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Efficacy and Safety of Tranexamic Acid in Bilateral Total Knee Replacement: A Meta-Analysis and Systematic Review

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Data Interpretation D
Manuscript Preparation E
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Background: Tranexamic acid (TXA) has been well documented to reduce blood loss and transfusion requirements in patients undergoing unilateral total knee arthroplasty (TKA). However, the efficacy and safety of TXA in simultaneous bilateral TKA have not been clearly defined. The aim of our study was to systematically review the existing evidence regarding the role of TXA in patients undergoing simultaneous bilateral TKA.

Material/Methods: A systematic search of all studies published through June 2014 was performed using Medline, EMBASE, OVID, and other databases. All studies that compared the efficacy and safety of TXA administration in simultaneous bilateral TKA patients were identified. The data from the included trials were extracted and analyzed regarding blood loss and transfusion rates. The evidence quality levels of the selected articles were evaluated using a grading system.

Results: Six studies were included, in which a total of 245 patients received TXA and 271 patients were controls. Overall, the results demonstrated that the use of TXA significantly reduced total blood loss by a mean of 371.1 ml (95% confidence interval (CI)=–412.12 to –330.09; p<0.001) and reduced the number of patients requiring blood transfusion (risk ratio (RR)=0.16; 95% CI=0.10 to 0.28; p<0.001). No significant differences in adverse effects such as deep vein thrombosis (DVT) or pulmonary embolism (PE) were noted in any group.

Conclusions: The intravenous use of TXA in patients undergoing simultaneous bilateral TKA is effective and safe and results in significantly reduced estimated blood loss and transfusion rates. No significant difference was observed in the incidence of side effects. Due to the limitations in the evidence quality of current meta-analyses, well-conducted, larger, high-quality randomized controlled trials (RCTs) are required.

MeSH Keywords: Arthroplasty • Meta-Analysis • Tranexamic Acid

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Background

Progressive aging has led to an increased incidence of knee degenerative joint disease, for which total knee arthroplasty (TKA) is an effective treatment. However, there are reports of some peri-operative complications, including pulmonary embolism, deep vein thrombosis, adverse cardiac event, neurological disorders, acute renal injury, wound infections, intensive care unit admissions and pseudo-patella baja in the TKA procedure [1–3]. Furthermore, TKA is associated with considerable blood loss, ranging from 1,000 to 1,500 ml [4], which has a significant influence on morbidity and mortality. It was reported increased need for blood transfusion, risks of pulmonary embolism, and higher rates of mortality in simultaneous bilateral TKA, compared with unilateral TKA [5]. Thus, blood loss management associated with TKA is an issue of worldwide importance, especially in simultaneous bilateral TKA. Various blood-conservation strategies have been used to decrease blood loss and postoperative transfusion rates, including preoperative autologous donation, the preoperative use of erythropoietin, intraoperative hemodilution, intraoperative blood salvage, intraoperative hypotensive techniques, the administration of thrombotic medications, and the use of postoperative reinfusion drains [6–8]. Whereas the efficacy of these techniques remains under debate, the intraoperative administration of tranexamic acid (TXA) has been reported in many studies to reduce postoperative bleeding after TKA [9,10].

Tranexamic acid is an antifibrinolytic agent, a synthetic analog of the amino acid lysine and a competitive inhibitor of the lysine-binding site of plasminogen, thereby leading to the inhibition of fibrinolysis [11]. Although TKA may activate fibrinolysis by promoting the release of tissue plasminogen activator, the preoperative use of TXA may prevent plasmin from binding to fibrinogen and fibrin structures after clot formation and thereby may reduce perioperative blood loss and the allogeneic blood transfusion rate [12].

Many studies have reported success in utilizing TXA in TKA to reduce blood loss and transfusion requirements [13–16]. However, some of these studies have been criticized for poor design, inconclusive results, and differences in surgical plans among the study surgeons. Furthermore, most studies were focused on unilateral TKA, and only a few studies have evaluated the blood management of bilateral TKA procedures, which is more challenging [17,18]. The aim of this study was to evaluate the effectiveness and safety of TXA in reducing perioperative blood loss and the transfusion rate in patients undergoing simultaneous bilateral TKA.

