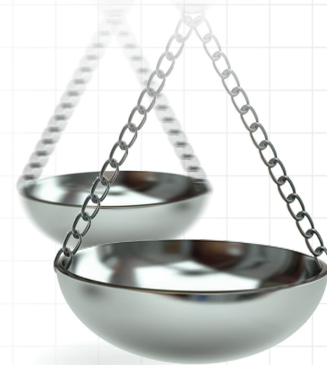




Intravenous tranexamic acid reduces blood transfusions in revision total hip arthroplasty: a meta-analysis

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Aim: We performed a meta-analysis to systematically assess the efficacy and safety of intravenous tranexamic acid in revision total hip arthroplasty. **Method:** Potential academic articles were identified from Cochrane Library, Medline, PubMed, EMBASE, ScienceDirect and other databases. The time range we retrieved from was that from the inception of electronic databases to February 2019. Gray studies were identified from the references of included literature reports. STATA version 11.0 was used to analyze the pooled data. **Results:** A total of eight articles were involved in our study. The overall participants of tranexamic acid (TXA) group were 3533, whereas it was 11,007 in the control group. Our meta-analysis showed that TXA is preferable for revision total hip arthroplasty because of its lower value of hemoglobin reduction (weighted mean difference = -1.277–1.405; 95% CI: -1.996 to -0.559; $p < 0.001$), the rate of blood transfusion (odds ratio: 0.233; 95% CI: 0.129–0.422; $p < 0.001$) and the number of red blood cell units transfused (weighted mean difference = -0.978; 95% CI = -1.631 to -0.324; $p = 0.003$). However, there was no difference in calculated blood loss ($p = 0.075$), operation duration ($p = 0.569$) and venous thromboembolism complications ($p = 0.338$). **Conclusion:** Based on available evidence, use of intravenous TXA for patients undergoing revision arthroplasty may reduce hemoglobin reduction, number of red blood cell units transfused and blood transfusion rate without increasing the risk of venous thromboembolism and length of operation duration. Given the relevant possible biases in our study, adequately powered and better-designed studies with long-term follow-up are required to reach a firmer conclusion.

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Keywords: intravenous tranexamic acid • meta-analysis • revision • total hip arthroplasty

Currently, patients with total hip arthroplasty (THA) for osteoarthritis, rheumatoid arthritis, femoral neck fracture and femoral head necrosis are increasing by years [1,2]. Similarly, there was an increase in the number of revision total hip arthroplasty (RHA) surgery due to infection, loose prosthesis and prosthetic wear [3–5]. It is estimated that RHA in 2030 may exceed 97,000 cases. The annual revision rate of the hip joint is about 19.05% and the rate of growth is 137% [6]. Perioperative hemorrhagic anemia is the main problem in orthopedic surgery, and the number of transfusions after total joint arthroplasty accounts for 40% of the total number of patients with orthopedic surgery [7–9]. The operation of the RHA still considered being operation with higher blood loss and blood transfusion rate during the perioperative period [10]. Though, surgeons and anesthesiologists have taken a number of steps to reduce perioperative blood loss and blood transfusion including controlled hypotension, local anesthesia, intraoperative blood recycling and erythropoietin [11,12]. Allogeneic blood transfusion could rapidly correct postoperative anemia, but there are obviously related complications: transfusion-related infectious diseases, intravascular hemolysis, transfusion-related acute lung loss and delayed recovery [7,13,14]. As an artificial synthesis of lysine analogs, tranexamic acid (TXA) could reduce calculated blood loss by blocking the antifibrinolysis of lysine binding sites [15]. Recently, some studies on primary THAs have suggested that a single or multiple uses of TXA (10 ~ 20 mg/kg) could reduce postoperative bleeding without an increase of deep venous thrombosis (DVT) or

pulmonary embolism [16–19]. Other studies have shown that intravenous TXA can reduce the bleeding of RHA [20]. Nevertheless, what is the effect of intravenous TXA reducing perioperative blood loss? Whether it will increase the risk of DVT and pulmonary embolism in patients will require further clinical study. Thus, we performed a meta-analysis pooling the relevant literature to definite the clinical effect in RHA.

Materials & methods

PRISMA [21], the abbreviation for Preferred Reporting Items for Systematic Reviews and Meta-Analyses, was used for the study guidelines.

Data sources & searches

Electronic databases including Cochrane Library, Medline (1966-2019.2), PubMed (1966-2019.2), EMBASE (1980-2019.2) and ScienceDirect (1985-2019.2) were searched for comparative studies involving intravenous TXA in patients undergoing revision THA. We retrieved the following keywords in combination with Boolean logic: total hip arthroplasty, total hip replacement, revision and intravenous TXA. Beyond that, the research of the appraisal reference list was manually checked to determine other potential qualification trials. The process iterates until no more articles could be determined.

Inclusion & exclusion criteria

The articles will be incorporated into the present meta-analysis if the literature meets the following preplanned criteria in accordance with PICOS: population: limited the comparison to patients undergoing RHA; intervention: used strictly intravenous TXA and placebo or nothing; comparison: compared the results about reducing blood loss and complications; outcome measures: the primary outcomes included transfusion requirements, hemoglobin (Hb) reduction, operation duration, calculated blood loss, venous thromboembolism (VTE) complications, number of RBC units transfused; and an official published full-text English-written randomized controlled trials (RCTs) or non-RCT. The exclusion criteria were as follows: conference or commentary articles and letters to the editor; animal trials; unclear patient characteristics and outcome data; case reports and case series; systematic reviews or meta-analyses.

