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Original article

Effect of topical tranexamic acid in total hip arthroplasty patients who receive continuous aspirin for prevention of cardiovascular or cerebrovascular events: A prospective randomized study

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ABSTRACT

Background: Due to differences in pharmacological mechanism of action, the effect of tranexamic acid (TA) on aspirin-related bleeding remains unknown. We therefore conducted a prospective randomized study to elucidate: (1) the effect of topical TA administration on blood loss and transfusion rate in total hip arthroplasty (THA) patients receiving continuous aspirin for prevention of cardiovascular or cerebrovascular events; (2) 90-day complications of topical TA administration; (3) possible variables contributing to blood transfusion.

Hypothesis: Topical TA administration reduces blood loss and transfusion rate in THA patients receiving continuous aspirin.

Patients and Methods: A total of 102 consecutive THA patients taking continuous aspirin were enrolled and randomized into two groups. In the topical TA (TTA) group ($n = 55$), topical TA was administered at three points during THA; in the control group ($n = 47$), the patients received saline solution as placebo. Based on drop in hemoglobin concentration, total estimated blood loss was calculated as the main assessment criterion. Secondary assessment criteria included transfusion rate and 90-day complications. Finally, a multivariate regression model was used to assess possible predictive factors for blood transfusion.

Results: (1) Significantly lower total blood loss was observed in the TTA group than in the control group (897 ± 177 ml vs. 1153 ± 345 ml, $p < 0.001$). Furthermore, lower transfusion rate was observed in the TTA group than in the control group (10.9% vs. 34.0%, $p = 0.005$). (2) No significant difference was observed between the two groups regarding 90-day complications. (3) We identified higher preoperative hemoglobin level (OR = 0.675, $p = 0.002$) and topical TA administration (OR = 0.002, $p = 0.012$) as negative predictive factors for blood transfusion.

Discussion: Topical application of TA was safe and beneficial in THA patients receiving continuous aspirin for prevention of cardiovascular or cerebrovascular events, to reduce blood loss and transfusion rate, without increasing the risk of 90-day complications.

Introduction

Aspirin, commonly used as an antiplatelet agent for primary or secondary prevention of thromboembolic events in joint arthroplasties [1], inhibits platelet release and aggregation, and prolongs bleeding time in patients undergoing invasive procedures [2–4].

Over the last decade, tranexamic acid (TA) has been demonstrated in numerous studies to reduce blood loss and transfusion rates in total hip arthroplasty (THA) [5,6]. As a synthetic antifibrinolytic agent, TA inhibits plasmin-induced fibrinolysis by binding plasmin and it is administered via topical and intravenous routes [7]. The safety of combined use of TA and aspirin has been demonstrated in a few prior studies, without increasing postoperative complications [8]. However, the effect of TA administration on aspirin-related bleeding remains unclear. To our knowledge, in THA patients, only one study by Heller et al. demonstrated that the association of aspirin and TA did not produce additional complications while reducing blood loss and transfusion [9]. However, it was retrospective and not randomized. Therefore, we conducted a prospective randomized study to establish the clinical evidence of combined use of topical TA and aspirin.

We hypothesized that topical TA administration was safe and could reduce blood loss and transfusion rate in THA patients receiving continuous aspirin for prevention of cardiovascular or

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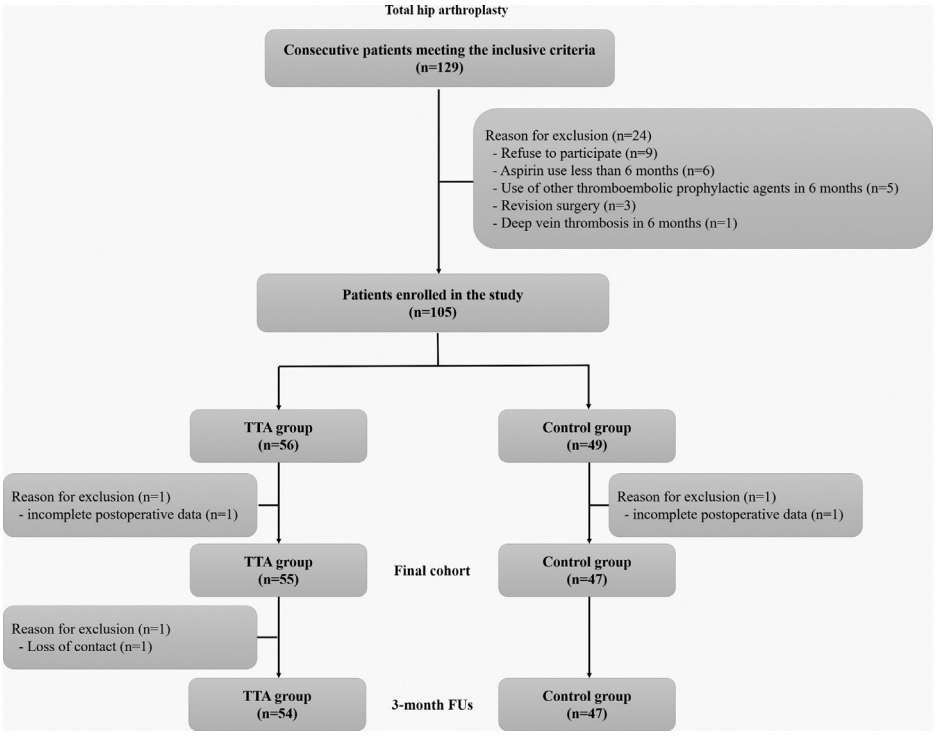

