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Efficacy and safety of tranexamic acid in orthopaedic trauma surgery: a meta-analysis

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Abstract. – OBJECTIVE: To systematically review the efficacy and safety of tranexamic acid (TXA) in reducing blood transfusion and total blood loss in patients undergoing orthopaedic trauma surgery.

MATERIALS AND METHODS: A systematic literature search was performed using PubMed, Embase and Cochrane Library databases. The search time was incepted to February 2019. Two reviewers independently screened literature, extracted data, and assessed risk of bias. Then, meta-analysis was performed using RevMan 5.3.

RESULTS: A total of 10 studies were included, with 936 patients. The pooled results indicated that TXA group was superior to control group in the total blood loss [MD=-157.61, 95%CI (-250.09, -65.13), *p*=0.0008], blood transfusion [OR=0.59, 95%CI (0.43, 0.81), *p*=0.001], and the wound complications [OR=0.59, 95%CI (0.43, 0.81), *p*=0.001]. There was no significant difference in risk of thromboembolic events [OR=1.27, 95%CI (0.78, 2.12), *p*=0.35] and the mortality [OR=0.79, 95%CI (0.35, 1.78), *p*=0.57] between TXA and control group.

CONCLUSIONS: TXA could effectively reduce blood transfusion, total blood loss, and wound complications in patients undergoing orthopedic trauma surgery. Furthermore, TXA does not significantly increase the incidence of thromboembolic events and mortality. Due to the limited quality of the included studies, more high-quality works are required to verify the above conclusions.

Key Words:
Tranexamic acid, Orthopaedic trauma surgery, Blood loss, Blood transfusion, Meta-analysis.

Introduction

Traumatic fracture is a common disease in clinic. It is caused by accident or violence[1]. Patients are often accompanied by tendon injury, vascular injury, and nerve injury in injured limbs. In severe cases, it could lead to visceral injury, shock, and even death[2]. Bleeding is the most common complication of traumatic fractures. Pelvic fractures and acetabular fractures could result in a total blood loss of 1230 to 2800 mL, while the total blood loss of patients undergoing hip fracture surgery could exceed 2000 mL[3]. Severe bleeding would increase the death rate and the rate of allogeneic blood transfusion. On the one hand, transfusion of allogeneic blood would increase medical costs, on the other hand, it would increase the risk of blood disease transmission, causing also an immune response and cardiovascular damage[4]. Therefore, reducing the amount of blood loss of patients is our top priority in the treatment of traumatic fractures.

Tranexamic Acid (TXA) is a lysine analogue that acts as an antifibrinolytic agent to stabilize blood clots and reduce bleeding[5]. Tan et al[6] have shown that TXA could reduce perioperative blood loss in osteoarthritis patients undergoing artificial joint replacement, without increasing the incidence of thrombotic events. Hui et al[7] also reported that TXA could reduce the amount of blood loss in spinal surgery and have good safety. Dakir et al[8] found in a prospective research that TXA also had a good effect on maxillofacial fractures. In addition, there have also been reports in obstetrics and gynecology that TXA could effectively reduce the mortality rate of postpartum hemorrhage[9]. However, TXA is not routinely used in patients with traumatic fractures because the surgeon worries that it may lead to the formation of thrombosis and increase the incidence of thrombotic events. Furthermore, current reports on the hemostatic effect of TXA in the operation of traumatic fractures are inconsistent. Therefore, we conducted this meta-analysis to systematically evaluate the effectiveness and safety of TXA in reducing perioperative total blood loss and blood transfusion in patients with traumatic fractures to provide a theoretical basis for its application in the surgery of traumatic fractures.

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Materials and Methods

Search Strategy

Two researchers independently screened the literature, extracted data, and cross-checked. In case of any disagreement, it would be settled through discussion or consultation with a third party. In the literature screening, the title of the article was read first and, after excluding the significantly irrelevant literature, the abstract and the full text were further read to determine whether to include them or not. If necessary, we contacted the author of the original study for undetermined information that was important to this study. The retrieved databases included PubMed, Embase and Cochrane Library databases. Retrieval search keywords included "tranexamic acid" and "orthopaedic trauma surgery". The retrieval time was from inception to February 2019.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) type of study is a randomized controlled trial (RCT); (2) subjects are patients undergoing surgical treatment for orthopedic traumatic fractures and the age, gender, fracture type, and other conditions were not limited; (3) intervention measures: the experimental group was given TXA treatment with no limitation on the administration time, cycle, and dose; control group was treated with saline, placebo or blank control.

