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Efficacy and safety of oral tranexamic acid in total knee arthroplasty
A systematic review and meta-analysis

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Abstract

Background: Tranexamic acid (TXA) is an antifibrinolytic drug widely used as a blood-sparing technique in total knee arthroplasty (TKA), and it is usually administrated by intravenous or intraarticular injection. Recently, the oral form of TXA has been applied in TKA patients. However, there is no final consensus regarding the effectiveness and safety of oral TXA. The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to evaluate the efficacy and safety of oral TXA versus control for blood loss after TKA.

Methods: We searched PubMed, Embase, Medline, Web of Science, and Cochrane Library databases for relevant studies through August 2017. The mean difference (MD) of total blood loss, hemoglobin (Hb) drop, hematocrit (Hct), drain output, and risk difference (RD) of transfusion rate and thromboembolic complications in the TXA and control groups were pooled throughout the study. The outcomes were pooled by Stata 12.0.

Results: A total of 5 RCTs (608 patients) were included in this study. All the included studies were randomized and the quality of included studies was relatively high. The pooled results indicated that the oral TXA group had significantly less Hb drop (standardized mean difference [SMD], −0.936; 95% confidence intervals [CI], −1.118,−0.754), Hct drop (SMD, −0.693; 95% CI, −1.113, −0.274), and drain output (SMD, −0.793; 95% CI, −0.959, −0.628) than the control group. No statistically significant differences were found in transfusion rate and the incidence of thromboembolic complications between the 2 groups. Total blood loss could not be evaluated for the insufficient date.

Conclusions: Our meta-analysis suggested that the administration of oral TXA provided significantly better results with respect to Hb drop, Hct drop, and drain output without increasing the transfusion rate and the risk of thromboembolic complications after TKA. Nevertheless, our current study with some limitations such as the small sample size only provided limited quality of evidence, confirmation from further meta-analysis with large-scale, well-designed RCTs is required.

Abbreviations: CI = confidence intervals, DVT = deep vein thrombosis, Hb = hemoglobin, Hct = hematocrit, MD = mean difference, PE = pulmonary embolism, RCTs = randomized controlled trials, RD = risk difference, SD = standard deviation, SMD = standardized mean difference, TKA = total knee arthroplasty, TXA = tranexamic acid.

Keywords: blood loss, meta-analysis, oral tranexamic acid, randomized controlled trial, total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) is widely used as an effective treatment for end-stage osteoarthritis and other joint diseases of the knee to help patients relieve pain and improve quality of life. The number of patients needing this surgical method has increased dramatically over the past several decades because of the aging population. However, intraoperative and postoperative

blood loss is one of the major complications following TKA.[1–3] Perioperative blood loss ranges from 1500 to 2000 mL with a predictable decrease in $3\,g\,dL^{-1}$ of hemoglobin (Hb) for every 1000 mL of blood loss[3] and the massive blood loss will be definitely related to the longer hospital stays and delayed rehabilitation. The extensive introduction of tourniquet in recent years can greatly decrease bleeding during the surgery. However, as the result of the activation of fibrinolytic system in the regional blood caused by both surgery and the use of the tourniquet, a more remarkable bleeding postoperatively may occur.[1,4–6] Postoperative allogeneic blood transfusion may be a life-saving measure in those with hemorrhage, but it also carries a substantial risk of hemolytic and non-hemolytic transfusion reactions and transmission of infectious diseases.[7,8] Additionally, allogeneic blood transfusion is sure to increase the costs.[9] Thus, several methods aiming at reducing blood loss have been applied including the use of hypotensive anesthesia, intraoperative blood salvage and antifibrinolytic agents such as tranexamic acid (TXA).[10,11]

TXA, a synthetic lysine analog, inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen.[7,12] TXA is thought to be of particular effects because of the significance of keeping balance between the fibrinolytic and procoagulant system both intraoperatively and postoperatively. Many clinical studies[13–15] and meta-analyses[16,17] have previously confirmed that the intravenous and topical administrations of TXA were effective on minimizing the risks of anemia and transfusion rate.

Recently, researchers have kept their eyes on the administration of oral TXA,[5,18,19] but the safety and efficacy remained controversial because of the small sample size and other limitations existed in individual studies. Up to now, we have not found any review or meta-analysis related to this topic, so we conducted this research to evaluate whether TXA is superior to control in the reduction of postoperative blood loss for TKA patients.

