

Intravenous tranexamic acid use in revision total joint arthroplasty: a meta-analysis

Feng-Chih Kuo¹
Pao-Yen Lin²
Jun-Wen Wang¹
Po-Chun Lin¹
Mel S Lee¹
Antonia F Chen³

¹Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kaohsiung, Taiwan; ²Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kaohsiung, Taiwan; ³Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Purpose: Massive perioperative blood loss in complex revision total joint arthroplasty (TJA) often requires blood transfusions. Tranexamic acid (TXA) has been used in elective primary TJA to minimize blood loss and transfusions. The purpose of this meta-analysis was to evaluate the safety and efficacy of intravenous TXA in revision TJA.

Methods: A literature search of PubMed, Scopus, and the Cochrane Controlled Trials Register was performed to identify studies published between January 2000 and May 2017. All randomized controlled trials (RCTs) and retrospective cohort observational studies evaluating the efficacy of intravenous TXA during revision total knee arthroplasty (TKA) and total hip arthroplasty (THA) were included. The mean differences (MDs) of blood loss, hemoglobin (Hb) change, and red blood cell (RBC) units transfused were compiled, and ORs of transfusion and venous thromboembolism (VTE) events in TXA and control groups were calculated.

Results: Seven studies involving 930 patients were included (501 TXA vs 429 control). Intravenous TXA use had a significantly less blood transfusion (OR=0.20, 95% CI=0.11–0.34, $P<0.001$), lower Hb drop (MD=−0.88, 95% CI=−1.31 to −0.44, $P<0.001$), and less number of RBC units transfused (MD=−0.44, 95% CI=−0.65 to −0.24, $P<0.001$) compared to control in the postoperative period. No significant difference was seen in blood loss (MD=−245, 95% CI=−556 to 66, $P=0.12$) and VTE events (OR=0.57, 95% CI=0.13–2.42, $P=0.45$) between groups.

Conclusion: Our meta-analysis suggests that intravenous administration of TXA can significantly reduce blood transfusion requirements following revision TJA, without increasing the risk of VTE. However, due to the variation in included studies, larger RCTs are required to draw firm conclusions.

Keywords: tranexamic acid, revision arthroplasty, transfusion, venous thromboembolism, meta-analysis

Introduction

More revision total joint arthroplasties (TJAs) are being performed as the number of primary TJAs has increased.¹ Revision TJA is often associated with greater blood loss, which may result in increased transfusion requirements. Allogenic red blood cell (RBC) transfusions can lead to transfusion reactions, are a risk factor for periprosthetic joint infections, and may increase costs. Blood-conserving techniques, such as the use of antifibrinolytic agents, have been implemented to decrease blood loss and blood transfusion rates.²

Tranexamic acid (TXA) is a commonly used antifibrinolytic in orthopedic surgeries that works by blocking the lysine-binding sites on plasminogen molecules, inhibiting the formation of plasmin.³ TXA can be administered intravenously (IV), topically in the surgical wound, or combined. All forms of TXA administration have successfully reduced blood loss after primary total knee arthroplasty (TKA) and total

Correspondence: Antonia F Chen
Department of Orthopaedic Surgery,
Brigham and Women's Hospital, Harvard
Medical School, 75 Francis Street, Boston,
MA, USA
Tel +1 617 525 5935
Fax +1 617 264 5226
Email uafchen@bwh.harvard.edu

hip arthroplasty (THA) over the last decade.³ IV TXA has been widely studied and has been shown to reduce blood loss and transfusion requirements in revision TJA.^{4–14} However, few of these studies characterized changes in hemoglobin (Hb) or venous thromboembolism (VTE) complications. Additionally, some of these studies were poorly designed and had a low power or inconclusive results. While various small studies have evaluated the use of IV TXA in revision TJA, there have been no studies to date that have compiled data from multiple studies.

Thus, the purpose of this meta-analysis was to investigate the efficacy of TXA in revision TJA, specifically assessing the following outcome measurements: 1) blood transfusion rate; 2) Hb change; 3) mean units of RBC transfused; 4) blood loss; and 5) VTE complications.