Exclusion criteria: (1) duplicated studies; (2) studies on non-orthopedic traumatic fractures such as cerebral trauma and maxillofacial surgery; (3) joint replacement for osteoarthritis, bone tumor or osteonecrosis; (4) literature without access to full-text data; (5) the blind method and the loss of follow-up rate of >20% were not adopted.

Data Extraction and Quality Assessment

Two reviewers independently extracted the data and cross-checked them. The content of data extraction includes: (1) basic information included in the study: research topic, researcher, year, country or region, etc.; (2) baseline characteristics and intervention measures of the subjects; (3) the key elements of bias risk assessment; (4) the outcome of the concern indicators and measurement indicators.

We used the modified Jadad scale to evaluate the quality of the included studies. In the modified Jadad scale, blinding, randomization, concealment allocation, and withdrawal were analyzed to give corresponding scores. The total score is 7. Studies with scores greater than or equal to 4 were considered high-quality, while those with scores less than 4 were considered low-quality. If the quality of the included studies was too low (1-2), we would exclude them.

Outcome Indicators

Outcome indicators in this meta-analysis included the total blood loss, blood transfusion rate, incidence of thrombotic events, postoperative mortality, and incidence of wound complications.

Statistical Analysis

We used RevMan5.3 (London, UK) for meta-analysis. For continuous variables, we used mean difference (MD) and 95%CI to analyze them. For dichotomous variables, odds ratio (OR) and 95% CI were used as effect statistics. Heterogeneity among the included results was analyzed by χ^2-test (α=0.1) and quantitatively evaluated by I^2. If there was no statistical heterogeneity among the results, we used a fixed-effect model for meta-analysis. If statistical heterogeneity existed among the results of various studies, we would further analyze the source of heterogeneity. After excluding the influence of evident heterogeneity, the random effect model would be adopted for meta-analysis. In addition, we used funnel plots to analyze publication bias for outcome indicators with greater than or equal to 9 included studies.

Results

Study Selection and Study Characteristics

A total of 1767 related literatures were preliminarily detected and 10 RCTs[10-19] were finally included after layer by layer screening. A total of 936 patients were analyzed, including 462 in the experimental group and 474 in control group. Fracture types in the study included 1 calcaneal fracture[18], 7 hip fractures[10,11,14-17,19], 1 femur fracture[12], and 1 acetabular fracture[13]. The literature screening process and results were shown in Figure 1. Baseline characteristics for included studies were shown in Table I.

Results of Meta-Analysis

The Total Blood Loss

A total of 5 studies[10,13,14,18,19], including 418 patients, were included. Heterogeneity analysis results showed that p=0.0004 and I^2=80%, indicating that there was significant heterogeneity between the studies. The results of meta-analysis of the random effect model showed that the total blood loss in TXA group was significantly lower than that in control group [MD=-157.61, 95%CI (-250.09, -65.13), p=0.0008] (Figure 2).

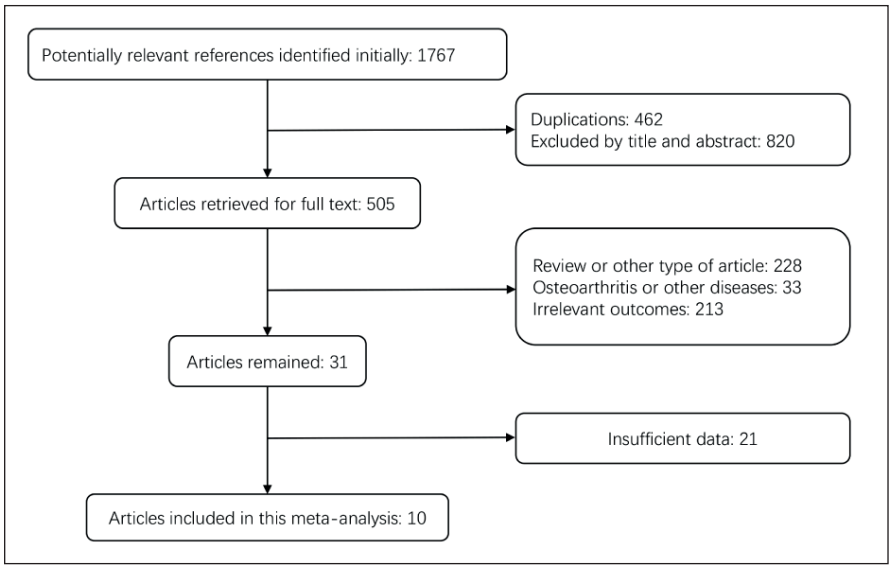

Figure 1. Study flow and selection diagram.