Material and Methods

Study design

A meta-analysis and systematic review was conducted according to the predefined guidelines provided by the Cochrane Collaboration (2008). All data were reported according to the Quality of Reporting for Meta-analyses provided by the Handbook for Systematic Reviews of Interventions, Version 5.0.0 [19].

Search strategy

We conducted a computerized search of electronic databases, including the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, ISI Web of Knowledge, Science Direct and Google Scholar, for studies published through the end of June 2014. The following key terms were used to maximize search specificity and sensitivity: tranexamic acid, total knee arthroplasty and bilateral. The search strategy, encompassing studies conducted in humans and written in the English language, is presented in Figure 1. Secondary searches for additional relevant studies, such as those of the European Federation of National Associations of Orthopaedics and the British Orthopaedic Association Annual Congress, as well as conference proceedings until the end of June 2014, were also performed along with reference searches of the included articles to identify any additional studies that were not previously identified in the initial literature search.

Inclusion and exclusion criteria

The studies that met the following criteria were included: (1) the study evaluated the effect of TXA on blood loss in patients undergoing bilateral TKA surgery; (2) the study was a randomized controlled trial (RCT) or a prospective or retrospective comparative study; and (3) the study provided sufficient raw data for the weighted mean difference (WMD) with 95% confidence intervals (CI). Articles were excluded from our meta-analysis if they did not contain raw or usable data or if they were duplicate publications.

Data extraction

Two authors (Ziji Zhang and Yumin Li) independently reviewed the titles and abstracts related to the inclusion criteria. Full-text article reviews were performed for final inclusion into the study. Any discrepancy between these reviews was resolved by discussion with a third author (Dongliang Xu). Two authors (Hua Wang and Peiheng He) independently extracted the following data: study demographic data, types of interventions, TXA administration, total blood loss, blood transfusion rate, amount of transfused allogeneic blood, hemoglobin

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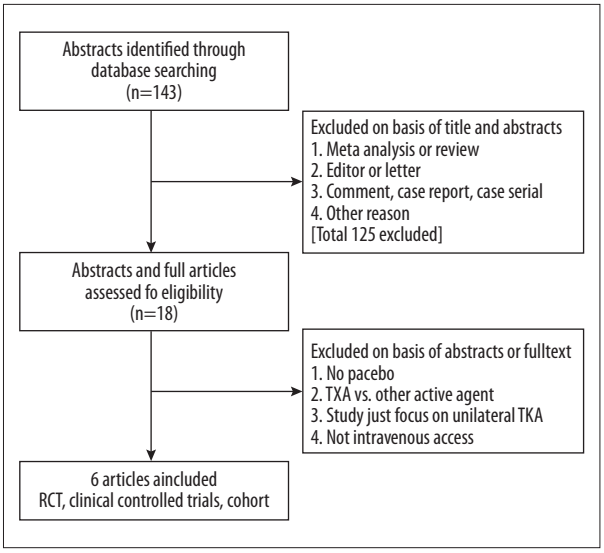

Figure 1. Summary of the article selection and exclusion process.

or hematocrit reduction, and thrombo-embolic complications. All of the extracted data were reassessed by a third author.

Outcome

The clinical outcomes included the total blood loss, allogeneic blood transfusion rate, amount of transfused allogeneic blood, and hemoglobin or hematocrit reduction. The complication outcomes included thrombo-embolic complications such as deep vein thrombosis (DVT) or pulmonary embolism (PE).

Assessment of methodological quality

The methodological quality of the included studies was independently assessed by two independent investigators according to the Cochrane guidelines. The individual methodological reporting domains (randomization sequence, allocation concealment, blinding, incomplete outcome data, and freedom from other biases) for the included studies were evaluated for risk of bias. Any conflicts were resolved by a third reviewer.