Materials and methods

Data and literature sources

Two independent reviewers searched for eligible studies between January 2000 and May 2017 in PubMed at the National Library of Medicine, Scopus, and Cochrane Controlled Trials Register. The search was performed by using the search terms (tranexamic acid) AND (revision) AND (hip or knee), without limitation in language. The references of relevant articles and review articles in this area were searched for citations not indexed in abovementioned databases. The titles and abstracts of studies obtained by this search strategy were screened by reviewers to determine if studies were potentially eligible for inclusion in this meta-analysis. The following studies were excluded based on titles and abstracts alone: review articles, non-human studies, articles commenting on other studies or case reports, and studies not mentioning TXA. In cases of disagreement, a third person was consulted to evaluate the articles.

Study selection and data extraction

After primary screening of titles and abstracts, the remaining studies comparing administration of IV TXA vs controls were evaluated for the following: 1) patients undergoing unilateral revision THA or TKA; 2) the use of IV TXA; and 3) outcome measurements including number of RBC units transfused, number of patients who received a blood transfusion, blood transfusion rate, mean and standard deviation values of postoperative blood loss via drainage (BLD), estimated blood loss (EBL), total blood loss (TBL) and change in Hb levels before and after surgery, and VTE complications. The full text of articles was obtained if the title and abstract did not supply adequate information, and authors of individual

trials were contacted directly to provide further information when necessary. Disagreements were resolved by consensus or consultation with the senior author, and studies were excluded if there were unavailable data. The process of study selection is described in Figure 1.

Assessment of methodological quality

To assess the methodological quality of included studies, two reviewers independently assessed the methodological quality of the prospective randomized controlled trials (RCTs) using the Jadad scale, including randomization, blinding, withdrawals and dropouts, inclusion and exclusion criteria, adverse reactions, and statistical analysis. A scale of 0 (very poor) to 5 (rigorous) was used to assess the methodological strength of a clinical trial.¹⁵ The Newcastle–Ottawa Scale (NOS), as recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used to assess retrospective or prospective cohort observational studies based on three criteria: the selection of study groups, the comparability of groups, and the ascertainment of either exposure or outcome of interest for case–control and cohort studies. The NOS ranged between 0 and 9, with 7+ points considered as a “high-quality” study.¹⁶ Any unresolved disagreements between reviewers were resolved by consultation with a third investigator.

Data synthesis and analysis

The Comprehensive Meta-Analysis Software, version 2 (Biostat, Englewood, NJ, USA) was used to analyze the selected studies. The treatment effect for continuous data was expressed as mean difference (MD) with a 95% CI. The treatment effect for dichotomous data was expressed as OR with a 95% CI. The data from included studies were synthesized by using a random-effects model. Missing data were sought from the authors. When this was not possible or data were missing due to loss of follow-up, intention-to-treat principles were used.

Heterogeneity was determined by estimating the proportion of between-study inconsistencies due to actual differences between studies, rather than differences due to random error or chance using the I^2 statistic, with values of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity, respectively. A P -value of <0.1 and an I^2 value of $>50\%$ were considered suggestive of statistical heterogeneity. It did not imply that there was necessarily homogeneity, as there may have been insufficient power to be able to detect heterogeneity. When the data allowed, we performed subgroup analysis of the trials according to the type of surgery location (hip or knee).

