

Efficacy and safety of tranexamic acid in total hip replacement

A PRISMA-compliant meta-analysis of 25 randomized controlled trials

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Abstract

Background: Hip osteoarthritis is one of the most prevalent musculoskeletal degenerative diseases in elderly. Total hip arthroplasty (THA) is the most effective surgical treatment for end stage hip osteoarthritis. Tranexamic acid (TA) is a potent drug to reduce surgical blood loss in surgery, therefore, as a potential drug for application in THA.

Objectives: To identify the combined efficacy of TA administration in THA. A meta-analysis including 25 randomized controlled trials was conducted for generating synthesized effects.

Methods: This meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines for reporting systematic reviews and meta-analysis. A total of 25 Randomized controlled trials (RCTs) were included for meta-analysis.

Results: The pooled results illustrated that total blood loss, intraoperative blood loss, postoperative blood loss, hemoglobin drop, transfusion rate, and average hospital stay were significantly lower than controls (standardized mean difference or odds ratio (OR) (95%CI): $-0.87, (-1.13, -0.61)$, $-0.68, (-0.96, -0.39)$, $-1.41, (-2.24, -0.59)$, $-1.11, (-1.63, -0.58)$, $0.28, (0.20, -0.38)$, $-0.17, (-0.49, 0.14)$, $P < .05$, respectively). Moreover, TA acts efficiently without increasing risk of thromboembolic events with $OR = 1.14$, $95\%CI = 0.50-2.62$, $P = .75$. Subgroup analysis indicated no statistically significant differences between a higher dose of topical TA ($\geq 2g$ or 15 mg/kg) or a lower dose ($< 2g$ or 15 mg/kg).

Conclusion: The findings indicated that TA is clinically effective and safe in patients receiving total hip arthroplasty.

Abbreviations: CI = confidence intervals, DVT = deep vein thrombosis, HB = hemoglobin, ICC = intraclass correlation coefficient, IV = intravenous, M-H = Mantel-Haenszel, OR = odds ratio, PE = pulmonary embolism, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SMD = standardized mean difference, TA = tranexamic acid, THA = total hip arthroplasty, WMD = weighted mean difference.

Keywords: blood loss, meta-analysis, total hip arthroplasty, tranexamic acid

1. Introduction

The increasing prevalence of total hip arthroplasty (THA) is simultaneously associated with considerable blood loss,^[1-3] thereby increasing a patient's risk of blood transfusion.^[4] Blood loss often leads to significant postoperative anemia predisposing to an increased risk for cardiopulmonary events, transfusion

reactions, and increased health care costs.^[1,5,6] Allogenic transfusions may also increase patient's risk for postoperative infection. Tranexamic acid (TA) is a synthetic amino acid^[7] which competitively blocks the lysine binding sites on plasminogen and thereby slows the conversion of plasminogen to plasmin.^[8] TA may be administered intravenous (IV)^[9] or topically^[10-13] in the surgical wound. TA has been reported to reduce blood loss and be cost-effective^[6] in many areas of orthopedic surgery, such as spinal surgery as well as knee and hip arthroplasty.^[4,14]

TA is widely utilized in THA surgery which perhaps reduces the risk of developing systemic thrombogenesis.^[15] A series of recent studies have sought to explain outcomes of TA in total joint arthroplasties. Most protocols have involved intravenous delivery of TA, revealing impressive results.^[16] An oral form of TA has also been shown to be clinically effective. While these studies have not shown adverse events caused by TA such as increased thromboembolic events,^[4] this continues to be a concern, and is perhaps why TA implementation has been slow to progress. An increasing number of researches indicate that intraarticular injection or topical administration^[10,11,18] may provide some advantages; these include potentially reduced costs with a single injection, surgeon control, and localization and concentration of the drug to the surgical site.^[12] Topical

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application increases pharmacologic efficacy as well as reduces the risk of developing systemic thromboembolic events at the same time.

Inspired by the safety concerns with intravenous administration, there has been a growing interest in the utilization of TA associated with major orthopedic surgeries. Thus, intravenous or topical TA application can directly target the source of bleeding, which is the local increase in fibrinolytic activity. However, the literature with regard to the definite measurements of TA efficacy and risk remains to be solved. Thus we undertook a meta-analysis of the literature in order to investigate the safety and efficacy of the intravenous or topical TA administration in patients receiving THA.