Blood Transfusion Rate

A total of 10 studies[10-19] included 936 patients. Heterogeneity analysis results showed p=0.26 and I^2=20%, indicated that there was no significant heterogeneity between the researches. The results of meta-analysis of fixed-effect models showed that blood transfusion rate in TXA group was significantly lower than that in control group [OR=0.59, 95%CI (0.43, 0.81), p=0.001] (Figure 3).

Occurrence of Thrombotic Events

A total of 9 studies[10,11,13-19] included 898 patients. Heterogeneity analysis results showed that p=0.66 and I^2=0% indicated that there was no significant heterogeneity between the works. The results of meta-analysis of fixed-effect models showed that there was no significant statistical difference between two groups [OR=1.27, 95%CI (0.78, 2.12), p=0.35] (Figure 4).

Postoperative Mortality

A total of 3 studies[15-17] included 280 patients. Heterogeneity analysis results showed that p=0.87 and I^2=0% indicated that there was no significant heterogeneity between the studies. The results of meta-analysis of fixed-effect models showed that there was no significant statistical difference between the two groups [OR=0.79, 95%CI (0.35, 1.78), p=0.57] (Figure 5).

Table I. Baseline characteristics of included studies.

Studies	Region	No. of patients	Mean ages (T/C, years)	Intervention measures		Outcomes
				T	C	
Baruah et al[10] 2016	India	30/30	57.7/55.3	TXA	Normal saline	abc
Drakos et al[11] 2016	Greece	100/100	81/80.7	TXA	Normal saline	bce
Haghighi et al[12] 2017	Iran	18/20	65.1/66.2	TXA	Normal saline	b
Lack et al[13] 2017	America	42/46	41.7/39.7	TXA	Normal saline	abc
Lei et al[14] 2017	China	37/40	77.8/79.18	TXA	Normal saline	abc
Tengberg et al[15] 2016	Denmark	33/39	79.8/75	TXA	Placebo	bcd
Wang et al[16] 2017	China	35/35	73.8/74.1	TXA	Normal saline	bcd
Watts et al[17] 2017	America	69/69	82.2/81	TXA	Normal saline	bcd
Xie et al[18] 2015	China	41/42	43.4/42.6	TXA	Normal saline	abce
Zufferey et al[19] 2010	France	57/53	81/82	TXA	Placebo	abce

T: tranexamic acid group; C: control group; a, the total blood loss; b, blood transfusion rate; c, occurrence of thrombotic events; d, postoperative mortality; e, occurrence of wound complications.

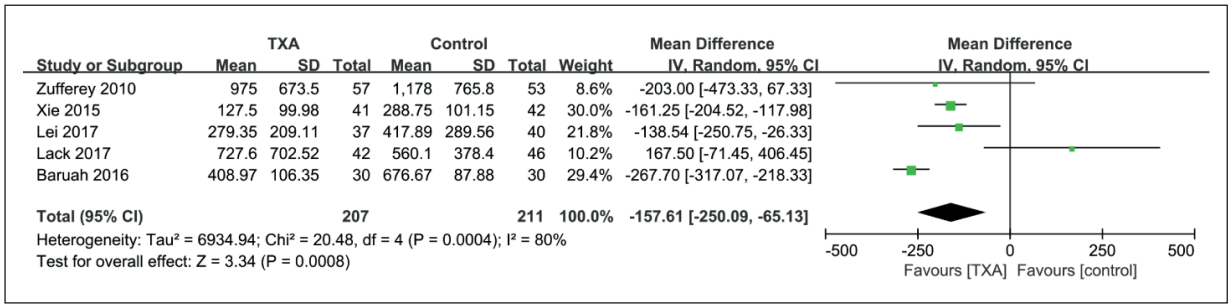

Figure 2. Forest plot for comparison of the total blood loss between two groups.