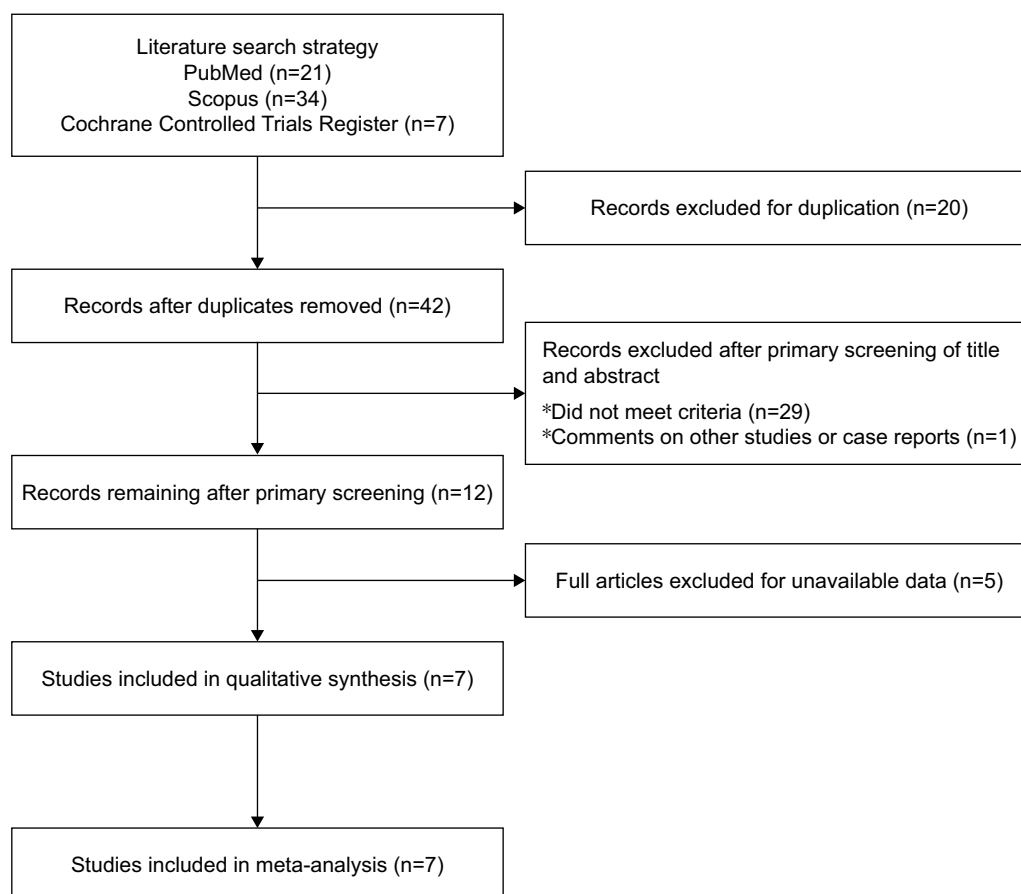


Figure 1 The flow chart of literature screening.

Results

Literature screening

There were 62 articles for initial consideration in the meta-analysis, and a total of 20 studies were excluded due to duplication. Based on title and abstract evaluation, 30 studies were excluded because they did not meet the specified criteria. When the text of the remaining 12 studies was examined, five of them were excluded because they did not have available data for meta-analysis (Figure 1). The remaining seven studies (one RCT, one prospective cohort observational study, and five retrospective cohort observational studies) were included in the meta-analysis, which included 501 revision TJA patients (149 revision THAs and 352 revision TKAs) who were administered intravenous TXA and 429 revision TJA control patients (91 revision THAs and 338 revision TKAs) who did not receive TXA. Different dosages of TXA were used in the studies (Table 1). In terms of dosages, the most commonly used doses of IV TXA were 10 mg/kg before skin incision and 10 mg/kg or 1 g 2–3 hours after the operation in revision THA. In revision TKA, IV TXA with a dose of 10–20 mg/kg before deflation of the tourniquet was

commonly used. Only one RCT study⁵ in this meta-analysis had a wider range of blood transfusion (Hb <10 g/dL and hematocrit [Hct] <30%) compared with the other six observational studies. This RCT study⁵ also lacked information about the change in Hb levels.

Methodological quality of included studies

Table 2 summarizes the quality assessment of the selected studies. One study was an RCT with a Jadad score of 5, demonstrating high quality. Among the other six nonrandomized studies, the NOS score ranged from 6 to 8, which indicated acceptable quality for these studies.

Allogenic blood transfusion rate

All seven studies provided data on the number of patients who underwent blood transfusions. A total of 75 (15.0%) transfusions occurred in the TXA group compared with 166 (38.7%) transfusions in the control group. Five retrospective cohort observational studies favored lower allogenic blood transfusion rate in patients with IV TXA compared with the control group.

