

Oral tranexamic acid reduces blood loss in total-knee arthroplasty

A meta-analysis

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Abstract

Background: Postoperative hemorrhage following total-knee arthroplasty (TKA) remains an important topic. The objective of the meta-analysis is to assess the effectiveness of oral antifibrinolytics for blood management in patients undergoing TKA.

Methods: We searched Medline (1966 to August 2018), PubMed (1966 to August 2018), Embase (1980 to August 2018), ScienceDirect (1985 to August 2018), and the Web of Science (1995 to August 2018) for randomized control trials (RCTs). To assess the heterogeneity of study trial and determine the model for analysis (random-effect model or fixed-effect model), I^2 tests and Chi-squared were conducted. We utilized the STATA 12.0 (StataCorp, College Station, TX) to perform all statistical analyses.

Results: A total of 5 RCTs met our inclusion criteria. This meta-analysis shows that there are significant differences between the 2 groups regarding total blood loss, hemoglobin reduction, and transfusion rates. In addition, no adverse effects were identified in treatment groups.

Conclusion: The oral form of antifibrinolytics in TKA is able to significantly decrease blood loss, postoperative hemoglobin reduction, as well as transfusion requirements. No increased risk of postoperative complications was observed. Higher quality RCTs is necessary to confirm our finding.

Abbreviations: PE = pulmonary embolism, DVT = deep vein thrombosis, RCT = randomized controlled trial, RD = risk difference, TKA = total-knee arthroplasty, TXA = tranexamic acid, WMD = weighted mean difference.

Keywords: antifibrinolytics, blood loss, meta-analysis, oral, total-knee arthroplasty

1. Introduction

Total-knee arthroplasty (TKA) is a common surgical procedure for treatment of the degenerative disorders and rheumatic arthritis.^[1] It has been estimated that more than 700,000 TKAs were performed throughout the United States annually.^[2] However, arthroplasties were associated with substantial bleeding. Previous articles have reflected that there was an estimated 750 to 1800 mL of calculated total blood loss during TKA.^[3–5] Although various methods such as hemostatic agent administration, hypothermic anesthesia, tourniquet, and minimally invasive procedures have been used, blood transfusion rates remain relatively high which may cause hemolysis, infection, and allergic reactions.^[6,7]

In recent years, antifibrinolytics have been well-documented in the field of surgery. Tranexamic acid (TXA) is a synthetic analog

of the amino acid lysine and it serves as an antifibrinolytic.^[8] Recently, it was widely used in major orthopedic surgery.^[9–11] Previous articles have demonstrated that it was effective and safe for patients who received intravenous administration or topical application of TXA. Alshryda et al^[12] indicated that topical use of TXA was effective in decreasing blood transfusion rates after TKA. Jaszczuk et al^[13] reported that 15 mg/kg of TXA could significantly decrease the need for postoperative transfusion of allogeneic blood due to a significant reduction in intra-, post-, and perioperative blood loss. Indeed, the oral form of TXA was cheap and easy to use and did not require specific equipment for administration.

However, the relatively small amount of patients meant the results of the present studies were inconclusive and there has been no systematic evaluation of the literature. Consequently, we applied a systematic and meta-analytical approach to determine the evidence for the safety and efficacy of oral TXA.

2. Methods

This systematic review and meta-analysis were conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement. No primary personal data will be collected; therefore no additional ethical approval needs to be obtained.

2.1. Search strategy

The electronic databases of PubMed, Embase, ScienceDirect, and the Web of Science were searched from the inception of the database to August 2018, without language restriction. The following key words were used in combination with Boolean

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operators AND or OR: “oral antifibrinolytics OR tranexamic acid,” “total-knee replacement OR arthroplasty,” and “blood loss OR bleeding OR transfusion.” Additionally, unpublished studies or gray literature were also searched. The selection process of all studies used in the literature was presented in a flow diagram (Fig. 1).

2.2. Inclusion and exclusion criteria

The inclusion criteria were: Participants: patients with a diagnosis of end-stage knee osteoarthritis and prepared for TKA; Interventions: the intervention group received the oral form of antifibrinolytics for postoperative blood management after TKA; Comparisons: the control group received a placebo; Outcomes: total blood loss, hemoglobin reduction, transfusion requirements, and postoperative complications, such as deep vein thrombosis (DVT) and pulmonary embolism (PE); Study design: randomized control trials (RCTs).

The exclusion criteria were: abstracts, case reports, letters, editorials, conference articles, repeated studies, and retrospective studies.

2.3. Selection criteria and date extraction

Two authors independently assessed the potentially eligible studies. Firstly, the titles and abstracts were screened to exclude the duplicated and apparently irrelevant ones or those that do not meet our inclusion criteria. After then, the remaining

potential studies were full-text downloaded and reviewed. Any disagreement between 2 above authors was sent and discussed with the 3rd independent author. Two reviewers independently extracted data. A standard form was used; the extracted items included the following: the general study information, for example, the authors, publishing date, study design, case number, age, gender, and follow-up term. Whenever necessary, we contacted the authors of the studies for the missing data and additional information. Primary outcomes included total blood loss, hemoglobin reduction, and transfusion rate. Secondary outcomes were postoperative complications such as DVT and PE.

2.4. Quality assessment

Quality assessment for the included articles was independently evaluated by 2 reviewers which used the Cochrane Collaboration’s tool. We conducted a “risk of bias” table including the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting and other bias, and each item was recorded by “Yes,” “No,” or “Unclear.” Each risk of bias item was then presented as a percentage across all included studies. The percentage indicated the proportion of different levels bias risk for each item. If there was disagreement between 2 reviewers, consensus was reached through discussion.

