Systematic Review and Meta-Analysis

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Tranexamic acid plus diluted-epinephrine versus tranexamic acid alone for blood loss in total joint arthroplasty

A meta-analysis

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Abstract

Background: We conducted the present meta-analysis to assess the efficacy and safety of tranexamic acid (TXA) plus diluted-epinephrine (DEP) for patients with total joint arthroplasty (TJA, including total knee arthroplasty (TKA) and total hip arthroplasty (THA)).

Methods: Electronic databases (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Wanfang databases, and Google databases) were systematically searched up to December 2016. Only randomized controlled trials (RCTs) were included. The primary outcomes were total blood loss and need for transfusion. The secondary outcomes were hemoglobin drop and the incidence of deep venous thrombosis (DVT) and hematoma. Continuous outcomes and discontinuous outcomes were compiled as the weighted mean difference (WMD) and relative risk (RR) with 95% confidence intervals (CI), respectively.

Results: A total of 5 RCTs with a total of 493 patients were eligible and ultimately included in the meta-analysis. Compared with the TXA group, TXA plus DEP yielded a significant reduction in total blood loss (WMD = –244.78; 95% CI –290.12 to –199.44; $P < .001$), need for transfusion (RR = 0.27; 95% CI 0.15–0.48; $P < .001$) and hemoglobin drop (WMD = –0.81; 95% CI –1.22 to –0.40; $P < .001$). There was no significant difference in incidence of DVT (RR=0.67; 95% CI 0.27–1.64; $P = .382$) or hematoma (RR=0.89; 95% CI 0.30–2.61; $P = .831$) between the TXA plus DEP group and the TXA group.

Conclusion: TXA plus DEP can decrease perioperative blood loss without increasing the incidence of DVT compared with TXA alone. However, considering the limited number of included RCTs, this conclusion should be interpreted cautiously, and more high-quality RCTs are needed to verify the efficacy and safety of TXA plus DEP for TJA patients.

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CIs = confidence intervals, DEP = diluted-epinephrine, DVT = deep venous thrombosis, PE = pulmonary embolism, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RR = relative risk, SD = standard deviation, THA = total hip arthroplasty, TJA = total joint arthroplasty, TJAs = total joint arthroplasties, TKA = total knee arthroplasty, TXA = tranexamic acid, WMD = weighted mean difference.

Keywords: epinephrine, meta-analysis, total hip arthroplasty, total knee arthroplasty, tranexamic acid

1. Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are associated with a large amount of perioperative blood loss.[1] Blood loss is often associated with a risk of anemia and increase the mortality and disability rates. What's more, blood loss will also increase the rate of blood transfusion.[2] Blood transfusion is certainly not a zero-risk procedure and may cause postoperative infections and disease transmission.[3] Therefore, it is necessary to explore an efficient protocol to decrease perioperative blood loss in TKA and THA. Although intravenous or topical tranexamic acid (TXA) can reduce perioperative total blood loss in TKA and THA,[4] intravenous TXA leads to a high concentration of TXA in the circulation, which has the potential to cause deep venous thrombosis (DVT) or pulmonary embolism (PE).[5] Topical TXA has equivalent efficacy for blood loss as intravenous TXA in TKA and THA with less concentration of TXA in the circulation.[6] In patients undergoing TKA or THA, "hidden blood loss" accounting for a large part of the total blood loss.[7] Diluted-epinephrine (DEP) causes platelets aggregation and stimulates platelet release coagulation factors to reduce blood loss.[8] Therefore, the peripheral blood vessels were contracted and the blood loss can be reduced. Theoretically speaking, TXA plus DEP may more effective in reducing postoperative blood loss than TXA alone. Several studies have investigated the efficacy of TXA

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plus DEP for controlling blood loss following THA and TKA.[9,10] However, the results for THA and TKA yield are conflicting, with some studies concluding that TXA plus DEP can decrease postoperative total blood loss and others concluding that it does not.[9,10] Therefore, the purpose of this meta-analysis was to assess the effect of TXA plus DEP in reducing exposure to allogeneic transfusion and total blood loss in both THA and TKA. Additionally, the safety of TXA plus DEP was evaluated.

2. Material and methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the meta-analysis of intervention trials.

2.1. Search strategies

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Wanfang databases, and Google databases were searched up to December 2016 for any relevant studies involving combined TXA and DEP versus TXA alone for blood loss control in patients undergoing TJA (TKA and THA). The search terms were as follows: "tranexamic acid," "epinephrine," "total knee arthroplasty," "total knee replacement," "total hip arthroplasty," "total hip replacement." The detailed search strategies can be seen in Supplement S1, http://links.lww.com/MD/B748. There was no language or publication date limited. Reference lists of all eligible studies were searched manually for additional studies. This meta-analysis collected data from published articles and thus no ethical approval was necessary for this article.