Table 1 Characteristics of included studies

Study, year	Study type	Location	No TXA/control	Intervention	VTE prophylaxis	Blood transfusion protocol
Gill et al, ⁵ 2009	RCT	Hip	5/5	TXA 10 mg/kg IV before induction of anesthesia, then 1 mg/kg/h infusion until wound closure	Warfarin+mechanical	Hb <10 g/dL and Hct <30%
Kazi et al, ⁷ 2012	Prospective cohort observational study	Hip	30/30	TXA 10 mg/kg IV 30 minutes before operation and 10 mg/kg IV further dose after 3 hours from operation	LMWH	Hb <7 g/dL or Hb <8 g/dL with cardiovascular disease
Park et al, ¹² 2016	Retrospective cohort observational study	Hip	114/56	TXA 1 g IV at incision and TXA 1 g IV further dose after 2 hours from operation	Unknown	Hb <7 g/dL or Hb <8 g/dL with ACS, CHF, or requiring oxygen
Aguilera et al, ⁸ 2012	Retrospective cohort observational study	Knee	19/49	TXA 1 g IV 15–30 minutes before inflation of the tourniquet and TXA 1 g IV before deflation of the tourniquet	LMWH	Hb <8 g/dL or Hb <8.5 g/dL with heart disease or older than 70 years Hb between 8.5 and 9 g/dL (does not tolerate sitting)
Smit et al, ⁹ 2013	Retrospective cohort observational study	Knee	246/178	TXA 20 mg/kg IV before deflation of the tourniquet	LMWH	Hb <7 g/dL or symptomatic or Hb between 8 and 9 g/dL with cardiac history
Samujh et al, ¹⁰ 2014	Retrospective cohort observational study	Knee	43/68	TXA 10 mg/kg IV 10 minutes before deflation of the tourniquet	Rivaroxaban	Hb <8 g/dL with symptoms of anemia
Ortega-Andreu et al, ¹³ 2016	Retrospective cohort observational study	Knee	44/43	TXA 15 mg/kg IV before deflation of the tourniquet and 15 mg/kg IV further dose after 3 hours after surgery	Unknown	Hb <8 g/dL or Hb <10 g/dL with symptoms of anemia or cardiac history

Abbreviations: ACS, acute coronary syndrome; CHF, congestive heart failure; Hb, hemoglobin; Hct, hematocrit; IV, intravenously; LMWH, low-molecular-weight heparin; RCT, randomized controlled trial; TXA, tranexamic acid; VTE, venous thromboembolism.

However, one RCT⁵ and one retrospective cohort observational study⁸ did not favor IV TXA to reduce the allogenic blood transfusion rate. The proportion of patients who received allogenic blood transfusion was lower in the TXA group (OR=0.20, 95% CI=0.11–0.34, $P<0.001$, $I^2=58\%$; Figure 2). Three studies were specific for revision THA, and four studies were specific for revision TKA. The revision THA subgroup had a significantly lower allogenic blood transfusion rate

compared to control (OR=0.19, 95% CI=0.09–0.37, $P<0.001$, $I^2=0\%$). Similarly, the revision TKA subgroup also had a lower allogenic blood transfusion rate compared to control (OR=0.22, 95% CI=0.08–0.60, $P=0.003$, $I^2=71\%$).

Change in Hb levels

Of the seven studies, four compared the change in preoperative and postoperative Hb levels between revision TJA patients

Table 2 Quality of selected studies

Study, year	Study type	Jadad scale			Total Score
		Randomization	Blinding	Cohort	
Gill et al ⁵ , 2009	RCT	2	2	1	5
NOS					
		Selection	Comparability	Outcome	
Kazi et al, ⁷ 2012	Prospective cohort observational study	3	1	2	6
Park et al, ¹² 2016	Retrospective cohort observational study	4	1	2	7
Aguilera et al, ⁸ 2012	Retrospective cohort observational study	3	1	2	6
Smit et al, ⁹ 2013	Retrospective cohort observational study	4	1	3	8
Samujh et al, ¹⁰ 2014	Retrospective cohort observational study	4	1	2	7
Ortega-Andreu et al, ¹³ 2016	Retrospective cohort observational study	3	1	2	6

Abbreviations: NOS, Newcastle–Ottawa Scale; RCT, randomized controlled trial.