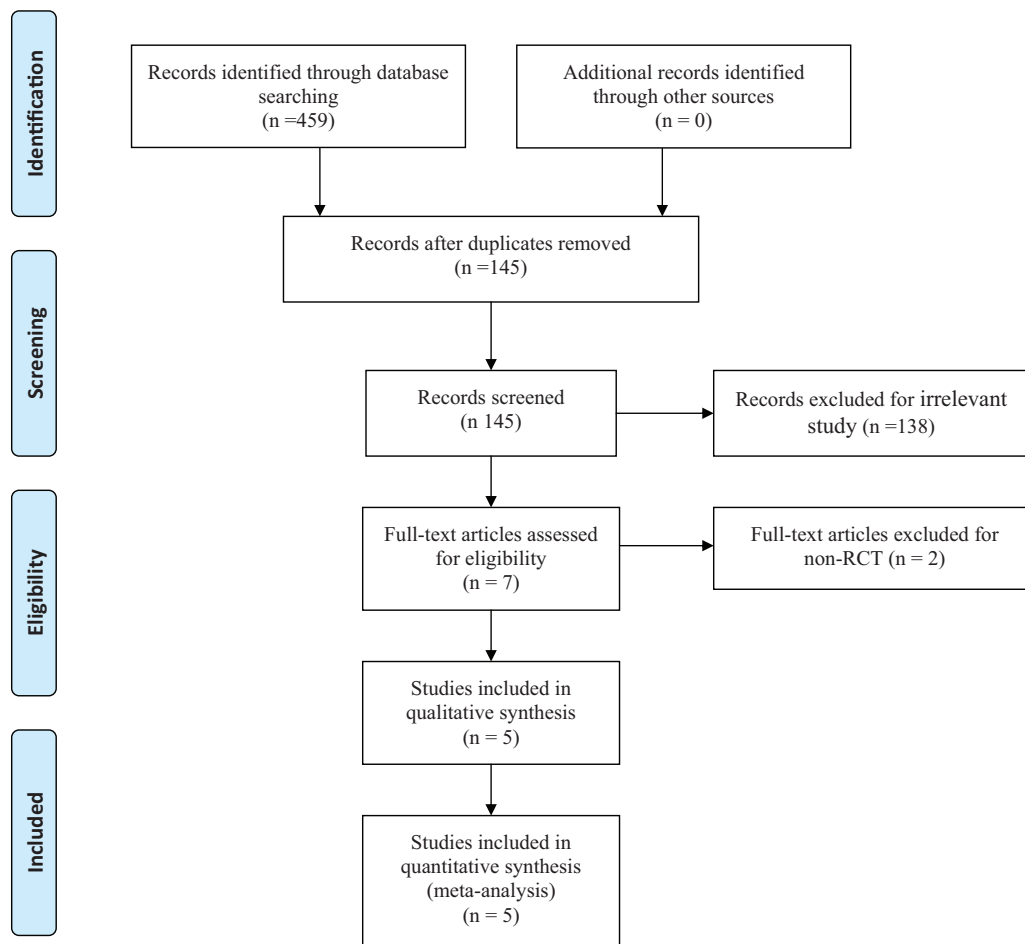


Figure 1. Search results and the selection procedure. RCT = randomized controlled trial.

The qualities of evidence in the main outcomes of the present meta-analysis were evaluated using the Recommendations Assessment, Development and Evaluation (GRADE) system including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The GRADE evidence was divided into the following categories: high-quality evidence, which indicated that further research was unlikely to change the confidence in an estimate of effect; (2) moderate-quality evidence, which indicated that further research was likely to have an important impact on confidence in an estimate of effect and may change the estimate; (3) low-quality evidence, which indicated that further research was likely to have an important impact on confidence in an estimate of effect and was likely to change the estimate; and (4) very low-quality evidence, which indicated that we were very uncertain about the results.

2.5. Data analysis and statistical methods

The data were collected and input into the STATA software (version 12.0; StataCorp, College Station, TX) for meta-analysis. Risk difference (RD) with a 95% confidence interval (CI) or weighted mean difference (WMD) with 95% CI were assessed for dichotomous outcomes or continuous outcomes, respectively. A random-effects model was applied when heterogeneity was detected or the statistical heterogeneity was high ($P < .05$ or $I^2 > 50\%$). Otherwise, a fixed-effects model was used ($P \geq .05$ or $I^2 \leq 50\%$).

3. Results

3.1. Search result

A total of 459 studies were preliminarily reviewed. About 314 articles were removed as duplicates and 138 were excluded due to irrelevant content. Two studies were removed for non-RCTs. No gray reference was included. Finally, 5 RCTs^[14-18] which had been published between 2004 and 2017 were included in our study. There were 307 participates in the intervention group and 301 patients in the control group.

3.2. Study characteristics

The characteristics of included studies are presented in Table 1. The sample size ranged from 40 to 280 and the mean age ranged from 63 to 70. All articles assessed the oral TXA for blood management in TKA. Four studies performed general anes-

sia.^[14-17] The intervention group received oral form TXA, while control groups received placebo or none. All articles indicated that TKA was performed by the same group of surgeon. Blood transfusions were performed following postoperative level of hemoglobin level or symptoms of anemia. The follow-up period ranged from 1 to 8.2 months.

3.3. Risk of bias assessment

A standardized assessment of the risk of bias in the 5 RCTs is summarized in Figure 2. All RCTs detailed the methods of randomization and stated allocate concealment was achieved by sealed envelope. Four RCTs reported the blinding of participants and personnel^[15-18] and 3^[15-17] of them had attempted to blind assessors. All of them suggest the outcomes for at least 95% of the participants. Each risk of bias item is presented as the percentage across all included studies, which indicates the proportion of different levels of risk of bias for each item (Fig. 3).

3.4. Outcomes for meta-analysis

3.4.1. Total blood loss. Five articles^[15-18] reported the total blood loss following TKA. There was significant heterogeneity among the studies ($\chi^2 = 31.89$, $df = 4$, $I^2 = 87.5\%$, $P = .000$); therefore, a random-effects model was used. Pooled results demonstrated there was significant difference regarding total blood loss between groups (WMD = -159.53, 95% CI: -256.95 to 62.11, $P = .001$; Fig. 4).

3.4.2. Hemoglobin decline. Five studies^[15-18] showed the postoperative hemoglobin decline following TKA. There was significant heterogeneity ($\chi^2 = 9.06$, $df = 4$, $I^2 = 55.9\%$, $P = .060$); therefore, a random-effects model was used. Significant difference was identified regarding the postoperative hemoglobin decline between groups (WMD = -0.492, 95% CI: -0.696 to -0.288, $P = .000$; Fig. 5).