Data analysis and evidence synthesis

The meta-analysis of the data, including the effects and outcomes of the treatments, was performed using RevMan Version 5.1 (The Cochrane Collaboration, Copenhagen, Denmark). For continuous outcomes such as blood loss, the means ± standard deviations were pooled to a mean difference (MD) and a 95% CI. For dichotomous outcomes, the risk ratio (RR) and 95% CI were applied. A probability of $p<0.05$ was regarded as statistically significant. The assessment for statistical heterogeneity was assessed using the chi-square and I-square tests. A p-value <0.1 and an I-square value >50% were considered suggestive of statistical heterogeneity. Sensitivity analysis was performed by rejecting the study with the higher statistical heterogeneity.

Results

Search results

A total of 143 citations were reviewed. All of the articles were strictly selected according to the criteria described above. Of the 143 reviewed titles and abstracts, 6 studies [20–27] met the inclusion criteria. These studies included three RCTs [28–30], two prospective cohort studies [31,32] and one retrospective cohort study [33]. Altogether, 516 patients were included in the 6 studies. The study selection process and the reasons for exclusion are summarized in Figure 1.

Quality assessment

Six articles directly comparing blood management with and without TXA administration in patients undergoing bilateral TKA were included in this meta-analysis: three RCTs, two prospective cohort studies and one retrospective cohort study. All of the articles aimed to evaluate the safety and efficacy of TXA in bilateral TKA. The sample size of the included studies, which were only focused on bilateral TKA surgery, ranged from 26 to 146. TXA was the only type of antifibrinolytic agent used, although the dose varied in some studies.

Table 1. Quality assessment of the RCT study.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Kakar PN et al. [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
MacGillivray RG [26]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Kim TK [27]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk

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Table 2. The study designs and MINORS appraisals cores for the non-RCTs.

Study	Study design	MINORs methodological criteria												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Dhillon MS et al. [28]	Retrospective cohort	2	1	0	1	0	0	2	0	2	1	2	2	13
Hegde C et al. [29]	CCT	2	1	2	2	0	0	2	0	2	1	2	2	16
Karam JA et al. [30]	Retrospective cohort	2	1	0	1	0	0	2	0	2	1	2	2	13

The MINORs criteria include the following items: 1. a clear stated aim; 2. inclusion of consecutive patients; 3. prospective data collection; 4. endpoints appropriate to the aim of the study; 5. unbiased assessment of the study end point; 6. a follow-up period appropriate to the aims of the study; 7. less than 5% loss to follow-up; 8. prospective calculation of the sample size; 9. an adequate control group; 10. Contemporary groups; 11. baseline equivalence of groups; and 12. Adequate statistical analysis. The items are scored as follows: 0 (not reported); 1 (reported but inadequate); 2 (reported and adequate). The ideal score for comparative studies is 24.

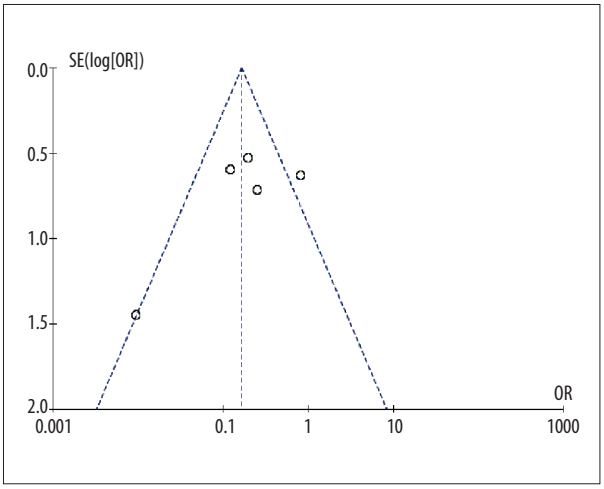

Figure 2. Trials of TXA versus placebo: funnel plot of allogenic transfusion rate. Funnel plot assess publication bias for the most frequently reported outcome. RR – risk ratio; SE – standard error. The asymmetrical funnel plot means publication bias could have existed in this meta-analysis.