2. Materials and methods

Our systematic review and meta-analysis was conducted strictly following the guidelines of the guidelines in PRISMA.^[19] Since all the data of this meta-analysis were collected from published literature and no patient consent were need, the ethical approval and written consent were not necessary in this study.

2.1. Outcome measurements

The primary outcome measure was to review the efficacy of intravenous or topical TA in THA by reviewing the proportion of patients who received blood transfusion, the amount of blood loss; hemoglobin (HB) and hematocrit drop, to check the safety of TA administration by reviewing complications such as deep vein thrombosis (DVT) and average hospital stay, etc.

2.2. Literature search

Two of the authors (JZ, YZ) searched the Web of Science, PubMed Medline; Embase; Cochrane Library, and the Chinese Biomedical Library to retrieve all relevant articles, using the terms tranexamic acid, AND total hip arthroplasty, OR topical, OR intravenous. The titles of the articles and their abstracts were then reviewed independently. When there was an issue requiring clarification the full article was retrieved for further scrutiny. The bibliographies of identified articles, including relevant reviews and meta-analyses were manually searched for potential eligible reports. No language restrictions were set during search process.

2.3. Criteria of eligibility

Studies selected were randomized controlled trials (RCTs) and prospective comparative studies that fulfilled the following inclusion criteria: (1) studies enrolled adult patients undergoing a THA regardless of the etiology and type or size of prosthesis used; (2) more than 20 patients were included; (3) the full text of each article was available. Exclusion criteria: (1) review articles, case reports, animal researches and no case-control design; (2) studies regarding other types of CP and patients who were previously diagnosed with other diseases that could lead to infertility; (3) patients with a mean age of less than 12 years or more than 60 years.

2.4. Extraction of data

Every citation was independently reviewed by 2 reviewers (JX, PL) strictly following PRISMA flowchart (Fig. 1). Most citations could be excluded due to irrelevance of topics provided by their

title or abstract. Otherwise, the complete manuscript was obtained and carefully scrutinized by the 2 reviewers. Any retrospective studies or nonrandomized researches were excluded then. Disagreement between them was resolved by consensus. Relevant information on author's name, publication year, Journal name, type of study, methods of blood conservation, preoperative use of anticoagulants, number of patients, dose of TA, postoperative thrombophylaxis, blood loss, transfusion, postoperative complications, and duration of follow-up were carefully scrutinized.

2.5. Study quality

The methodological quality of each component study was assessed by using Jadad score.^[20] This scale comprises a list of 4 criteria, (each one conferring 0–2 points). We only include articles with Jadad score >2. The agreement between the 2 reviewers was evaluated with the intraclass correlation coefficient (ICC).

2.6. Statistical analysis

The meta-analysis program of the Cochrane Collaboration (Review Manager 5.3 and STATA 12.1) was employed for quantitative analysis, using the inverse variance statistical method and either a fixed or random effects model, depending on the absence or presence of statistical heterogeneity, accordingly. Binary outcome data were summarized using odds ratio (OR) and 95% confidence intervals (95% CI). Continuous outcomes were analyzed using the weighted mean differences and their respective 95% CIs. Both weighted mean difference (WMD) and standardized mean difference (SMD) were recorded. Summary estimates of the overall effect of treatment are provided in the form of a forest plot. The Mantel-Haenszel (M-H) method was utilized to synthesize combined result using fixed or random effect models depending on sample heterogeneity.^[21] Subgroup analysis was introduced in every parameter, dosage ≥ 2 g or 15 mg/kg was defined as high dose and vice versa. The presence of statistical heterogeneity was assessed through Q and I^2 statistics, with a value of $I^2 > 50\%$ considered substantial heterogeneity. Publication bias was tested by generating Begg's funnel plot and Egger's regression plot. Sensitivity analysis was undertaken by sequentially omitting every study to find out the independent influence of each study on the total effective size.