2. Material and methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] reporting guidelines for the conduct of meta-analysis of intervention trials. Ethical approval for this study was unnecessary because it was a review of existing literature and did not involve any handling of individual patient data.

2.1. Data sources and searches

PubMed, Embase, Medline, Web of Science, and Cochrane Library databases were searched to identify randomized controlled trials (RCTs) comparing oral TXA with control for reducing blood loss in patients who underwent TKA. The following search term was used for the initial literature search: (tranexamic acid or TXA) and (oral) and (total knee arthroplasty or total knee replacement). Two authors independently searched for relevant studies through July 2017. The study selection was then independently performed by 2 of the authors, and any different opinions were resolved through discussion. In addition, we checked the reference lists of the articles manually to identify other potentially eligible publications.

2.2. Study selection

We identified RCTs comparing oral TXA with control in patients undergoing TKA. Studies were considered eligible if they met the

following criteria: the study population was adult patients that underwent TKA, with a trial group receiving oral TXA and a control group that received either a placebo or no treatment at all; and the study design was RCT. Articles that reported at least 1 outcome were included and those without the outcome measures of interest were excluded. Quasi-RCT or non-RCT, observational studies, letters, comments, editorials, and practice guidelines were excluded. If the same population was reported in several publications, we retained the most informative article or complete study to avoid duplication of information.

2.3. Data extraction and quality assessment

Two authors independently reviewed all titles and abstracts of the studies identified by searchers according to the eligibility criteria described above. Full texts of articles that met the inclusion criteria were reviewed thoroughly. Disagreements were resolved by discussion to reach consensus. Data on patient characteristics (age, sex, and other baseline characteristics), intervention and outcomes were extracted in duplicate by 2 authors using a standardized form. For continuous outcomes, if 1 group was divided into several subgroups, we combined those into a single sample size and calculated mean and standard deviation (SD) according to the method introduced by the Cochrane Handbook.[21] And data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval [CI]) were converted to mean ± SD according to the Cochrane Handbook.[21] If data were not reported numerically, we extracted them by manual measurements from published figures. We only extracted the outcomes related to the oral TXA and control group if a study also reported groups of TXA in other forms.

Methodological quality and risk of bias of RCTs was assessed using a modified version of the Jadad Scale and the tools from Cochrane Handbook. The Jadad Scale contains 2 questions, one on randomization and masking, and the other on the reporting of dropouts and withdrawals.[22] The total score is 7 points, 0 to 3 points means poor quality, and 4 to 7 points means high quality. A total of 7 domains were assessed according to the standard from the instructions provided in the Cochrane Handbook: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Disagreement was resolved by a third author. Based on the information provided from included studies, each item was recorded by "Yes," "No," or "Unclear"; "Yes" indicates low risk of bias, "No" indicates high risk of bias, "Unclear" indicates lack of information or unknown risk of bias. We used the RevMan v5.3.5 to draw the risk of bias figure.

2.4. Data synthesis and analysis

Stata 12.0 (Stata Corp, College Station, TX) was used for graphical representation of the pooled data. Statistical heterogeneity was assessed by both a Cochran's χ^2 test (Q test) and an I^2 test. The primary outcomes in our meta-analysis included total blood loss, Hb drop, hematocrit (Hct) drop, drain output, and transfusion rate. Thromboembolic complications (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) were our secondary outcomes. Continuous outcomes such as Hb drop were expressed as the mean ± SD, and they were summarized using the standardized mean differences (SMD) and 95% CI. For dichotomous outcomes, the risk ratio or risk difference (RD) with 95% CI was applied. A probability of $P < .05$ was regarded as statistically significant. The assessment for statistical heterogeneity was assessed using the χ^2
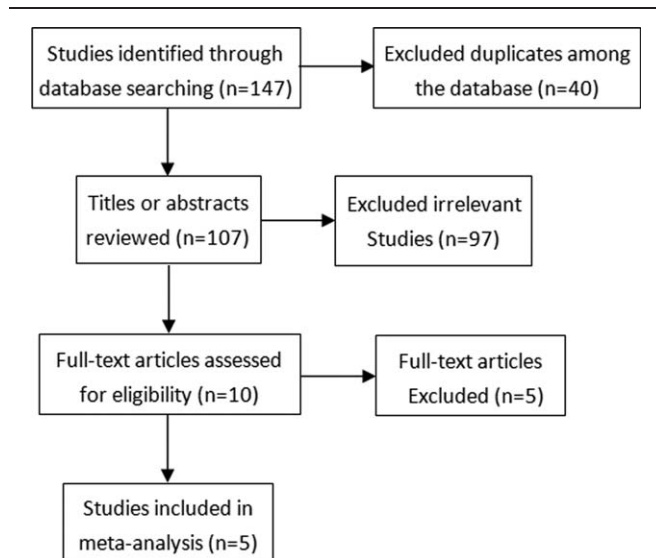
Figure 1. The selection process of this meta-analysis.