Data extraction & outcome measures

Two of the reviewers respectively extracted data from the included studies. The following essential information was captured: first author names, publication year, samples size, study design, and outcomes and other relevant data. The extracted data (median, range and the size of the trial, and mean difference and standard deviation) are put into the designed standardized table according to the Cochrane Handbook. When there are differences of opinion, another authority author has the final decision. The outcome measurements were transfusion requirements, Hb reduction, operation duration, calculated blood loss, VTE complications and number of RBC units transfused.

Quality assessment & statistical analysis

We used the STATA version 11.0 (Stata Corporation, TX, USA) for statistical analyses. When $I^2 < 25\%$, we considered the data have no obvious heterogeneity, and we conducted a meta-analysis using the fixed-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Otherwise, the random-effect model was performed. The results of continuous outcomes (Hb reduction, operation duration, calculated blood loss and number of RBC units transfused) were expressed as weighted mean difference (WMD) with 95% CIs. For discontinuous various outcomes (transfusion requirements and VTE complications) odds ratio (OR) with 95% CIs was applied for the assessment.

Results

Search results

A total of 68 studies were identified as potentially relevant literature reports. Fifty reports were removed because of duplication. By scanning the title and abstract, eight reports were excluded according to the eligibility criteria. Eight reports are eliminated after browsing the full text. No additional studies were obtained after the reference review. Ultimately, eight studies were eligible for data extraction and meta-analysis. The searching process is shown in Figure 1.

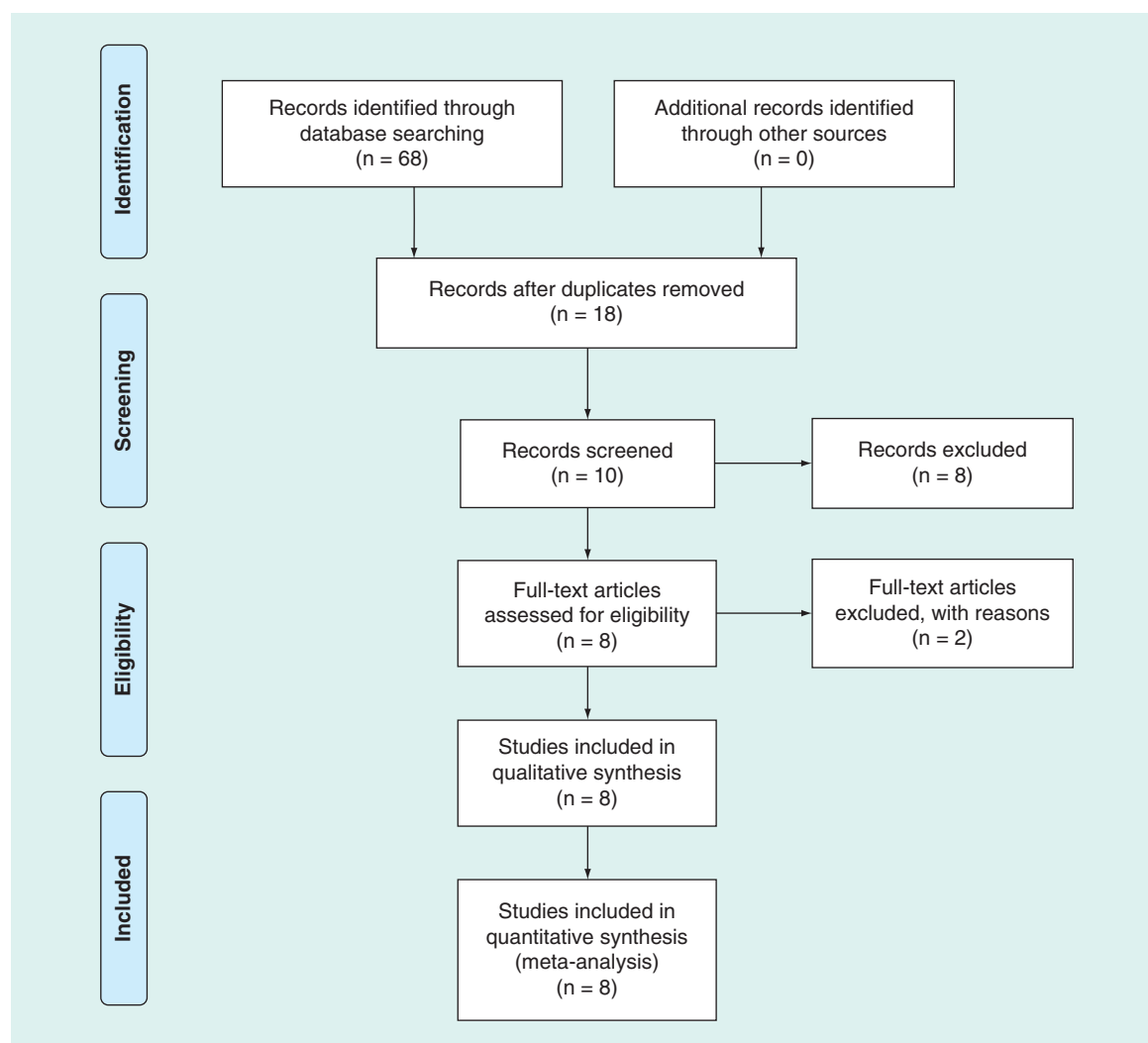


Figure 1. Flowchart of the study selection process.