2.2. Inclusion criteria and study selection

Participants: patients prepared for TKA or THA. Intervention: combined local TXA with DEP. Comparison: administration with local TXA alone. Outcomes: primary outcomes were total blood loss and need for transfusion; secondary outcomes were hemoglobin drop and the incidence of DVT and hematoma. Study: only RCTs were included. Quasi-RCT or non-RCT, retrospective studies, letters and comments were excluded.

2.3. Data extraction

Two authors (ZXY and LLY) independently reviewed all titles and abstracts of the included studies. Disagreements were resolved by a joint review of the article to reach a consensus. Data on patients' general characteristics (number, the ratio of male patients, and mean age), intervention (including the dose of TXA and DEP), outcomes, study design and follow-up were extracted by 2 authors (ZXY and LLY) and recorded in a pre-generated standard Microsoft Excel (Microsoft Corporation, Redmond, Washington, DC) file. Data in other forms were converted to mean ± standard deviation (SD) according to the guideline of Cochrane Handbook.[11] If data were not reported numerically, we extracted them by manual measurements from published figures.

2.4. Quality assessment

Two reviewers (ZXY and QY) assessed the methodological quality according to the following items recommended by the Cochrane Handbook version 5.1.0.[11] A total of 7 fields (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias) need to assess as low risk of bias, unclear risk of bias and high risk of bias. Any disagreement in assessments was resolved by discussing with a third author (LLY) to reach a consensus.

2.5. Statistical analysis

All the outcomes were calculated by the Stata 12.0 software (Stata Corp., College Station, TX). Weighted mean difference (WMD) with a 95% CI was calculated for continuous data (total blood loss and hemoglobin drop). Risk ratios (RR) with 95% CI were calculated for dichotomous data (need for transfusion, the incidence of DVT and hematoma). Heterogeneity was measured by the I^2 statistic ($I^2 > 50\%$ indicated there was a high heterogeneity). A random-effects model was used if the heterogeneity $I^2 > 50\%$. Sensitivity analysis was performed to explore the impact of an individual study by deleting 1 study each time. A P value less than 0.05 was considered statistically significant.

3. Results

3.1. Search results

In the initial search, we identified 185 potentially relevant studies, of which 40 duplicates were removed by Endnote software (Thomson Reuters, America). According to the inclusion criteria, 145 studies were excluded after reading the titles and abstracts. Finally, we included 5 clinical trials with 493 patients in the meta-analysis.[9,10,12–14] The search details are shown in Fig. 1. The characteristics of the included studies are shown in Table 1. In the included studies, a total of 493 TJAs were performed, and the numbers of TJAs using TXA plus DEP and TXA alone were 244 and 249, respectively. All articles were published in the year 2014. The dose of TXA ranged from 1 g to 3 g and the dose of DEP ranged from 0.25 mg to 0.33 mg. Three studies compared TXA plus DEP versus TXA in TKA, and 2 studies compared these treatments in THA.

3.2. Quality assessment

The quality assessment of RCTs can be seen in Figs. 2 and 3. Only 1 study appropriately described the random sequence generation,[14] and 3 studies [9,12,14] performed the appropriate allocation concealment and blinding of participants and personnel. Four studies [9,10,12,14] provided enough information and thus were evaluated as low bias for blinding of outcome assessments. Attribution bias, reporting bias, and other bias were all low in each of the included studies.[9,10,12–14]

3.3. Meta-analysis results

3.3.1. Total blood loss. Five studies [9,10,12–14] with 493 patients showed the total blood loss. The meta-analysis revealed that the TXA combined with the DEP group had a lower volume of total blood loss compared to the TXA group (Fig. 4) (WMD = –244.78; 95% CI –290.12 to –199.44; $P < 0.001$). There was no statistical heterogeneity ($I^2 = 0.0\%$, $P = 0.723$); therefore, a fixed-effects model was performed. Subgroup analysis results are presented in Supplement S2, http://links.lww.com/MD/B748. Results indicated that a TXA dose of 1 g or 3 g can decrease total

