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Review Article

Efficacy of combined tranexamic acid for total hip arthroplasty patients: a meta analysis of randomized controlled trials

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Abstract: Background: The efficacy and safety of combined intravenous (IV) and topical administration of tranexamic acid (TXA) compared with IV-only administration of TXA for reducing blood loss during total hip arthroplasty (THA) is controversial. We performed a meta-analysis of randomized controlled trials (RCTs) to compare the efficacy and safety of combined IV and topical TXA with IV-TXA after THA. Methods: PubMed, Medline, Embase, Web of Science and the Cochrane Library were searched to identify studies comparing combined IV and topical TXA with IV-TXA for THA patients. The mean difference (MD) of blood loss, hemoglobin drop, surgical duration, length of hospital stay and risk ratios (RR) of transfusion rate and the occurrence of deep venous thrombosis in combined TXA and IV-TXA groups were pooled throughout the study. Relevant data were analyzed using Stata 12.0. Results: Five RCTs involving 682 patients were included (339 combined TXA vs. 343 IV-TXA). The application of combined TXA in THA had a significantly lower total blood loss than IV-TXA [MD = -185.72; 95% CI: -250.69 to -120.74, P = 0.000], lower transfusion rate [RR = 0.31; 95% CI: 0.14 to 0.69; P = 0.004] and lower hidden blood loss without increasing the risks of deep venous thrombosis (DVT). No significant differences were seen in hemoglobin drop and length of hospital stay between the two groups (P>0.05). Conclusions: Our meta-analysis suggests that combined application of IV and topical TXA for patients undergoing THA may reduce calculated total blood loss compared with IV use alone without increasing the risks of postoperative complications. However, owing to the variation of included studies, no firm conclusions can be drawn.

Keywords: Total hip arthroplasty, blood loss, intravenous, topical, combined, tranexamic acid

Introduction

Total hip arthroplasty (THA) is an excellent surgical procedure for patients with end-stage hip disease: femoral head necrosis and femoral neck fracture [1]. However, perioperative blood loss and subsequent blood transfusion is still an unsolved problem [2, 3]. It is reported that perioperative blood loss could reach as much as 2000 ml, and blood transfusion rate is 16% to 37% [4, 5]. Although the incidence of blood transfusion is low, the blood transfusion may cause immunological reaction and disease transmission [6]. Moreover, blood transfusion may increase the incidence of infection. The reason for blood loss may include surgical bleeding and fibrinolysis [7]. The blood loss due to fibrinolysis accounts for approximately 60% of total blood loss [8]. To reduce the total blood loss after THA and the subsequent blood transfusion complications, multimodal blood management has been introduced. Of these, the antifibrinolytic agent tranexamic acid (TXA) is potentially the most effective choice [9]. TXA competitively inhibits the activation of plasminogen by blocking lysine binding sites. Thus, the thrombin clot is not broken down and blood loss is reduced. There is a large amount of evidence provided by randomized controlled trials (RCTs) and meta-analysis that have shown that TXA, applied intravenously, can be effective in reducing the total blood loss without risking

deep venous thrombosis (DVT). However, the optimal regimen, dosage, and timing still remain unclear. Traditionally, TXA was injected intravenously prior to the skin incision in primary THA, and concerns about the safety of systemic administration of TXA in high dosage hindered its wide application. Compared with IV-TXA, local administration is easy to administer, inhibiting clot breakdown directly with maximum concentration at the bleeding site. Except for the above protocol, combining topical and intravenous TXA is a preferable protocol and has shown satisfactory results in THA. However, the efficacy and safety of combined topical and intravenous TXA versus intravenous TXA alone has not been identified. Thus, we carried out a systematic review and meta-analysis to compare combined topical and intravenous TXA versus intravenous TXA alone for reducing total blood loss in THA.

Materials and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines for the meta-analysis of intervention trials.

Search strategies

PubMed, Embase, Web of Science and the Cochrane Library were searched up to October 2016 for comparative studies involving combined TXA and IV-TXA for reducing blood loss in patients undergoing THA. The search terms were as follows: "combined tranexamic acid", "intravenous tranexamic acid", "intravenous and topical tranexamic acid", "intravenous and intra-articular (IA) tranexamic acid", "hip arthroplasty", and "hip replacement". The detailed search strategies can be seen in Supplementary S1. The language of publications was not limited. The title and abstract of studies identified in the search were reviewed to exclude clearly irrelevant studies. Reference lists of all eligible studies and relevant reviews were searched manually for additional trials.

Inclusion criteria and study selection

Inclusion criteria: Participants: patients undergoing primary THA; Intervention: combined topical with intravenous TXA; Comparison: intravenous TXA alone; Outcomes: the primary outcomes included total blood loss, hidden blood loss, transfusion rate, and postoperative complications (including DVT/PE). Secondary outcomes included hemoglobin drop and length of hospital stay. Study: only RCTs were included. Articles that reported at least one outcome were included and those without the outcome measures of interest were excluded. Quasi-RCT or non-RCT, retrospective studies, letters, comments, editorials and practice guidelines were excluded.