and I^2 tests. A fixed effects model was used when there was no significant statistical heterogeneity ($P > .1$ and an $I^2 < 50\%$). Otherwise, a random effects model statistical method was employed. And if there were still some huge statistical heterogeneities, a sensitivity analysis investigating the influence of every single study on the overall outcome estimate was conducted by omitting one study at each turn.

3. Results

3.1. Search result and quality assessment

A total of 147 potentially relevant articles were initially searched from the PubMed, Embase, Medline, Web of Science, and Cochrane Library databases, and 40 duplicates were discharged by EndNote. Then 97 were excluded after scrutiny of their titles or abstracts, leaving 10 articles to be evaluated through full text scrutiny according to the selection criteria and then 5 were excluded. Eventually, 5 studies[4,5,18,19,23] consisting of 55 patients were included in this meta-analysis. Figure 1 showed the progress and details of our search work. The basic characteristics of the included studies were listed in Table 1 and Table 2.[4,5,18,19,23] Totally there are 306 patients in TXA group and 302 in the control group. Participant numbers in these studies ranged from 40 to 280 patients. All the patients received primary TKA. Osteoarthritis was the main diagnosis, followed by rheumatoid arthritis. Three trials[4,5,18] used general anesthesia and the remaining trials did not mention this information. Placebo was used by 2 trials, 1 used non-active medicine[23] and the other used calcium tablets,[18] and control groups in the rest of the included researches did not receive any treatment. A pneumatic tourniquet was applied in all the included studies. Only 1 study did not describe the transfusion trigger,[5] the rest studies associated it with Hb level or Hct level or clinical symptoms. To prevent thromboembolic complications, 3 trials used enoxaparin,[4,5,23] one used rivaroxaban[18] and the rest one did not mention any preventative measures. Outcome of total blood loss was only reported in one study,[19] which was not analyzed owing to insufficient data.

The average modified Jadad score was 5 points, and the details were showed in Table 3. Risk of bias in the included studies was shown in Figure 2. Sensitivity analysis was used to determine whether modification of the inclusion criteria affected the final results.

3.2. Meta-analysis results

3.2.1. Hb drop. Three studies[18,19,23] including 260 patients in TXA group and 255 in the control group reported the outcome of postoperative Hb drop. No heterogeneity was detected in the

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Table 1					
The characteristics of included studies[4,5,18,19,23].					
Author/year	**Cases (n) (TXA/Control)**	**Male (n) (TXA/Control)**	**Mean age (year) (TXA/Control)**	**Intervention (TXA/Control)**	**Outcomes**
Zohar[4]/2004	20/20	8/7	69/73	1 g TXA at 1 hour preoperatively and the same dose at 6 hours, 12 hours and 18 hours postoperatively/None	d,e,f
Bradshaw[23]/2012	26/20	14/13	67/68	1.5 g TXA at 8-hour intervals preoperatively for 24 hours and the same dose at 6 hours postoperatively/Non-active medicine	b,c,d,e,f
Alipour[5]/2013	26/27	11/11	68/63	1 g TXA at 2 hours preoperatively and the same dose at 6 hours, 12 hours and 18 hours postoperatively/None	c,d,f
Lee[19]/2017	94/95	31/29	70/68	1g TXA at 2 hours preoperatively and the same dose at 6 hours and 12 hours postoperatively/None	a,b,d,e,f
Yuan[18]/2017	140/140	68/65	63/65	20 mg/kg TXA at 2 hours preoperatively and the same dose at 12 hours postoperatively/Calcium tablets	b,d,e,f

TXA = tranexamic acid, a = total blood loss, b = hemoglobin drop, c = hematocrit drop, d = drain output, e = transfusion rate, f = thromboembolic complications.