Quality assessment

The literature quality evaluation was conducted separately by two reviewers. The study scores of RCT was assessed by Jadad scale. The study scores of all non-RCTs were assessed by Newcastle–Ottawa Scale, maximum of 9 points. The quality of most of the included publications was high, more details were shown [Table 1](#).

Study characteristics

A total of eight articles (one RCTs [22] and seven non-RCTs [23–29]) were involved in our study. The overall participants of intravenous TXA group were 3533, whereas it was 11,007 in the control group. Demographic characteristics and details concerning the literature type of the included studies are shown in [Table 2](#). Statistically similar baseline characteristics were observed between both the two groups. The methods of intravenous TXA use in RHA are shown in [Table 3](#).

Outcomes of meta-analysis

Six outcomes were assessed with our meta-analysis: calculated blood loss, Hb reduction, transfusion requirements, number of RBC units transfused, operation duration and VTE complications ([Table 4](#)).

Table 1. Quality assessment scores of the included studies.

Study (year)	Design	Jadad scale			Total scores
		Randomization	Blinding	Cohort	
Gill <i>et al.</i> (2009)	Randomized controlled trial	2	2	1	5
NOS					
		Selection	Comparability	Exposure	Total scores
Phillips <i>et al.</i> (2006)	Retrospective cohort study	2	1	2	5
Kazi <i>et al.</i> (2012)	Prospective cohort study	3	1	2	6
Duncan <i>et al.</i> (2015)	Retrospective cohort study	3	1	2	7
Park <i>et al.</i> (2016)	Retrospective cohort study	4	1	2	7
Mariani <i>et al.</i> (2017)	Retrospective cohort study	4	1	2	7
Peck <i>et al.</i> (2018)	Retrospective cohort study	3	1	2	6
Reichel <i>et al.</i> (2018)	Retrospective cohort study	4	1	3	8

NOS: Newcastle–Ottawa Scale.

Table 2. Characteristics of trials.

Study	Year	Design	Recruitment	Sample		Mean age (years)		Gender (M/F)		VTE prophylaxis
				TXA	Control	TXA	Control	TXA	Control	
Phillips <i>et al.</i>	2006	Non-RCT	2003–2005	40	40	Un	Un	Un	Un	LMWH
Gill <i>et al.</i>	2009	RCT	2005–2007	5	5	61.4	66.6	1/4	2/3	Warfarin + mechanical
Kazi <i>et al.</i>	2012	Non-RCT	2008–2010	30	30	72	73	20/10	19/11	LMWH
Duncan <i>et al.</i>	2015	Non-RCT	2005–2010	2785	10,477	67	67	Un	Un	Aspirin + LMWH
Park <i>et al.</i>	2016	Non-RCT	2012–2014	114	56	63	69	61/48	30/22	Unclear
Mariani <i>et al.</i>	2017	Non-RCT	2011–2014	61	64	67.5	69.7	34/27	23/41	LMWH
Peck <i>et al.</i>	2018	Non-RCT	2008–2016	402	232	Un	Un	133/269	93/193	Un
Reichel <i>et al.</i>	2018	Non-RCT	2014–2016	96	103	66.1	68.6	39/57	47/56	Enoxaparin

F: Female; LMWH: Low-molecular-weight heparin; M: Male; non-RCT: Nonrandomized controlled trial; RCT: Randomized controlled trial; TXA: Tranexamic acid; VTE: Venous thromboembolism; Un: Unclear.

Table 3. Intervention of tranexamic acid.

Study	Year	Intervention of tranexamic acid
Phillips <i>et al.</i>	2006	TXA 10 mg/kg iv. 30 min before incision, then 10 mg/kg further dose after 6 h from operation
Gill <i>et al.</i>	2009	TXA 10 mg/kg iv. before induction of anesthesia, then 1 mg/kg/h infusion until wound closure
Kazi <i>et al.</i>	2012	TXA 10 mg/kg iv. 30 min before operation and 10 mg/kg iv. further dose after 3 h from operation
Duncan <i>et al.</i>	2015	TXA 1 g was infused before incision, then 1 g was infused immediately before closure
Park <i>et al.</i>	2016	TXA 1 g iv. at incision and TXA 1 g iv. further dose after 2 h from operation
Mariani <i>et al.</i>	2017	TXA 1 g iv. before skin incision and TXA 1 g iv. further dose until wound closure
Peck <i>et al.</i>	2018	TXA 20 mg/kg iv. before operative in all revision total hip arthroplasty cases
Reichel <i>et al.</i>	2018	TXA 10 mg/kg bodyweight was received by every patient suffering revision total hip arthroplasty and 1 mg/kg bodyweight/h further dose intraoperatively

iv.: Intravenously; TXA: Tranexamic acid.

Calculated blood loss

Four literatures provided the number of calculated blood loss. The results show 642 cases in the experimental group and 421 cases in the control group. Significant heterogeneity was observed, and a random effects model was used ($I^2 = 72.9\%$, $p = 0.011$). The calculated blood loss between the experimental and the control groups was not statistically significant (WMD = -177.255, 95% CI: -372.430, 17.919; $p = 0.075$; Figure 2).

Hemoglobin reduction

Two literatures provided the values of Hb reduction. A moderate heterogeneity was found ($I^2 = 42.5\%$, $p = 0.187$), we used random-effect model. The results show that there was a statistical difference between the experimental and the control groups (WMD = -1.277, 95% CI: -1.996, -0.559; $p < 0.001$; Figure 3). The present meta-analysis

Table 4. Meta-analysis results.