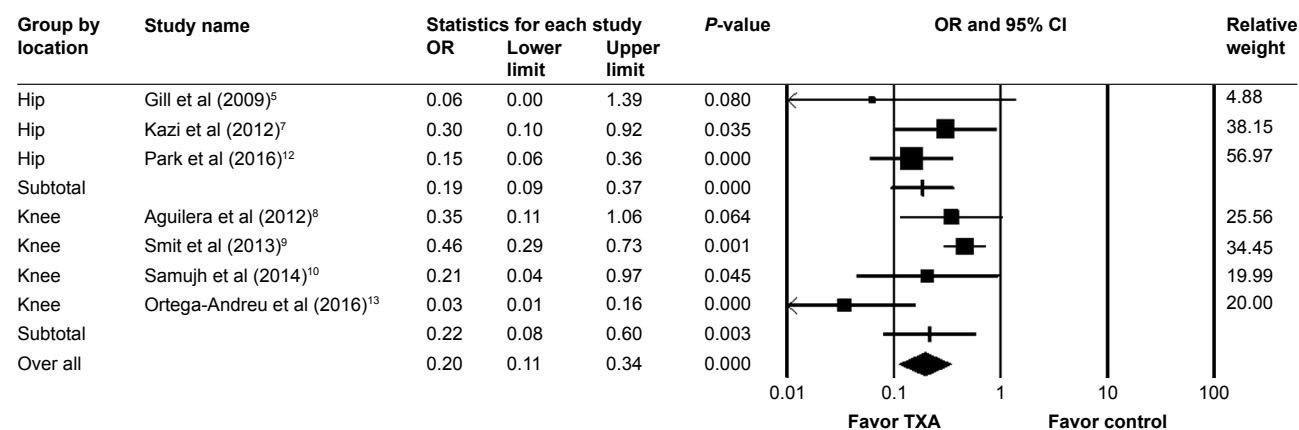


Figure 2 Results of aggregate analysis for comparison of allogenic blood transfusion rate between revision TJA patients who received intravenous TXA and control, including subgroup analysis by hip and knee.

Note: 95% CI shown as "Lower limit" and "Upper limit".

Abbreviations: TJA, total joint arthroplasty; TXA, tranexamic acid.

who did and did not receive IV TXA. The pooled MD in the Hb level change was -0.88 g/dL (95% CI= -1.31 to -0.44 g/dL, $P=0.001$, $I^2=83\%$; Figure 3), as there was less Hb drop when revision TJA patients received IV TXA (3.18 g/dL Hb drop) compared to control (4.06 g/dL Hb drop).

Number of RBC units transfused per patient

This outcome was measured in six studies. The number of RBC transfusions per patient was significantly lower in the TXA group (0.50 unit per person) compared to the control group (0.94 unit per person), with an MD of -0.44 units (95% CI= -0.65 to -0.24 units; $P=0.001$, $I^2=54\%$; Figure 4).

Blood loss

Five studies provided data on blood loss. Two of them were EBL, while the others were TBL, intraoperative blood loss (IBL), and BLD. There was high statistical heterogeneity between studies ($P=0.001$, $I^2=87\%$). The

meta-analysis (Figure 5) showed a slightly lower amount of blood loss with TXA use, but this did not reach statistical significance (MD= -245 mL, 95% CI= -556 to 66 mL, $P=0.123$, $I^2=82\%$).

VTE complications

Of the seven studies, five reported data on the proportion of patients who developed VTE complications. There were no significant differences between revision TJA with IV TXA (3/436, 0.69%) and without TXA (5/383, 1.31%; OR=0.57, 95% CI=0.13–2.42, $P=0.45$; $I^2=0\%$; Figure 6).

Discussion

There were significantly lower blood transfusion rates, less drop in Hb and less units of RBC units transfused when comparing IV TXA administration to control in revision TJA patients. Concomitantly, administration of IV TXA did not increase the rate of VTE in revision TJA patients compared to controls.