Data extraction and quality assessment

Two authors (Jing Wu and Xiang Wang) independently reviewed all titles and abstracts of studies identified by searches 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. The data on patient characteristics (age, sex and other baseline characteristics), interventions and outcomes were extracted in duplicate by the two authors using a standardized form. The data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to mean ± standard deviation (SD) according to the Cochrane Handbook [10]. If data were not reported numerically, we extracted them by manual measurements from published figures.

Two authors (Bao-fang Tian and Tao Li) independently assessed the risk of bias of the included studies, based on the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias [10]. Disagreement was resolved by the third author. The quality of evidence of outcomes was judged according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [11, 12]. The two authors independently evaluated five factors (risk of bias, inconsistency, indirectness, imprecision and publication bias) that may downgrade the quality level of evidence. The recommendation level of evidence was classified into four categories: high, moderate, low or very low [11, 12]. High quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and

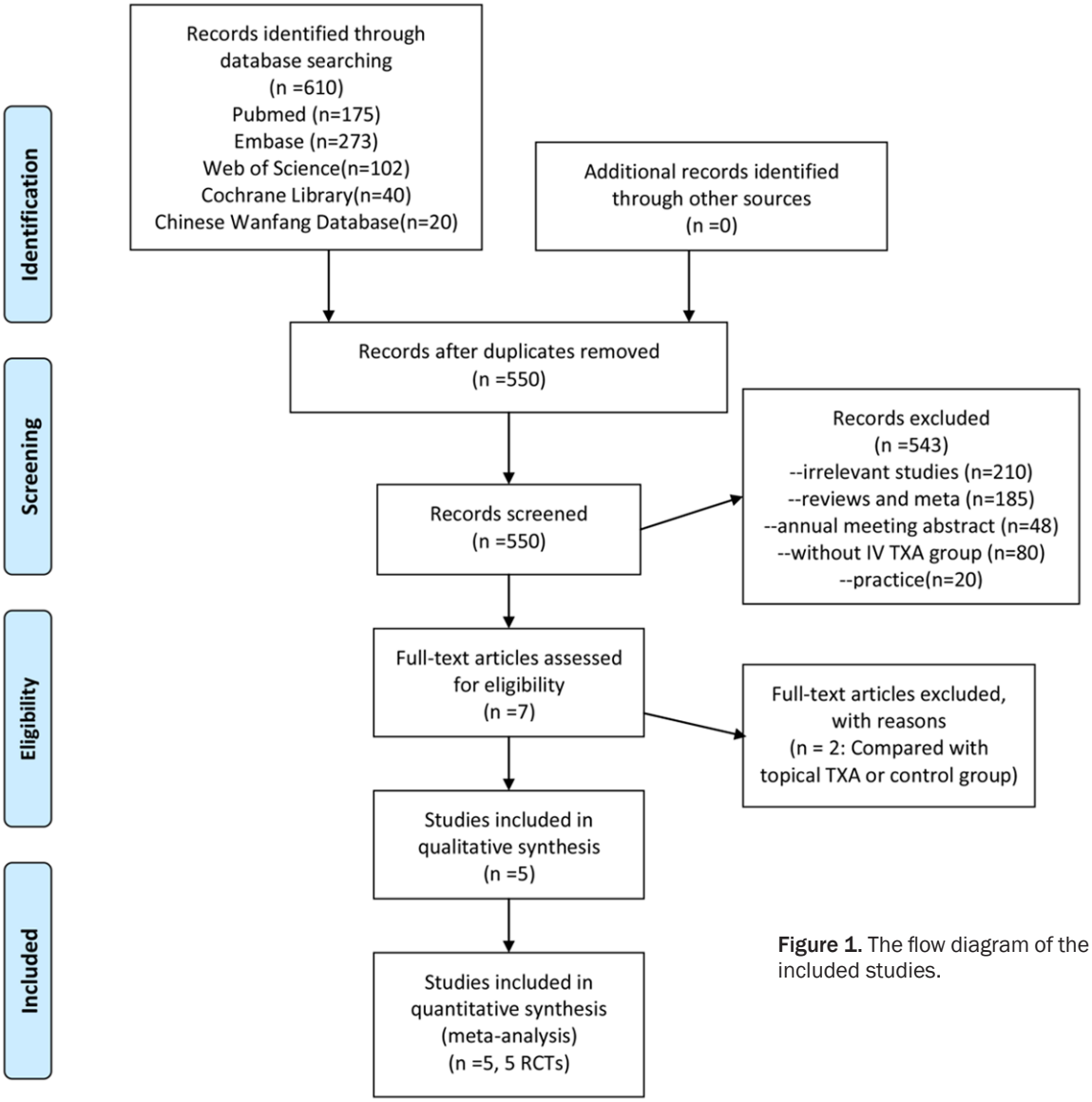

Figure 1. The flow diagram of the included studies.

may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.