Fig. 1. Flow chart of patient enrollment.

cerebrovascular events. Therefore, we asked the following questions:

- did topical TA administration decrease total blood loss and transfusion rate?
- did the rate of thromboembolic and bleeding complications increase within postoperative 90 days?
- what were the potential risk factors contributing to blood transfusion after THA?

Patients and Methods

Patients

From January 2016 to July 2017, 114 consecutive patients, who were scheduled for unilateral primary THA and received low-dose (100 mg/d) aspirin (Bayer Pharma AG, Berlin, Germany) for prevention of cardiovascular and cerebrovascular events, were eligible to be included in the prospective study. The exclusion criteria included:

- aspirin use for less than six months;
- thromboembolic prophylaxis use within six months before THA other than aspirin (including warfarin, heparin, enoxaparin, or oral factor Xa inhibitors);
- thromboembolic and major bleeding events within six months before THA;
- coagulation or fibrinolytic system dysfunction;
- allergy to TA.

The institutional review board of our center approved this study (file number: WMU-3-15-527).

Nine patients declined participation leaving 105 individuals for evaluations. The patients were randomized into two groups using computer-generated random numbers: the TTA group in which patients received topical TA, and the control group in which a standard protocol was followed for patient blood management.

Of 105 enrolled patients, three were excluded due to incomplete postoperative data (Fig. 1). Thus, the cohort consisted of 102 patients including 55 patients in the TTA group and 47 patients in the control group. Demographic characteristics of the two groups were not significantly different (Table 1). One patient in the TTA group was unable to complete the 3-month follow-up due to loss of contact.

As described previously [10], to detect a difference of 200 ml in total estimated blood loss (EBL) between groups with a standard deviation of 456 ml, 36 patients per group were needed to achieve a power of 0.80, using an alpha (two-tailed) of 0.05 and a standard effect size (d) of 0.25, assuming that 25% decrease in total blood loss would be needed to significantly reduce clinical symptoms and transfusions. Therefore, a sample size of 102 participants in this study was determined to be enough.

Methods

Cementless THA was performed under general anesthesia through a posterolateral approach, using standard surgical technique. In the TTA group, a solution of 3 g TA dissolved in 150 ml saline, described by Konig et al. [10], was used in three steps. First, 50 ml TA was used to soak the acetabulum for three minutes just after the acetabular preparation. Thereafter, a cementless acetabular cup was impacted followed by a polyethelene or ceramic liner. Second, after final broaching on the femoral side, another 50 ml TA was injected and left in the femoral canal. Then, a cementless femoral stem was implanted into place. Third, the remaining 50 ml TA was poured into the wound and was left after hip reduction. Subsequently, capsule and external rotators were repaired through a hole in the great trochanter. In the control group, TA was substituted by saline solution during these steps. No surgical drainage was used in all the cases. All the patients in two groups received the same rehabilitation protocols.

Table 1
General characteristics of patients in the TTA and control group.

