

Effects of tranexamic acid on vascular occlusive events and perioperative resuscitation in patients with atrial fibrillation undergoing total joint arthroplasty

Shangkun Tang, Zongke Zhou, Jing Yang, Pengde Kang, Bin Shen, Fuxing Pei, Xiaojun Shi

Department of Orthopedics, Orthopedic Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

To the Editor: Tranexamic acid (TXA) has recently become popular for use in orthopedic surgeries owing to its efficacy in reducing blood loss, transfusion rates, and mortality without increasing the risk of deep venous thrombosis.^[1] Although the ideal dosage and route for TXA administration remain unclear, it has become one of the most important parts of the perioperative blood conservation strategy. However, it remains controversial to prescribe TXA to patients with cardiovascular diseases, because of prothrombotic and proconvulsant effects, which potentially increases cardiovascular risk. Atrial fibrillation (AF), being the most common sustained cardiac arrhythmia, affects over 33 million individuals worldwide and is associated with a fivefold increase in the risk of stroke.^[2] Oral anticoagulants are administered to these patients toward preventing stroke and systemic embolism, and anticoagulant therapy would increase the perioperative blood loss during total joint arthroplasty. Although a previous study demonstrated no detrimental effect of TXA on the risk of cardiovascular events and death following total hip arthroplasty, the population investigated in that study included patients without cardiovascular diseases, which might cover up the real incidence of postoperative cardiovascular complication in these patients and thereby lead to statistical bias.^[1] Therefore, the retrospective cohort study aimed to assess the effects of perioperative TXA administration on cardiovascular occlusive events, perioperative resuscitation in patients with AF undergoing total joint arthroplasty.

This study was conducted using the data from the Joint Register Database of West China Hospital of Sichuan University. The Institutional Review Board of West China Hospital of Sichuan University approved this study (No. 2012268). The requirement for informed consent was waived because of the retrospective study design and anonymized patient data were used. Details of all patients

with AF who underwent total joint arthroplasty at our hospital, between January 2008 and April 2019, were collected through a prospective database and retrospectively reviewed. For patients who underwent ≥ 2 arthroplasties at different periods, each surgery was included in the present study. Operations were conducted by five senior orthopedic surgeons who have annually performed >500 hip and knee arthroplasties. Patients were divided into two groups based on the TXA administration: the TXA group and the non-TXA group. Patients in the TXA group were treated with at least a single dose of intravenous TXA at 10, 15, or 20 mg/kg before skin incision. Patients in the non-TXA group did not receive TXA treatment. The decision administering TXA or not in individual patients was at the discretion of the senior surgeon. Considering the different characteristics between the hip and knee arthroplasties, we established a subgroup analysis to examine the effects of TXA administration in patients with primary total joint arthroplasties. Each patient underwent routine blood examinations on postoperative days 1 and 3 and Doppler ultrasound examinations of both lower limbs at discharge as well as whenever deep venous thrombosis was clinically suspected during the follow-up period. Overall, 470 patients with AF were identified from 23,947 patients who underwent total joint arthroplasty. Among them, eight patients were lost to follow-up due to address and phone number change and were hence excluded from the study, 34 patients lacked the postoperative blood tests results and were only excluded from the blood loss calculation. Of the remaining 462 patients, there were 246 patients in the TXA group and 216 patients in the non-TXA group. All 462 patients were followed up for at least 3 months postoperatively. The vital outcome measured was as follows: postoperative vascular occlusive events evaluated at 1 month and 3 months postoperatively, perioperative resuscitation, blood loss, and transfusion rates. Continuous data were presented as means and standard deviations. Categorical

Access this article online	
Quick Response Code:	Website: www.cmj.org
	DOI: 10.1097/CM9.0000000000002114

Correspondence to: Xiaojun Shi, Department of Orthopedics, Orthopedic Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: shixjoint@scu.edu.cn

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(19)

Received: 26-07-2021; Online: 12-10-2022 Edited by: Ningning Wang

Table 1: Comparison of TXA administration in patients with AF undergoing total joint arthroplasty.