Statistical analysis

All calculations were made using Stata 12.0 software. Mean difference (MD) with a 95% CI was calculated for continuous data. Risk ratios (RR) with 95% CI were calculated for dichotomous data. Heterogeneity among studies was estimated using the I^2 statistic; substantial heterogeneity was represented by I^2>50%. A fixed-effects model was used if the heterogeneity test did not reveal significance (I^2<50%; P>0.1). Otherwise, we adopted the random-effects model. P<0.05 was considered significant. Sensitivity analysis was performed to explore the impact of an individual study by deleting one study each time.

Results

Search results

The initial search yielded 610 citations, of which 60 were excluded owing to duplication. After screening the titles and abstracts and reading full text, 543 studies were excluded based on inclusion criteria. Finally, five studies [13-17] involving 682 patients were eligible for

Table 1. The general characteristic of the included studies

Reference	No. of patients		Male, %	Mean age, y	Intervention		Outcomes	Study design	Follow up
	Combined	IV			Combined	IV			
Xie 2016	70	70	44/40	60.5/59.5	1 g IV+2 g topical	1.5 g	a, b, c, d, e, f	RCTs	30 days
Zhao 2016	44	48	50/52	57.6/59.9	1 g IV+1 g topical	1 g/250 ml	a, c, e, f	RCTs	5 days
Zhang 2015	34	34	29.4/32.4	64.7/63.4	1 g IV+100 mg topical	1 g/250 ml	a, b, c, f	RCTs	Discharge
Lu 2016	141	141	53.2/50.9	65.0/66.0	15 mg/kg IV+2 g topical	15 mg/kg	a, f	RCTs	5 days
Yi 2016	50	50	42/52	53.6/54.1	15 mg/kg IV+200 mg topical	15 mg/kg	a, c, c, d, f	RCTs	15 days

IV, intravenous, RCTs, randomized controlled trials, a, total blood loss, b, hidden blood loss, c, need for transfusion, d, length of hospital stay, e, hemoglobin drop, f, the occurrence of deep venous thrombosis (DVT).

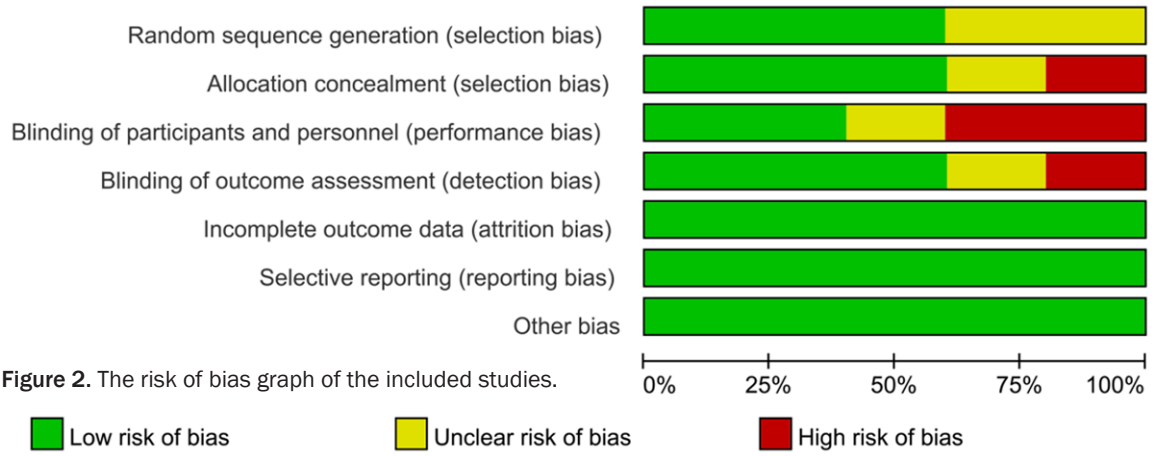

Figure 2. The risk of bias graph of the included studies.

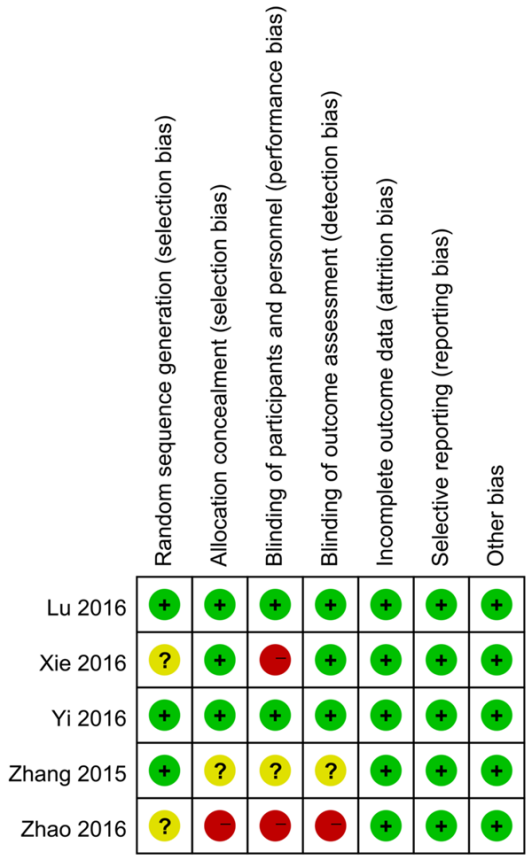

Figure 3. The risk of bias summary of the included studies; "+" means no risk of bias, "-" means high risk of bias; "?" means unclear of bias.

data extraction and meta-analysis (**Figure 1**). Of these 682 patients, 339 patients belonged to the combined TXA group and 343 to the IV-TXA group.