Of the six studies, only three trials [28–30] reported an adequate sequence generation and three trials [28–30] reported allocation concealment. Three studies [28–30] reported using double-blinded assessors, whereas the remained three studies did not specify a blinding method. The methodological quality of the RCTs is presented in Table 1. The methodological quality of the included non-RCT studies was assessed using MINORS quality scores, as shown in Table. 2. The scores ranged from 13–16, indicating little variability in the evidence base.

The funnel plots shown in Figure 2 were used to probe the existence of bias in the included studies of patients undergoing TKA. We evaluated the WMD in the allogeneic transfusion rate as a measure of the TXA treatment effect (Figure 3).

Demographic characteristics

Three RCTs, two prospective cohort studies and one retrospective cohort study were eligible for inclusion; among a total of 516 patients, 245 patients underwent bilateral TKA with TXA administration and 271 patients underwent bilateral TKA without TXA. All of the included studies had defined exclusion

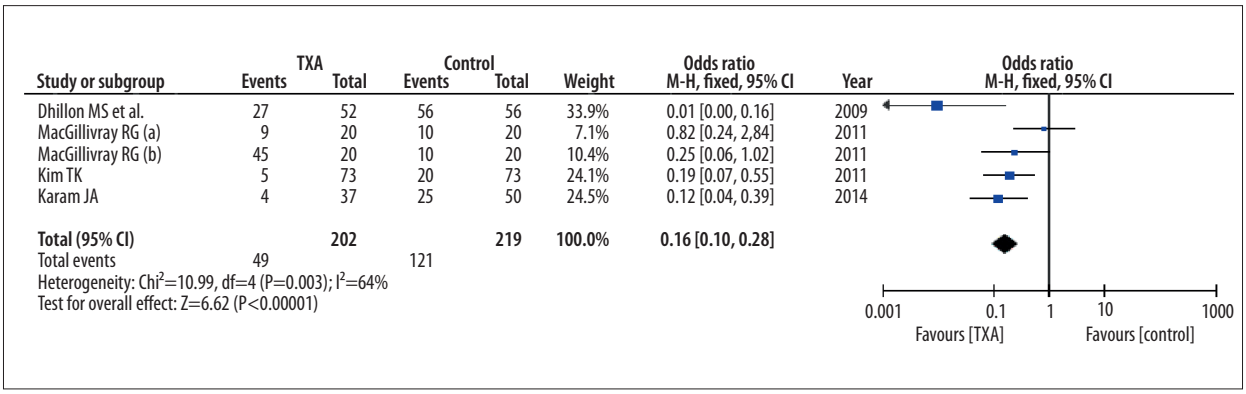

Figure 3. Forest plot and tabulated data illustrating the MD in the allogenic transfusion rate between the TXA and placebo group, showing that TXA administration significant decrease the allogenic transfusion rate.

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Table 3. The demographic characteristics of the included studies.