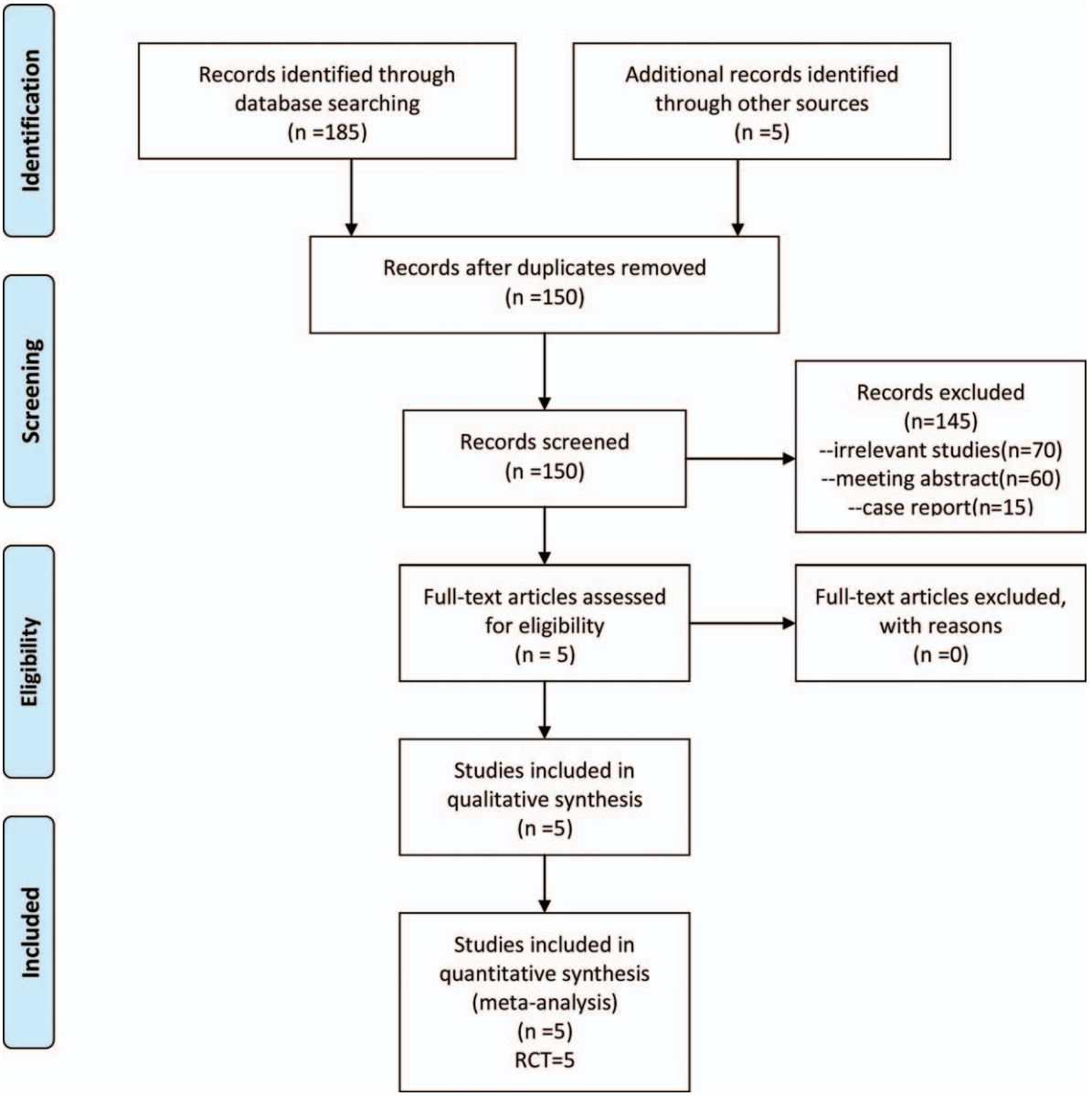

Figure 1. The flow diagram of the included studies. RCT = randomized controlled trial.

Table 1

The general characteristics of the included studies.

Reference	No. of patients		Male,%	Mean age, years	Intervention		Outcomes	Study design	Follow up	Joint arthroplasty
	TXA+DEP	Control			TXA+DEP	Control				
Zhao 2014	43	47	47.1	65.3/65.6	TXA (1 g, intra-articular injection)+DEP (0.33 mg)	TXA (1 g)	1, 2, 3, 4, 5	RCTs	6 month	TKA
Gao et al 2015	53	54	52.3	58.6/61.7	TXA (3 g, intra-articular injection)+DEP (0.25 mg)	TXA (3 g)	1, 2, 3, 4, 5	RCTs	2 week	THA
Jans et al 2016	50	50	49.6	67/68	TXA (1 g, intra-articular injection)+DEP (0.05 μg/kg/min)	TXA (1 g)	1, 5	RCTs	1 day	THA
Gao et al 2015	50	50	50.2	68.5/67.4	TXA (3 g, intra-articular injection)+DEP (0.25 mg)	TXA (3 g)	1, 2, 3, 4, 5	RCTs	3 month	TKA
Wei et al 2016	48	48	55.3	68.6/67	TXA (1 g, intra-articular injection)+DEP (0.25 mg)	TXA (1 g)	1, 2, 3, 4, 5	RCTs	3 month	TKA

1 = total blood loss, 2 = need for transfusion, 3 = hemoglobin drop, 4 = incidence of deep venous thrombosis, 5 = occurrence of hematoma, DEP = diluted-epinephrine, RCTs = randomized controlled trials, TKA = total knee arthroplasty, THA = total hip arthroplasty, TXA = tranexamic acid.