Table 1 summarizes the characteristics of the five included RCTs, which were published between 2014 and 2016. The sample size of the studies ranged from 30 to 92. All of the trials involved primary unilateral THA, and baseline characteristics between the two groups in each study were well matched. The sample ranged from 34 to 134 and patient age ranged from 53.6 to 64.7. Variation in the combined TXA and IV-TXA used was noted.

Study quality and GRADE of evidence

Risk of bias in the included studies is shown in **Figures 2** and **3**, respectively. Among the included studies, three studies were randomized by computer-generated numbers [13, 14, 17], and the remaining [15, 16] one did not report the method of random sequence generation.

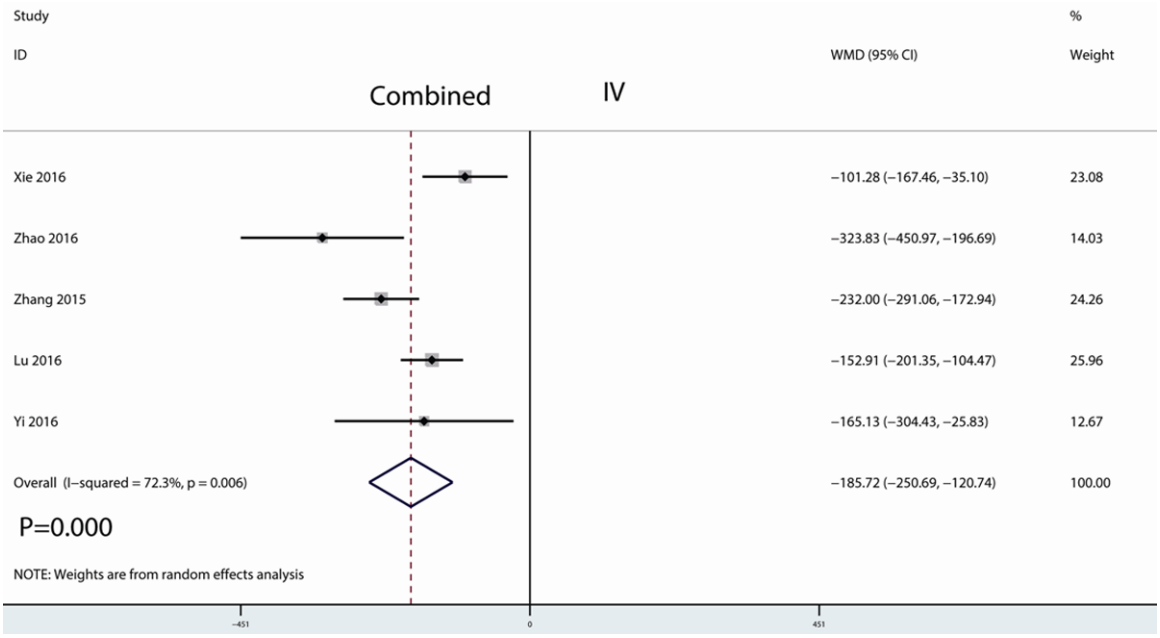

Figure 4. The forest plot comparing the total blood loss between the two groups. Forest plot showed combined intravenous and topical TXA associated with less total blood loss after THA than intravenous TXA alone (P = 0.000).