3. Results

3.1. Total blood loss

Relevant data were available in 15 component studies including 1073 patients that had been equally allocated into treatment and control groups (Fig. 2A). Pool data showed statistically significant less total blood loss in the TA group compared with the CG with weighted mean difference: -348.81 mL, 95% CI: -434.59 mL, -263.02 mL, $P < .001$ and SMD = -0.87 , $(-1.13, -0.61)$. Nevertheless, these results should be interpreted with caution due to the presence of significant statistical heterogeneity ($\text{Chi}^2 = 35.8$, $\text{df} = 14$, $P < .001$, $I^2 = 68\%$)

3.2. Intraoperative blood loss

A total of 11 studies with 722 patients concerning intraoperative blood loss record are meta-analyzed (Fig. 2B). It shows that the

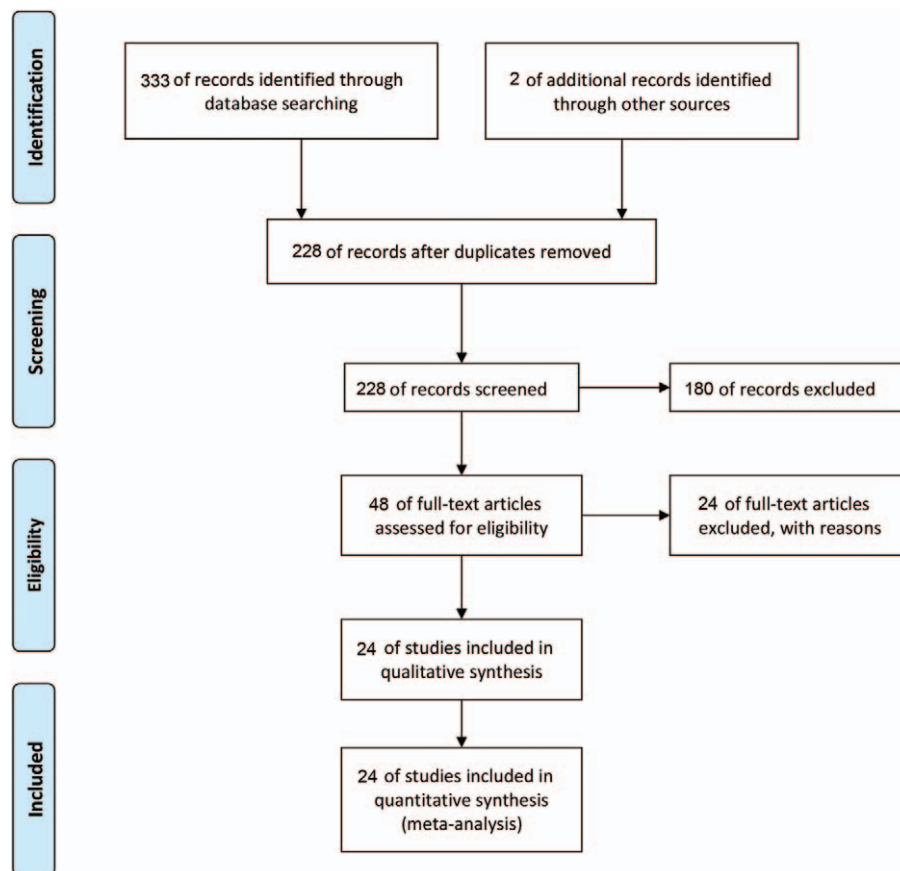


Figure 1. Flow chart of study selection.

TA groups have a less amount of intraoperative blood loss than control groups with weighted mean difference: -99.48 mL, 95% CI: -152.51 mL, -46.44 mL, $P < .001$ and SMD = -0.68 , $(-0.96, -0.39)$. These results should be interpreted with caution due to the presence of significant statistical heterogeneity ($\text{Chi}^2 = 24.7$, $\text{df} = 10$, $P = .006$, $I^2 = 60\%$),

3.3. Postoperative blood loss

A total of 11 studies with 718 patients concerning postoperative blood loss record are meta-analyzed (Fig. 2C). It shows that the TA groups have a less amount of postoperative blood loss than control groups with weighted mean difference: -211.39 mL, 95% CI: -279.66 mL, -143.11 mL, $P < .001$ and SMD = -1.41 , $(-2.24, -0.59)$. These results should be interpreted with caution due to the presence of significant statistical heterogeneity ($\text{Chi}^2 = 90.25$, $\text{df} = 10$, $P < .001$, $I^2 = 89\%$),