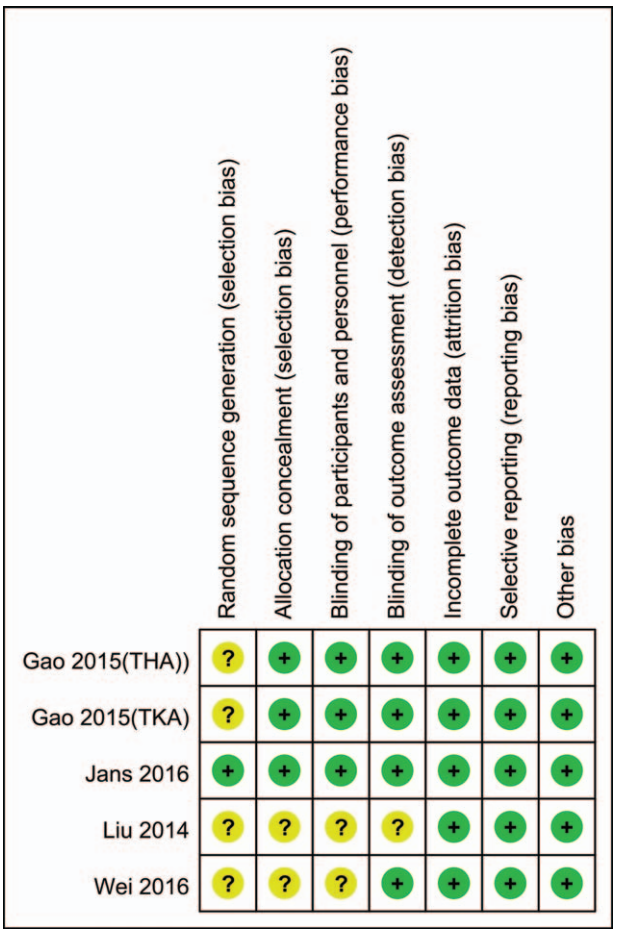

Figure 2. The risk of bias summary.

blood loss, and TXA combined with DEP can decrease total blood loss in TKA and THA.

3.3.2. Need for transfusion. A total of 4 component studies [9,10,12,13] (393 patients) provided data on the need for transfusion. The pooled results indicated that TXA plus DEP can decrease the need for transfusion more than TXA alone (RR = 0.27; 95% CI 0.15–0.48; $P<.001$, Fig. 5). There was little statistical heterogeneity (χ^2=46.39, df=4, I^2=39.3%, P=.176); therefore, a fixed-effects model was performed.

3.3.3. Hemoglobin drop. A total of 4 component studies [9,10,12,13] (393 patients) provided data on postoperative hemoglobin drop. The pooled results indicated that TXA plus DEP was associated with a significant reduction of the hemoglobin drop postoperatively (Fig. 6) (WMD = –0.81; 95% CI –1.22 to –0.40; $P<.001$). There was large statistical heterogeneity (χ^2 = 15.47, df=3, I^2=79.9%, P=.002); therefore, a random-effects model was performed.

3.3.4. Incidence of DVT. A total of 4 component studies [9,10,12,13] (393 patients) included the postoperative incidence of DVT. There was no statistically significant difference between the groups with respect to incidence of DVT postoperatively (RR = 0.67; 95% CI 0.27–1.64; P=.382, Fig. 7). There was no statistical heterogeneity (χ^2=12.16, df=3, I^2=0.0%, P=.602); therefore, a fixed-effects model was performed.

3.3.5. Occurrence of hematoma. A total of 5 component studies [9,10,12–14] (493 patients) included the postoperative occurrence of hematoma. There was no statistically significant difference between the groups with respect to occurrence of hematoma postoperatively (RR = 0.89; 95% CI 0.30–2.61; P=.831, Fig. 8). There was no statistical heterogeneity (χ^2=1.90, df=4, I^2=0.0%, P=.755); therefore, a fixed-effects model was performed.

4. Discussion

This is the first systematic review and meta-analysis of RCTs comparing the efficacy and safety of TXA plus DEP for patients prepared for total joint arthroplasty (TKA and THA). Based on the pooled estimates, TXA plus DEP was associated with a significant reduction in the volume of total blood loss, hemoglobin drop, and need for transfusion compared with TXA alone. TXA plus DEP was not associated with a significantly increased risk of serious adverse events (incidence of DVT).