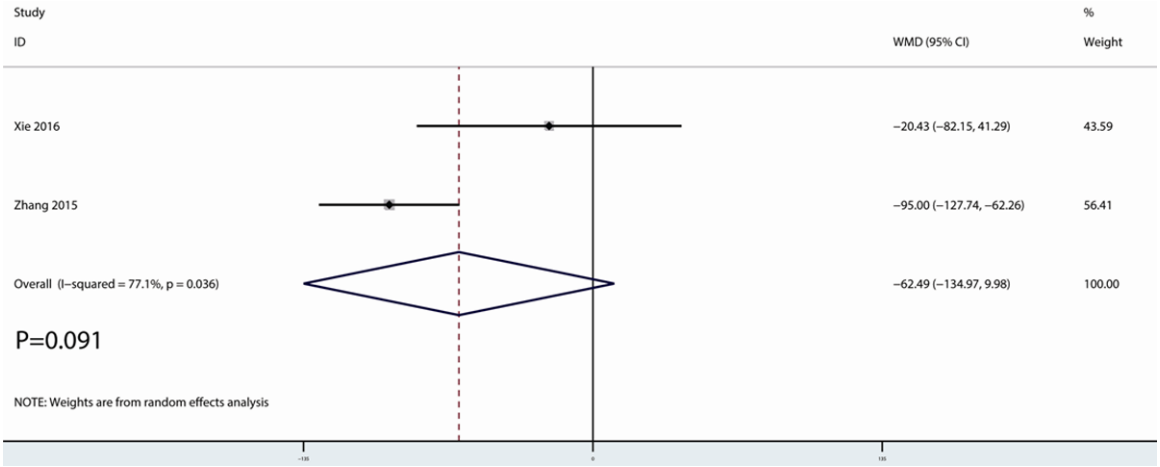

Figure 5. The forest plot of the hidden blood loss between the two groups. Pooled outcome of two studies showed no significant difference between the two groups (P = 0.091).

One study [15] did not report allocation concealment, one study [14] presented unclear risk, and the rest [13, 16, 17] all used a sealed envelope or box. Two studies [13, 17] were double-blind to participants and outcome assessors except one in which this information was not reported. We used the GRADE criteria to measure the strength of recommendations. A summary of the quality of the evidence according to the GRADE approach is shown in Supplementary S2. The GRADE level of evidence was low for total blood loss, moderate for need for transfusion, hidden blood loss, and Hb drop. It was high for LOS and the occurrence of DVT.

Results of the meta-analysis

Total blood loss: Data from five studies [13-17] involving 682 patients were available to examine the total blood loss assessed by the Gross formula. The formula was proven to be an accurate method. The application of combined TXA in THA had a significantly lower calculated total blood loss than IV-TXA [MD = -185.72; 95% CI:

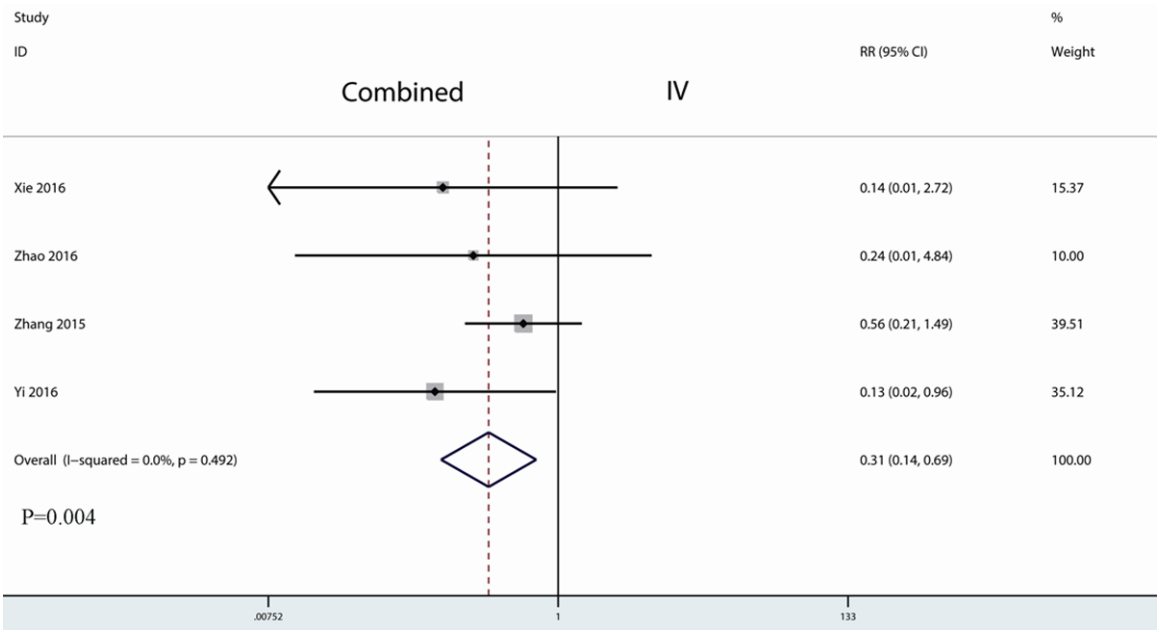

Figure 6. The forest plot of the transfusion rate between the two groups. Forest plot showed combined intravenous and topical TXA associated with less transfusion rate after THA than intravenous TXA alone (P = 0.000).