Table 2					
The characteristics of included studies[4,5,18,19,23].					
Author/year	**Anesthesia**	**Transfusion trigger**	**Thromboprophylaxis**	**Follow-up time**	**Jadad Score**
Zohar[4]/2004	General anesthesia	Hematocrit < 28%	Enoxaparin	3 months	5
Bradshaw[23]/2012	Not available	Hemoglobin < 7g/dL or clinical symptoms of anemia	Enoxaparin	3 months	6
Alipour[5]/2013	General anesthesia	Not available	Enoxaparin	6 weeks	4
Lee[19]/2017	Not available	Hemoglobin < 8g/dL	Not available	8.2 months	4
Yuan[18]/2017	General anesthesia	Hemoglobin < 8g/dL or clinical symptoms of anemia	Rivaroxaban	3 weeks	6

Table 3

The details of each outcome.

Outcomes	Studies (n)	Patients (n)		P	Standardized mean differences (95% CI) or risk difference (95% CI)	Heterogeneity P (I^2)
		TXA	Control			
Total blood loss[a]	1	94	95	–	–	–
Haemoglobin drop[a]	3	260	255	.000	−0.936 (−1.118, −0.754)	.803 (0%)
Hematocrit drop[a]	2	52	47	.001	−0.693 (−1.113, −0.274)	.921 (0%)
Drain output[a]	5	306	302	.000	−0.793 (−0.959, −0.628)	.184 (35.60%)
Transfusion rate[b]	4	280	275	.118	−0.087 (−0.197, 0.022)	.000 (87.20%)
Thromboembolic complications (DVT and PE) [b]	5	306	302	.719	0.003 (−0.015, 0.021)	.997 (0%)

CI = confidence interval, TXA = tranexamic acid, a = measured by Standardized mean differences, b = measured by risk difference.

studies (P=.803; I^2=0%), so the fixed-effects model was used. The pooled results showed that the Hb decline was significantly lower in TXA group than in the control group (SMD=−0.936, 95% CI: −1.118 to −0.754, P=.000; Fig. 3).

3.2.2. Hct drop. The Hct drop was reported in 2 studies[5,23] involving 99 patients. A fixed-effects model was applied because no significant heterogeneity was found among these studies (P=.921; I^2=0%). The results showed the TXA group had lower Hct drop than the control group (SMD=−0.693, 95% CI: −1.113 to −0.274, P=.001; Fig. 4).

3.2.3. Drain output. The results of drain output were assessed in all of the included studies, and all were reported the results in 24 hours after the operation except one,[18] which in 48 hours. The fixed-effects model was preformed due to the small heterogeneity (P=.184; I^2=35.6%). Meta-analysis showed that there was significant difference in drain output between TXA groups and control groups (SMD=−0.793, 95%CI: −0.959 to −0.628, P=.000; Fig. 5).

3.2.4. Transfusion rate. All studies reported the requirement of blood transfusion. There was significant heterogeneity among studies (P=.000; I^2=87.2%), so random-effects model was applied to pool the effect size. Meta-analysis revealed no significant difference in transfusion rate between the 2 groups (RD=−0.087; 95% CI:−0.197 to 0.022; P=.118; Fig. 6A). Sensitivity analysis was conducted to find out the source of heterogeneity. The results indicated that no study influences the final large heterogeneity, and the results did not show materially difference with that from the original analysis when omitting any of the included studies (Fig. 6B).

3.2.5. Thromboembolic complications. All of the included studies reported the incidence of DVT and PE. Pooled results indicated that there is no significant difference between the 2 groups (RD=0.003, 95% CI:−0.015 to 0.021, P=.719, Fig. 7) in a fixed-model. There is no heterogeneity between the trials (P=.997; I^2=0%).

4. Discussion

Intravenous and intraarticular administrations of TXA have been reported to be effective on reducing blood loss in TKA patients. However, 1 previous study reported a complication of anaphylactic shock in patients receiving intravenous TXA during coronary artery bypass graft surgery.[24] The topical form may be associated with the theoretical risk of staphylococcal infection and sepsis.[12] And the topical administration of TXA have a risk of forming clots in the knee joint and blocking drainage tubes.[18] The oral form is easy to access and administrate and its absorption is quick and complete. Additionally, its cost could be decreased dramatically. Those reasons led researchers to carry out studies to evaluate the effectiveness and safety of oral TXA. In order to provide a convincing conclusion, we conducted this meta-analysis.