	TTA group ($n = 55$)	Control group($n = 47$)	p value
Age (years)			0.167 [a]
Mean (SD)	71.2 (7.9)	69.0 (8.2)	
Median (range)	71 (50–86)	68 (51–88)	
Gender, No. (%)			0.779 [b]
Female	36 (65.5)	32 (68.1)	
Male	19 (34.5)	15 (31.9)	
BMI (kg/m^2)			0.339 [a]
Mean (SD)	25.4 (3.4)	26.1 (4.3)	
Median (range)	25.3 (18.3–33.6)	26.4 (19.0–33.5)	
Preoperative hemoglobin (g/L)			0.536 [a]
Mean (SD)	132 (14.1)	131 (13.3)	
Median (range)	133 (107–155)	139 (102–159)	
INR			0.517 [a]
Mean (SD)	0.99 (0.64)	1.00 (0.53)	
Median (range)	1.00 (0.81–1.33)	0.99 (0.91–1.12)	
APTT (s)			0.171 [a]
Mean (SD)	33.0 (2.8)	32.4 (2.5)	
Median (range)	33.0 (28.3–38.5)	32.7 (27.2–38.3)	
PLT ($\times 10^9$/L)			0.603 [a]
Mean (SD)	206 (36)	202 (48)	
Median (range)	207 (128–291)	200 (115–308)	
History, No. (%)			0.941 [b]
Coronary atherosclerotic heart disease	8 (14.6)	6 (12.8)	
Atrial fibrillation	5 (9.1)	4 (8.5)	
Hypertension	23 (41.8)	17 (36.2)	
Sequelae of myocardial infarction	2 (3.6)	1 (2.1)	
Carotid stenosis	2 (3.6)	3 (6.4)	
Stroke	15 (27.3)	16 (34.0)	
ASA, No. (%)			0.093 [b]
I	27 (49.1)	15 (31.9)	
II	23 (41.8)	26 (55.3)	
III	5 (9.1)	6 (12.8)	
Disease, No. (%)			0.912 [b]
FNF	18 (32.7)	15 (31.9)	
ONFH	22 (40.0)	17 (36.2)	
DDH	12 (21.8)	13 (27.7)	
OA	3 (5.5)	2 (4.2)	

SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists; INR: international normalized ratio; APTT: activated partial thromboplastin time; FNF: femoral neck fracture; ONFH: osteonecrosis of the femoral head; DDH: developmental dysplasia of the hip; OA: osteoarthritis.

[a] Student's *t*-test.

[b] Chi^2 test.

$$\text{Total EBL (L)} = \text{EBV} \times \frac{\text{Hct}_{\text{preoperative}} - \text{Hct}_{\text{postoperative}}}{\text{Hct}_{\text{mean}}}$$

$$\text{EBV}_{\text{male}} = \text{height (m}^3) \times 0.356 + \text{body weight (kg)} \times 0.033 + 0.183$$

$$\text{EBV}_{\text{female}} = \text{height (m}^3) \times 0.367 + \text{body weight (kg)} \times 0.032 + 0.604$$

Fig. 2. The formula used to calculate total estimated blood loss, described by Gross and Nadler et al. [12,13]. EBV represents estimated blood volume; $Hct_{preoperative}$, the preoperative hematocrit level; $Hct_{postoperative}$, the minimum postoperative hematocrit; Hct_{mean}, the mean of the $Hct_{preoperative}$ and $Hct_{postoperative}$.

Aspirin was continuously administrated as prophylaxis against postoperative thromboembolic events, without additionally using low-molecular-weight heparin or oral anticoagulants. Patients were discharged when they met the strict criteria described in our previous study [11].

Methods of assessment

Primary assessment criterion (total EBL): Total EBL was evaluated based on the drop in hematocrit (Hct) between the preoperative and the lowest Hct during hospitalization, using the Gross formula based on estimated blood volume) [12], and calculating the total blood volume per individual according to Nader [13] (Fig. 2).

Secondary assessment criteria (transfusion rate and complications): The guidelines recommending transfusion were a postoperative hemoglobin (Hb) level of < 80 g/l or < 100 g/l with the symptoms of anemia. Within 90 days after THA, thromboembolic and bleeding events as well as other postoperative complications were recorded. Ultrasound doppler was used before discharge to evaluate deep vein thrombosis (DVT).

Several vital perioperative variables including operative time, postoperative Hb, Hb loss, and intraoperative EBL were documented. Hb loss was calculated based on the drop in Hb between the preoperative and postoperative Hb.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois). Data were expressed as mean ± standard deviation for normally distributed continuous variables, and as total number and percentage for categorical

Table 2
Surgery related variables in the TTA group and the control group.