Parameters	Non-TXA group (n = 216)	TXA group (n = 246)	P value
Preoperative oral anticoagulation			0.680
Warfarin	54	48	
Aspirin	36	39	
Clopidogrel	33	30	
B-receptor blocker	90	87	0.165
Accumulated vascular occlusive event			
Postoperative 30 days	6	3	0.227
Postoperative 90 days	15	12	0.345
Total blood loss (mL)	1149.6 ± 556.6	748.5 ± 338.4	<0.001
Maximum Hb change (g/L)	31.3 ± 12.0	22.8 ± 8.7	<0.001
Patients given transfusion	60 (27.8)	15 (6.1)	<0.001
Patients experienced perioperative rescue	66 (30.6)	18 (7.3)	<0.001
Length of hospital stay (days)	12.4 ± 4.1	9.5 ± 3.0	<0.001

Data were presented as *n*, *n* (%), or mean ± standard deviation. AF: Atrial fibrillation; Hb: Hemoglobin; TXA: Tranexamic acid.

data were presented as frequency. Continuous variables were compared using Student's *t*-test and categorical variables using the chi-squared test or Fisher's exact test, as appropriate. $P \leq 0.05$ was considered significant. Statistical analyses were performed using SPSS® software version 19.0 (IBM, Armonk, New York, USA).

No statistical significant difference was found in the comparisons of the demographic and clinical characteristics between the TXA and non-TXA groups in all indexes. The distribution of diagnoses, American Society of Anesthesiologists (ASA) classification, Charlson comorbidity index, and type of surgery were not statistically significantly different between the two groups. Comparisons of the clinical outcomes between the TXA and non-TXA groups are summarized in Table 1. The number of death, myocardial infarction, or stroke were observed during the perioperative period. Within 3 months postoperatively, 27 vascular occlusive events occurred including 25 cases of stroke and two sudden deaths with unknown etiology, involving 12 patients in the TXA group and 15 patients in the non-TXA group ($P = 0.345$). No significant difference was noted in the incidence of accumulated vascular occlusive events between the two groups within 30 days and 90 days postoperatively. In addition, the perioperative resuscitation rate was significantly lower in the TXA group than in the non-TXA group ($P < 0.001$). Compared with patients in the non-TXA group, those in the TXA group had less total blood loss ($P < 0.001$) and less reduction in the maximum hemoglobin level ($P < 0.001$). The transfusion rate was significantly lower in the TXA group than in the non-TXA group ($P < 0.001$). In the subgroup analyses, no significant differences in terms of the preoperative anticoagulant therapy, beta-blocker use, or hemoglobin levels, hematocrit levels, and platelet count were observed between the two groups in primary total joint arthroplasty. However, the perioperative resuscitation rate and transfusion rate were significantly lower in the TXA group than in the non-TXA group in subgroup analyses ($P < 0.001$).

Total joint arthroplasty is a major orthopedic surgery with total blood loss of >1000 mL which is an independent risk

factor for perioperative cardiocerebral vascular system complication, thus a safe and effective blood conservation scheme is urgently required for these patients, especially for those with cardiovascular diseases because of the poor tolerance to blood loss. AF is a common cardiac disease and an epidemiological study revealed that the annual incidence of AF was 5.38% per year in Asian populations and that its prevalence increases with age.^[3] Postoperative AF is the most common perioperative cardiac arrhythmia and its most detrimental effect is a consequent increased risk of stroke, heart failure, systemic embolism, hospitalization day, and mortality.^[4] The present study results showed that TXA administration indeed reduces the total blood loss and transfusion rate. Furthermore, this study provides the evidence that perioperative intravenous TXA administration in patients with AF undergoing total joint arthroplasty did not increase the incidence of vascular occlusive events postoperatively, as found in the 3-month postoperative follow-up period. In addition, the risk of vascular occlusive events in the present study was similar to the results of systematic review literature in Asian populations, which reported an annual incidence of ischemic stroke in patients with AF to be 3.0%.^[3] Importantly, in the present study, the postoperative anticoagulant therapy with the half dose of low-molecular-weight heparin was initiated 6 h postoperatively rather than the conventional 12 h. This approach is expected to balance the risk of bleeding and thrombosis and reduce the risk of vascular occlusive events along with TXA administration.

Surprisingly, the present study suggested that TXA administration could significantly reduce the perioperative resuscitation rate. Our result proved the hypothesis that TXA is much more urgently required in patients with cardiovascular diseases as these patients are more susceptible to blood loss compared with others.^[5] The effect of TXA on reducing perioperative resuscitation rates could be attributed to the hemostatic and anti-inflammatory mechanisms of plasminogen antagonism. Endogenous plasminogen produced during trauma and surgery reduces clot stability and worsens bleeding. TXA, a competitive antagonist of the lysine binding sites on

plasminogen, can inhibit the production of plasmin and thereby reduce the total blood loss and minimize the need for blood transfusion. Severe bleeding induces hypoxemia, sympathetic nerve activity, and hemodynamic instability, which in turn distends and remodels the atrial chambers and activates stretch receptors, and alters diastolic function, which are significant risk factors of AF recurrence.^[5] Furthermore, inflammation and oxidative stress are believed to be strongly associated with AF pathogenesis.^[6] Considering that surgery is a strong inflammatory stimulus, its consequent inflammatory response and plasminogen activation would enhance the vulnerability of surgical patients to atherosclerotic plaque rupture and AF recurrence. Previous studies have demonstrated that TXA could dramatically reduce postoperative inflammation in patients undergoing total joint arthroplasty, as evidenced by decreased C-reactive protein and interleukin-6 levels.^[7]