Outcome	Studies	Groups		Overall effect			Heterogeneity	
		TXA	Placebo	Effect estimate	95% CI	p-value	I ² (%)	p-value
Calculated blood loss	4	642	421	-177.255	-372.430 to 17.919	0.075	72.9	0.011
Hemoglobin reduction	2	144	86	-1.405	-1.810 to -0.999	0.000	42.5	0.187
Transfusion requirements	7	748	530	0.233	0.129 to 0.422	0.000	66.2	0.007
RBC units transfused	4	192	202	-0.978	-1.631 to -0.324	0.003	55.8	0.079
Duration of operation	2	210	159	-6.037	-26.775 to 14.702	0.568	51.2	0.152
VTE complications	5	3384	10,916	0.846	0.601 to 1.191	0.338	0.0	0.759

RBC: Red blood cell; TXA: Tranexamic acid; VTE: Venous thromboembolism.

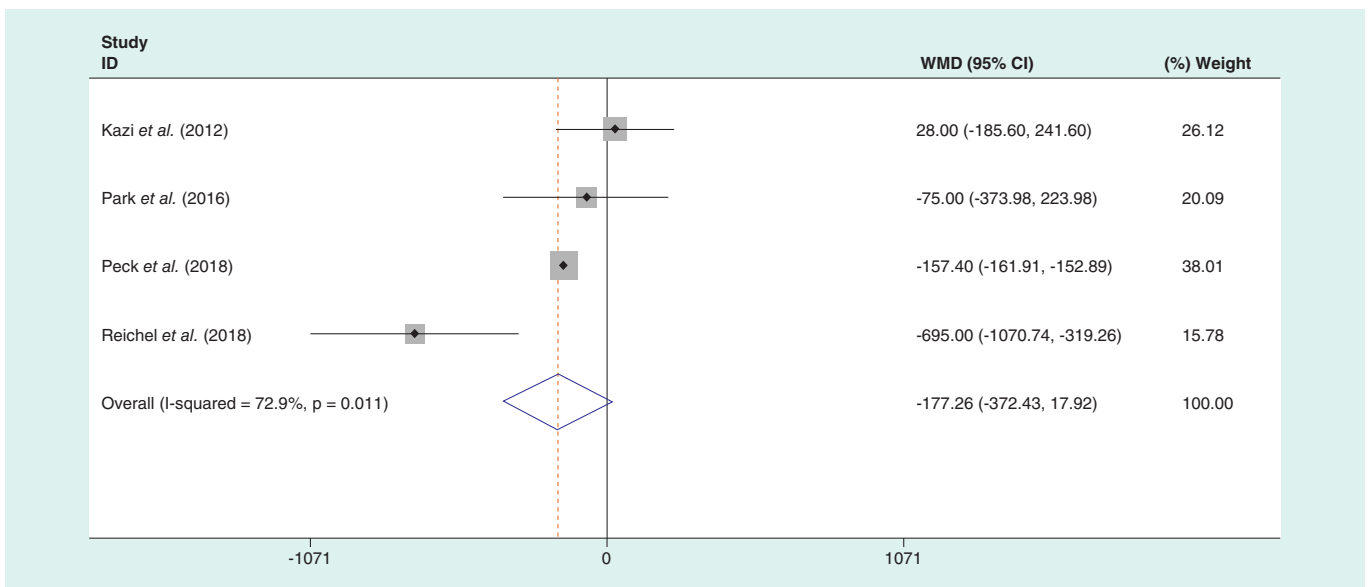


Figure 2. Forest plot on the assessment of the calculated blood loss.
WMD: Weighted mean difference.

demonstrates intravenous TXA with a lower value of Hb reduction than placebo or nothing in RHA.

Transfusion requirements

Seven literatures concentrated on the blood transfusion rate. Significant heterogeneity was found ($I^2 = 66.2\%$, $p = 0.007$), we used random model. The results show that there was a significant difference between experimental and control groups (OR: 0.233; 95% CI: 0.129–0.422; $p < 0.001$; Figure 4). The present meta-analysis demonstrates intravenous TXA with a lower rate of blood transfusion than placebo or nothing in RHA.

Number of RBC units transfused

Four articles mentioned the number of RBC units transfused and data pooled by a random effects model to reveal that there was a significant difference between the two groups (WMD = -0.978, 95% CI: -1.631 to -0.324; $p = 0.003$; Figure 5). The present meta-analysis demonstrates intravenous TXA with a lower number of RBC units transfused than placebo or nothing in RHA.

