Injury xxx (xxxx) xxx

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Blood loss and transfusion rate compared among different dosing regimens of tranexamic acid administration in patients undergoing hip hemiarthroplasty for femoral neck fracture: A randomized controlled trial

Rapeepat Narkbunnam, Apivuth Chompoonutprapa, Pakpoom Ruangsomboon, Pacharapol Udomkiat, Keerati Chareancholvanich, Chaturong Pornrattanamaneewong*

Division of Adult Reconstructive Surgery, Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok, 10700, Thailand

ARTICLE INFO

Article history:
Accepted 1 August 2021
Available online xxx

Keywords:
Blood loss
Transfusion rate
Tranexamic acid administration
Patients
Hip hemiarthroplasty
Femoral neck fracture

ABSTRACT

Background: Intravenous tranexamic acid (TXA) administration is a proven safe and effective method for reducing both blood loss and transfusion in total joint arthroplasty. However, data specific to its efficacy in hip hemiarthroplasty (HHA) for femoral neck fracture are scarce. Furthermore, no study has investigated the efficacy of an additional dose of TXA administration. Accordingly, this study aimed to assess blood loss and the transfusion rate compared among different regimens of TXA administration in patients undergoing HHA for femoral neck fracture.

Methods: Between January 2019 to December 2020, 90 HHA patients were randomized into one of three groups (30 patients/group). Control group patients received intravenous normal saline solution (NSS) 20 mL before skin incision, and NSS 20 mL at 3 hours after surgery. one-dose (1D) group patients received 750 mg of intravenous TXA before skin incision, and NSS 20 mL at 3 hours after surgery. Two-dose (2D) group patients received 750 mg of intravenous TXA before skin incision, and 750 mg of TXA at 3 hours after surgery. The primary outcome was blood transfusion rate. Intraoperative blood loss, hemoglobin levels at 24- and 48-hours postoperation, and calculated total blood loss were compared among the three groups.

Results: The mean age of the study population was 79.7 years, and 76.7% of participants were women. The transfusion rate in the control, 1D and 2D groups was 43.3%, 16.7%, and 3.3%, respectively. Total hemoglobin loss; total red blood cell loss; intraoperative blood loss; hemoglobin level at 24- and 48-hours postoperation; change in hemoglobin level between 0 and 24 hours, and between 0 and 48 hours; blood transfusion rate; and, the number of patients who did not require blood transfusion were all significantly improved in the 2D group compared to baseline. No parameters were significantly improved in the 1D group compared to controls.

Conclusions: The results of this study demonstrate both the efficacy of TXA administration in HHA, and the superiority of two-dose TXA administration over one-dose TXA administration in HHA for femoral neck fracture.

Introduction

Hip hemiarthroplasty (HHA) is one of the most common procedures for treating older adult hip fracture patients. Blood loss resulting from the initial fracture and during HHA can be as high as 1,500 mL [1]. The combination of the fracture and the HHA procedure often results in postoperative acute anemia and the potential requirement for blood transfusion. Postoperative anemia can lead to delayed functional recovery, longer hospital stay, and increased mortality [2]. Allogeneic blood transfusion increases the risk of immunological reaction, disease transmission, and surgical site infection [3]. Therefore, minimizing perioperative blood loss and transfusion during surgery is an important concern.

Tranexamic acid (TXA) is an antifibrinolytic agent that competitively inhibits plasminogen, and it impedes fibrinolysis and clot breakdown. Intravenous TXA administration is a proven safe and

* Corresponding author.
E-mail address: toonchaturong@gmail.com (C. Pornrattanamaneewong).

https://doi.org/10.1016/j.injury.2021.08.001
0020-1383/

effective method for reducing both blood loss and transfusion in total joint arthroplasty [4]. However, studies of this drug for HHA in femoral neck fracture patients are limited. Concerning TXA dosing, previous studies reported that a low-dose regimen (<30 mg/kg or 1 g) is acceptable for most patients [5–8]. However, no study has investigated the efficacy of an additional dose of TXA administration. Accordingly, the aim of this study was to evaluate blood loss and the transfusion rate compared among different regimens of TXA administration in patients undergoing HHA for femoral neck fracture.