To our knowledge, this is the first meta-analysis of RCTs comparing the efficacy and safety of oral TXA with control for the reduction of blood loss in patients after TKA. A total of 5
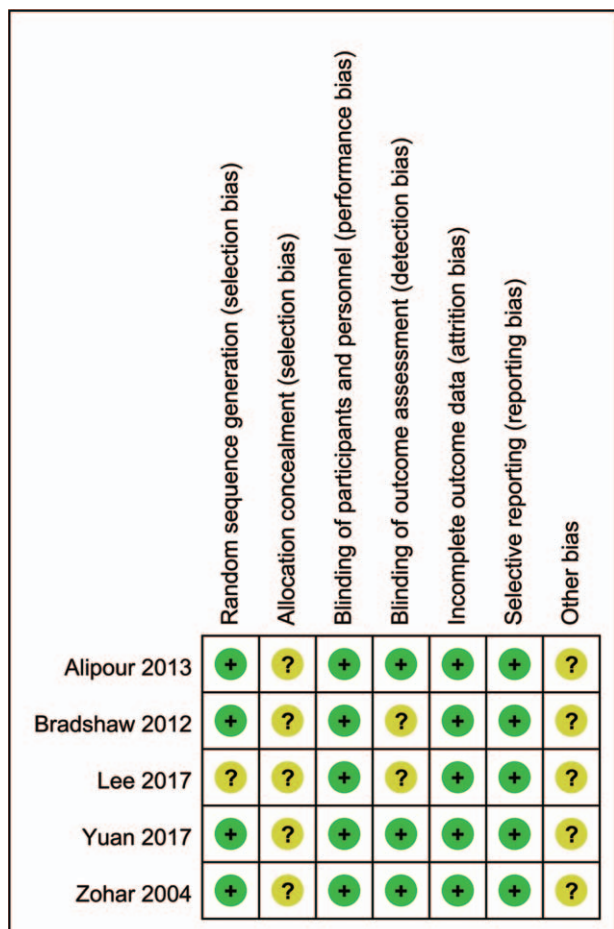

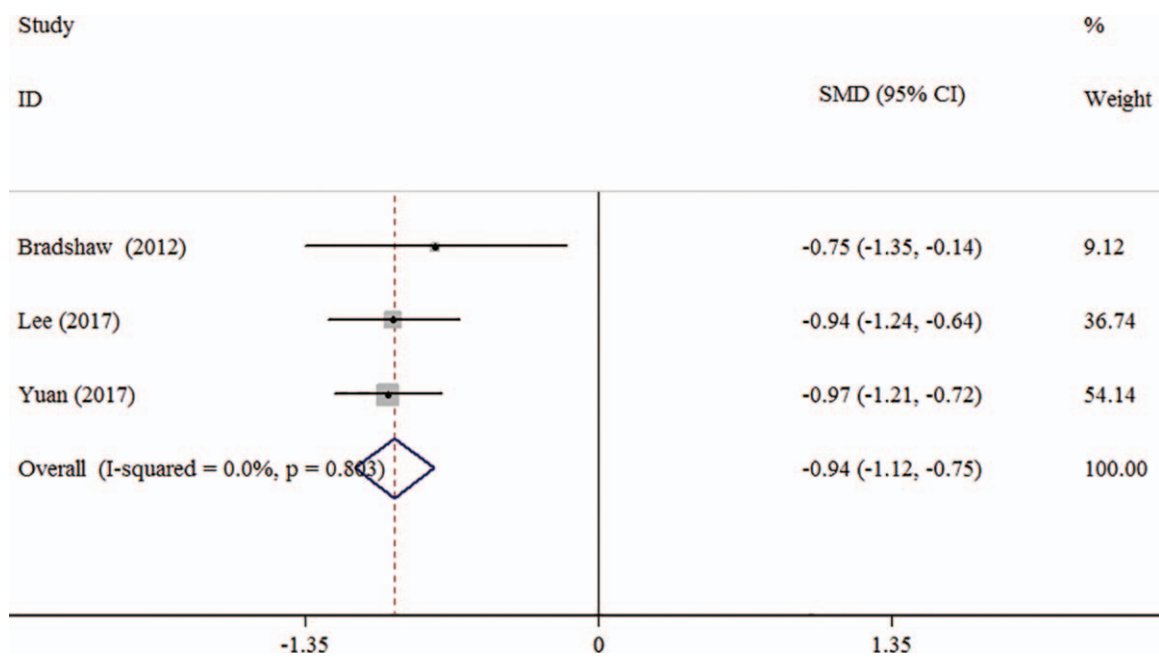**Figure 2.** Risk of bias assessment of the included studies.