3.4. Transfusion rate

Relevant data for transfusion were obtained from 20 component studies, including 1219 patients (661 patients in the TA group and 658 patients in the CG) (Fig. 2D). The pooled estimate of effect size for transfusion rate showed a significantly lower risk of transfusion requirements in the TA group compared with the CG (odds ratio = 0.28 , $P < .001$, 95% CI = $0.20-0.38$) in the absence of statistical heterogeneity ($\text{Chi}^2 = 15.63$, $\text{df} = 16$, $P = .55$, $I^2 = 0\%$).

3.5. Hemoglobin drop

This outcome was described in 5 papers (224 and 175 patients allocated in TA and control group, respectively) (Fig. 3A). The summarized estimate of effect size indicated that topical use of TA reduced the maximum postoperative Hb drop at approximately 1 g/L: weighted mean difference = -10.81 g/L, 95% CI = -14.03 g/L, -7.58 g/L, $P < .001$ and SMD = -1.11 , $(-1.63, -0.58)$ in the absence of statistical heterogeneity ($\text{Chi}^2 = 7.64$, $\text{df} = 4$, $P = .11$, $I^2 = 48\%$)

3.6. Average hospital stay

A total of 6 studies with 593 patients concerning average hospital stay are meta-analyzed. It shows that the TA groups manifest no statistical difference concerning hospital stay with control groups (Fig. 3B) with WMD: -99.48 mL, 95% CI: -152.51 mL, -46.44 mL, $P < .001$; SMD = -0.17 , $(-0.49, 0.14)$. These results should be interpreted with caution due to the presence of significant statistical heterogeneity ($\text{Chi}^2 = 24.7$, $\text{df} = 10$, $P = .006$, $I^2 = 60\%$). Subgroup analysis revealed high dose of TA ($z = 3.22$, $P = .001$) may relatively delay hospital stay than low dose of TA ($z = 1.84$, $P = .066$).

3.7. Deep vein thrombosis

Relevant data for transfusion were obtained from 21 component studies, including 1365 patients (685 patients in the TA group and