Reference	Country	Sample size	Intervention	Age (y)	Weight (kg)	VTE prophylaxis	BT protocol	Year
Kakar PN [25]	India		TXA 10 mg/kg IV bolus before inflation of the tourniquet, followed by 1 mg/kg/h until skin closure			NA	Hb <80 g/L or Hb <80 g/L for patients over 60 yr associated with cardiopulmonary disease	2009
TXA		13 /9F/4M		63.13±16.8	69.23±11.2			
Placebo		13 /10F/3M		67.15±6.9	64.23±9.7			
MacGillivray RG. [26]	United Arab Emirates		Group 1: TXA 10 mg/kg IV bolus 10 minutes before deflation of the first tourniquet and TEA 10 mg/kg IV 3 h after the first Group 1: TXA 15 mg/kg IV bolus 10 minutes before deflation of the first tourniquet and TEA 15 mg/kg IV 3 h after the first			Oral warfarin	Hb <80 g/L	2011
TXA (gourp1)		20 /13F/7M		62±4.3	79 ±17.3			
TXA (Group2)				62 ±4.3	79 ±17.3			
Placebo		20 /15F/5M		66±7.3	73 ±16.6			
Kim TK [27]	Korea		TXA 10 mg/kg IV bolus 30 min before deflation of the first tourniquet, followed by 10 mg/kg IV blous 30 min before deflation of the second tourniquet,and 10 mg/kg IV blous 3 h after second			Enoxaparin	Hb <70 g/L or Hb between 70–80 with anaemic dyspnea or tachycardia	2014
TXA		73 /72F/1M		74.3±5.3	64.5±8.			
Placebo		73 /70F/3M		73.9±5.1	65.2 ±9.8			
Dhillon MS [28]	India		TXA 10 mg/kg IV bolus 10 min before deflation of the first tourniquet, followed by 10 mg/kg IV blous 3 h after first			LMWH	Hb <80 g/L Hct <28%	2011
TXA		52 /34F/18M		65.75±8	74±8.5			
Placebo		56 /36F/20M		67.25±7.75	77±11			
Hegde C [29]	India		TXA 1000 mg IV bolus before inflation of the tourniquet			NA	Hb <70 g/L or Hb <90 g/L in patients with heart disease	2013
TXA		30		66.57±8.48	NA			
Placebo		30		64.93±4.87				
Karam JA [30]	USA		TXA 20 mg/kg IV bolus before inflation of the tourniquet			Aspirin	Hb <80 g/L	2014
TXA		37		63.5±8.7	NA			
Placebo		50		65.5±8.5	NA			

M – male; F – female; TXA – tranexamic acid; DVT – deep-vein thrombosis; LMWH – low-molecular-weight heparin; BT – blood transfusion; Hb – hemoglobin; Hct – hematocrit; NA – not applicable, age and weight was described as mean ±SD.

criteria by which patients were excluded for the following reasons: allergy to TXA, a history of hepatic or renal dysfunction, severe cardiac or respiratory disease (myocardial infarction within 6 months, unstable angina, aortic or mitral valvular stenosis), defective coagulation, previous stroke, or a history of thromboembolic disease. The demographic characteristics of these studies are shown in Table 3.

Blood loss

Total blood loss was evaluated in 4 trials, in which a total of 178 patients received TXA and 162 patients served as controls. The pooled WMD for all patients was calculated, and the data demonstrated that TXA administration significantly reduced total blood loss by a mean of 371.1 ml (95% CI=–412.12 to –330.09; p<0.001). However, significant heterogeneity was observed (p<0.001; I^2=92%) among the included studies (Figure 4).

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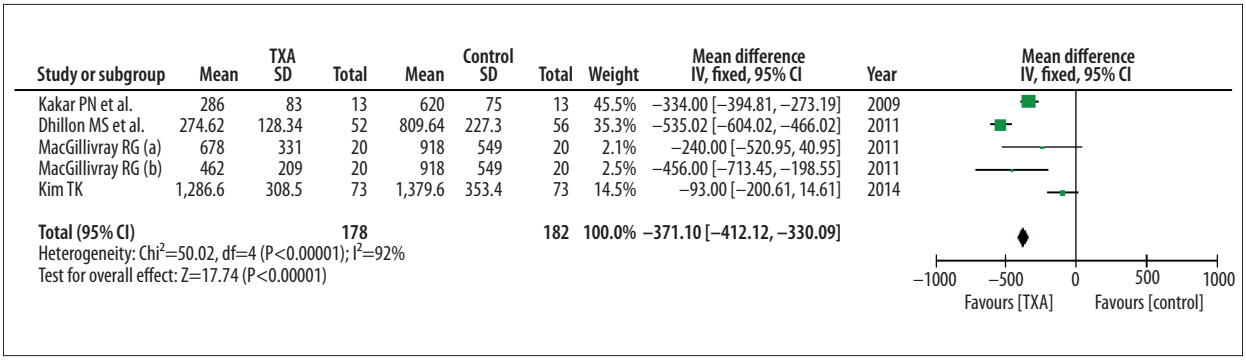

Figure 4. Forest plot and tabulated data illustrating the mean difference (MD) in the blood loss between TXA and placebo group, showing that TXA administration significantly reduce the total blood loss.