The current meta-analysis demonstrated that TXA plus DEP has a beneficial effect on the total blood loss. TXA plus DEP group can decrease appropriately by 244.78 mL blood loss when compared with control group. Studies shown that administration hemostasis agent alone is not sufficient to reach the satisfactory results.[15,16] A previous meta-analysis identified the efficacy of TXA in reducing blood loss after TKA and THA.[16] Anderson et al[17] reported that intra-articular injections of DEP decreased total blood loss after TKA. A local injection of DEP before the tourniquet induces the peripheral vessels contracting.[8,18] Furthermore, DEP stimulate

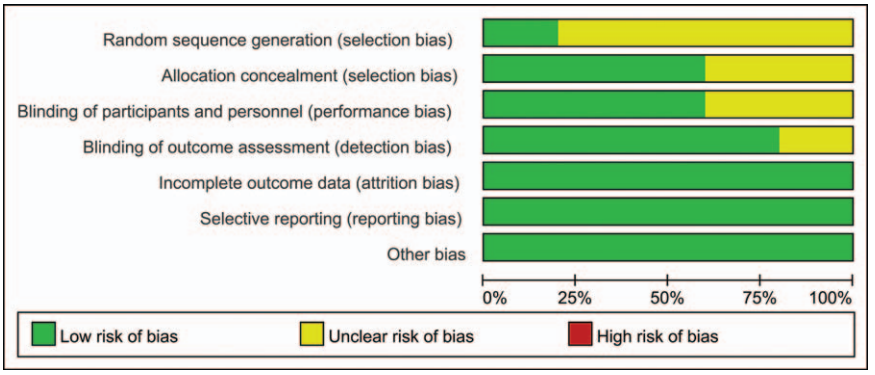

Figure 3. The risk of bias graph.

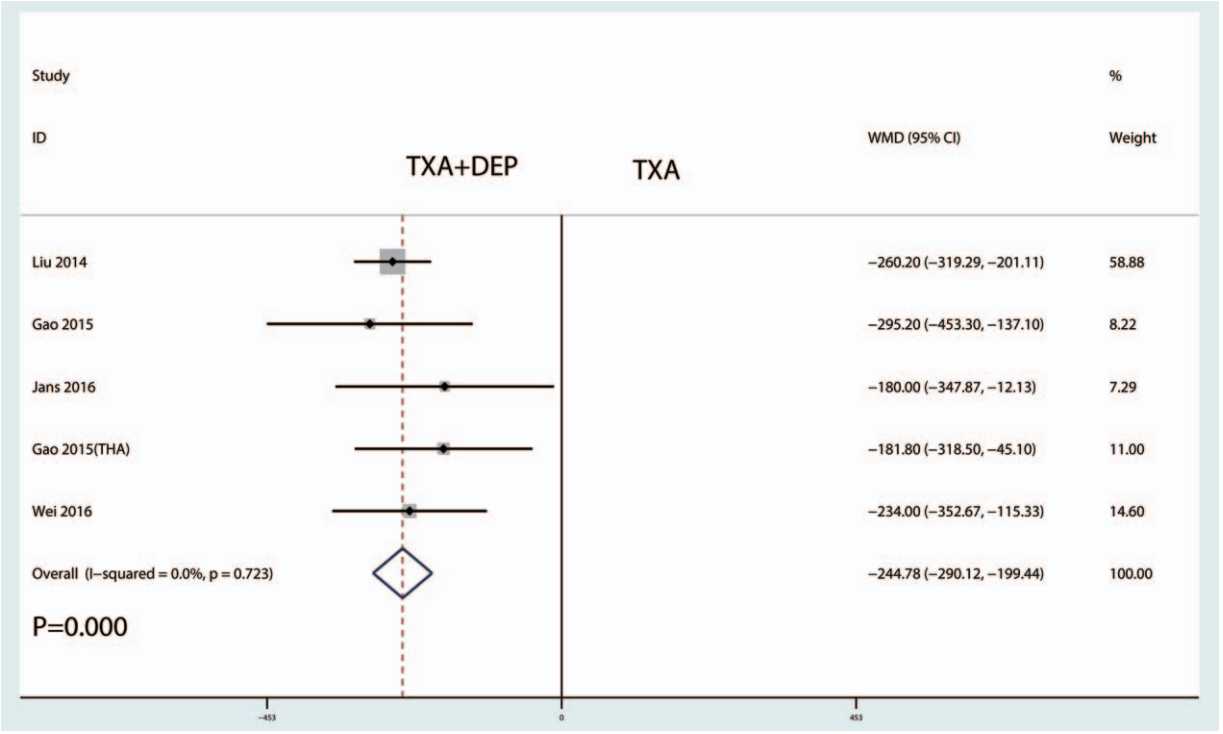

Figure 4. The forest plot comparing TXA combined with DEP versus TXA alone for total blood loss after total joint arthroplasty (TJA). An inverse-variance fixed-effects model was used. DEP = diluted-epinephrine, TJA = total joint arthroplasty, TXA = tranexamic acid.

