively, all in the placebo group ($p = 0.014$). Three patients were diagnosed with symptomatic DVT at 18, 86 and 93 postoperative days, three others had a cerebral stroke at 25, 38 and

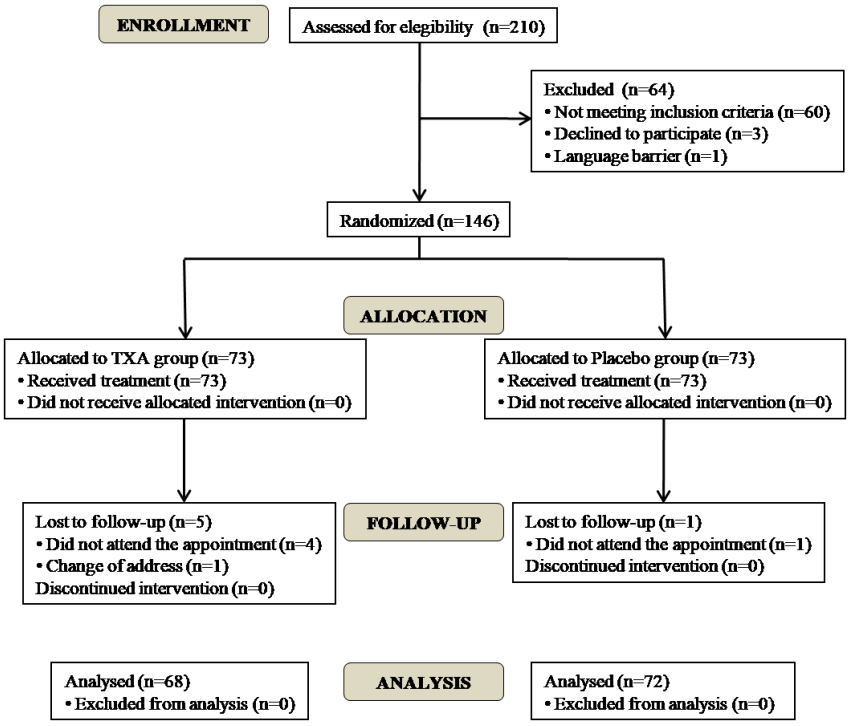

Figure 2 — CONSORT flow chart.

Table I. — Baseline data in both groups

	TXA group (n=68)	Placebo group (n=72)	p-value
Mean age, yrs (SD)	82.4 (10.5)	83.9 (9.1)	0.841 ¥
Gender, F:M	52:16	56:16	0.876 ‡
Mean BMI, kg/m^2 (SD)	26.4 (5.6)	28.3 (5.7)	0.078 ¥
ASA score, I-II:III	32:36	36:36	0.728 ‡
Charlson index, 0-2:>2	68:0	68:4	0.120 ‡
Admission Hb, gr/dl (SD)	13.0 (1.4)	12.9 (1.0)	0.764 ¥
Patient blood volume, l (SD)	3.9 (0.8)	4.2 (0.8)	0.166 ¥
Surgery delay, days (SD)	1.5 (0.6)	1.6 (0.5)	0.286 ¥
Surgery time, min (SD)	52.7 (12.7)	50.5 (15.4)	0.410 ¥
Stay length, days (SD)	5.9 (2.1)	5.6 (2.1)	0.323 ¥

TXA, tranexamic acid. F, female. M, male. SD, standard deviation. BMI, bone mass index. ASA, American Society of Anesthesiologists. Hb, haemoglobin. ‡Chi-square or Fisher exact test. ¥ Mann-Whitney test.

Table II. — Postoperative outcomes

	TXA group (n=68)	Placebo group (n=72)	p-value
Total blood loss, ml (SD)	699.7 (229.3)	1233.8 (578.2)	0.000 ¥
Transfused patients, n	1 (1.4%)	20 (27.7%)	0.000 ‡
Thromboembolic events, n	0 (0%)	7 (9.7%)	0.014 ‡
Cumulative mortality, n 30-day 90-day 1-year	 8 (11.8%) 8 (11.8%) 8 (11.8%)	 4 (5.6%) 4 (5.6%) 13 (18.0%)	 0.235 ‡ 0.235 ‡ 0.297 ‡
Infections, n	1 (1.5%)	8 (11.1%)	0.034 ‡

TXA, tranexamic acid. SD, standard deviation. RBC, red blood cell. ‡chi-square or Fisher exact test. ¥ Mann-Whitney test.

Table III. — Predictors of blood transfusion in multivariate analysis

	No transfused (n=119)	Tranfused (n=21)	Univariate p-value	Multivariate analysis	
				OR (95% CI)	p-value
Admission Hb, g/dl (SD)	13.1 (1.2)	12.5 (1.0)	0.023 ¥	0.618 (0.3-0.9)	0.034
Treatment, n Placebo TXA	 52 67	 20 1	 < 0.001 ‡	 Ref. 0.03 (0.004-0.2)	 0.001

Only data with univariate p-value < 0.1 are shown. Ref, OR = 1; CI, confidence interval Hb, haemoglobin. SD, standard deviation. TXA, tranexamic acid. OR, odds ratio. ¥, Mann-Whitney test. ‡, Chi-square or Fisher exact test.