Figure 3. Forest plot of hemoglobin drop in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences].

studies were ultimately included in our meta-analysis. Based on the pooled results, oral TXA was associated with significant reduction in Hb drop, Hct drop, drain output compared with the results from control group. However, no significant differences were found in the transfusion rate and thromboembolic complications between the two groups. The result of total blood loss was only reported by Lee et al.[19] They indicated that the total blood loss was significantly lower in oral group than in control group. Owing to the insufficient date, we could not pool the outcome of total blood loss.

Several studies have demonstrated that oral TXA could significantly decrease the Hb drop, Hct drop, and drain output after TKA. Our findings were consistent with most of the findings from previously published studies. In a prospective cohort study[25] in TKA patients, McGrath et al indicated the Hb drop for the oral TXA group was significantly less compared with the control group. Fillingham et al[26] also revealed that the Hb drop for the oral TXA group was significantly lower than that for the intravenous TXA group, which has been reported to be effective and safe in reducing blood loss and lowering Hb drop in many trails and meta-analysis. However, they did not demonstrated

Figure 4. Forest plot of hematocrit drop in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences].

significant difference when compared drain output. Only 2 studies[5,23] assessed the Hct drop, and they all indicated the significant difference between the TXA group and the control group. We just found 1 study[27] that evaluated the fall of Hct in patients receiving oral TKA and THA, and they reported no significant reduction. Further studies with a larger sample size are required to clarify this issue.

We did not find a significant difference in the rates of transfusion in TKA patients when compared oral TXA group with the control one. McGrath et al[25] also evaluated this outcome, and they found the number of patients transfused was significantly lower in the TXA group versus the control group. We found significant heterogeneity among the included studies. The methodological quality of our included studies was relatively high, so we thought the result was derived from clinical heterogeneity. Clinical heterogeneity may be caused by blood transfusion triggers, one study[5] did not mention the standard of transfusion, another one[4] used the Hct level to make a decision to conduct the transfusion and the rest of those employed either the Hb level or clinical symptoms to assess anemia. Clinical heterogeneity may also be caused by different surgical approaches. Three studies[18,19,23] preformed TKA through medial parapatellar approach; the rest did not mention the approach. Then, different TXA doses were used by those studies ranging from 1 to 1.5 g, which may be another source of clinical heterogeneity. However, subgroup analysis could not be performed for lack of adequate data. Sensitivity analysis indicated that no study influenced the final large heterogeneity and meta-analysis results.

DVT and PE, 2 serious complications after TKA, are major health concerns and are responsible for significant mortality, morbidity, and resource expenditure.[28,29] And an important finding of this meta-analysis was that oral TXA did not appear to increase the risk of DVT and PE compared with the control groups. However, the difference screening protocols were applied in those studies. Three studies[4,18,19] used clinical symptom and Doppler ultrasound to detect thromboembolic complications, the
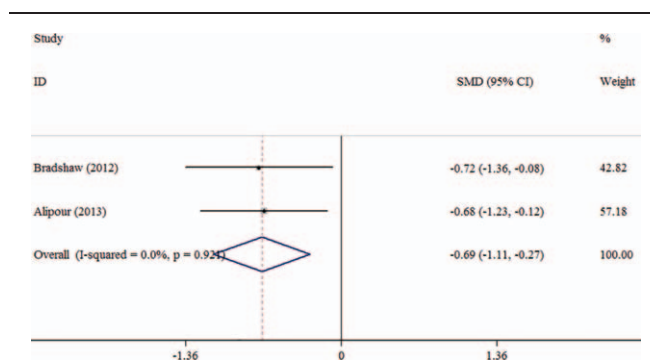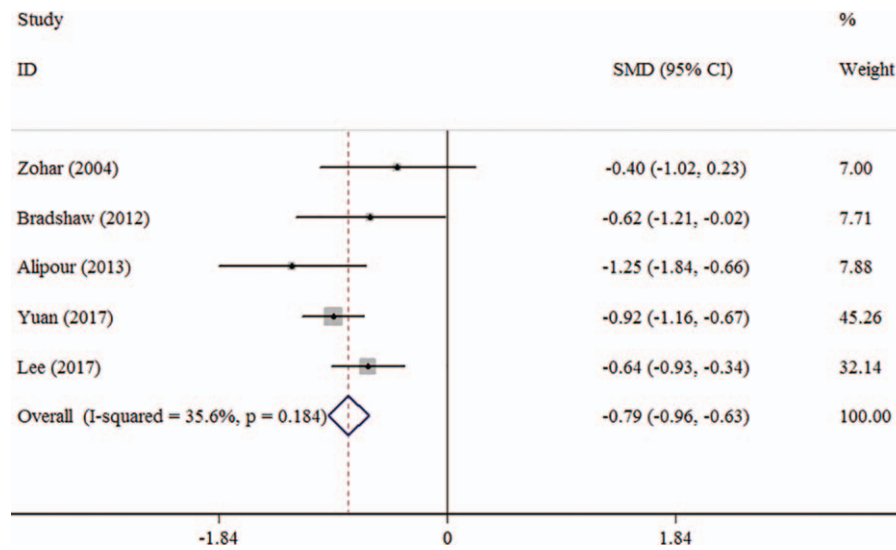
Figure 5. Forest plot of drain output in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences].