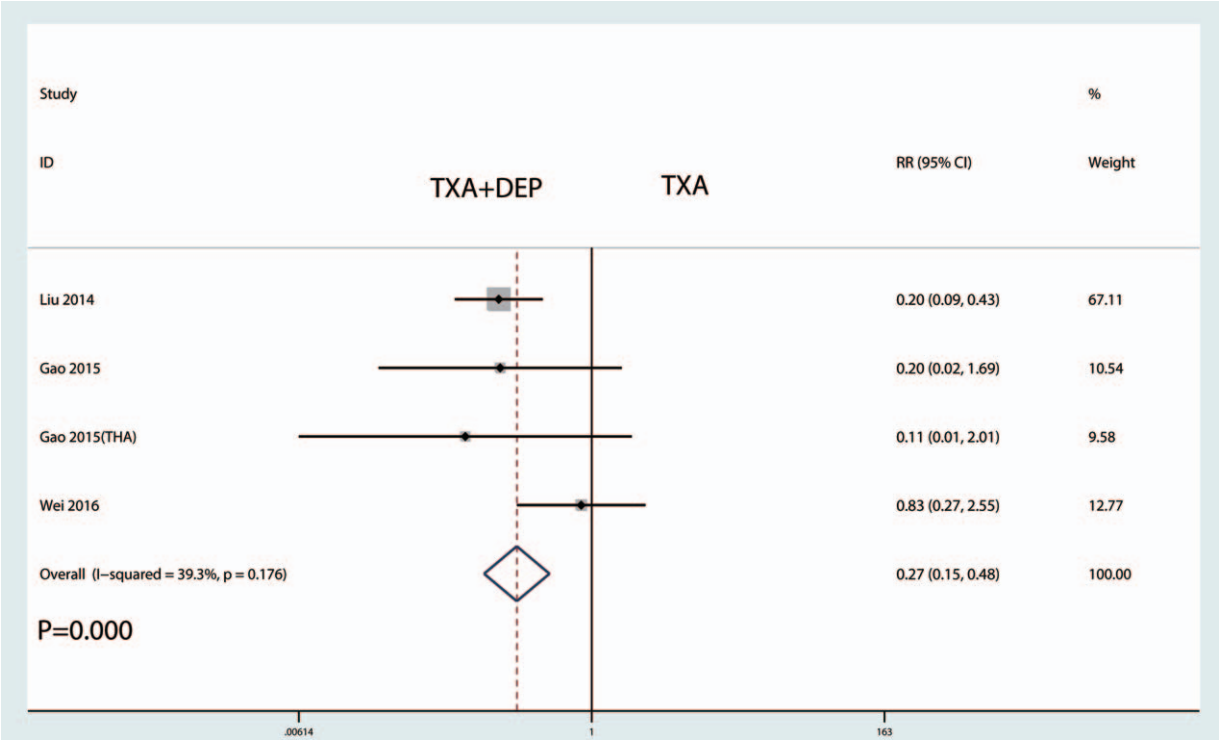

Figure 5. The forest plot comparing TXA combined with DEP versus TXA alone for need for transfusion after total joint arthroplasty (TJA). DEP = diluted-epinephrine, TJA = total joint arthroplasty, TXA = tranexamic acid.