	TTA group($n=55$)	Control group($n=47$)	p value
Operation time (min)			0.382
Mean (SD)	74 (14.2)	76 (12.0)	
Median (range)	74 (49–106)	74 (55–101)	
Intraoperative EBL (ml)			0.399
Mean (SD)	312 (91)	297 (90)	
Median (range)	321 (98–527)	298 (105–545)	
Total blood loss (ml) [a]			<0.001
Mean (SD)	897 (177)	1153 (345)	
Median (range)	902 (476–1292)	1148 (495–1869)	
Hemoglobin loss (g/L) [a]			<0.001
Mean (SD)	37 (6.9)	47 (6.9)	
Median (range)	38 (21–51)	45 (32–65)	
Postoperative hemoglobin (g/L) [a]			<0.001
Mean (SD)	95 (14.7)	84 (12.4)	
Median (range)	94 (65–126)	83 (62–117)	
Blood transfusion, No. (%)	6 (10.9)	16 (34.0)	0.005

SD: standard deviation; EBL: estimated blood loss.
[a] Difference of data statistically significant ($p<0.05$)

variables. Univariate analyses, using Student's t-test for quantitative data and Chi^2 test or Fisher's exact test for categorical variables, was performed to identify the risk factors of blood transfusion between the TTA and control group. Thereafter, statistically significant variables were included in a multivariate logistic regression model to investigate any independent predictors of blood transfusion, using a computation stepwise method. Odds ratio (OR) was used to describe the risk of blood transfusion. A p value < 0.05 was considered significant. Additionally, we tested overall calibration of the regression model using a Hosmer-Lemeshow goodness-of-fit test.

Results

Primary assessment criterion: Less total EBL as observed in the TTA group, when compared to that in the control group (897 ± 177 ml vs. 1153 ± 345 ml, $P<0.001$) (Table 2). Secondary assessment criteria: The transfusion rate in the TTA group (6/55, 10.9%) was significantly lower than that in the control group (16/47, 34.0%, $p=0.005$) (Table 2). The most common 90-day complication was incisional ecchymosis (6.9%), followed by DVT (3.0%) and wound bleeding (3.0%) (Table 3). Overall, the 90-day complication rate in the control group (12/47, 25.5%) was significantly higher than that in the TTA group (5/54, 9.3%, $p=0.029$). With regard to each 90-day complication, no significant difference was found between the two groups (Table 3). In the TTA group, dislocation was found in one patient at one month postoperatively and was reduced under anesthesia at the outpatient clinic. One patient in the TTA group and two patients in the control group were found with symptomatic DVT and readmitted for clinical observation. Upper gastrointestinal bleeding was found in one patient in the control group and was managed under endoscope after readmission. The other two patients in the control group were readmitted due to incisional hematoma and superficial infection and were cured after debridement. Finally, we identified lower preoperative Hb level (OR = 0.675, $p=0.002$) and absence of topical TA administration (OR = 0.002, $p=0.012$) as the potential predictive factors for blood transfusion (Table 4). Moreover, the Hosmer–Lemeshow goodness-of-fit test showed that the regression model offered a good fit for the data ($p=0.742$), indicating good calibration.

Table 3
Ninety-day complications in the TTA and control group[a].

	TTA group($n=54$)	Control group($n=47$)	p value
Thromboembolic Events, No. (%)			
DVT	1 (1.9)	2 (4.3)	0.596
PE	0	0	
Myocardial infarction	0	0	
Stroke	0	0	
Bleeding Events, No. (%)			
Wound bleeding	1 (1.9)	2 (4.3)	0.596
Incisional hematoma	0	1 (2.1)	0.465
Incisional ecchymosis	2 (3.7)	5 (10.6)	0.246
Gastrointestinal bleeding	0	1 (2.1)	0.465
Hemoptysis	0	0	
Epistaxis	0	0	
Hematuria	0	0	
Conjunctival bleeding	0	0	
Other, No. (%)			
Dislocation	1 (1.9)	0	1.000
Death	0	0	
Infection	0	1 (2.1)	0.465
Reoperation	0	2(4.3)	0.214
Readmission	1 (1.9)	4 (8.5)	0.181

DVT: deep vein thrombosis; PE: pulmonary embolism.
[a] Fisher exact test

Table 4
Results of multivariate logistic analysis to predict blood transfusion.

	Regression Coefficient	OR	95%CI	p value
Preoperative hemoglobin [a]	−0.393	0.675	0.526–0.867	0.002
Topical tranexamic acid use [a]	−6.069	0.002	0–0.268	0.012

OR: odds ratio; CI: confidence intervals.
[a] Difference of data statistically significant ($p<0.05$).

Discussion

Our prospective study showed that in THA patients receiving continuous aspirin, topical TA administration could significantly reduce perioperative blood loss and transfusion rate without increasing 90-day complications. Besides, preoperative Hb level and topical TA administration were identified as negative predictive factors for blood transfusion. Safety and feasibility of topical TA use were further demonstrated in patients receiving continuous aspirin for prevention of cardiovascular or cerebrovascular events.