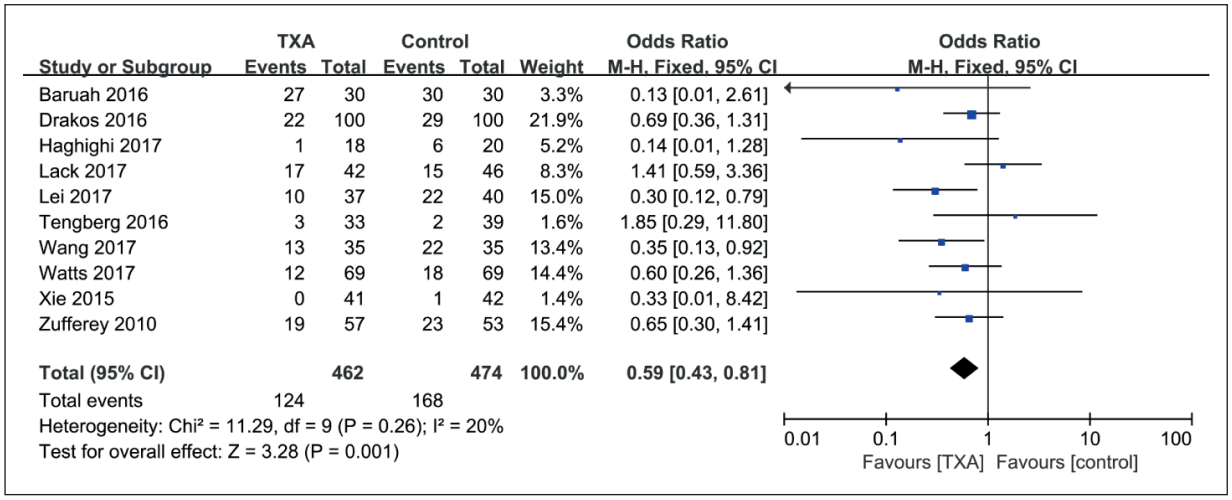

Figure 3. Forest plot for comparison of blood transfusion rate between two groups.

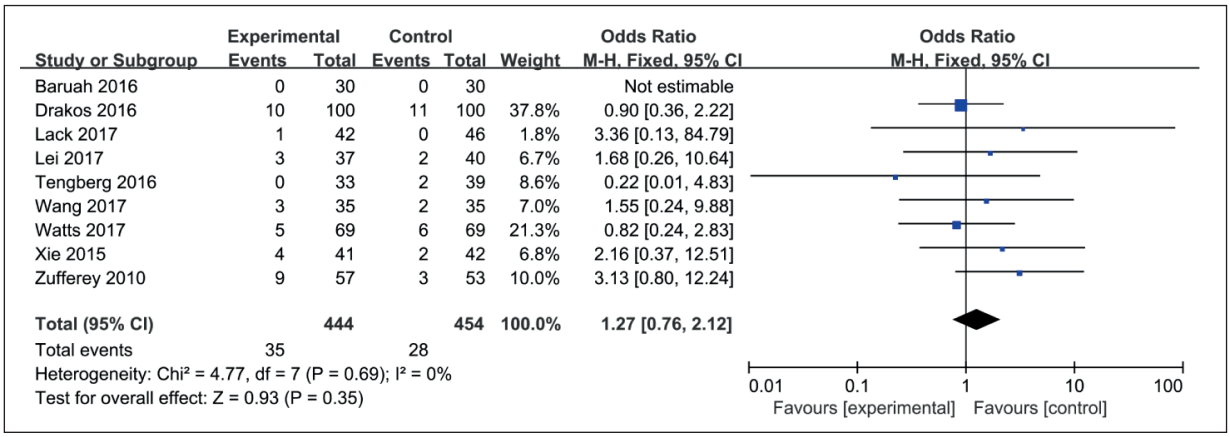

Figure 4. Forest plot for comparison of occurrence of thrombotic events between two groups.