3.4.3. Transfusion rates. Four studies^[15-18] reported data regarding the transfusion rates following TKA. There was significant heterogeneity ($\chi^2 = 14.87$, $df = 4$, $I^2 = 73.1\%$, $P = .005$) and a random-effects model was applied. The present meta-analysis indicated that there was significant difference between the TXA and control groups in terms of transfusion rates (RD = -0.108, 95% CI: -0.214 to -0.001, $P = .048$; Fig. 6).

3.4.4. Deep vein thrombosis. The occurrence of DVT was provided in 4 studies.^[15-18] No significant heterogeneity among these studies was found; therefore, a fixed-effects model was used

Table 1
Cohort characteristics.

Studies	Locate	Cases (T/C)	Mean age (T/C)	Female patients (T/C)	Surgical procedure	Anesthesia method	TXA intervention	Transfusion trigger	Follow-up	Quality assessment score
Zohar et al, 2004	Israel	20/20	69/69	12/16	TKA	General anesthesia	T:oral 1 g TXA C:none	Hematocrit <28%	3 mo	5
Bradshaw et al, 2012	USA	26/20	67/68	12/10	TKA	General anesthesia	T:oral 1.5 g TXA C:none	Hemoglobin <7 g/dL	2 mo	7
Alipour et al, 2013	Iran	27/26	68.6/63.1	15/16	TKA	General anesthesia	T:oral 1 g TXA C:none	Hemoglobin <7 g/dL	1.5 mo	7
Yuan et al, 2017	China	140/140	63/64	72/75	TKA	General anesthesia	T:oral 1 g TXA C:none	Hemoglobin <8 g/dL	2 mo	7
Li, 2017	Hong Kong	94/95	70/68	47/66	TKA	NS	T:oral 3 g TXA C:none	Hemoglobin <8 g/dL	8.2 mo	7

C=control group, NS=not stated, RCT=randomized controlled trial, T=TXA group.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alipour 2013	+	+	+	+	+	?	?
Bradshaw 2012	+	+	+	?	+	?	?
Li 2017	+	+	+	+	+	?	?
Zohar 2004	+	+	-	?	+	?	?

Figure 2. Methodologic quality of the randomized controlled trials.

($\chi^2 = 1.07$, $df = 3$, $I^2 = 0\%$, $P = .784$). There was no significant difference between the 2 groups (RD = -0.001, 95% CI: -0.024 to 0.022, $P = .942$; Fig. 7).

3.4.5. Pulmonary embolism. The occurrence of PE was shown in 4 articles.^[15-18] There was no significant heterogeneity among these studies; therefore, a fixed-effects model was used ($\chi^2 = 0.70$, $df = 4$, $I^2 = 0\%$, $P = .952$). There was no significant difference between the 2 groups (RD = -0.004, 95% CI: -0.024 to 0.017, $P = .728$; Fig. 8).

3.4.6. Publication bias and subgroup analysis. Publication bias was assessed for the main outcomes. A low risk of publication bias was found (Figs. 9-11); however, publication bias is an inherent weakness that exists in all meta-analyses.

Subgroup analysis is summarized in Table 2.

4. Discussion

The objective of the meta-analysis is to assess the effectiveness and safety of oral antifibrinolytics for blood management in patients undergoing TKA. Pooled results indicated that oral TXA was associated with further decrease in total blood loss and transfusion rate when compared with the control. In addition, no difference in thromboembolic complication was found.

All outcomes in this meta-analysis were evaluated using the GRADE system. The overall scores of the included studies are presented in Table 3. Based on the concerns regarding the serious limitations and inconsistencies, we downgraded the evidence to low quality for the main outcomes. In addition, we also found significant heterogeneity for the total blood loss ($I^2 = 87.5\%$, $P = .000$), hemoglobin decline ($I^2 = 55.9\%$, $P = .060$) and transfusion requirement ($I^2 = 73.1\%$, $P = .005$). Differing from anesthesia methods, a dose of TXA and transfusion trigger would be a cause of heterogeneity. Thus, more RCTs are needed to confirm our conclusion. Overall, the evidence quality for the present meta-analysis is low which indicated that further research is likely to have a significant impact on the confidence in an estimate of effect and is also likely to change the estimate.

The present meta-analysis indicated that oral TXA was able to effectively reduce total blood loss (WMD = -159.53, 95% CI: -256.95 to 62.11, $P = .001$; Fig. 4) and hemoglobin decline after TKA (WMD = -0.492, 95% CI: -0.696 to -0.288, $P = .000$;

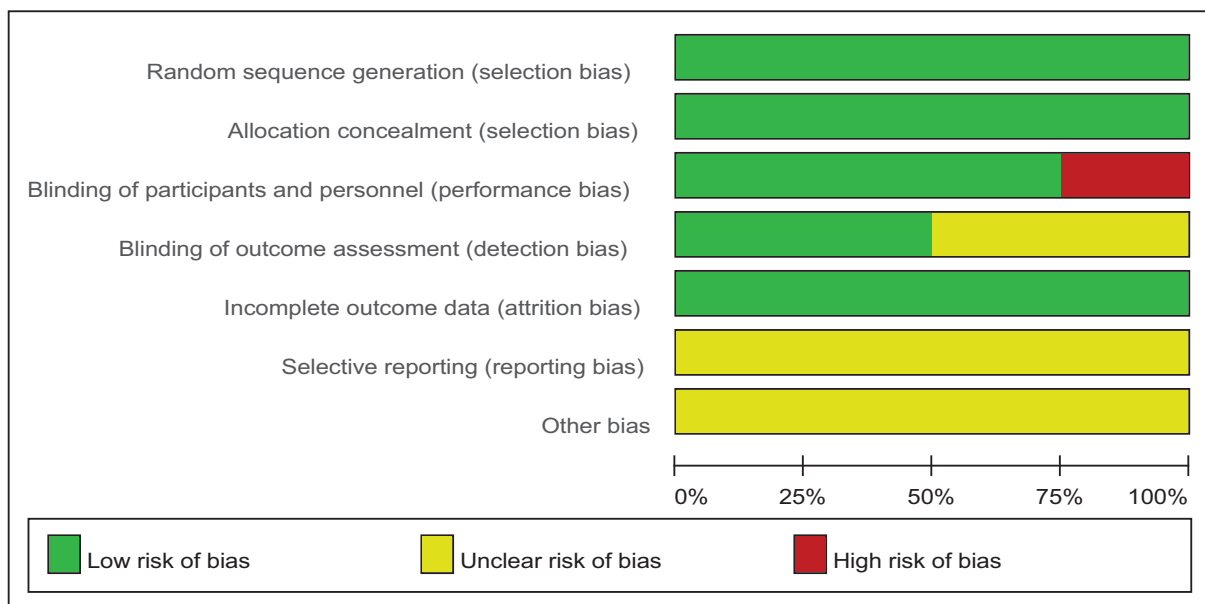


Figure 3. Risk of bias.