rest 2 only clinically examined the result but did not evaluate the asymptomatic DVT and PE. Furthermore, follow-up time and prophylaxis varied from each other, which also may influence the conclusion. Our study did not show any heterogeneity in DVT and PE among studies although the differences mentioned above.

The consensus has not been determined on the most efficacious timing and dose protocol for TXA administration, and it is particular rare for the oral usage. In our included articles, Zohar et al[4] used a regimen of 1 g oral TXA 1 hours before surgery and then two doses at 6 hours, 12 hours, and 18 hours postoperatively.
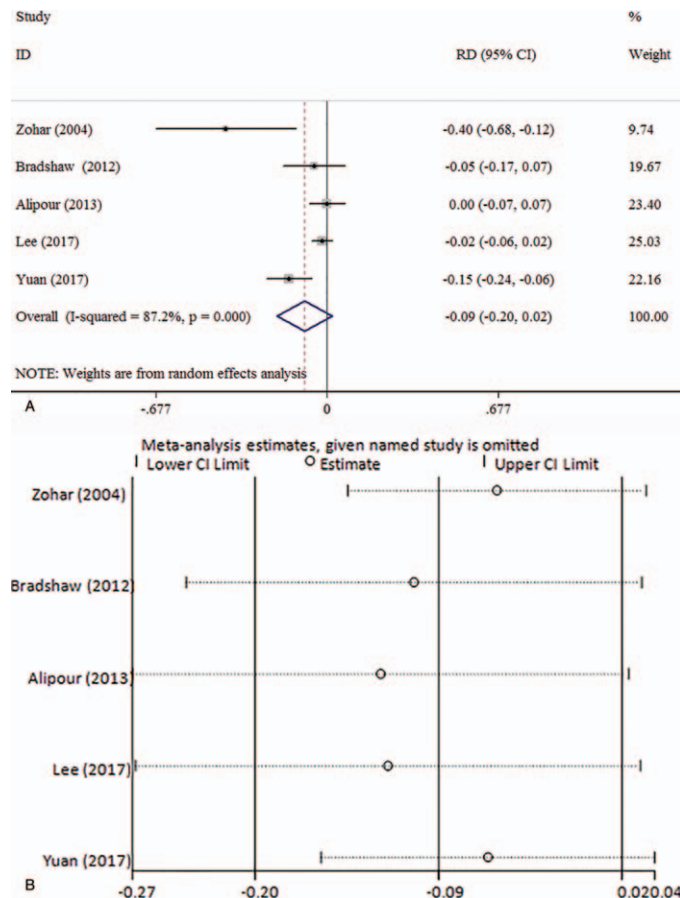
Figure 6. A, Forest plot of transfusion rate in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences]. B, Sensitivity analyses plot of transfusion rate in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences].
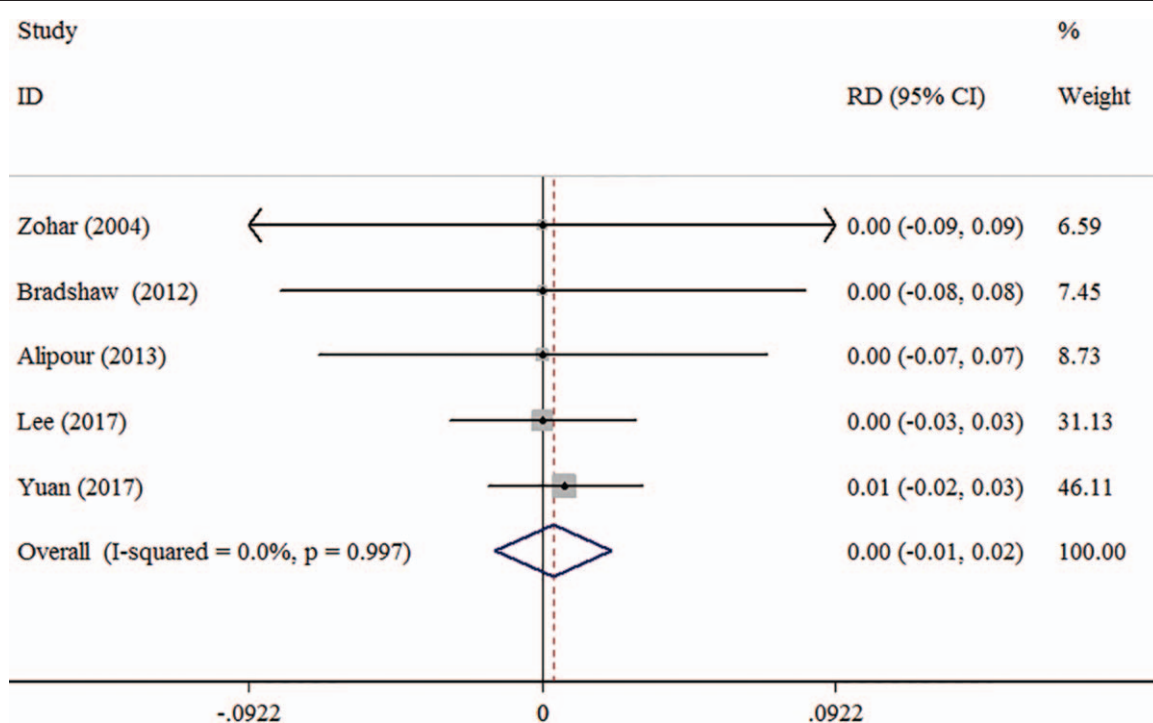
Figure 7. Forest plot of thromboembolic complications in total knee arthroplasty. [CI = confidence intervals, SMD = standardized mean differences].