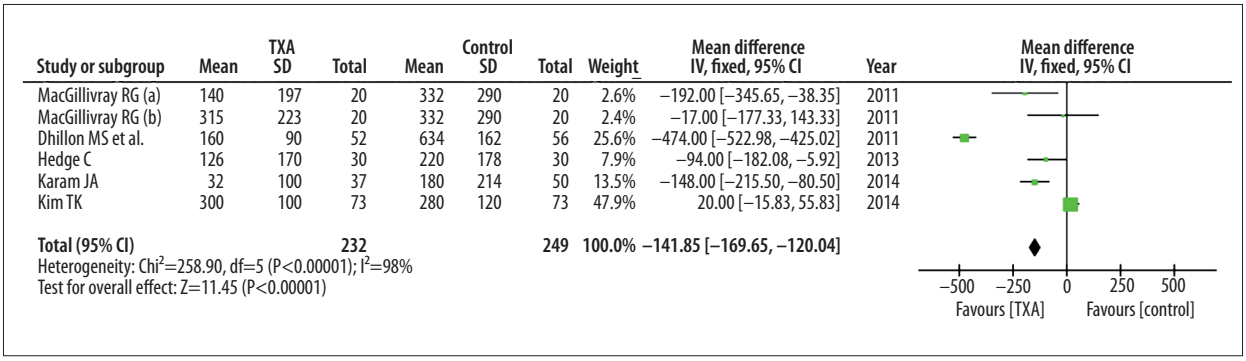

Figure 5. Forest plot and tabulated data illustrating the volume of allogenic transfusion between the TXA and placebo group, showing that TXA group has a significant lower allogenic transfusion volumes per patient.

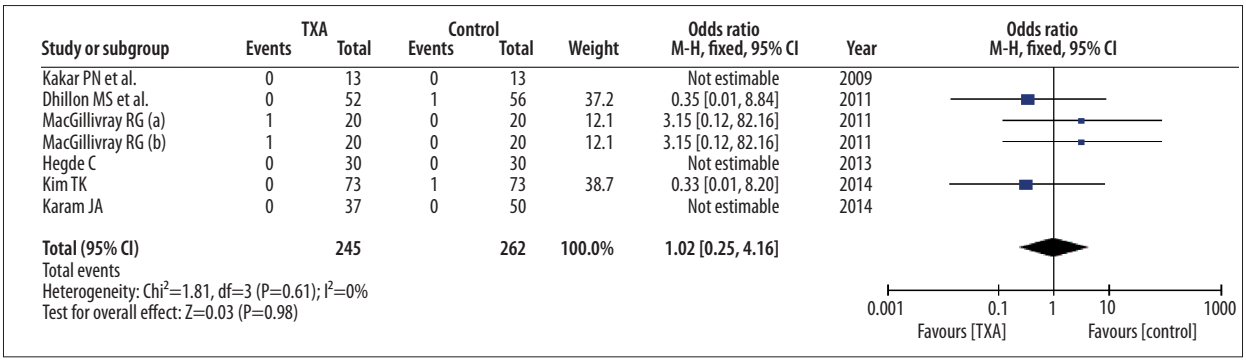

Figure 6. Forest plot diagram show the effect of TXA on DVT, showing that the ratio of DVT in the two administrations are not significantly different.

Blood transfusion requirement

The number of patients requiring transfusion after bilateral TKA was provided in four studies. The allogeneic transfusion rate was significantly lower in patients administered TXA compared with the control group (RR=0.16; 95% CI=0.10 to 0.28; p<0.001), with significant heterogeneity again observed (p=0.03; I^2=64%) (Figure 3).