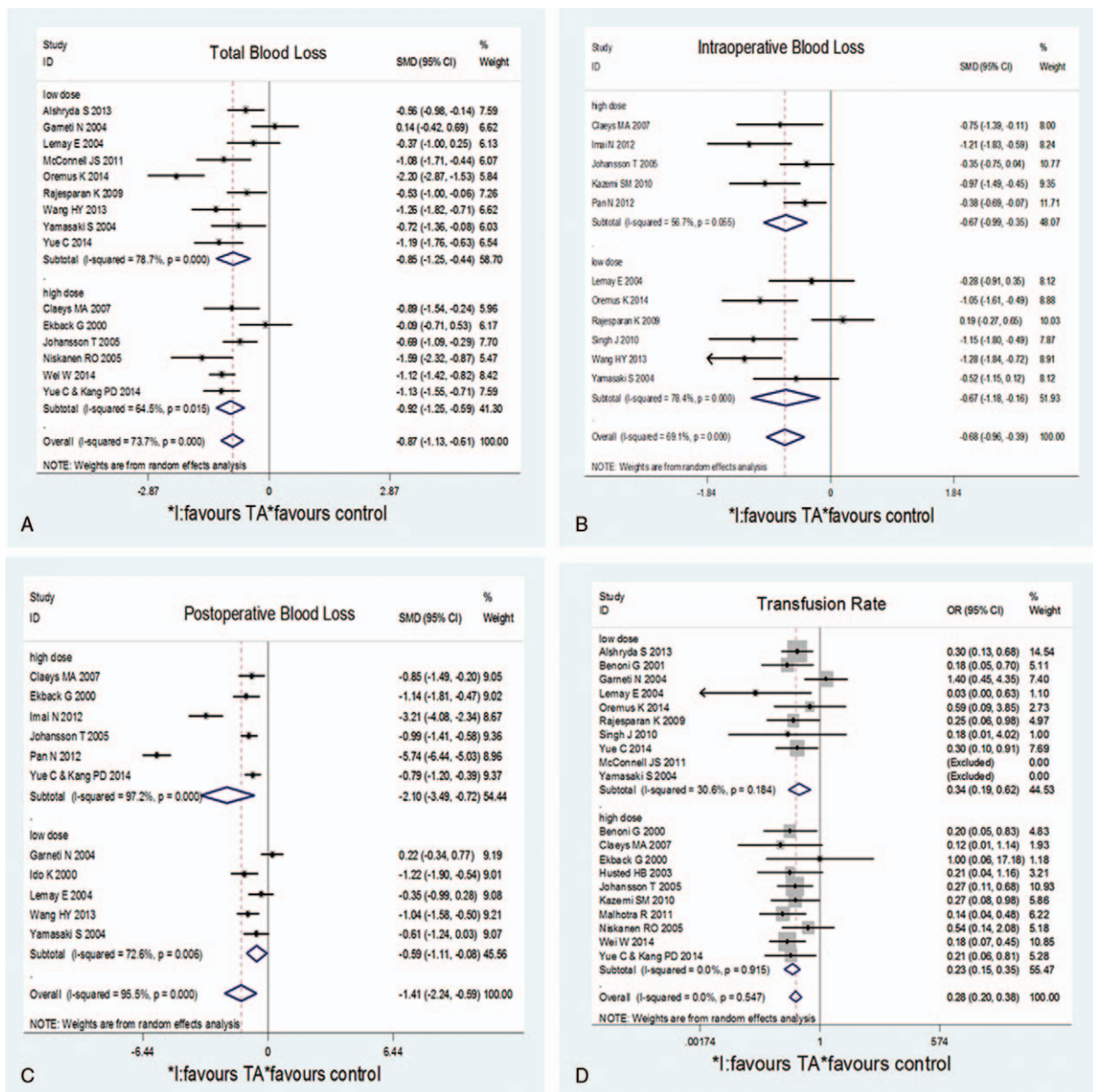


Figure 2. Forest plot of (A) total blood loss, (B) intraoperative blood loss, (C) postoperative blood loss, and (D) transfusion rate after THA. THA=total hip arthroplasty,

680 patients in the CG) (Fig. 3C). The pooled estimate of effect size for transfusion rate showed the risk of DVT development was not significantly elevated in the TA group compared with the CG (OR=1.14, $P=0.75$, 95%CI=0.50–2.62) in the absence of statistical heterogeneity ($\text{Chi}^2=4.54$, $\text{df}=8$, $P=0.87$, $I^2=0\%$).

3.8. Publication bias

For each main outcome of interest respective funnel plots were generated for evaluation of publication bias. Begg’s funnel plot did not show any substantial asymmetry (Fig. 4A). Egger’s regression test indicated little evidence of publication bias ($P > 0.05$).

3.9. Sensitivity analysis

We omitted 1 study sequentially, and the calculated combined SMD for the remaining studies yielded consistent results. In the

overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (Table 1) (Fig. 4B).

4. Discussion

Perioperative bleeding stands as a significant concern in major orthopedic surgery due to large exposure of surgical area and activation of fibrinolysis.^[3,9,22] As a synthetic amino acid, TXA is a competitive inhibitor of plasminogen and therefore acts to decrease fibrinolysis.^[23,24] Due to the high efficacy of blood loss reduction and safety, surgical implication of TA is broadly distributed especially in joint arthroplasties. A series of randomized clinical trials were conducted to investigate the relative benefit and potential risk of TA utilization. For the primary outcomes, the total blood loss, intraoperative blood loss, postoperative blood loss are significantly reduced in TA group