Alipour et al[5] applied a similar protocol, but the first dose was used at 2 hours preoperatively. And the only difference between the studies of Lee et al[19] and Alipour et al was that Lee et al employed 2 postoperative doses instead of 3. Bradshaw et al[23] used a regimen of four 1.5 g doses given 6-hourly with the first 3 doses given preoperatively. Yuan et al[18] used 20 mg kg^{-1} oral TXA at 2 hours preoperatively and the same dose at 12 hours postoperatively. Because of the similar protocol, we were not able to identify the optimum one. Further studies with high quality were needed to explore the optimal dose and administration of oral TXA in TKA.

We only found one meta-analysis[30] comparing oral versus intravenous application of TXA in total knee and hip arthroplasty. However, we think our study provided the more exact conclusion for patients after TKA. And all of the studies included in our article were RCTs, which had a more convincing persuasive result. Moreover, our results included the Hct drop and drain output after the surgery, which could be a supplement for the previous meta-analysis.

In our study, most of the trials were of high quality, which makes the conclusions drawn from this meta-analysis more reliable, but various limitations presented in our review should not be ignored. First, our analyses were based on a limited number of studies. Although all of the studies had adequate sample size according to the pre-study statistical analysis, most of them enrolled small number of participants. And total blood loss was not evaluated because of insufficient data in included studies. Second, the variations in the administration of TXA, anesthesia methods, operation modes and follow-up time in the included studies may have some influence on the final conclusions. Finally, any uncontrolled confounding factors that were inherited from the original studies might affect our final results, which is also a common problem with most evidence-based medicine.

5. Conclusions

This meta-analysis of the current literatures indicates that oral TXA administration leads to a statistically significant reduction in Hb drop, Hct drop, and drain output, without increasing the risk of thromboembolic complications compared with the control group in patients undergoing TKA. No significant differences were seen in the transfusion rate between the 2 groups. However, our current study with some limitations such as the small sample size only provided limited quality of evidence, confirmation from further systemic reviews and meta-analyses with large-scale, well-designed RCTs are required to illustrate the efficacy and safety of oral TXA in patients following TKA.

Author contributions

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