Patients and methods

This randomized controlled trial enrolled patients aged ≥60 years who were diagnosed with unilateral femoral neck fracture and scheduled to undergo HHA at our institute during January 2019 to December 2020. The exclusion criteria were high-energy fracture, pathological fracture, bleeding disorders, contraindication for the use of TXA, and refusal to participate. The contraindications for TXA included end-stage renal disease, previous ischemic stroke, ischemic heart disease, venous thromboembolism (VTE), and drug allergy. Patients who required a long femoral stem during surgery or who had acetabular pathology that required total hip arthroplasty (THA) were also excluded. This study was approved by our Institutional Review Board, and was registered in the Thai Clinical Trials Registry (TCTR20200506007). Written informed consent to participate was obtained from all study participants.

The 90 included patients were consecutively enrolled and randomly assigned to one of three groups using block-of-nine randomization method. Each patient's group assignment was concealed in an opaque envelop and opened by a scrub nurse before the operation. The surgeons, patients, and outcome assessors were blinded to the intervention. The flow of patients is summarized in a CONSORT flow diagram (Fig. 1).

HHA patients were randomized into one of three groups (30 patients/group). Control group patients received intravenous normal saline solution (NSS) 20 mL before skin incision, and NSS 20 mL at 3 hours after surgery. One-dose (1D) group patients received 750 mg of intravenous TXA [Transamin (250 mg/5 mL); OLIC (Thailand) Limited, Bangpa-In, Thailand] before skin incision, and NSS 20 mL at 3 hours after surgery. Two-dose (2D) group patients received 750 mg of intravenous TXA before skin incision, and 750 mg of TXA at 3 hours after surgery.

Before surgery, all patients underwent preoperative medical optimization by the geriatric physician team. All HHA were performed within 48 hours after admission, and all procedures were performed under regional anesthesia. Four experienced arthroplasty surgeons performed all the operations using a posterior approach with the same surgical technique among all patients. For implant selection, cementless bipolar HHA was considered the first priority. However, cemented bipolar HHA was indicated in the following situations: 1) rotational instability was detected when inserting the optimal size femoral rasp, and 2) the desired anteversion, leg length, and offset could not be achieved during the trial placement of the cementless component. The final decision was made according to surgeon discretion. No surgical drain was used. In the postoperative period, an intermittent pneumatic compressive device was applied for VTE prophylaxis. All patients were mobilized under the care of a physiotherapist on the first operative day.

Outcome measurement

Demographic and anthropometric data, including age, gender, weight, height, and body mass index (BMI), were recorded. Operative time, type of implant fixation, and length of hospital stay were documented as perioperative outcomes. Surgical site infection, clinical VTE, cardiovascular complications, cerebrovascular complications, and mortality were also determined at 2, 6, and 12 weeks after surgery.

Regarding blood loss and transfusion outcomes, the hemoglobin (Hb) level was determined preoperatively, and at 24- and 48-hours, postoperatively. One unit of packed red cells (PRC) transfusion was given if the Hb level was <9 g/dL, or if compromised clinical criteria, including lightheadedness, orthostatic hypotension, and/or tachycardia, were detected. The Hb level was reassessed at 6 hours after transfusion, and blood replacement was considered again using the same criteria. Intraoperative blood loss, change in Hb level at each time point, transfusion rate, and amount of transfusion (number of units) were also recorded.

To calculate total blood loss, the Hb balance method was used with the following steps [9, 10]: the total blood volume (TBV) was calculated using the Nadler formula [9], as follows: TBV (mL) = (k1 x height (m^3) + k2 x weight (kg) + k3) x 1000, when k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men; and, k1 = 0.3561, k2 = 0.03308, and k3 = 0.18331 for women.

Total Hb loss and total red blood cell (RBC) loss were calculated using the following formula: Total Hb loss (g) = TBV x (10x (Hb_{pre} – Hb_{post})) x 0.01 + Hb_t and Total RBC loss (mL) = 1000 x (total Hb loss/Hb_{pre}) when Hb_{pre} (g/dL) = preoperative Hb level, Hb_{post} (g/dL) = postoperative Hb level at 48 hours, Hb_t (g) = total volume of blood transfusion that generally contains 52 g of Hb per unit [10].

Sample size calculation and statistical analysis

The primary outcome was the transfusion rate within 48 hours after operation. Based on data from previous studies [5, 6, 11], the average reduction in transfusion rate using TXA was 20%. A sample size of 26 patients per group was calculated to have 80% power to detect the significance level of 0.05. Assuming a drop-out rate of approximately 20%, we aimed to recruit a total of 90 patients (30 patients per group) in this study.