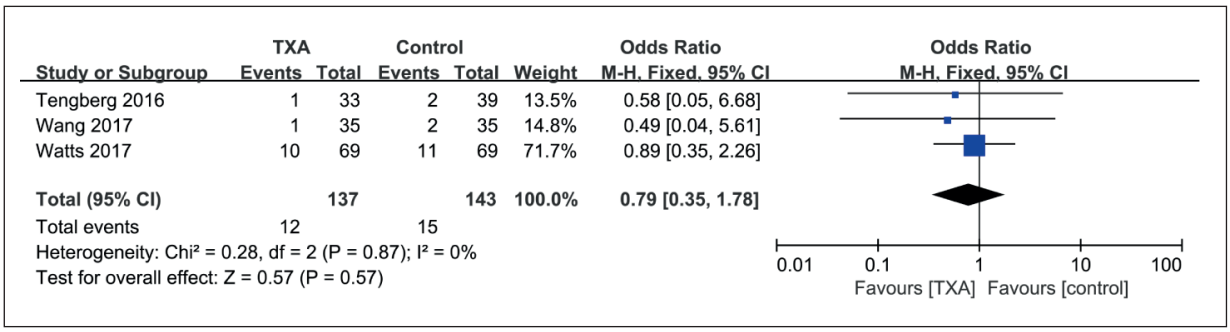

Figure 5. Forest plot for comparison of postoperative mortality between two groups.

Occurrence of Wound Complications

A total of 3 studies[11,18,19] included 393 patients. Heterogeneity analysis results showed that p=0.86 and I^2=0% indicated that there was no significant heterogeneity between the researches. The results of meta-analysis of fixed-effect models showed that the occurrence of wound complications in TXA group was significantly lower than that in control group [OR=0.59, 95% CI (0.43, 0.81), p=0.001] (Figure 6).

Publication Bias and Quality Assessment

We analyzed the publication biases of results of the blood transfusion rate and incidence of thrombotic events by funnel plots (Figure 7). The funnel plot of the result of blood transfusion rate was slightly asymmetric, suggesting possible publication bias. The funnel plot of the result of the incidence of thrombotic events showed good symmetry and thus no evident publication bias was observed.

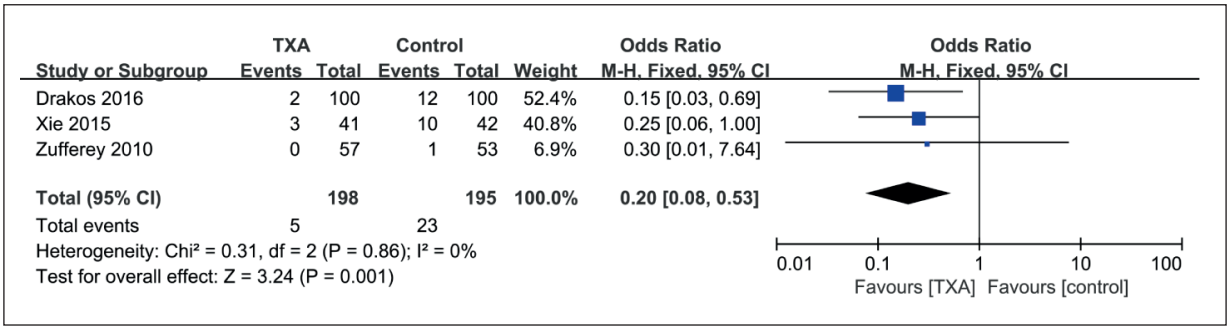

Figure 6. Forest plot for comparison of occurrence of wound complications between two groups.