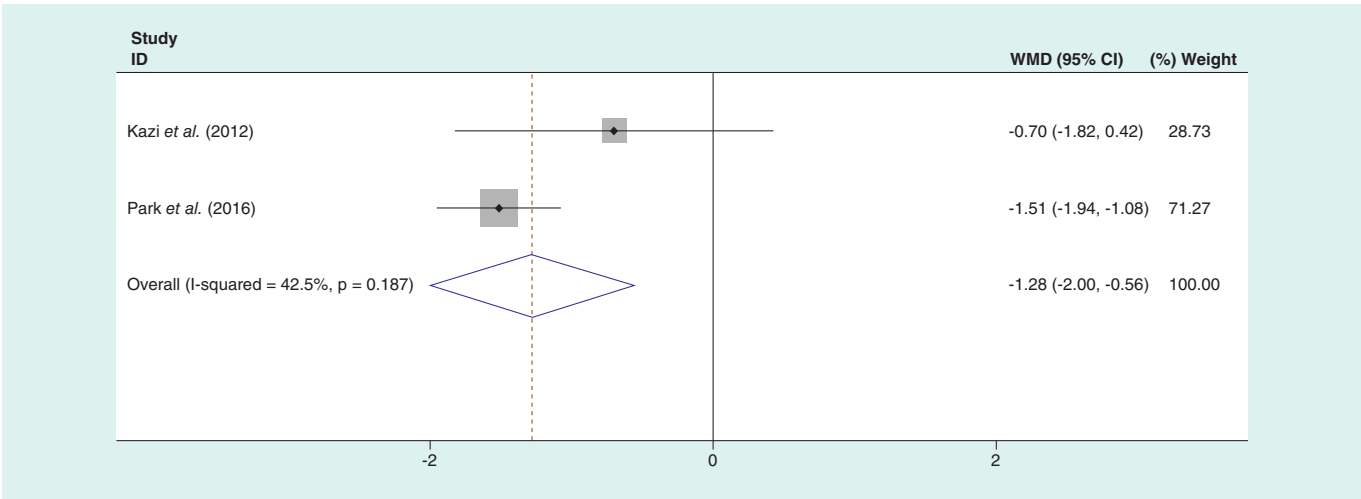


Figure 3. Forest plot on the assessment of the hemoglobin reduction.
WMD: Weighted mean difference.

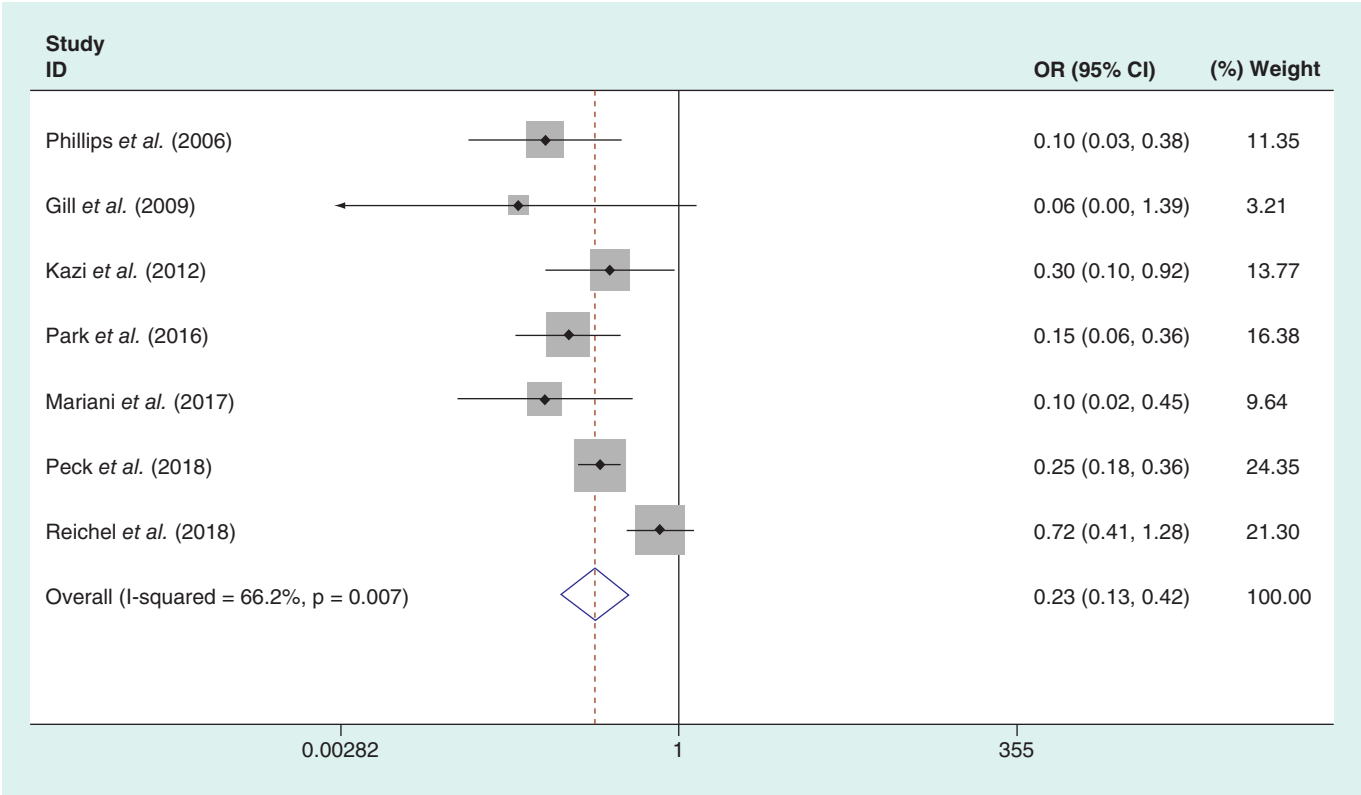


Figure 4. Forest plot on the assessment of the transfusion requirements.
OR: Odds ratio.

Operation duration

Two articles mentioned the operation duration and data pooled by a random effects model to reveal that there was no significant difference between the two groups (WMD = -6.037, 95% CI: -26.775–14.702; p = 0.569; Figure 6).