There are several limitations in the current study. First, our study only included patients receiving oral aspirin with and without TA use. Undoubtedly, the participation of patients without aspirin administration (with and without TA usage) would provide higher level of evidence. Second, the small sample size may lead to a bias when evaluating the incidence of postoperative complications. Third, some post-discharged mild and self-limiting complications may have been omitted at the follow-up. Therefore, some missing data, which could not be possibly handled, might not be included in the data of 90-day follow-up. Fourth, when calculating total EBL, we used the Gross's method instead of the Mercuriali and Inghilleri formula [14], taking into account both non-compensated and compensated blood loss. Although our method did not include transfused blood volume, results were not underestimated because calculated based on the lowest Hct level prior to blood transfusion. Finally, the dose-effect relationship of topical TA was not investigated. The optimal dose of TA in patients receiving oral aspirin requires further investigation.

Due to different drug targets in the blood coagulation pathway, the mechanism of interaction between TA and aspirin has not yet been completely understood. Weber et al. [15] observed that TA administration could partially improve platelet function in patients treated with dual antiplatelet therapy (aspirin and clopidogrel), although the platelet function was not assessed by light transmission aggregometry, the gold standard for platelet function testing. Furthermore, a recent prospective, randomized, double-blind pilot study [16] showed that TA administration decreased the magnitude of cardiopulmonary bypass-induced platelet dysfunction in patients who did not receive preoperative aspirin. Nevertheless, in patients receiving continuous aspirin, TA did not significantly improve platelet function. These results seemed somewhat in disagreements with our study. As the platelet function was not investigated in our study, further investigations are needed to assess and confirm the substantive relationship between TA and aspirin.

Although a large number of previous studies have demonstrated that topical TA use did not increase postoperative thrombotic complications, there are only few studies aiming to investigate these complications in patients receiving oral aspirin. Heller et al. [9] showed that in patients undergoing THA and receiving aspirin as VTE prophylaxis, the incidence of VTE, bleeding events, and wound complications was similar between the intravenous TA group and the no TA group. Shi et al. [8] compared the clinical outcomes of intravenous TA and placebo in patients receiving dual antiplatelet therapy during coronary artery bypass grafting, and observed similar results between these two groups regarding postoperative adverse outcomes, mortality, and morbidity at 1-year follow-up. However, dual antiplatelet therapy was discontinued in that study during the procedure. Our study [9] also showed a similar incidence of 90-day thromboembolic or bleeding events between patients, who received topical TA and placebo along with continuous aspirin. We found no interaction between aspirin and TA regarding the risk of major hemorrhage and thromboembolism, which has also been showed in a previous 2-by-2 factorial design, including 2127 patients, scheduled to undergo coronary artery surgery [17].

Our study identified topical TA administration as negative predictive factors for blood transfusion, in agreement with other previous studies [9,18,19]. Recently, Kang et al. [20] reported that topical TA usage in the THA patients reduced the transfusion rate to 27.5%, nearly half of that in the control group (without TA use). Another meta-analysis identified seven randomized and seven non-randomized control trials, and revealed that compared to placebo, topical TA significantly reduced total blood loss (mean, 297.65 ml) as well as transfusion rates (OR = 0.26) [21]. Recently, few studies showed that novel strategies including oral TA [22,23] and combined use of intravenous and topical TA [24,25] were equivalent or superior to single use of intravenous or topical TA for reducing blood loss and transfusion rate. Whether these strategies are effective in THA patients receiving continuous aspirin is still unclear and will be the focus of our further research.

Apart from surgical technique, the advances in TA administration, as demonstrated previously [10], contributed in reducing blood loss and transfusion rate in conventional THA and eventually led to shortened hospital stay. Previous studies on total hip and knee arthroplasty have affirmed the equivalent effect of intravenous and topical TA on reduction of blood loss [26,27]. Recently, Wei et al. found similar blood transfusion rate and total blood loss in THA between the topical and intravenous TA group [27]. Therefore, we finally used topical TA to avoid the side effects of intravenous TA, including nausea, vomiting, and anaphylactic reaction [28–30].

To summarize, topical TA application was safe and beneficial in THA patients receiving continuous aspirin for prevention of cardiovascular or cerebrovascular events, to reduce blood loss and transfusion rate, without increasing the incidence of 90-day complications.

Disclosure of interest

The authors declare that they have no competing interest.

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None.

Contribution of authors

J.Q.: data analysis, writing and correction of the manuscript.
X.S.: data collection, writing of the manuscript.
W.Z.: data analysis, contribution to the writing of the manuscript.
X.K.: grouping, correction of the manuscript.
G.Y.: statistical analysis, correction of the manuscript.
L.Z.: study design, main surgeon of the study, correction and submission of the manuscript.

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