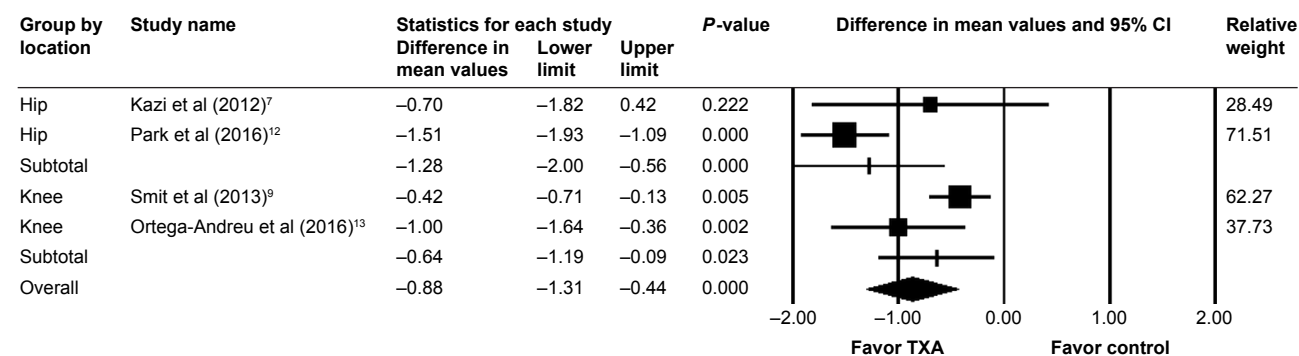


Figure 3 Results of aggregate analysis for comparison of change in Hb levels between revision TJA patients who received intravenous TXA and control, including subgroup analysis by hip and knee.

Note: 95% CI shown as "Lower limit" and "Upper limit".

Abbreviations: Hb, hemoglobin; TJA, total joint arthroplasty; TXA, tranexamic acid.

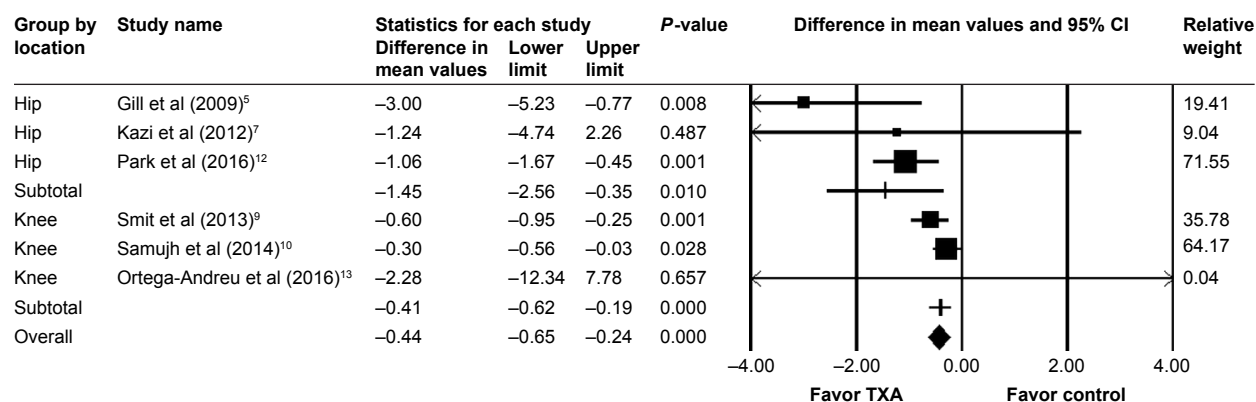


Figure 4 Results of aggregate analysis for comparison of RBC units transfused per patient between revision TJA patients who received intravenous TXA and control, including subgroup analysis by hip and knee.

Note: 95% CI shown as "Lower limit" and "Upper limit".

Abbreviations: RBC, red blood cell; TJA, total joint arthroplasty; TXA, tranexamic acid.