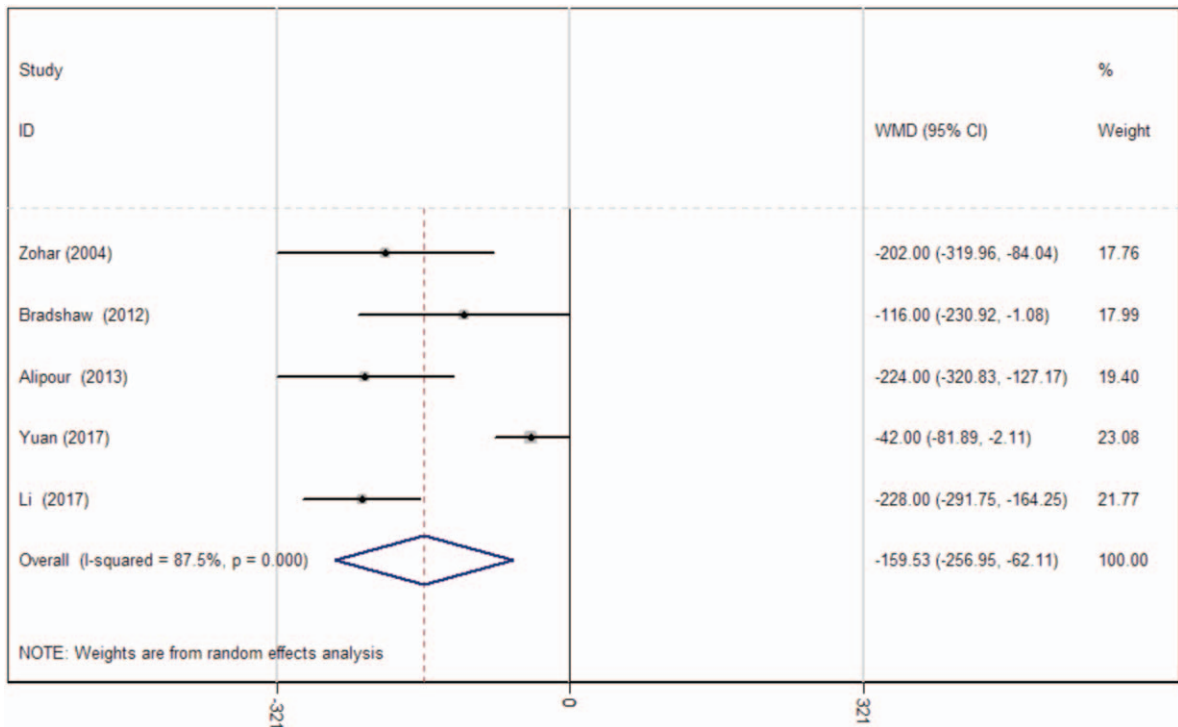


Figure 4. Forest plot diagram showing effect of oral tranexamic acid on total blood loss. CI = confidence interval, WMD = weighted mean difference.

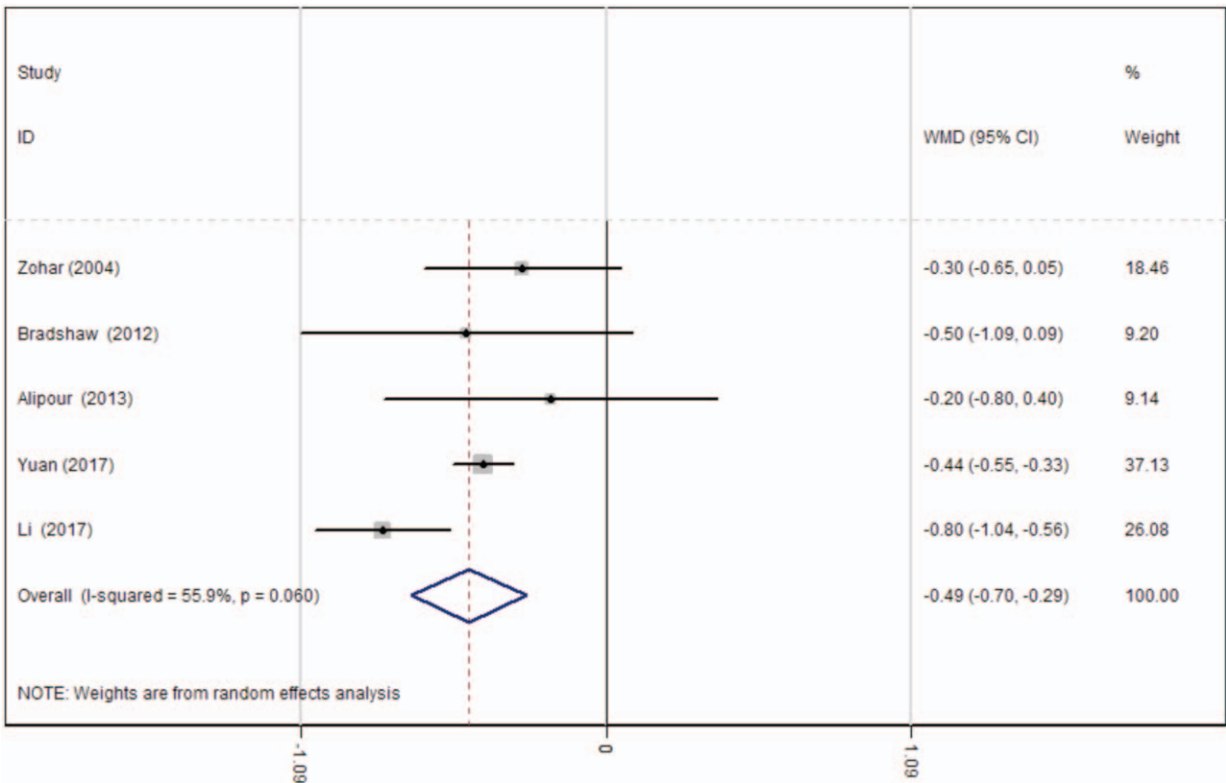


Figure 5. Forest plot diagram showing effect of oral tranexamic acid on hemoglobin decline. CI = confidence interval, WMD = weighted mean difference.