The data were analyzed using SPSS Statistics v18.0 (SPSS, Inc., Chicago, Illinois, USA). Shapiro-Wilk test was used to examine for normal distribution of continuous data. For descriptive statistics, normally distributed continuous data are presented as mean ± standard deviation, and non-normally distributed data are shown as median and range. Categorical data are reported as frequency and percentage. To compare continuous data among the three groups, analysis of variance (ANOVA) and Kruskal-Wallis test was used for normally and non-normally distributed data, respectively. For post hoc pairwise comparison of significant parameters, Bonferroni and Dunn-Bonferroni test were used for normally and non-normally distributed data, respectively. Chi-square test or Fisher's exact test was used to compare categorical data among groups. Statistical significance was set at a *p*-value less than 0.05.

Results

Among the 90 patients that were included, the mean age was 79.7 years, and 76.7% were women. The demographic, anthropometric, and perioperative characteristics were similar among the three groups (Table 1). There were also no significant differences in TBV or preoperative Hb level among the three groups. The total Hb loss in the control, 1D, and 2D groups was 118.3±57.4, 80.8±39.6, and 67.3±35.1 g, respectively. The 1D and 2D groups had significantly lower total Hb loss than the control group. However, no significant difference was detected between the 1D and 2D groups (Table 2).

Concerning intraoperative blood loss and total RBC loss, the 2D group had significantly lower values than the control group. How-