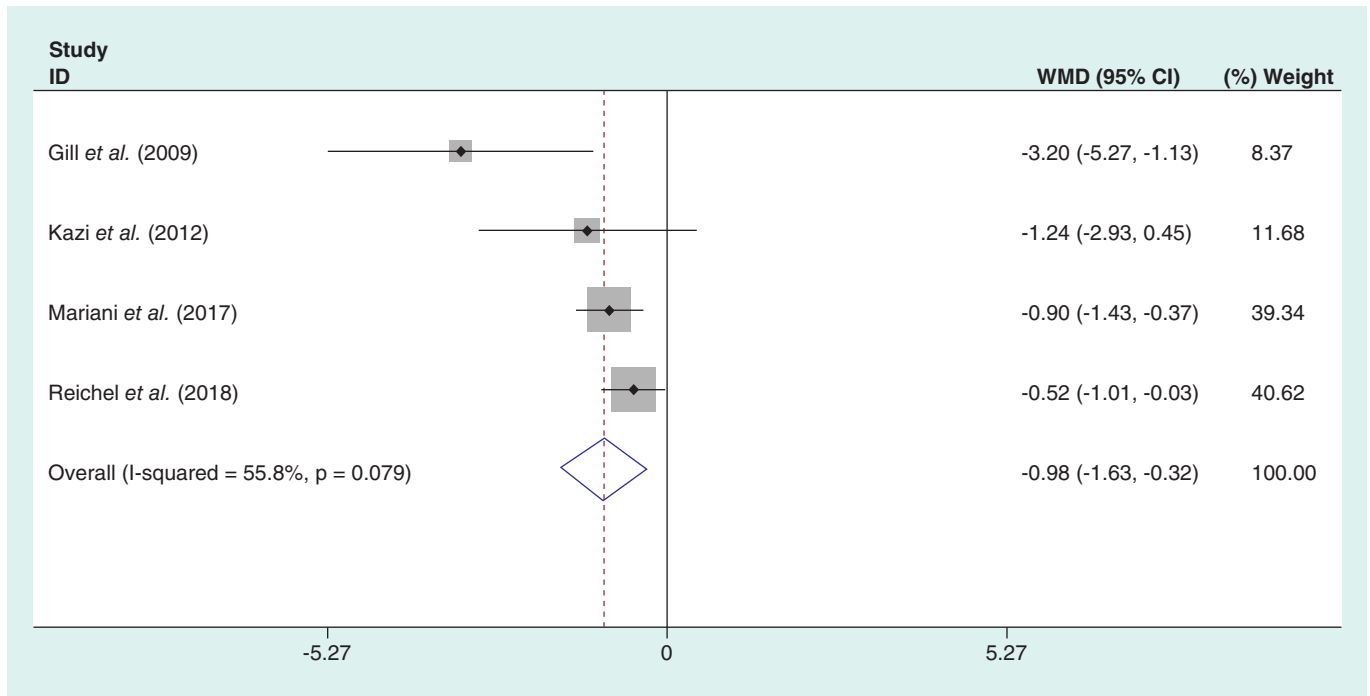


Figure 5. Forest plot on the assessment of the number of red blood cell units transfused.
WMD: Weighted mean difference.

VTE complications

Five literatures provided the numbers of VTE in patients. No significant heterogeneity was found, fixed model was used ($p = 0.759$, $I^2 = 0.0\%$). The results show that there was no statistical difference between the experimental and the control groups (OR: 0.846; 95% CI: 0.601–1.191; $p = 0.338$; Figure 7).

Discussion

At present, most of the studies suggest that for patients with primary joint replacement, using small doses of intravenous TXA can effectively reduce the patients with perioperative blood loss, postoperative transfusion rate, the risk of surgery and hospitalization expenses and length of hospital stay [30–33]. Recently, intravenous TXA has applied in revision joint replacement. Extensive tissue damage and longer operation duration in the revision arthroplasty are usually associated with increased intraoperative and calculated blood loss [34]. The tissue damage caused by revision surgery could activate the fibrinolytic system, which is one of the reasons for the inevitable hemorrhage after surgery. As an artificial synthesis of lysine analogs, TXA could reduce perioperative blood loss by blocking the antifibrinolysis of lysine binding sites [15,35]. Yamasaki [36] found that the most bleeding time in 2 h after joint arthroplasty was followed by a gradual decrease in drainage volume per hour over time. Although TXA has been widely used to reduce blood loss and transfusion requirements in primary THA [37–40], little is known about the efficacy and safety of the use of TXA in RHA. This is the first meta-analysis, aimed to intravenous TXA, reduces blood transfusions in RHA and showed that intravenous TXA is preferable for RHA because of its lower value of Hb reduction, rate of blood transfusion and the number of RBC units transfused. However, there was no difference in calculated blood loss, operation duration and VTE complications.