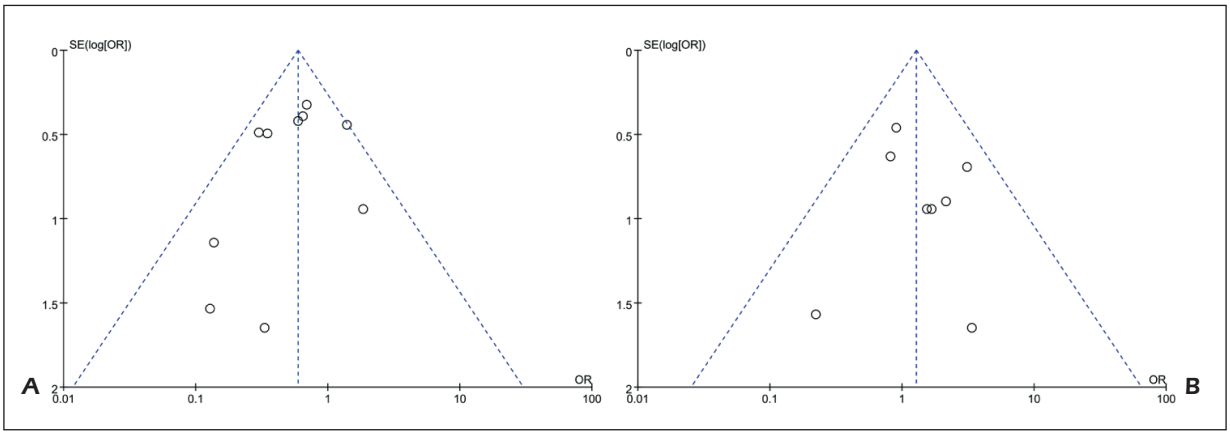

Figure 7. Funnel plots for publication bias assessment. **A**, Blood transfusion rate. **B**, Occurrence of thrombotic events.

Table II. Modified Jadad scale.

Studies	Blinding	Randomization	Concealment allocation	Withdrawal	Total scores
Baruah et al[10] 2016	2	1	1	1	5
Drakos et al[11] 2016	1	1	1	1	4
Haghighi et al[12] 2017	2	2	2	1	7
Lack et al[13] 2017	2	2	1	1	6
Lei et al[14] 2017	1	2	2	1	6
Tengberg et al[15] 2016	2	1	2	1	6
Wang et al[16] 2017	2	2	1	1	6
Watts et al[17] 2017	1	2	2	1	6
Xie et al[18] 2015	2	2	2	1	7
Zufferey et al[19] 2010	2	2	1	1	6

As shown in Table II, the quality assessment results of the included studies showed that their quality scores were all greater than 4 points. Therefore, they had good methodological quality and the results were highly credible.

Discussion

Ten RCTs were included in this study, with a total of 936 patients. Meta-analysis results showed that TXA could effectively reduce the blood transfusion rate and total blood loss in patients with traumatic fractures. The results of this work are consistent with recent reports that TXA could reduce blood loss and transfusion rates in osteoarthritis patients undergoing artificial joint replacement. There was heterogeneity in the total blood loss between the studies included in this meta-analysis, which may be due to differences in surgical methods and techniques of patients with fractures in different locations.

The results of this meta-analysis showed that TXA did not significantly increase the mortality and occurrence of thrombotic events in patients with traumatic fractures. Therefore, it had good safety. Zhang et al[20] analyzed the effect and safety of TXA in hip fracture surgery and concluded that TXA could reduce blood loss and transfusion rate, while not increasing the occurrence of thrombotic events, which was consistent with the results of this meta-analysis.

Although many works have confirmed TXA in spinal fusion, joint replacement surgery showed good effect and security, but the patients of traumatic fracture have not been administrated with TXA routinely. Most doctors held a hesitant attitude and even gave up using TXA directly and the reason was that patients with traumatic fracture had a higher risk of thromboembolic events of 0.4-7.5% compared to patients undergoing elective artificial joint replacement[21]. Therefore, TXA was less used in patients with traumatic fracture due to safety concerns. In addition, some studies[22] have detected that the application of TXA within 3 h after trauma could give a good hemostatic effect. This meta-analysis found that TXA not only could effectively reduce the amount of blood loss, blood transfusion rate, and wound complications in patients with traumatic fractures, but also had good safety. These results suggested that TXA has certain advantages in the treatment of patients with traumatic fractures.

Although this meta-analysis achieved some significant results, it also had some limitations. First of all, the number of trials included in this meta-analysis is small and the total sample size is not large enough, so there may be bias. Secondly, this meta-analysis included works from many different countries. Due to the differences in physical function between different ethnic groups, the results of this meta-analysis may vary among people from different countries. Thirdly, due to the limited number of included studies, the subgroup analysis was not conducted according to the effects and safety of different fracture sites. Furthermore, this meta-analysis did not retrieve high-quality studies on TXA for upper limb fractures. Finally, as the postoperative evaluation indexes of included studies and the follow-up time were different, future trials would need to increase the monitoring items and extend the follow-up time to achieve long-term efficacy and safety.

Conclusions

TXA could effectively reduce the blood transfusion rate and total blood loss in patients with traumatic fracture surgery and reduce the occurrence of postoperative wound complications, without significantly increasing the prevalence of thrombotic events and mortality. In the future, further studies need to be included to evaluate the effectiveness and safety of TXA in the treatment of traumatic fractures.

Conflict of Interests

The Authors declared that they have no conflict of interests.

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