Blood volumes transfused per patient

Data were available on the volumes of blood transfused per patient in 5 trials encompassing 461 patients. The pooled results indicated that the allogeneic transfusion volume per patient was significantly reduced by a mean of 144.85 ml following TXA administration (95% CI=−169.65 to −120.04; p<0.001) (Figure 5).

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Safety of TXA administration

All 6 trials described the incidence of DVT, with 4 patients who developed DVT postoperatively in only 3 trials. The incidence of DVT in the TXA and placebo groups was 2 of 245 and 2 of 242 patients, respectively. The rate of DVT was not affected by the administration of TXA compared to the control groups (RR=1.02; 95% CI=0.25 to 4.16; p=0.98) (Figure 6).

Discussion

With the aging of the population, knee replacement rates have increased dramatically [34]. Because TKA is associated with significant postoperative blood loss, the increased performance of TKA will be associated with increased bleeding risks and other complications, such as myocardial infarction, PE, postoperative confusion, the need for intensive monitoring, and DVT, all of which are more frequent in patients undergoing simultaneous bilateral TKA [18,35]. Blood loss require blood transfusion, and up to 76% of patients undergoing bilateral TKA required allogeneic blood transfusion, with 2.6 RBC units per patient on average [35]. Allogeneic blood transfusion has potential risks, such as the transmission of infectious disease, allergic reactions, transfusion reactions, and acute lung injury, heavy economical cost, and so on [36]. Therefore, the importance of blood management in the TKA procedure is essential.

A variety of methods have been used to reduce blood loss during TKA, including autologous blood transfusion, the preoperative use of erythropoietin, intraoperative hemodilution, intraoperative blood salvage, intraoperative hypotensive techniques, the administration of thrombotic medications, and the use of postoperative reinfusion drains.

TXA is an antifibrinolytic agent that has been widely used to reduce blood loss in different types of surgery, such as cardiac, liver, spinal, and hip and knee replacement surgery, all showed good results without an increase in the DVT rate or other related complications [15,37]. The mechanism of TXA action is to decrease the physiologic process of fibrinolysis and to prevent the degradation of fibrin. Moreover, TXA has an antiplasmin effect and may inhibit platelet-activating factor, whereby it may protect platelets. As occurs during TKA surgery, fibrinolysis is stimulated by surgical trauma, and tourniquet use can further enhance the fibrinolytic effect. Thus, TXA may be useful in TKA. Additionally, TXA is inexpensive and widely available, which may enable its development as a promising treatment for attenuating blood loss [38].

In previous meta-analyses, TXA was used in cardiac surgery, emergency surgery, spinal surgery, total hip arthroplasty, unilateral surgery, and other surgical procedures. Results showed that the use of TXA for surgical patients was effective and safe, TXA reduced blood loss and blood transfusion requirements without appearing to increase complication risks such as DVT and PE [16,39,40]. Ker et al. [27] demonstrated that topical application of TXA reduced bleeding and blood transfusion in surgical patients, whereas the risk of thrombo-embolic events was uncertain. Perel et al. [41] found that TXA reduced blood transfusion in patients undergoing emergency or urgent surgery, without increase mortality and thromboembolic events. In addition, Ker et al. [38] demonstrated that TXA reduced the probability of receiving a blood transfusion by one-third and mortality rate.