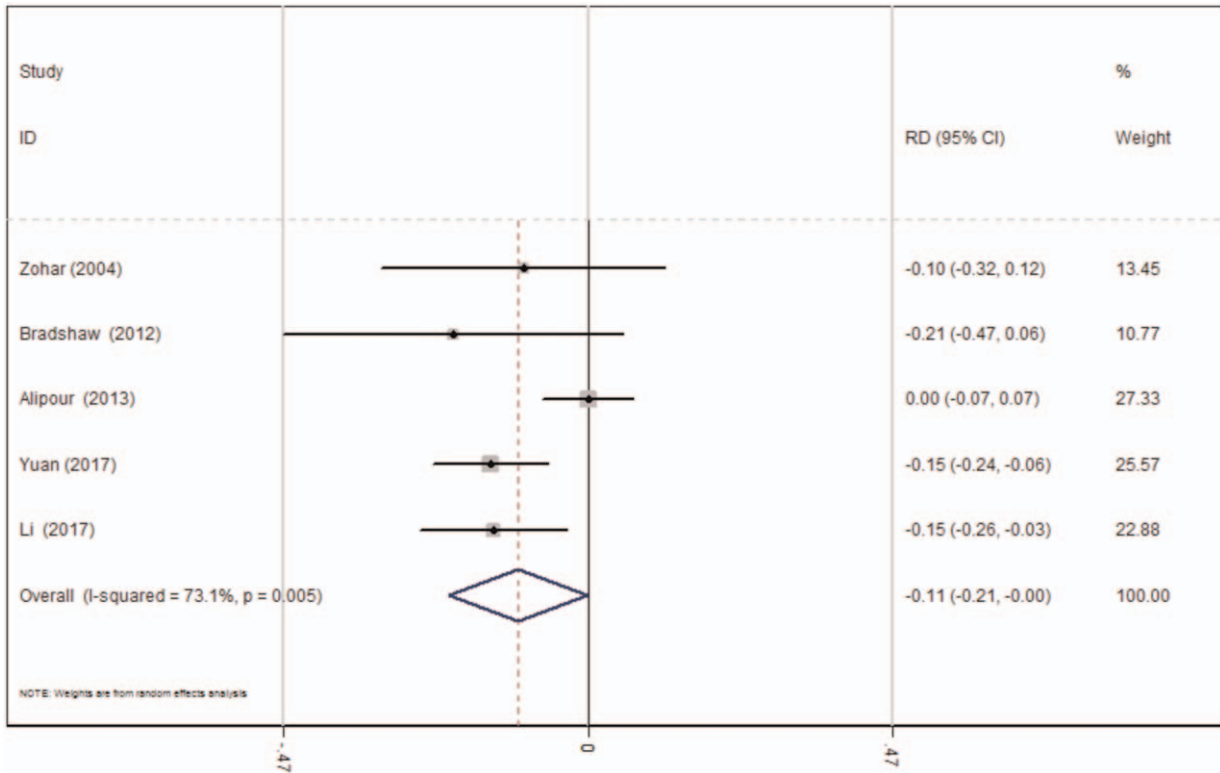


Figure 6. Forest plot diagram showing effect of oral tranexamic acid on transfusion rate. CI = confidence interval, RD = risk difference.

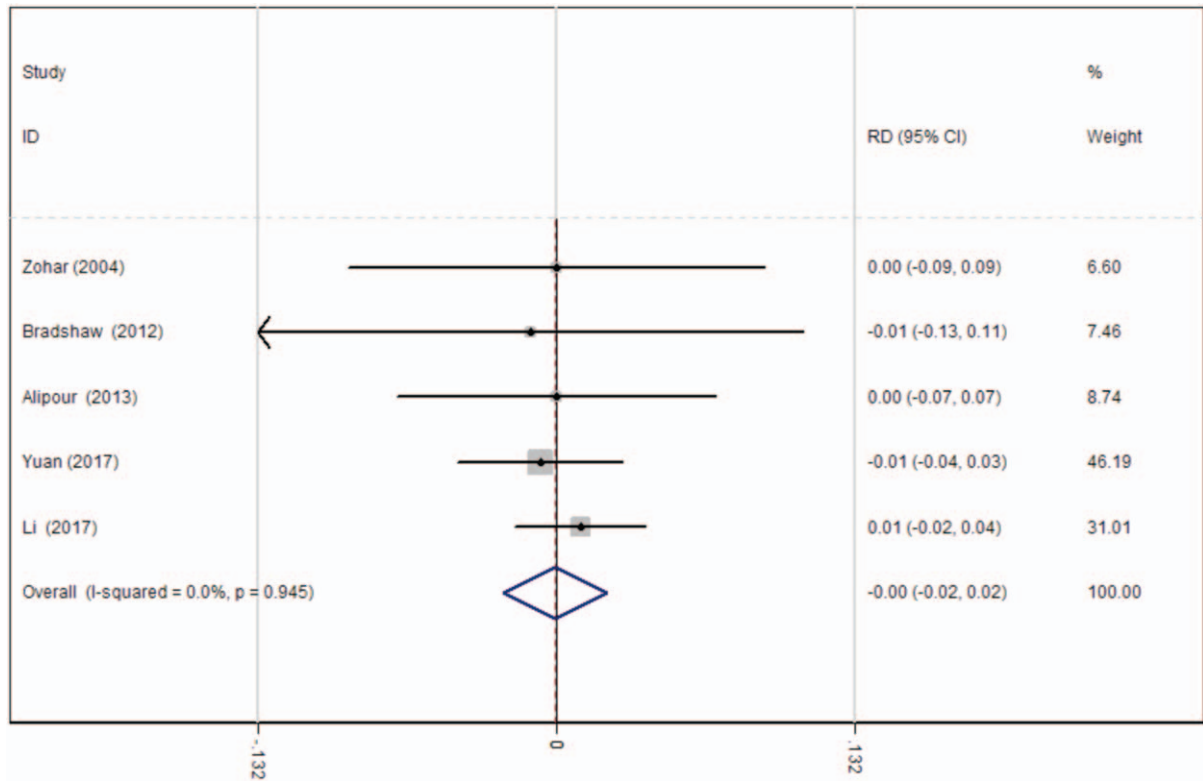


Figure 7. Forest plot diagram showing effect of oral tranexamic acid on the risk of deep vein thrombosis. CI = confidence interval, RD = risk difference.