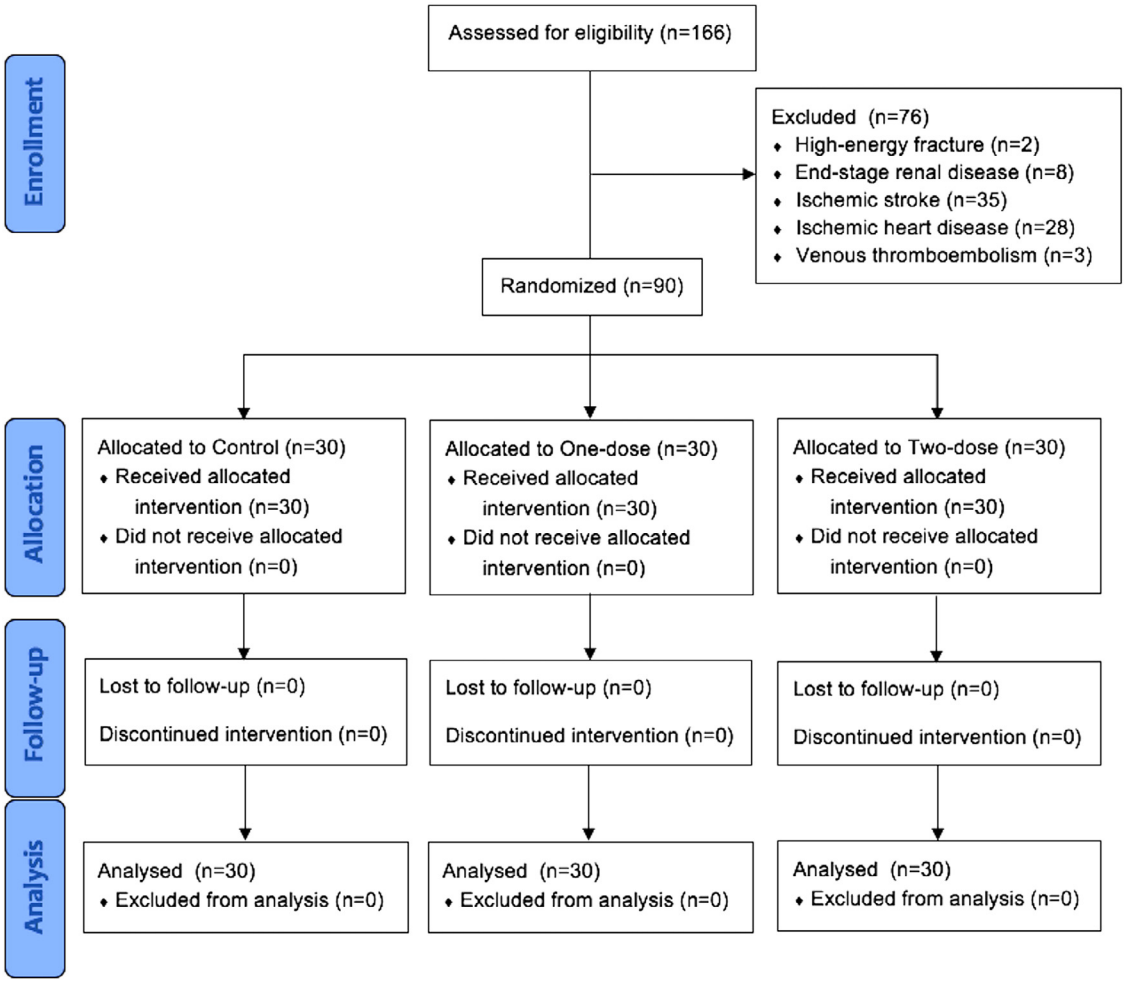

Fig. 1. The CONSORT flow diagram in this study

Table 1
Demographic, anthropometric, and perioperative characteristics compared among groups

Characteristics	Control (n=30)	One-dose (n=30)	Two-dose (n=30)	*p*-value
Age (yrs)	81.8±8.1	78.8±6.5	78.4±10.3	0.253
Female gender	21 (70.0%)	23 (76.7%)	25 (83.3%)	0.475
Weight (kg)	55.8±9.1	58.1±12.8	56.1±12.4	0.703
Height (cm)	156.6±9.6	158.3±8.1	155.5±7.9	0.436
Body mass index (kg/m^2)	22.8±3.8	23.1±4.6	23.1±4.4	0.959
Operative time (min)	82.0±22.2	78.3±20.9	82.3±18.0	0.703
Implant: Cemented	5 (16.7%)	9 (30.0%)	6 (20.0%)	0.434
Cementless	25 (83.3%)	21 (70.0%)	24 (80.0%)	
Length of hospital stay (days)	9 (6-26)	10 (5-21)	9 (5-19)	0.830$^{\#}$

Data presented as mean ± standard deviation, number and percentage, or median and range
A *p*-value<0.05 indicates statistical significance ($^{\#}$Kruskal-Wallis test)

ever, there were no significant differences for those two parameters between the 1D and control groups. The 2D group had significantly higher Hb levels at 24- and 48-hours postoperation than the control group. No significant difference was found for this parameter between the 1D and control groups. The reduction in Hb levels during 0-24 and 0-48 hours was significantly lower in the 2D group than in the control group. In contrast, no significant difference was observed for reduction in Hb levels during 24-48 hours among the three groups (Table 2).

Regarding the primary outcome, the transfusion rate in the control, 1D and 2D groups was 43.3%, 16.7%, and 3.3%, respectively. The difference was statistically significant between the 2D and control groups, but not between the 1D and control group. The same statistical relationship was observed for the amount of transfusion (number of units) (Table 2). No surgical site infection, clinical VTE, cardiovascular complications, cerebrovascular complications, or mortality were observed in this study.

Discussion

Hip fracture patients tend to be older and at greater risk for postoperative complications compared to elective hip surgery patients [12]. Minimization of blood loss in these susceptible older adult patients is essential. Intravenous TXA administration is a recognized method for reducing blood loss and blood transfusion. Two recent meta-analyses of randomized controlled trials reported