Systematic reviews and meta-analyses have demonstrated that IV TXA is efficacious at reducing blood loss and decreasing allogenic transfusion rates in primary TJA.^{3,17} This study is the first meta-analysis in revision TJA patients that demonstrated that IV TXA reduced allogenic blood transfusions in revision THA and revision TKA patients. However, our meta-analysis did not show that IV TXA significantly reduced blood loss in revision TJA. These results may be attributed to the fact that the measuring methods of blood loss were not consistent, as the most consistent method of blood loss measurement from the pooled studies was EBL.¹⁸ Blood loss measurement using IBL or drain blood loss were not reliable, as these measurements underestimated the true TBL from TJA, since hidden blood loss is calculated and makes up ~50% of TBL.¹⁹ TXA can effectively decrease drainage blood loss by ~50% in the postoperative period, but TXA has not been shown to significantly reduce hidden blood loss, which is not mediated in the initial phase of fibrinolysis.¹⁹

However, there was a trend toward IV TXA resulting in less blood loss, with an MD of 359 mL less blood loss in revision THA and 234 mL less blood loss in revision TKA.

IV TXA has been effectively shown to reduce Hb drop in primary TKA and THA.^{20,21} In a recent meta-analysis in primary TKA patients, IV TXA significantly reduced Hb loss compared to control patients who did not receive TXA (MD=-0.85, $P=0.000$, 95% CI=-1.26 to -0.44).²⁰ In a meta-analysis of primary THA patients, the use of IV TXA reduced Hb loss up to 6.03 g/L compared to that in controls ($P=0.001$, 95% CI=3.90-8.15 g/L).²¹ In our meta-analysis, we also found a lower reduction in preoperative to postoperative Hb levels for IV TXA revision TJA patients (MD=0.88 g/dL). In the four studies that were pooled, only one study did not have a significant difference in Hb change.⁷ Another study showed a significant difference in Hb change at 24 and 48 hours, but the Hb change at postoperative day 5 was not significant.¹³ Another study in THA patients demonstrated no difference

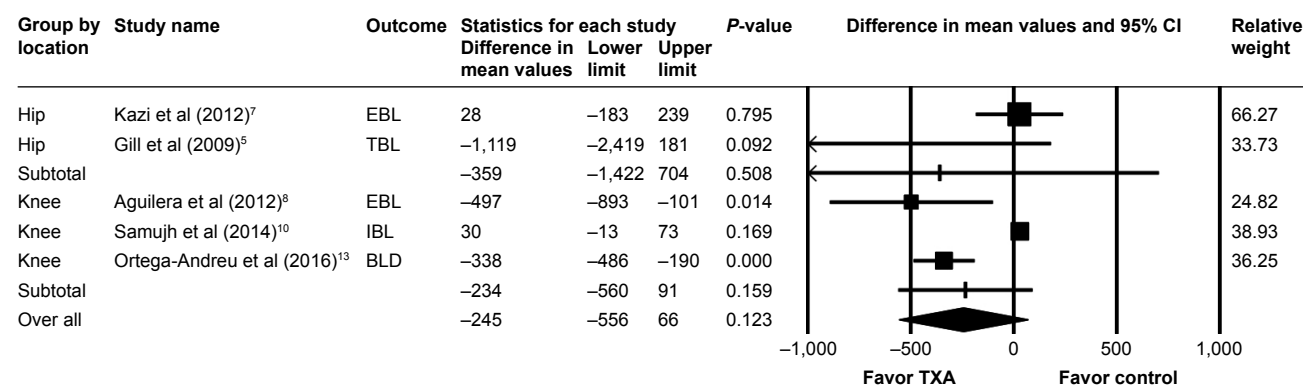


Figure 5 Results of aggregate analysis for comparison of blood loss between revision TJA patients who received intravenous TXA and control, including subgroup analysis by hip and knee.

Note: 95% CI shown as "Lower limit" and "Upper limit".

Abbreviations: BLD, blood loss via drainage; EBL, estimated blood loss; IBL, intraoperative blood loss; TBL, total blood loss; TJA, total joint arthroplasty; TXA, tranexamic acid.