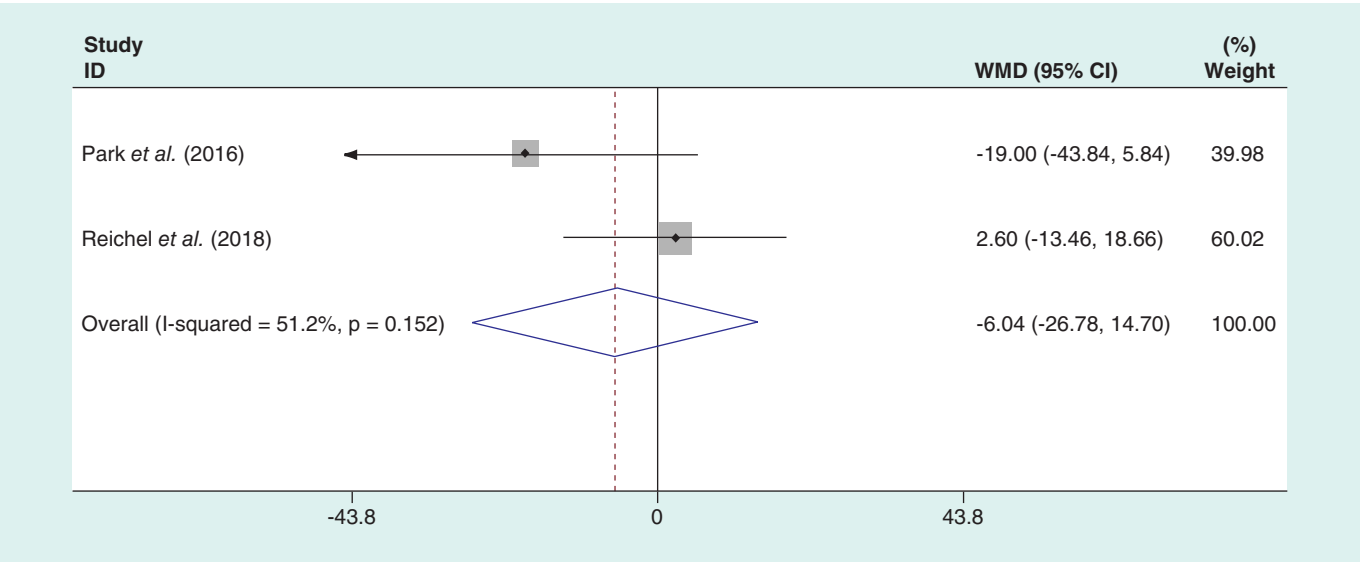


Figure 6. Forest plot on the assessment of the operation duration.
WMD: Weighted mean difference.

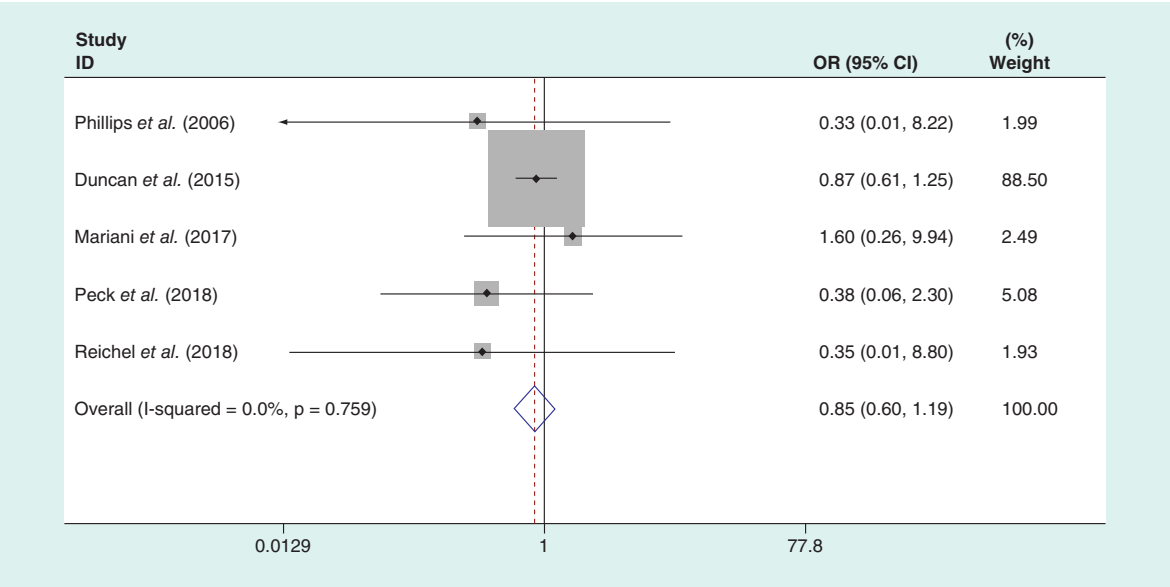


Figure 7. Forest plot on the assessment of the venous thromboembolism complications.
OR: Odds ratio.

As we all know, intravenous TXA has been effectively demonstrated to reduced Hb loss in THA [41,42]. One recent meta-analysis in THA patients showed that intravenous TXA was significantly associated with a lower reduction of Hb drop compared with control group (mean difference [MD] = -0.85; $p < 0.001$; 95% CI: -1.26 to -0.44) [42]. Intravenous TXA could reduce Hb loss up to 6.03 g/l compared with that in the control group in THA patients ($p = 0.001$; 95% CI: 3.90–8.15 g/l) [41]. Kzai *et al.* [24] use a large hospital database to assess the efficacy of intravenous TXA in patients undergoing RHA and found that the mean Hb reduction was 2.7 g/dl in the TXA group and 3.4 g/dl in the control group. There was a significant reduction in Hb reduction (TXA: 2.02 ± 1.27 g/l vs Control [CON]: 3.53 ± 1.40 g/l; $p < 0.001$) in the study of Park *et al.* [26]; the data of 144 participants in TXA group and 86 participants in the control group were extracted to make a further credible investigation. Similarly, the result of our meta-analysis (WMD = -1.405, 95% CI: -1.810, -0.999; $p < 0.001$) shows that intravenous TXA could significantly reduce the Hb reduction compared with the control group.