Table 2
Perioperative and postoperative blood parameters compared among groups

Blood parameters	Control (n=30)	One-dose (n=30)	Two-dose (n=30)	*p*-value
Total blood volume (mL)	3,534.6±602.7	3,625.9±652.2	3,456.4±634.5	0.583
Total hemoglobin loss (g)	118.3±57.4	80.8±39.6	67.3±35.1	*<0.001* [a b]
Total red blood cell loss (mL)	1,095.6 (349.6-11,157.0)	624.6 (211.7-5,797.6)	500.5 (61.5-4,399.3)	*<0.001* [# a]
Intraoperative blood loss (mL)	275.0 (100.0-450.0)	200.0 (100.0-500.0)	200.0 (50.0-300.0)	*0.004* [# a]
Hemoglobin level (g/dL)				
Preoperative	12.0±1.2	12.0±1.2	12.3±1.2	0.456
At 24 hours	9.7 (7.8-12.7)	10.0 (8.2-13.3)	10.4 (8.3-12.7)	*0.017* [# a]
At 48 hours	9.5 (6.9-11.6)	9.7 (8.1-12.6)	10.3 (8.2-12.1)	*0.008* [# a]
Change in hemoglobin level (g/dL)				
0-24 hr	2.2±1.1	1.7±0.8	1.6±1.0	*0.029*[a]
24-48 hr	0.6 (-1.9 to 2.9)	0.5 (-2.1 to 1.9)	0.3 (-1.3 to 1.3)	0.439#
0-48 hr	2.6±1.1	2.0±1.0	1.9±1.0	*0.032*[a]
Transfusion rate (%)	13 (43.3%)	5 (16.7%)	1 (3.3%)	*0.001*[a]
0-24 hr	7 (23.0%)	3 (10.0%)	1 (3.3%)	
24-48 hr	6 (20.0%)	2 (6.7%)	0 (0.0%)	
Amount of blood transfusion (units)				
No transfusion	17 (56.7%)	25 (83.3%)	29 (96.7%)	*0.003* [a]
1 unit	11 (36.7%)	5 (16.7%)	1 (3.3%)	
2 units	2 (6.7%)	0 (0.0%)	0 (0.0%)	

Data presented as mean ± standard deviation, median and range, or number and percentage
A *p*-value<0.05 indicates statistical significance (#Kruskal-Wallis test)
[a] Significant difference between the control and two-dose groups
[b] Significant difference between the control and one-dose groups

the efficacy of intravenous TXA for reducing blood loss and transfusion during hip fracture surgery. However, most of the trials included in those two meta-analyses were conducted in internal fixation patients [13, 14].

Only two randomized controlled trials investigated the use of TXA in patients who underwent hip arthroplasty for femoral neck fracture. Emara, *et al.* [5] found that either intravenous or topical TXA in HHA could reduce blood loss and transfusion during the first postoperative day compared to placebo. Watt, *et al.* [8] reported that intravenous TXA reduced blood loss without a significantly decreased transfusion rate in HHA and THA. Thus, there remains a limited volume of level-I evidence regarding the use of TXA in HHA.

Regarding the dosage of TXA for HHA, some studies used a titrated low dose of TXA (10-15 mg/kg) [5, 7], whereas other studies used a fixed low dose (1-1.5 g) [11, 15]. Since our patients were relatively small (mean BMI among all groups: 23.0 kg/m^2), we decided to use a fixed low dose (750 mg) of TXA in this study. Moreover, 750 mg of TXA is equal to 3 ampules, which makes it easy for administration.

Concerning the timing of TXA administration, previous studies reported several different protocols. Emara, *et al.* [5] reported that the use of TXA 10 mg/kg prior to incision followed by infusion of 5 mg/kg/hour until the end of surgery significantly lowered the transfusion rate compared to placebo (5% *vs.* 35%, $p<0.05$). A historical cohort study by Ashkenazi, *et al.* [15] found that the use of TXA 1.5 g prior to incision, and another 1.5 g during wound closure could significantly reduce the transfusion rate compared to the control group. (17.5% *vs.* 44.4%, $p<0.001$). Regarding one-dose regimens, a retrospective cohort study by Xie, *et al.* [7] found that 15 mg/kg of TXA prior to surgery was effective for reducing blood transfusion compared to the control group (8.7% *vs.* 24.1%, $p<0.001$). Another retrospective cohort study by Lee, *et al.* [11] concluded that patients who received 1 g TXA on induction were 3 times less likely to require transfusion than control group patients (6% *vs.* 19%, $p=0.005$).

To the best of our knowledge, this is the first study to compare among different dosing regimens of intravenous TXA for HHA. The important finding of this study was that the two-dose regimen was more effective than one-dose regimen for reducing both blood loss and transfusion without increasing the risk of complications. Even though no significant difference in blood transfusion was observed between 1D and the control group, the 1D group showed a trend towards a decreased transfusion rate. Possible reasons for this finding include too small a sample size to detect the difference between 1D and controls, or inadequate dose of TXA. Regarding the timing of TXA administration, all of the above-mentioned studies administered TXA prior to incision. In the double-dose regimen, another dose of TXA was given at the end of the operation. In the present study, we also gave the first dose of TXA prior to the incision. The time required for TXA to reach its maximum plasma level was reported to be 5-15 minutes after intravenous injection. Thus, suppression of fibrinolysis was started at the beginning of the operation. The second dose was given at 3 hours after surgery because a therapeutic level of TXA can be maintained for approximately 8 hours after surgery. This protocol is routinely used for hip and knee arthroplasty at our institute [16, 17].