To the best of our knowledge, this is a rare study to focus on TXA administration in patients with AF undergoing non-cardiac surgery. However, there exist concerns that TXA should not be intravenously administered to patients with a history of thrombotic events including cardiac disease and stent placement. Although a previous study included 20,211 patients with trauma under a randomized, placebo-controlled study design reported that TXA treatment was not associated with an increased risk of vascular occlusive events, and there was no information regarding the history of cardiac diseases in the enrolled patients.^[8] The present study also presented several limitations. First, the retrospective design involves an inherent risk of bias. Second, patients were enrolled between 2008 and 2019, during which time our concepts of TXA treatment gradually evolved. This inevitable drawback may cause an unknown risk of bias. Third, in the context of limited sample size due to the relatively low incidence of AF, it is impossible to conduct subgroup analysis to provide insights into the effect of different formulations of TXA administration. We cannot exclude the possibility that the higher doses of TXA can increase the risk of vascular occlusive events in patients with AF undergoing total joint arthroplasty. Nevertheless, the present study showed that at least a single dose of intravenous TXA administration in patients with AF did not increase the risk of vascular occlusive events. To overcome these limitations, a prospective, multicenter, randomized controlled trial of TXA is required in the future.

To conclude, among patients with AF undergoing total joint arthroplasty, perioperative TXA intravenous admin-

istration was associated with reduced total blood loss, blood transfusion, and perioperative resuscitation, without increasing vascular occlusive events within 3 months postoperatively.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Nos. 81871780 and 82072420) and the Special Scientific Research Projects of China - The safety and effectiveness evaluation of arthroplasty (No. 201302007).

Conflicts of interest

None.

References

1. Dastrup A, Pottegård A, Hallas J, Overgaard S. Perioperative tranexamic acid treatment and risk of cardiovascular events or death after total hip arthroplasty: a population-based cohort study from National Danish Databases. *J Bone Joint Surgery Am* 2018;100:1742–1749. doi: 10.2106/jbjs.17.01518.
2. Quinn G, Severdija O, Chang Y, Singer D. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation* 2017;135:208–219. doi:10.1161/circulationaha.116.024057.
3. Bai Y, Wang Y, Shantsila A, Lip G. The global burden of atrial fibrillation and stroke: a systematic review of the clinical epidemiology of atrial fibrillation in Asia. *Chest* 2017;152:810–820. doi: 10.1016/j.chest.2017.03.048.
4. Frost L, Johnsen S. Age and risk of stroke in Asians with atrial fibrillation. *Stroke* 2018;49:1809–1810. doi: 10.1161/strokeaha.118.022038.
5. Roberts I. Scientific letter: could tranexamic acid use in surgery reduce perioperative myocardial infarction? *Heart* 2013;99:1785. doi: 10.1136/heartjnl-2013-304292.
6. Vizzardi E, Curnis A, Latini M, Salghetti F, Rocco E, Lupi L, *et al*. Risk factors for atrial fibrillation recurrence: a literature review. *J Cardiovasc Med (Hagerstown)* 2014;15:235–253. doi: 10.2459/JCM.0b013e328358554b.
7. Huang Z, Xie X, Li L, Huang Q, Ma J, Shen B, *et al*. Intravenous and topical tranexamic acid alone are superior to tourniquet use for primary total knee arthroplasty: a prospective, randomized controlled trial. *J Bone Joint Surg Am* 2017;99:2053–2061. doi: 10.2106/jbjs.16.01525.
8. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, *et al*. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23–32. doi: 10.1016/s0140-6736(10)60835-5.

How to cite this article: Tang S, Zhou Z, Yang J, Kang P, Shen B, Pei F, Shi X. Effects of tranexamic acid on vascular occlusive events and perioperative resuscitation in patients with atrial fibrillation undergoing total joint arthroplasty. *Chin Med J* 2022;135:2354–2356. doi: 10.1097/CM9.0000000000002114