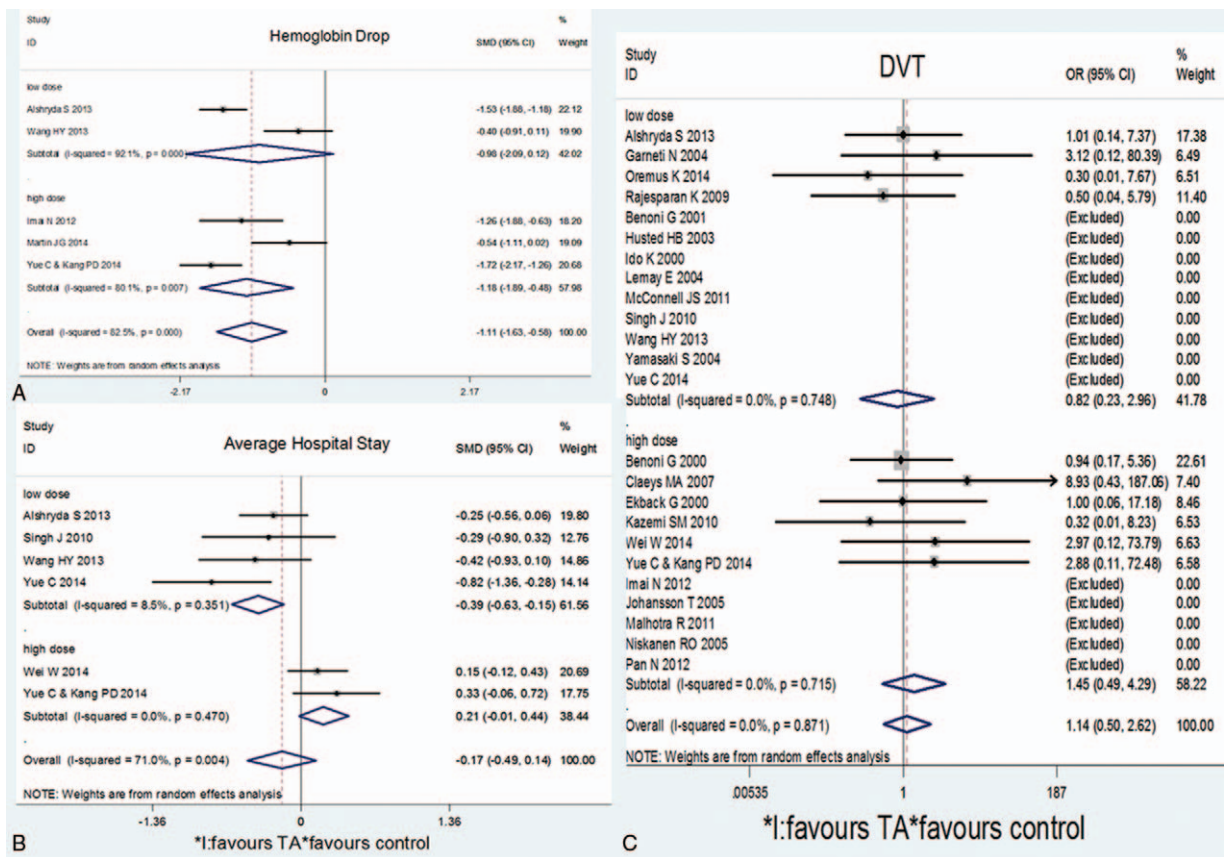


Figure 3. Forest plot of (A) hemoglobin drop, (B) average hospital stay, and (C) DVT rate after THA. DVT = deep vein thrombosis, THA = total hip arthroplasty,

than in control groups.^[25] As with transfusion rate and maximum hemoglobin drop measurements, TA administration group also show preferred performance compared with control groups. Since transfusion alone may raise a series of problems like additional expenditure, transfusion associated infections and transfusion reactions, etc. As a reason, TA is highly recommended in revision THA where bleeding may predominately outweigh primary THA due to larger exposure of cancellous bone.^[26]

Hospital stay^[27] is determined by various factors majorly including surgical complications like DVT, PE (pulmonary embolism), and infections. Although our total effect confirmed TA administration would not significantly influence hospital stay, subgroup analysis revealed that higher. Furthermore, cost-benefit analysis showed that TA may reduce \$8372.66 per 100 patients based on transfusion cost alone.^[19] Greater healthcare savings may be recognized if variables such as transfusion complication or infection rates are included in the cost analysis.^[28] For DVT risk, TA theoretically elevates the opportunity for developing hypercoagulation.^[5] Many orthopedic surgeons remained cautious about the risk of symptomatic DVT events particularly when less aggressive chemical prophylaxis methods such as aspirin or warfarin with a target INR of less than 2.5 were needed after THA. Although our result indicates that TA might not elevate risk of developing DVT, we did not include result of pulmonary embolism or other rare vascular complications.