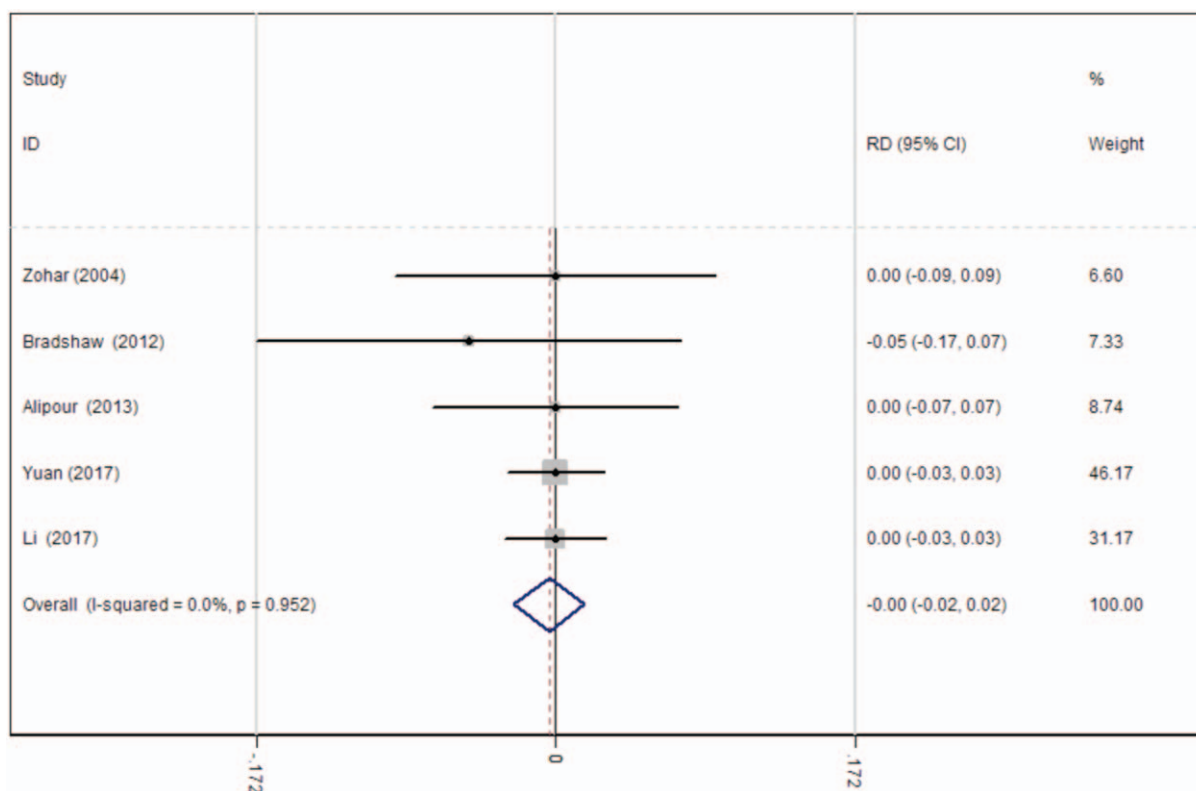


Figure 8. Forest plot diagram showing effect of oral tranexamic acid on the risk of pulmonary embolism. CI = confidence interval, RD = risk difference.

Fig. 5). Substantial evidence has demonstrated that the use of TXA was associated with excellent outcomes for patients undergoing TKA.^[19,20] The oral form is cheap, easy to use and does not require specific equipment for administration. Since the oral form of TXA is available and is quick acting, is estimated that it has the comparative effect in blood management compared with the topical or intravenous form. Despite previous clinical research, the efficacy of the oral form of TXA in primary TKA was seldom reported. Therefore, no reliable conclusion has been reached regarding the effectiveness for blood sparing by oral routine of TXA. Meta-analysis is conducted as the main statistical method in our study. It could strengthen statistical power while also enlarging the sample size by pooling results of published studies that could provide stronger evidence. The present meta-analysis indicates that oral TXA can significantly reduce the calculated total blood loss and hemoglobin decline after TKA. Minimally invasive surgery, diathermy coagulation, the position of the knee, sealing of the intramedullary femoral canal, and the use of tourniquet were also effective method of reducing the requirement for blood transfusion.^[21-24] Due to the limited number of the included studies, we did not perform a meta-analysis regarding these factors. Further investigation was still required.

Blood sparing is not the only concern when evaluating the effectiveness of the oral form of TXA. TXA is a synthetic fibrinolytic inhibitor that competitively inhibits plasmin, plasminogen, and fibrin from combining. Theoretically, it would increase the prevalence of thromboembolic complications. The most common thrombotic events were DVT and PE which could induce severe results and even death after major orthopedic surgery. Published studies have demonstrated that no increased

risk of DVT or PE was observed with the topical or intravenous administration of TXA. Similarly, all included articles in the present meta-analysis reflected no significant difference in the incidence rate of DVT or PE in the oral TXA groups which was in accordance with the previous studies. However, due to the small amount of included studies, more RCTs with longer follow-ups are required to confirm our conclusion. Surgical site infection remains a devastating complication that is a deep concern for many patients and surgeons alike. It may lead to periprosthetic joint infection which prolongs hospital stays, delays recoveries, and subsequent revision surgeries, leading to greater subsequent revision surgeries which are a financial burden. It has been reported that the infection rate of TKA is approximately 1% to 3%.^[25] The present meta-analysis shows that there is no significant difference in the incidence of infection. More RCTs with long-term follow-ups are needed for further investigation.