The seven included studies evaluate the effect of intravenous TXA on postoperative blood transfusion rate. Phillips *et al.* [20] found the application of TXA in RHA could effectively reduce the postoperative blood transfusion rate. The present meta-analysis shows that blood transfusion rate in the TXA group (40.37%) was significantly lower than that in control group (71.13%). Our pooled data demonstrated that intravenous TXA could effectively reduce the postoperative blood transfusion rate (OR: 0.233; 95% CI: 0.129, 0.422; $p < 0.001$), which is in accordance with the research of Noordin *et al.* [43] and Kzai *et al.* [44]. At the same time, a reduction in the number of RBC unit transfused per patient is also a concern in RHA. In primary THA, one meta-analysis showed that reduction of the number of RBC units transfused per patient was not significantly in TXA group compared with the placebo group (WMD = 0.3, 95% CI: -0.49–1.09; $p = 0.45$) [41]. Our meta-analysis found that the number of RBC units transfused was significantly lower in the TXA group compared with the control group in RHA (WMD = -0.978, 95% CI: -1.631 to -0.324; $p = 0.003$). However, a high heterogeneity appeared in these results, we hypothesized that the transfusion trigger was the source of high heterogeneity.

Andreu *et al.* [45] measured blood loss in the drain at 24 h and found it is significantly differed in both groups, confirming more visible blood loss in the control group (TXA: 256.4 ± 266.6 , CON: 594.6 ± 422.3 , $p = 0.009$); they believes intravenous TXA administration appeared as an effective means of reducing blood loss in revision total knee arthroplasty operation. Based on the existing research results, Blanie *et al.* [46] believed that the fibrinolysis effect of the body will reach the peak around 6 h after surgery, and reduced to the preoperative level at 24 h after an operation. The optimal time for control and reduction of blood loss due to the activation of the fibrinolytic system during the perioperative period was from the beginning of surgery to 6 h after surgery [47–49]. The antifibrinolytic effect of TXA can last about 8 h, so it could limit the body's hyperfibrinolysis to the maximum extent [47–49]. However, from our meta-analysis, four articles mentioned the number of calculated blood loss were pooled and showed that no statistically significant difference was found in the calculated blood loss between the experimental group and the control group. It may be due to the relatively small sample size of the included literatures. In our study, three articles measured calculated blood loss excluding the hidden blood loss while Reichel *et al.* [29] measured calculated blood loss according to the Brecher formula [50] that the hidden blood loss was included. Meanwhile, the heterogeneity reduced a lot when this article was excluded ($I^2 = 37.2$; $p = 0.204$). The conclusion is still to be proved, more powered and better-designed studies are necessary to reach a firmer conclusion.

The security of antifibrinolytic agents in orthopedics major surgery has always been a topic of discussion, and whether the use of intravenous TXA will increase the risk of DVT after surgery is also a hot concern for surgeons. Although many scholars believe that the risk of VTE in Asian population is lower than that in the European and American populations, the literature reports that it still has a higher incidence of VTE [51,52]. Fargen *et al.* [53] showed that the preoperative TXA 10 mg/kg dose was widely believed to reduce blood loss and to prevent DVT, but several foreign studies [35,54–56] reported that the use of TXA in the perioperative period of primary joint arthroplasty surgery did not increase the incidence of VTE compared with the control group. The present meta-analysis demonstrated that intravenous TXA was not associated with an increased complication rate of VTE. At the same time, the results of our pooled data demonstrated that there was no statistic difference in length of operation duration (WMD = -6.037; 95% CI: -26.775–14.702; $p = 0.569$).

Our research also has some limitations that should be considered. First, the sample size of the included literature is too small. Second, different administrations of TXA, operation methods and study designs, especially in retrospective cohort study (RCSs), might have a biased impact on our results. Third, lacking long-term evaluation indexes such as Keen Society Score and range of motion. Fourth, the heterogeneity of hidden blood loss was still moderate due

Summary points

- We performed a meta-analysis pooling the relevant literature to define the clinical effect in revision total hiparthroplasty. Potential academic articles were identified from Cochrane Library, Medline, PubMed, EMBASE, ScienceDirect and other databases. STATA version 11.0 was used to analyze the pooled data.
- The overall participants of tranexamic acid (TXA) group were 3533, whereas it was 11,007 in the control group.
- Our meta-analysis showed that TXA is preferable for revision total hiparthroplasty because of its lower value of hemoglobin reduction, the rate of blood transfusion and the number of red blood cell units transfused.
- However, there was no difference in calculated blood loss, operation duration and venous thromboembolism complications.
- Based on available evidence, use of intravenous TXA for patients undergoing revision arthroplasty may reduce hemoglobin reduction, number of red blood cell units transfused, and blood transfusion rate without increasing the risk of venous thromboembolism and length of operation duration.

to no gold standard; more powered and better-designed studies are necessary to reach a firmer conclusion. Finally, the sample sizes of the included studies are relatively small in the present meta-analysis.

Conclusion

Based on available evidence, use of intravenous TXA for patients undergoing revision arthroplasty may reduce Hb reduction, number of RBC units transfused and blood transfusion rate without increasing the risk of VTE and length of operation duration. Given the relevant possible biases in our study, adequately powered and better-designed studies with long-term follow-up are required to reach a firmer conclusion.

Financial & competing interests disclosure

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