Regarding orthopedic surgical procedures, Huang et al. [42] demonstrated that TXA significantly reduced the blood loss and blood transfusion requirements in patients undergoing major orthopedic surgery and did not appear to increase the risk of DVT. Yang et al. [23] found that the mean blood loss in patients treated with perioperative intravenous TXA was decreased by 128.28 ml intraoperatively and by 98.49 ml postoperatively in spinal surgery, TXA treatment decreased the number of patients who required blood transfusions by 35%, which is similar to our findings. Gandhi et al. [43] suggested that TXA be considered for routine use in primary TKA and THA. Tan et al. [14] demonstrated that intravenous TXA could significantly reduce blood loss and blood transfusion requirements in primary unilateral TKA, but didn't increase the risk of VTE or other severe adverse events. While Fu et al. [44] demonstrated TXA appeared to reduce the occurrence of DVT and PE in TKA patients [44]. With respect to the route of TXA administration, Kim et al. [45] demonstrated that both systemic and topical administration reduced blood loss after TKA and the effect of TXA was influenced by the dose and time of administration [45]. In terms of the effective dose of TXA, Yang et al. [46] suggested that the intravenous administration of 10 to 20 mg/kg of TXA 30 minutes before deflation of the tourniquet followed by 10 to 15 mg/kg every 3–8 hours for 24 hours appeared to be a safe and effective method. Another method is the intraarticular injection of 50 mg/kg once postoperatively [46].

However, the previously cited meta-analysis studies of TKA all focused on unilateral TKA. In this study, we only included bilateral TKA. To our knowledge, this is the first meta-analysis of studies comparing the effectiveness and safety of TXA in reducing perioperative blood loss and the transfusion rate in patients undergoing simultaneous bilateral TKA. The most important finding of our meta-analysis was that the use of TXA in patients undergoing bilateral TKA was effective in reducing blood loss, allogeneic blood transfusion requirements, and the number of patients requiring transfusion. Concurrently, TXA did not increase the prevalence of DVT and PE, and no other severe adverse effects of TXA administration were reported in the included trials. These data are similar to the previous

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meta-analysis in unilateral TKA procedures [13–16]. In addition, a significant difference was observed for intraoperative, postoperative, and total blood loss between the TXA and the control groups, and our meta-analysis demonstrated that TXA reduced total blood loss by a mean volume of 371.1 ml.

In terms of complications, DVT has been reported as a common complication after TKA. Because of its mechanism of action, TXA presents an increased risk of thrombosis in TKA, possibly leading to PE, with high morbidity and mortality. A slight increase in thrombosis risk may outweigh the benefits of TXA in reducing blood loss and transfusion rates. However, in our meta-analysis, no significant increase was observed in the occurrence of thrombo-embolic complications. Only one study reported a 3.3% incidence of non-life-threatening pulmonary embolus in the TXA group, and one study reported a patient with DVT in the placebo group. The rates of DVT in the TXA and control groups were 2 of 245 patients and 2 of 242 patients, respectively; therefore, no conclusive evidence was obtained to confirm that TXA leads to an increased risk of DVT. Pulmonary embolism is one of the related complications in TKA; patients with simultaneous bilateral TKA had a higher rate of pulmonary embolism than unilateral TKA. The risk factors are use of a pneumatic tourniquet, intramedullary guides, and cement, and the most common reason for PE was fat embolism [47]. TXA did not increase the risk of pulmonary embolism [47]. Prior studies also reported higher incidence of cardiac complications in patients underwent simultaneous-bilateral TKA compared with unilateral TKA [48], while TXA didn't increase the occurrence of adverse cardiac event [12]. Moreover, TXA administration didn't increase hospitalization stay, rate of readmission, deep infection, stroke, myocardial infarction [49].

Except for the limitation in most other meta-analyses, such as the range of databases due to language selection, publications biased towards positive results, and data heterogeneity among the included studies. Regarding the limitations of the current meta-analysis, the statistical efficacy may have been improved with the inclusion of additional studies, the low-evidence-based, non-RCT articles may have led to various types of bias, and the administered dose varied in some studies.

Conclusions

According to the results presented in our meta-analysis and in related previous meta-analyses, the use of TXA for patients undergoing bilateral TKA surgery is effective and safe in reducing blood loss and allogeneic blood transfusion requirements, without any additional thrombo-embolic risk. However, large and clinically relevant high-quality RCTs are needed to evaluate the potential risk of thrombo-embolic complications related to TXA in patients undergoing bilateral TKA.

Conflict of interest

Peiheng He, Ziji Zhang, Yumin Li, Hua Wang and Dongliang Xu declare that they have no conflict of interest.

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