Limitations existed in the current review that needed further attention, describing as follows: the limited number of studies and the small number of samples may have weakened our analysis; the analysis of some outcome measures such as total blood loss and hemoglobin decline were based on a high heterogeneity; follow-up duration was relatively short; only English studies were included, publication bias is unavoidable.

Implications for practice: Oral form of TXA should be considered for patients undergoing TKA. Although no significant difference in the incidence rate of DVT or PE were found, the risk of such complications should still be carefully considered. Implications for research: an adequately sized, well designed RCT for assessing TXA-related side-effects are required to shed more light on the efficiency of TXA given perioperatively to decrease blood loss during TKA.

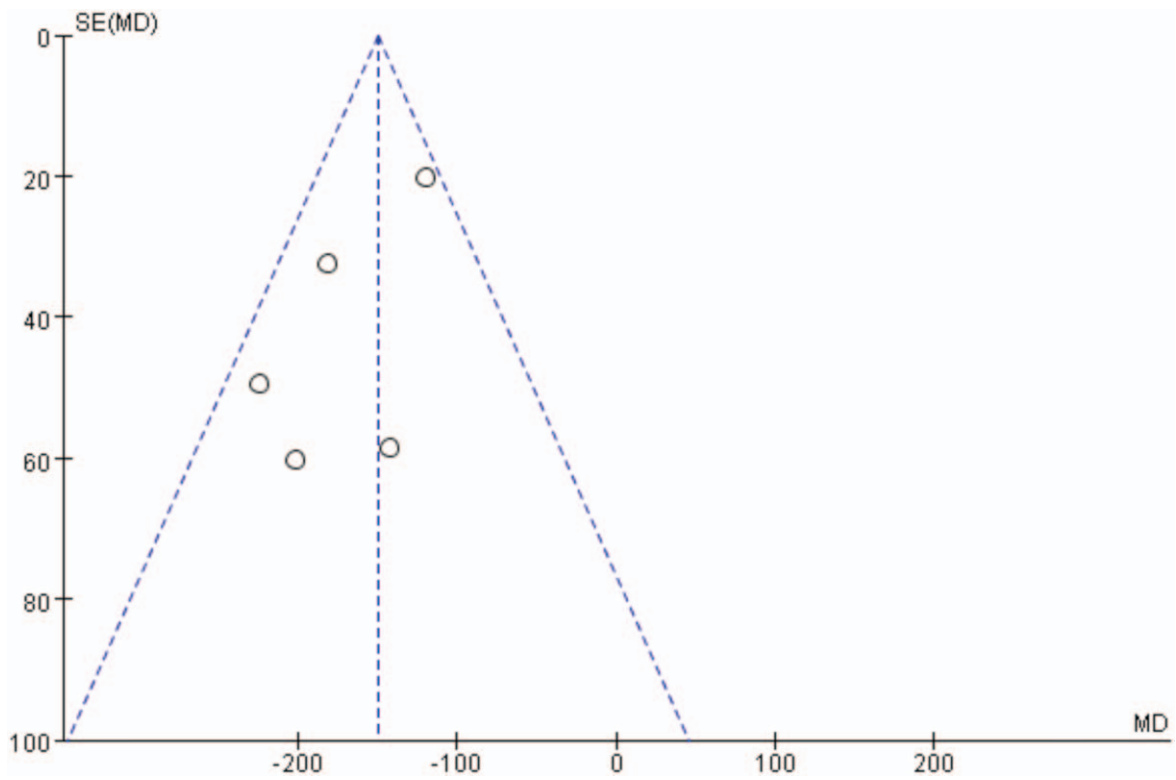


Figure 9. Funnel plot of total blood loss.

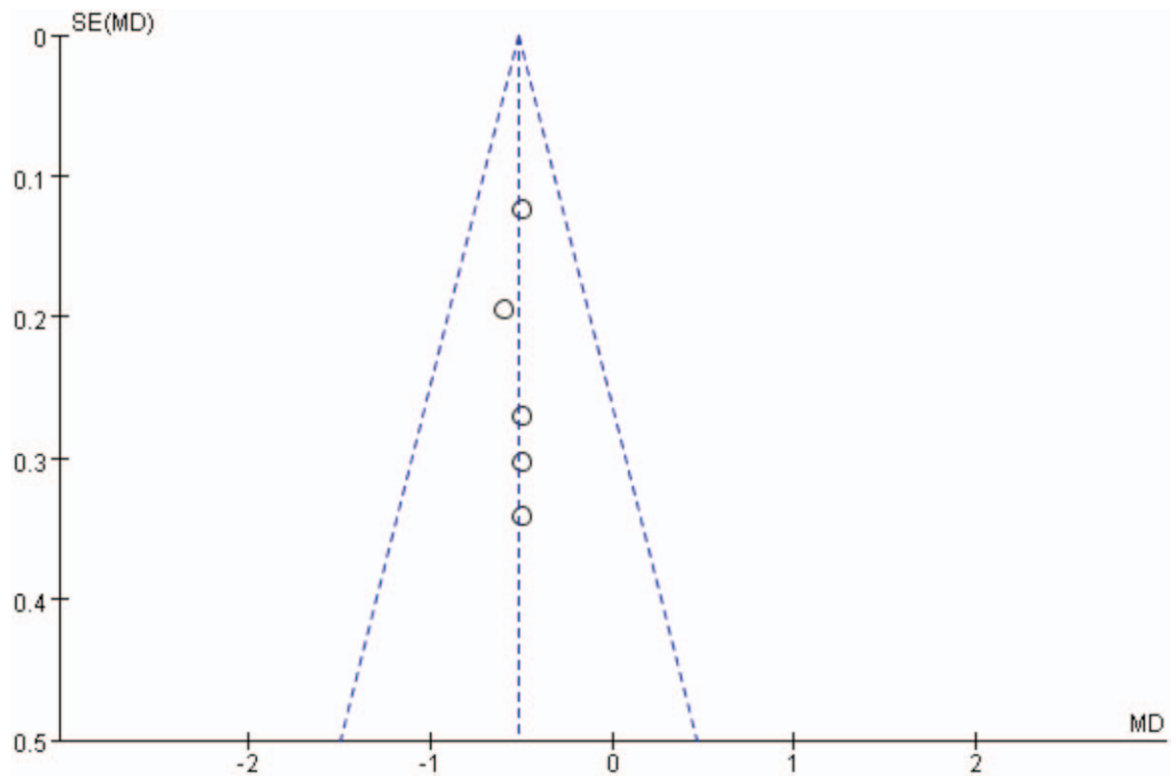


Figure 10. Funnel plot of hemoglobin decline.