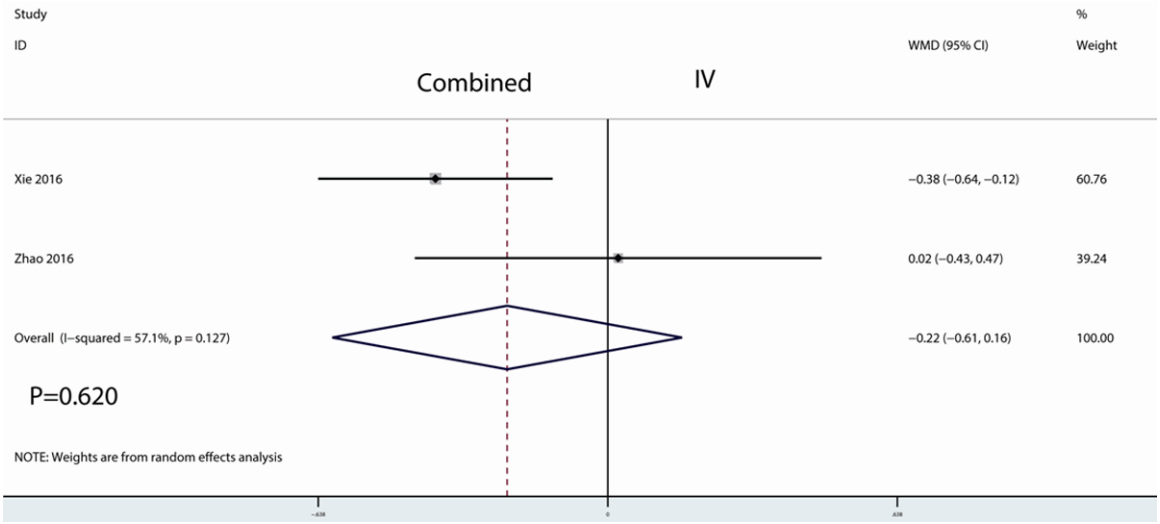

Figure 7. The forest plot of the hemoglobin drop between the two groups. Pooled outcome of two studies showed no significant difference between the two groups (P = 0.620).

-250.69 to -120.74, P = 0.000, **Figure 4**]. There was, however, moderate heterogeneity between studies [I^2 = 72.3%, P = 0.006, **Figure 4**].

Hidden blood loss: Two studies [14, 16] involving 208 patients reported the hidden blood loss after THA. The application of combined TXA in THA had a significantly lower hidden blood loss than IV-TXA [MD = -62.49; 95% CI: -134.97 to 9.88, P = 0.091, **Figure 5**] after THA with moderate heterogeneity [I^2 = 77.1%, P = 0.036, **Figure 5**].

Transfusion rate: Four studies [15-18] involving 396 patients were used to carry out a meta-analysis on the requirements of blood transfusion. Postoperative prevalence of transfusion was 3.1% and 10.9% in combined and IV-TXA groups, respectively (**Figure 5**). Meta-analysis revealed no significant difference in transfu-

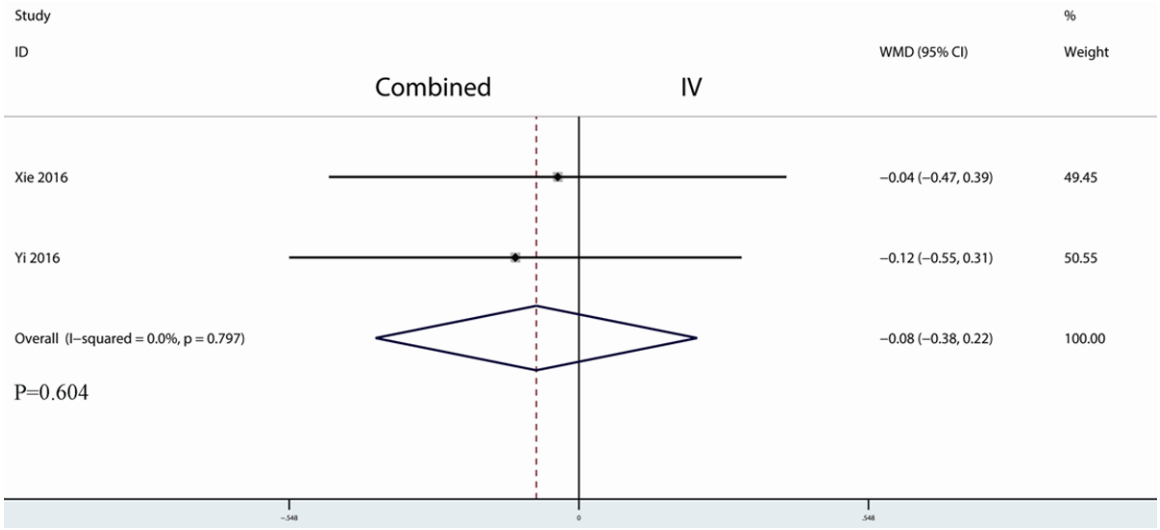

Figure 8. The forest plot of the length of hospital stay between the two groups. Pooled outcome of two studies showed no significant difference between the two groups (P = 0.604).