117 postoperative days, and one patient suffered a myocardial infarction 27 days after surgery. There was no case of pulmonary embolism. Multivariate analysis for the risk of thromboembolic events was not performed due to the low rate. The postoperative infection rate was 4.4% (three patients) in the TXA group compared with 8.3% (six patients) in the placebo group (p = 0.495). All those patients required early revision surgery. There was no significant relationship between infection and surgery time (p = 0.524) or blood transfusion (p = 0.598). Except for deceased patients, there were no cases of readmission.

The cumulative mortality (Table II) was not significantly different between groups at 30 (p = 0.235) or 90 days (p = 0.235). At one year, eight patients in the TXA group and 13 in the placebo group had died, but this difference was not significant (p = 0.297). Only postoperative infection (p = 0.004) showed a significant association with 1-year mortality in the univariate analysis.

DISCUSSION

The main finding of this study was that the administration of 1 gr of intravenous TXA at the start of the surgery significantly reduced total blood loss and transfusion rate in patients older than 75 years with intracapsular hip fracture undergoing cemented hip hemiarthroplasty. Furthermore, the use of TXA was not associated with an increased risk of thromboembolic events or 1-year mortality. As in the present study, Nikolaou et al[5] also found that preoperative Hb level and TXA treatment were the only significant predictor of packed red blood cell transfusion.

There is clear evidence of the effectiveness and safety of tranexamic acid in knee and hip prosthetic surgery[21]. However, there is a paucity of high evidence level studies on intracapsular hip fractures treated by cemented hemiarthroplasty[12,22,23]. Narkbunnam et al.[12] studied the blood loss and transfusion rate in patients undergoing hemiarthroplasty for femoral neck fracture, but comparing among different regimens of TXA administration. Emara et al.[22] compared topical versus intravenous use of tranexamic acid in this type of patient, while Watts et al.[23] included both total hip replacements and hemiarthroplasties after femoral neck fractures. Moreover, other non-randomized studies analyzed the use of tranexamic acid in patients with hip fractures, mixing types of fracture and implants used, therefore, with series of great heterogeneity.

Significant reduction of blood loss and need for transfusion were also reported by most randomized studies that used a single dose[5,7,24], two doses[4,12,23,25], or three doses[8] of intravenous TXA. Conversely, Zufferey et al.[26] found no significant difference in blood loss or transfusion rate between the TXA and placebo groups, while Nikoloau et al[5] did report a significant decrease in blood loss and transfusion rate in patients with extracapsular fracture who received intravenous TXA compared to those who received placebo, but found no such differences in patients with intracapsular fractures.

In the only study[12] randomizing one dose, two doses and placebo, the authors found no significant difference between one-dose and two-dose groups in blood loss, but the transfusion rate was significantly lower in the two-dose group. Nevertheless, data suggested that the effectiveness of intravenous TXA was similar regardless of the number of doses[4,6,8,23,25,27]. Recent metaanalyses also found that the frequency and dosage of intravenous TXA did not influence its beneficial effect[28,29].

Randomized studies with a follow-up of at least three months reported similar rates of thromboembolic event, complication, and 90-day mortality between TXA and placebo groups using two[23,25] or one[7] dose of intravenous TXA. Only Zufferey et al[26] raised some concerns about the safety of the treatment, based on the results of their study, reporting nine (16%) thromboembolic events with two doses of intravenous TXA, and three (6%) in the placebo group. Although that difference was not statistically significant, the authors did not recommend TXA for hip fracture surgery. Tengberg et al[4] found a higher 90-day mortality rate in the TXA group (27%) compared to the placebo treatment (10%), but although this difference seems important, it was not statistically significant and the influence of TXA on excess mortality could not be determined.

With one dose of intravenous TXA, as in the present study, Ma et al[7] reported 14% of DVT in the TXA group, and 13% in the placebo group. No other thrombotic events were observed after a follow-up of three postoperative months. Zhou et al.[24], also using one dose and follow-up of one month, found three (3%) thromboembolic events in the TXA group, and seven (7%) in the placebo group, although that difference was not significant. Similar findings were found in other randomized studies that used only one dose of intravenous TXA, although their follow-ups were between 48 hours and four days[5,16]. The use of intravenous TXA appears to be safe even in patients with a prior venous thromboembolic event[30].

To our knowledge, only one randomized study[12] had previously studied the effectiveness and safety of intravenous TXA only in patients with cemented hemiarthroplasty after intracapsular hip fracture. However, they focused their research on analyzing the efficacy of an additional dose of TXA, using cemented and cementless hip systems according to intraoperative criteria, and with less postoperative follow-up. The present study had several limitations. Due to safety considerations, high-risk patients were excluded from the study. Thus, the results may not be generalizable, and the safety of TXA in those patients remains unproven. For the primary effectiveness outcome, the mathematical calculation of the blood loss based on clinical measurements proposed by Good et al[20] was used. Like others, this method is not validated and could be a source of error with a tendency to overestimate blood loss, although other first level studies[4,5,12] used the same method. Nevertheless, it was applied to compare two groups, with a standardized postoperative fluid therapy used to minimize the effect of isovolumetric hemodilution. Regarding the safety outcome, subclinical or asymptomatic DVT might have gone undetected. On the other hand,

the sample size was based on blood loss. Given the low frequency of thromboembolic events, the study may be underpowered to detect differences in these complications.

CONCLUSION

The use of a single dose of 1 gr of intravenous TXA at the start of the surgery reduces blood loss and requirement for transfusion significantly without increasing the risk of thromboembolic events or mortality within one year postoperatively in patients older than 75 years with hip fracture undergoing cemented hemiartrhoplasty.

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