Limitations

There are some limitations of our study that need to be discussed. First, we used a fixed dose of 750 mg of intravenous TXA given prior to incision and/or at 3 hours after surgery. The use of a titrated dose, a different route of administration, different timing, and different regimens might have yielded different results. Second, due to ethical considerations, a large number of previous ischemic stroke or ischemic heart disease patients were excluded from this study. Thus, the clinical application of our results may not be generalizable to patients with those two conditions. Third, we calculated blood loss using the Hb balance method. Even though this method may be the most reliable method [10], the influence of hemodilution and fluid shift still exists.

Conclusion

The results of this study demonstrate both the efficacy of TXA administration in HHA, and the superiority of two-dose TXA administration over one-dose TXA administration in HHA for femoral neck fracture.

Conflict of interest declaration

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Funding disclosure

This was an unfunded study.

Acknowledgements

The authors gratefully acknowledge the patients that agreed to participate in this study, and Miss Nichakorn Khomawut for assistance with data collection and statistical analysis.

References

[1] Smith GH, Tsang J, Molyneux SG, White TO. The hidden blood loss after hip fracture. Injury 2011;42(2):133–5.
[2] Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL. Higher Hb level is associated with better early functional recovery after hip fracture repair. Transfusion (Paris) 2003;43(12):1717–22.
[3] Shokoohi A, Stanworth S, Mistry D, Lamb S, Staves J, Murphy MF. The risks of red cell transfusion for hip fracture surgery in the elderly. Vox Sang 2012;103(3):223–30.
[4] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis. J Arthroplasty 2018;33(10):3083–9 e4.
[5] Emara WM, Moez KK, Elkhouly AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesth Essays Res 2014;8(1):48–53.
[6] Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, et al. Tranexamic acid in hip fracture surgery: a randomized controlled trial. Br J Anaesth 2010;104(1):23–30.
[7] Xie J, Hu Q, Huang Q, Chen G, Zhou Z, Pei F. Efficacy and safety of tranexamic acid in geriatric hip fracture with hemiarthroplasty: a retrospective cohort study. BMC Musculoskelet Disord 2019;20(1):304.
[8] Watts CD, Houdek MT, Sems SA, Cross WW, Pagnano MW. Tranexamic Acid Safely Reduced Blood Loss in Hemi- and Total Hip Arthroplasty for Acute Femoral Neck Fracture: A Randomized Clinical Trial. J Orthop Trauma 2017;31(7):345–51.
[9] Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962;51(2):224–32.
[10] Gao F-Q, Li Z-J, Zhang K, Sun W, Zhang H. Four Methods for Calculating Blood--loss after Total Knee Arthroplasty. Chin Med J (Engl) 2015;128(21):2856–60.
[11] Lee C, Freeman R, Edmondson M, Rogers BA. The efficacy of tranexamic acid in hip hemiarthroplasty surgery: an observational cohort study. Injury 2015;46(10):1978–82.
[12] Wu VJ, Ross BJ, Sanchez FL, Billings CR, Sherman WF. Complications Following Total Hip Arthroplasty: A Nationwide Database Study Comparing Elective vs Hip Fracture Cases. J Arthroplasty 2020;35(8):2144–8 e3.
[13] Haj-Younes B, Sivakumar BS, Wang M, An VV, Lorentzos P, Adie S. Tranexamic acid in hip fracture surgery: A systematic review and meta-analysis. J Orthop Surg Hong Kong 2020;28(1):2309499019887995.
[14] Xiao C, Zhang S, Long N, Yu W, Jiang Y. Is intravenous tranexamic acid effective and safe during hip fracture surgery? An updated meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg 2019;139(7):893–902.
[15] Ashkenazi I, Schermann H, Gold A, Lin R, Pardo I, Steinberg E, et al. Tranexamic acid in hip hemiarthroplasty. Injury 2020;51(11):2658–62.
[16] Eriksson O, Kjellman H, Pilbrant A, Schannong M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol 1974;7(5):375–80.
[17] Charoencholvanich K, Siriwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. Clin Orthop 2011;469(10):2874–80.