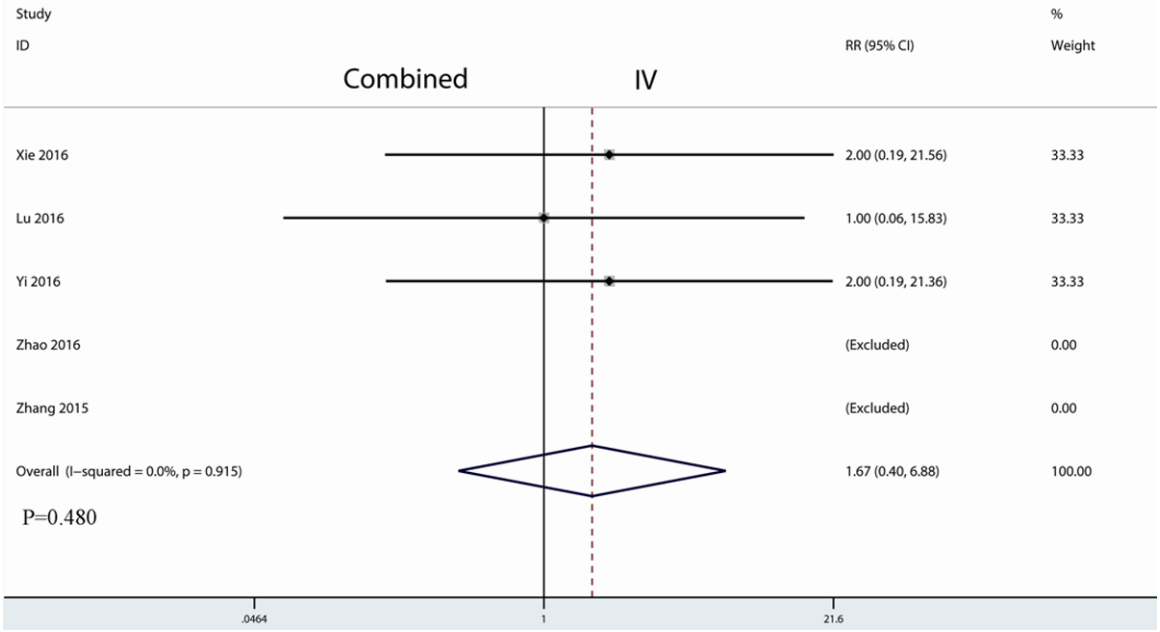

Figure 9. The forest plot of the DVT between the two groups. Pooled outcome of five studies showed no significant difference between the two groups (P = 0.480).

sion rate between the two groups [RR = 0.31; 95% CI: 0.14 to 0.69; P = 0.004]. There was no significant heterogeneity between studies [I^2 = 0%, P = 0.492, **Figure 6**].

Hemoglobin drop: Two studies [15, 16] involving 228 patients reported a hemoglobin drop after THA. The application of combined TXA in THA had a significantly lower hemoglobin drop than IV-TXA [MD = -0.22; 95% CI: -0.61 to 0.16, P = 0.620, **Figure 7**] after THA with moderate heterogeneity [I^2 = 57.1%, P = 0.127, **Figure 7**].

Length of hospital stay: Data were available from two studies [16, 17] involving 240 patients. There were no significant differences in the length of hospital stay between the two groups [MD = -0.08, 95% CI: -0.38 to 0.22, P = 0.604, **Figure 8**] and no heterogeneity [I^2 = 0.0%, P = 0.797].

The occurrence of DVT: Five studies [13-17] involving 682 patients were used to carry out a meta-analysis on the occurrence of DVT. There were no significant differences in the occurrence of DVT between the two groups [RR = 1.67, 95% CI: 0.40 to 6.88, P = 0.480, **Figure 9**].

Discussion

To the best of our knowledge, this is the first meta-analysis of RCTs comparing the efficacy and safety of combined administration of TXA with IV administration of TXA for reduction of blood loss after THA. We found that combined application of IV and topical TXA for patients undergoing THA reduced more total blood loss, hidden blood loss, hemoglobin drop and transfusion rate compared with IV use alone in the early postoperative period; furthermore, combined TXA did not increase the risk of postoperative DVT.

Perioperative bleeding is an inevitable complication of THA that often leads to anemia. Acute anemia (low levels of hemoglobin) can be associated with tachycardia and hypotension and may result in myocardial infarction and heart failure [19]. Blood transfusion is frequently required to correct severe anemia [20]. IV administration of TXA has been shown to be effective and safe in reducing blood loss and blood-transfusion requirements in THA compared with controls [21]. Compared with the IV-TXA in THA, the topical TXA has the advantages of less systemic absorption and better local hemostasis effect by stopping fibrin clot dissolution in the affected area [22]. In addition, topical TXA could reduce the severity of knee swelling and promote earlier postoperative rehabilitation exercise [23]. Thus, a large number of studies have focused on the topical application of TXA in THA and reported that topical application seemed to be more effective in terms of lowering blood loss and transfusion rate than IV administration. However, one meta-analysis by Li et al. detected no significant difference in blood loss and transfusion requirements between topical and IV TXA in THA [5]. Until now, the efficacy and safety of topical TXA compared to IV-TXA for controlling blood loss and transfusions in THA still remains controversial. Therefore, the new strategy of TXA administration, the combined regimen, has been explored.