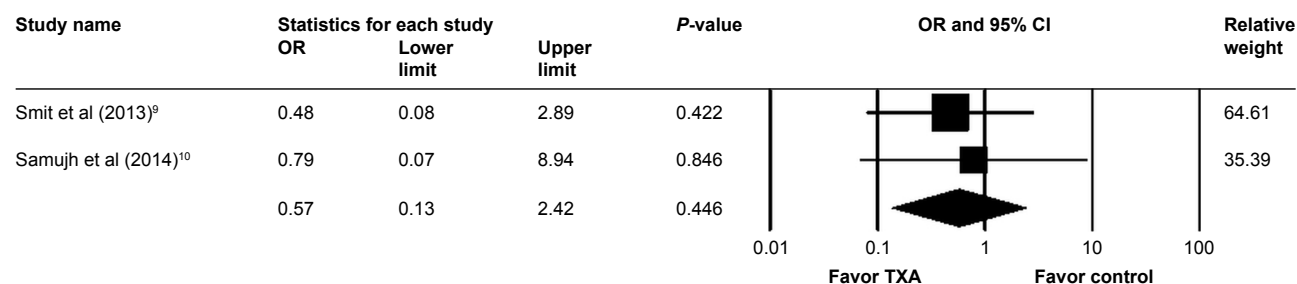


Figure 6 Results of aggregate analysis for comparison of VTE complications between revision TJA patients who received intravenous TXA and control.

Note: 95% CI shown as "Lower limit" and "Upper limit".

Abbreviations: TJA, total joint arthroplasty; TXA, tranexamic acid; VTE, venous thromboembolism.

in Hb change on postoperative day 7.²¹ The Hb levels on postoperative days 5 and 7 may have been compensated by transfusions in the control group.

Reduction in allogenic RBC unit transfused per patient is also a concern in revision TJA. In primary THA, allogeneic RBC units transfused per patient was not significantly reduced in IV TXA patients compared to those in placebo (weighted MD=0.3 units; 95% CI=−0.49 to 1.09 units, $P=0.45$) in a meta-analysis.²¹ However, there was a reduction in RBC units transfused per patient in primary TKA patients who received IV TXA (MD=−1.14, $P=0.000$, 95% CI=−1.53 to −0.76).²⁰ This meta-analysis found that the number of RBC units transfused was significantly lower in the IV TXA group with a mean reduction of 0.44 unit per person ($P<0.001$) compared to that in the control group in revision TJA cohorts.

However, concerns still exist regarding the safety of systemic TXA administration and the risk of VTE events in high-risk patients undergoing revision TJA. One recent review demonstrated no correlation between TXA and any major thromboembolic or nonthromboembolic complications in primary TJA.²² In a prospective randomized study, Wu et al¹¹ reported that the combined administration of IV and topical TXA in revision THA did not increase the risk for VTE complications. Similarly, our meta-analysis also determined that IV administration of TXA did not increase the risk of VTE complication in revision TJA. Thus, TXA may be a relatively safe drug to administer during primary and revision TJA.

This study has several limitations. Of the seven studies, six were observational, resulting in some inherent heterogeneity due to uncontrolled bias. The heterogeneity of the included studies could explain the slight differences in factors affecting parameters of blood loss and postoperative complications, such as anesthesia type, surgical techniques, and operative time. Additionally, the type of revision TKA/THA (partial vs total) was not stratified in studies, which can also affect

blood loss and blood transfusion rates due to differences in surgical exposure and operative time. We were also unable to differentiate between VTE complications, such as deep vein thrombosis and pulmonary embolism, as most studies reported aggregate VTE complications. The administration of IV TXA was heterogeneous with different dosages, and we cannot recommend a specific dosage of administration in revision TJA cases. The criteria for transfusion were also heterogeneous, which may affect outcomes. Finally, since we focused on IV TXA in this meta-analysis, we were unable to compare topical TXA to IV TXA in revision TJA.

Conclusion

Intravenous TXA reduced allogenic blood transfusions and had lower drop in Hb levels postoperatively without increasing VTE complications in patients undergoing revision TJA. Further prospective RCTs should be performed to examine the efficacy and safety of TXA in revision TJA patients.

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Disclosure

The authors report no conflicts of interest in this work.

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