As with the method of administration, the majority of studies choose intravenous administration.^[26] It is hypothesized that intravenous TA is distributed throughout the circulation thereby

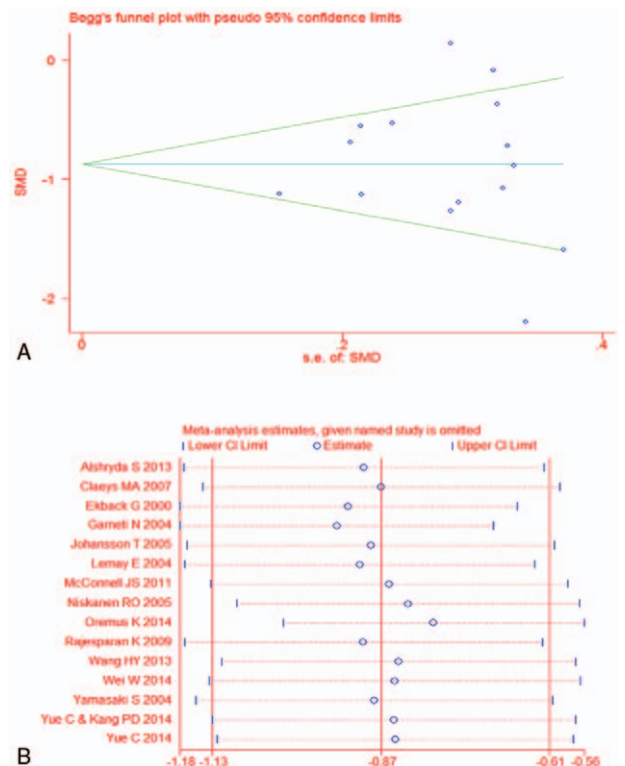


Figure 4. (A) The Begg funnel plot and (B) sensitivity analysis.

Table 1**Basic characteristics of included citations.**

Citation	Size	Intervention	Control	Thromboprophylaxis	Transfusion criteria	Jadad score
Benoni et al ^[1]	20/19	IV:10 mg/kg at end of operation + again 3 hours later	S	Klexane	Clinical condition	5
Benoni et al ^[3]	18/20	IV: 10 mg/kg - max=1 g over 5–10 min before operation started.	S	Klexane	Clinical condition	5
Claeys et al ^[29]	20/20	IV: 15 mg/kg.	S	Fraxiparine.	Hb < 85 g/L or Hemocrit < 27%	5
Ekback et al ^[2]	20/20	IV: (1)10 mg/kg before surgery, for 10 h. (2)10 mg/kg 3 h after surgery	S	LMWH	Hemocrit < 27%	4
Garneti and Field ^[8]	25/25	IV: 10 mg/kg.	S	Stockings + pumps	N/A	5
Husted et al ^[22]	20/20	IV: 10 mg/kg for 10 min, 15 min prior to incision + 1 mg/kg/h for 10 h	S	LMWH	Hb < 25% + clinical symptoms	5
Ido et al ^[4]	20/20	IV: 100 mg before and after surgery	Blank	N/A	N/A	3
Imai et al ^[25]	22/26	IV: 1 g 10 min before surgery, 1 g 6 h after surgery	S	Enoxaparin	Hct changes	4
Lemay et al ^[17]	20/19	IV: 10 mg/kg prior to surgery. 1 mg/kg/h until wound closure.	S	Dalteparin	90 g/L or 70 g/L dependent on patient.	4
Martin et al ^[18]	25/25	IV:2 g before closure	S	N/A	N/A	4
McConnell et al ^[15]	22/22	IV: 10 mg/kg when surgery starts	S	Stockings and aspirin	Hct changes	3
Oremus et al ^[23]	20/22	IV: 1 g before surgery	S	Enoxaparin	HB<80 g/L, clinical condition	5
Singh et al ^[16]	21/21	IV: 10 mg/kg 10 min before surgery	Blank	N/A	HB<85 g/L	3
Wei and Wei ^[12]	101/100	IV: 3 g 10 min before incision	S	LMWH	HB<90 g/L	5
Yamasaki et al ^[9]	20/20	IV: 1 g 5 minutes prior to operation.	Blank	N/A	N/A	4
Yue et al ^[13]	52/49	Topical: 1 g before incision, 1 g for acetabulum, 1 g for femoral canal	Blank	LMWH, foot pumps	HB<70 g/L, clinical	6
Yue et al ^[13]	31/26	IV: 10 mg/kg 10 min before incision	Blank	LMWH, foot pumps	HB<70 g/L, clinical	5