Pooled results indicated that combined TXA can reduce total blood loss and need for transfusion after THA more than IV TXA alone. It was reported that TXA could maintain a biological half-life of 2 to 3 hours within joint fluid and enhance micro-vascular hemostasis. The routine dose of IV TXA in THA is 10 to 15 mg/kg and always administered at 5 to 10 min before operation. For hidden blood loss, there was no significant difference between the two groups. Topical TXA administration could reduce intraoperative and drainage blood loss, while IV TXA could reduce hidden blood loss and systemic blood loss during THA. Compared with IV TXA alone, combined TXA can decrease the transfusion rate by 7.8%. The transfusion trigger of the included studies was different; in one study it was set at hemoglobin less than 80 g/L, whereas the other studies set it at less than 70 g/L. Only two RCTs were included, and more RCTs are needed to identify the effects of combined TXA for hidden blood loss. For the length of hospital stay and the occurrence of DVT, there was no significant difference between the two groups. When added to topical TXA, IV-TXA might reduce joint swelling, improve wound healing, and permit rapid rehabilitation.

There are three main limitations in our meta-analysis. First, only five reports were included, and the sample size of each study was small, which limited the statistical power of our meta-analysis. Second, the variation of the doses of combined TXA and IV-TXA between the studies might also be a problem. Finally, outcomes of drain output volume, functional scores, range of motion, cost and postoperative swelling were not analyzed owing to insufficient data. Hence, further research into the comparative efficacy and complications between combined application of TXA and IV administration of TXA for blood preservation is required.

Conclusion

The combined administration of TXA appeared to be more effective in decreasing total blood loss and transfusion rate without increasing the risk of DVT compared with IV application of TXA for blood management in patients undergoing THA. No significant differences were seen in the hemoglobin drop, and length of hospital stay between the two groups. However, due to the limitations in the included studies, more large-sample and high-quality clinical trials and

systemic reviews are needed in the future to demonstrate the efficacy and safety of combined TXA compared to IV-TXA after THA.

Disclosure of conflict of interest

None.

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Supplementary S1

History

Download history Clear history

Search	Add to builder	Query	Items found	Time
#39	Add	Search **(("Tranexamic Acid"[Mesh]) OR tranexamic acid)) AND (((((total hip arthroplasty) OR total hip replacement) OR THA) OR THR) OR "Arthroplasty, Replacement, Hip"[Mesh])**	175	03:16:47
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#37	Add	Search **((((total hip arthroplasty) OR total hip replacement) OR THA) OR THR) OR "Arthroplasty, Replacement, Hip"[Mesh]**	56424	03:16:25
#36	Add	Search **"Tranexamic Acid"[Mesh]**	2332	03:16:01
#34	Add	Search **tranexamic acid**	3464	03:15:31
#33	Add	Search **"Arthroplasty, Replacement, Hip"[Mesh]**	20049	03:15:23
#29	Add	Search **THR**	22754	03:14:57
#28	Add	Search **THA**	7170	03:14:51
#27	Add	Search **total hip replacement**	27914	03:14:44
#26	Add	Search **total hip arthroplasty**	28911	03:14:34

Pubmed

Search date: October 26, 2016

Results: 175

EMBASE

Search date: October 26, 2016

Results: 273

Supplementary S2

Quality assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With outcome		Risk with control	Risk difference with outcome (95% CI)
Total blood loss (CRITICAL OUTCOME; Better indicated by lower values)											
678 (5 studies)	serious[1]	serious[2]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, inconsistency	343	335	-		The mean total blood loss in the intervention groups was 185.72 lower (250.69 to 120.74 lower)
Need for transfusion (CRITICAL OUTCOME)											
396 (4 studies)	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[3] due to risk of bias	22/202 (10.9%)	6/194 (3.1%)	OR 0.26 (0.1 to 0.64)		Study population
										109 per 1000	78 fewer per 1000 (from 36 fewer to 97 fewer)
											Moderate
										101 per 1000	73 fewer per 1000 (from 34 fewer to 90 fewer)
Hidden blood loss (Better indicated by lower values)											
208 (2 studies)	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[4] due to inconsistency	104	104	-		The mean hidden blood loss in the intervention groups was 78.62 lower (107.55 to 49.69 lower)
LOS (Better indicated by lower values)											
240 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ HIGH	120	120	-		The mean los in the intervention groups was 0.08 lower (0.38 lower to 0.22 higher)
Hb drop (Better indicated by lower values)											
228 (2 studies)	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[5] due to inconsistency	118	110	-		The mean hb drop in the interven-tion groups was 0.22 lower (0.61 lower to 0.16 higher)
DVT (IMPORTANT OUTCOME)											
678 (5 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ HIGH	3/343 (0.9%)	5/335 (1.5%)	RR 1.67 (0.4 to 6.88)		Study population
										9 per 1000	6 more per 1000 (from 5 fewer to 51 more)
											Moderate
										7 per 1000	5 more per 1000 (from 4 fewer to 41 more)

[1]3 studies did not state the random sequence generation; [2]I^2 = 72.3%; [3]2 studies did not state the random sequence generation; [4]I^2 = 77.1%; [5]I^2 = 57.1%.