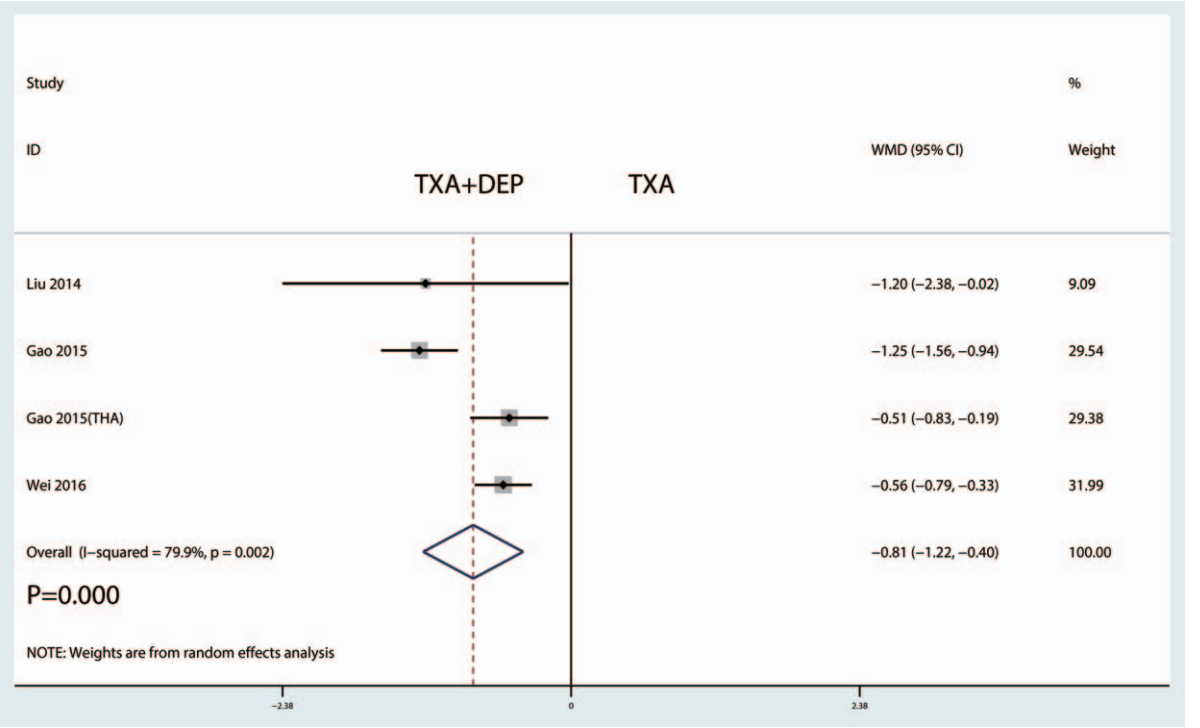

Figure 6. The forest plot comparing TXA combined with DEP versus TXA alone for hemoglobin drop after total joint arthroplasty (TJA). DEP = diluted-epinephrine, TJA = total joint arthroplasty, TXA = tranexamic acid.

the platelet aggregation and thus the blood loss can be further reduced. A previous retrospective study found that an intra-articular administration epinephrine has no statistically significant with control in terms of blood loss after TKA.[19]

The pooled results indicated that there was a lower transfusion rate and less hemoglobin drop in the TXA plus DEP group than in the TXA alone group. TXA plus DEP may prolong the duration of action of TXA after major joint arthroplasty. The combination

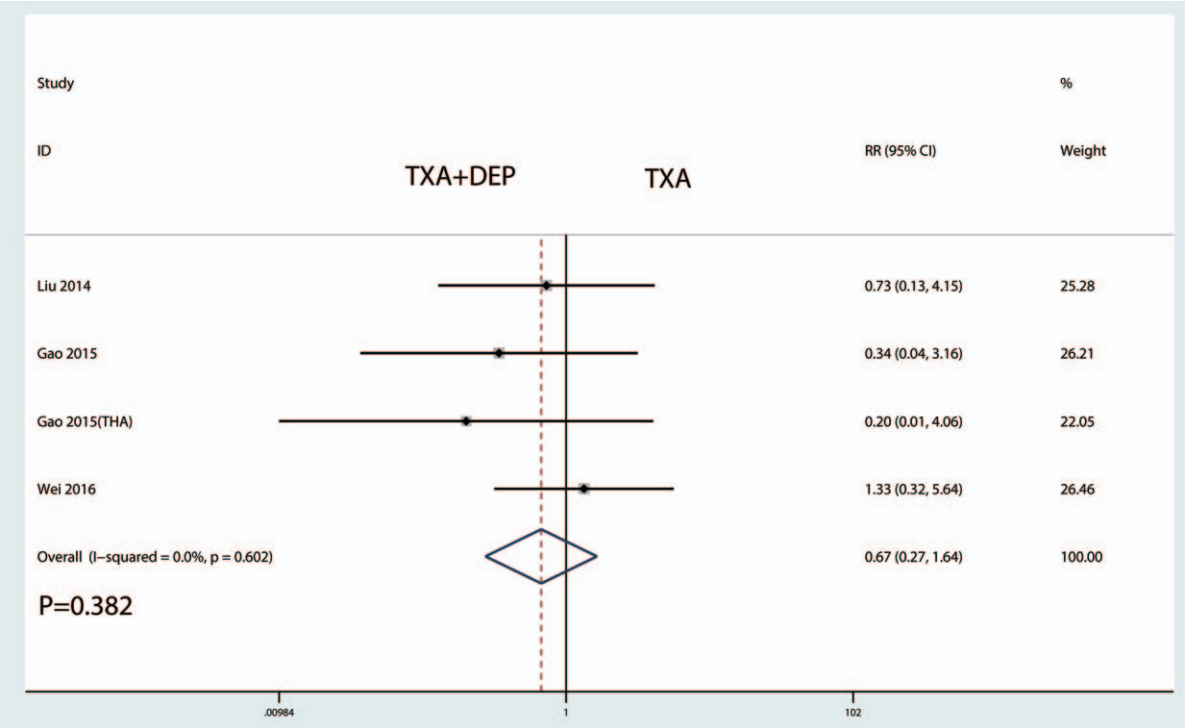

Figure 7. The forest plot comparing TXA combined with DEP versus TXA alone for the incidence of DVT after total joint arthroplasty (TJA). DEP = diluted-epinephrine, TJA = total joint arthroplasty, TXA = tranexamic acid.