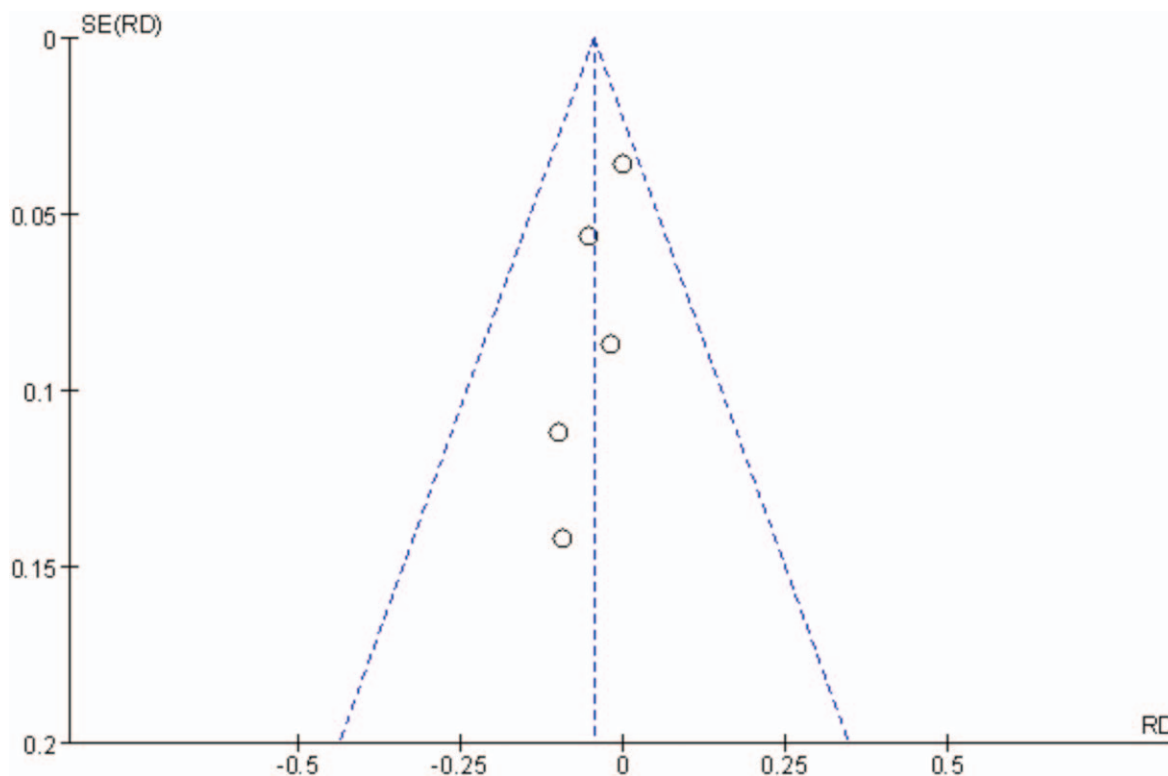


Figure 11. Funnel plot of transfusion rates.

Table 2

Outcome of subgroup analysis for main results.

Variables	Studies (n)	Patients (n)	P	WMD or RD (95% CI)	Heterogeneity P-value (I ²)	Model
Total blood loss						
Dosage of TXA = 1 g	3	373	.031	-149.0 (-284.7, -13.3)	0.000 (87.6%)	Random
Dosage of TXA > 1 g	2	235	.001	-182.6 (-290.4, -74.9)	0.095 (64.2%)	Random
Postoperative hemoglobin decline						
Dosage of TXA = 1 g	3	373	.000	-0.42 (-0.52, -0.32)	0.577 (0%)	Fixed
Dosage of TXA > 1 g	2	235	.000	-0.76 (-0.98, -0.53)	0.359 (0%)	Fixed
Transfusion rates						
Dosage of TXA = 1 g	3	373	.310	-0.08 (-0.23, 0.07)	0.002 (83.5%)	Fixed
Dosage of TXA > 1 g	2	235	.004	-0.16 (-0.26, -0.05)	0.671 (0%)	Random

RD = risk difference, TXA = tranexamic acid, WMD = weighted mean difference.

Table 3

The GRADE evidence quality for main outcome.

No of studies	Design	Quality assessment					Other considerations	No of patients		Effect Absolute	Quality	Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Oral TXA groups		Control groups				
Total blood loss (follow-up 1.5–8.4 mo; better indicated by lower values)												
5	RCT	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	None	307	301	WMD = -159.53, 95% CI: -256.95 to 62.11, P = .001	Low	Critical	
Hemoglobin decline (follow-up 1.5–8.4 mo; better indicated by lower values)												
5	RCT	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	None	307	301	WMD = -0.492, 95% CI: -0.696 to -0.288, P = .000	Low	Critical	
Transfusion requirements (follow-up 1.5–8.4 mo)												
5	RCT	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	None	35/307 (11.4%)	75/301 (24.9%)	RD = -0.108, 95% CI: -0.214 to -0.001, P = .048	Low	Critical	

CI = confidence interval, RCT = randomized controlled trial, RD = risk difference, TXA = tranexamic acid, WMD = weighted mean difference.

5. Conclusion

The oral form of antifibrinolytics in TKA is able to significantly decrease blood loss, postoperative hemoglobin reduction, as well as transfusion requirements. No increased risk of postoperative complications was observed. Higher quality RCTs is necessary to confirm our finding.

Author contributions

Hua Li finishes the manuscript. Liqun Bai collects data. Yunhai Li and Zhiyuan Fang design the study. All authors read and approved the final manuscript.

Data curation: Liqun Bai, Yunhai Li, Zhiyuan Fang.

Writing – original draft: Hua Li.

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