IV = intravenous, LMWH = low molecular weight heparin, S = saline.

reducing its therapeutic concentration at the bleeding site of, while topical TA is predominantly distributed in the joint cavity and thus reaches a higher therapeutic concentration at the site of bleeding. But for THA, intraoperative blood loss could be systemically minimized when delivering TA intravenously prior to surgical incision.^[8,29] Also only a part of trials have reported the effect of topical TA in THA. It was not possible to pool these study findings because of their different modes of reporting. However, there was a smaller trend towards reduced blood loss and transfusion. This is expected because TKA is frequently performed using a tourniquet which causes negligible intraoperative blood loss but significant postoperative blood loss to use topical TA. Concerning the preferred dose of TA, we introduce high dose and low dose of TA administration into subgroup analysis to define the dose–effect relationship. In a previous review majorly on TKA,^[30] a larger and more homogeneous effect on blood transfusion was found greater reductions in blood loss and transfusion when increasing TA dose. But in our results, high dose and low dose only manifests a slight difference in developing DVT. The optimum homogeneous dose of topical TA to reduce blood loss and the rate of transfusion needs further study. There is a tendency to utilize TA in a conjoined way combining local and intravenous administrations. The advantage of this method was explainable since local administration lowers adverse effect like DVT and PE, etc. Moreover, local intraoperative TA administration could help reduce joint swelling, improve wound-healing, and accelerate rapid rehabilitation progress.

For the statistical analysis part, we utilized sensitivity analysis to reduce the heterogeneity raised in different studies considering the relative broad spectrum of patients and studies we included.

We also introduce subgroup analysis by subdividing the patients into low dosage and high dosage groups. By analyzing all the parameters in the pooled data, we claimed that higher dose of TA administration was more beneficial without raising safety issues like PE and DVT. Nevertheless, limitations of this meta-analysis still wait for further investigations to fill the gap. Firstly, some of the parameters like complications other than DVT were not recorded or combined because of the rare prevalence like pulmonary embolism, superficial or deep infections, prosthesis dislocations, etc. Although TA administration did not elevate DVT risk, it might be insufficient to detect longer term safety issues, such as accelerated wear of the joint, hip functional scores or life quality measurements. Secondly, some of the pooled results are with relatively large heterogeneities. These heterogeneities mainly originate in 3 aspects: (1) Clinical diversity that comes from the clinical aspect of diseases, different clinical interventions, differences in the results of measurement. (2) Methodological diversity that are derived from the differences in trial design, risk bias, such as randomization, blindness, sample size, research objectives, outcome definitions, and differences in measurement methods. (3) Statistical diversity that include sampling errors and the existence of various biases. Fortunately, for some of the parameters like postoperative blood loss, shows a large effect size favoring treatment groups even with a considerable heterogeneity. Future homogeneous studies with larger sample size are required to update the meta-analysis pool to reduce these heterogeneities. Thirdly, biomechanical studies should be conducted to explore the longer term effect of tranexamic acid on the mechanical performance of the replacement joint since revision THA may be another challenge for patients and doctors.

5. Conclusion

This meta-analysis showed a statistically significant reduction of blood loss, transfusion requirements, and hospital stay with intravenous or topical use of TA in THA, without any additional thromboembolic risk. The relative high or low dose does not significantly influence the efficacy or risk of applying. However, the clinical importance of the respective estimates of effect size is equivocal.

6. Author contributions

JZ and YZ searched and evaluated citations, PL WS, and MZ conducted statistical analysis. YH, YZ wrote the main manuscript; JZ prepared all the figures. All authors reviewed the manuscript.

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