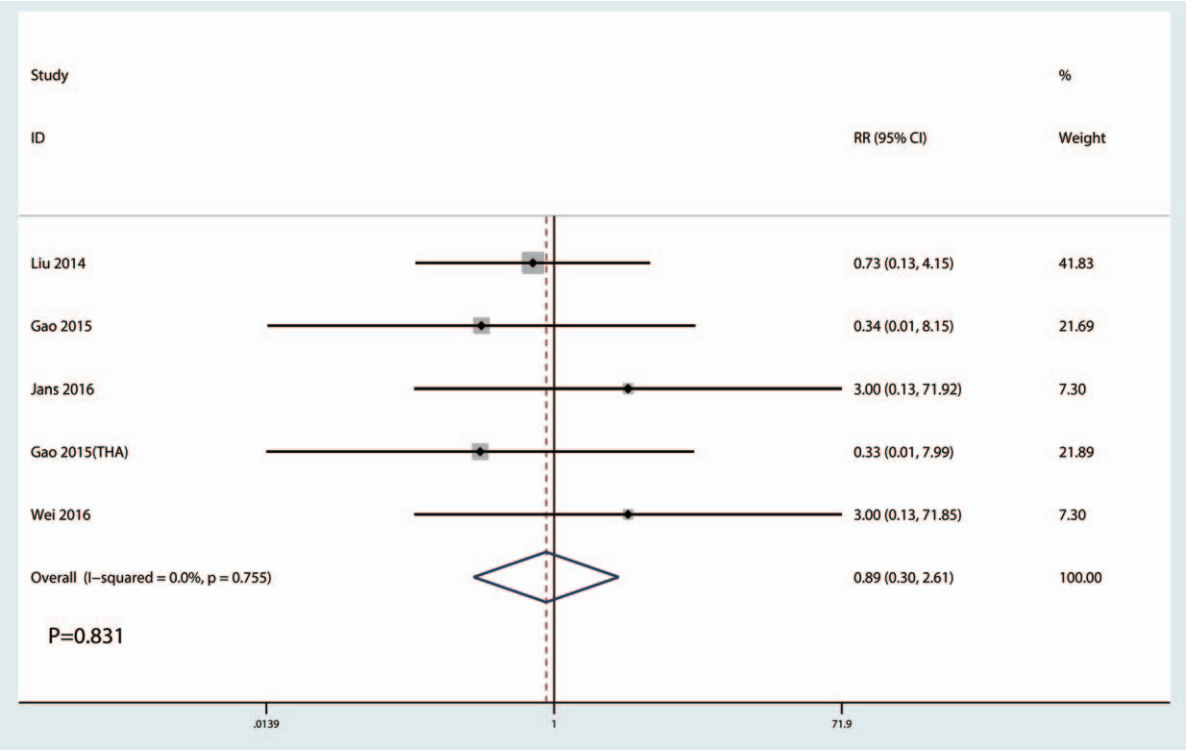

Figure 8. The forest plot comparing TXA combined with DEP versus TXA alone for the occurrence of hematoma after total joint arthroplasty (TJA). DEP = diluted-epinephrine, TJA = total joint arthroplasty, TXA = tranexamic acid.

of tissue injection with TXA plus DEP resulted in the application of higher doses of TXA. Yamada et al[20] found that the hemostatic effect of epinephrine was more effective than the control group. The dose of TXA ranged from 1 g to 3 g and the dose of DEP ranged from 0.25 mg to 0.33 mg.

Regarding the safety of TXA plus DEP, there was no significant difference between the incidence of DVT (RR = 0.67; 95% CI 0.27–1.64; $P = .382$) or hematoma (RR = 0.89; 95% CI 0.30–2.61; $P = .831$). A previous retrospective study reported that the use of an epinephrine wash in patients undergoing THA was of minimal impact on the occurrence of DVT.[21] Another meta-analysis indicated that administration with TXA did not increase the occurrence of DVT.[3] Other previous studies revealed that vasoconstrictors have a nominal risk of delayed wound healing, wound edge necrosis, pulmonary edema, and an increased risk of DVT.[8,22] However, these complications did not occur more frequently in the study by Sasanuma et al.[23] Additionally, no studies reported complications such as pulmonary embolism or wound healing.

Our meta-analysis also has several potential limitations. First, our analysis included only 5 randomized controlled trials, and the sample size was limited in the included studies. Second, the potential risk of publication bias may exist due to the small number of included studies. In addition, the limited number of studies may also have influenced our conclusions. Furthermore, follow-up was limited in the included studies and no study compared the functional recovery at final follow-up.

The present meta-analysis indicated that TXA plus DEP, compared with TXA alone, was associated with less blood loss and need for transfusion. However, the number of included studies was limited, and more RCTs are needed to identify the optimal dose of TXA and DEP for controlling blood loss in total joint arthroplasty.

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