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Tranexamic acid reduces blood loss in intertrochanteric fractures

A meta-analysis from randomized controlled trials

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Abstract

Background: This meta-analysis aims to assess the efficacy and safety of tranexamic acid for reducing blood loss and transfusion requirements in patients with intertrochanteric fractures.

Methods: We conduct electronic searches of Medline (1966–2017.09), PubMed (1966–2017.09), Embase (1980–2017.09), ScienceDirect (1985–2017.09), and the Cochrane Library. Only randomized controlled trials (RCTs) are included. The quality assessments are performed according to the Cochrane systematic review method. Fixed/random-effect model is used according to the heterogeneity tested by I^2 statistic. Meta-analysis is performed using Stata 11.0 software.

Results: A total of 4 RCTs are retrieved involving 514 participants. The present meta-analysis indicated that there were significant differences between groups in terms of total blood loss (weighted mean differences = −131.49, 95% confidence interval (CI): −163.63 to −99.35, $P = .00$), hemoglobin decline (weighted mean differences = −0.31, 95% CI, −0.44 to −0.19, $P = .00$), and transfusion rate (risk differences = −1.11, 95% CI, −0.19 to −0.04, $P = .00$). In addition, no increased risk of adverse effects was identified in both groups.

Conclusion: Local administration of tranexamic acid is associated with a reduced total blood loss, postoperative hemoglobin decline, and transfusion requirements in patients with intertrochanteric fractures. High-quality RCTs are still required for further investigation.

Abbreviations: DHS = dynamic hip screw, PFNA = proximal femoral nail antirotation, RCT = randomized controlled trials, TXA = tranexamic acid.

Keywords: blood loss, intertrochanteric fracture, meta-analysis, tranexamic acid

1. Introduction

Hip fractures are common and comprise approximately 20% of the operative workload of an orthopedic trauma unit.[1] Intertrochanteric fracture comprises half of hip fractures.[2] They are commonly caused by low energy damage such as falls and may result in morbidity and mortality, especially in elderly individuals. Internal fixations such as dynamic hip screws (DHS) or proximal femoral nail antirotations (PFNA) are frequently used to treat intertrochanteric fractures.[3,4] However, these surgical procedures are associated with substantial perioperative blood loss which increases the risk of cardiocerebrovascular events. Although numerous methods have been implemented to minimize blood loss, including administration of antifibrinolytic agents, autologous donation, and the use of erythropoietin, anemia may still occur.[5,6] Allogenic blood transfusions increase the risk of adverse events, such as virus infections, immunologically mediated diseases, and cardiovascular dysfunction, resulting in financial burdens and potentially life-threatening side effects for patients.[7,8]

Recently, the use of tranexamic acid (TXA) on hip fractures has become popular in orthopedics.[9,10] TXA is a synthetic analog of an amino acid whose biological activity inhibits plasminogen from dissolving clots, thereby reducing blood loss and transfusion requirements.[11,12] It is reported that the administration of TXA has a proven outcome in major orthopedic surgeries, such as total joint arthroplasty and spine surgery.[13,14]

Recent studies have focused on the use of TXA in reducing perioperative blood loss in patients with intertrochanteric fractures. Currently, the use of TXA in reducing blood loss in intertrochanteric fracture surgery remains controversial, due to small sample sizes and a lack of published articles. Therefore, we perform the present meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and safety of TXA in reducing blood loss and transfusion requirements in patients with intertrochanteric fractures.

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Authors' contributions: JCY conceived the design of the study. WDW performed and collected the data and contributed to the design of the study. WDW finished the manuscript. All authors read and approved the final manuscript.

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2. Methods

This meta-analysis was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy

We conduct electronic searches of Medline (1966–2017.9), PubMed (1966–2017.9), Embase (1980–2017.9), ScienceDirect (1985–2017.9) and the Cochrane Library. The following key words are used in combination with Boolean operators AND or OR: "tranexamic acid," "intertrochanteric fractures," "blood loss," and "transfusion." References in the included articles are also scanned for potentially relevant studies. No restrictions are placed on the publication language. Two reviewers independently assess the titles and abstracts of all the reports identified by the electronic and manual searches. Subsequently, the full text of potential articles which meet the inclusion criteria are screened, and a final decision is made. Disagreements are resolved by consulting a third reviewer.

2.2. Inclusion criteria and study selection

(Participants: only published studies enrolling adult human subjects with intertrochanteric fractures who prepared for internal fixation are included in our study; interventions: the intervention groups received TXA in the area of postoperative blood loss; comparisons: the control groups received placebos; outcomes: the primary outcomes are total blood loss, hemoglobin decline, and transfusion rates. The secondary outcomes include length of stay and postoperative complications (infection, deep vein thrombosis, and pulmonary embolism); study design: RCTs are regarded as eligible for our study. The exclusion criteria are as follows: insufficient clinical outcome data in articles, and reviews, case reports, letters, or conference articles.

2.3. Data extraction

Two of the authors independently extract the data from each full-text reports using a standard data extraction forms. The following data are extracted: article titles, first author' names, publication year, samples size, population, age, sex, intervention procedures, duration of follow-up, and outcome parameters. Corresponding authors are consulted to obtain any required information that is missing. The clinical outcomes include total blood loss, hemoglobin decline, transfusion rates, length of stay, and postoperative complications (infection, deep vein thrombosis, and pulmonary embolism).

2.4. Assessment of methodological quality

Quality assessment of the included RCTs is assessed by 2 authors independently according to the Cochrane Handbook for Systematic Reviews of Interventions 5.0. We apply assessing the "risk of bias" table, which includes the following key domains: adequate sequence generation, allocation of concealment, blinding, incomplete outcome data, free of selective reporting, and free of other bias. Each item is checked by "Yes," "No," or "Unclear." Each risk of bias item is presented as a percentage across all included studies. The percentage indicates the proportion of different levels of risk of bias for each item.

2.5. Evidence synthesis

The evidence grade for the main outcomes is assessed using the guidelines of the Recommendations Assessment, Development and Evaluation (GRADE) system[15] including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence is divided into the following categories: high, which means that further research is unlikely to change confidence in the effect estimate; moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate; low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and very low, which means that any effect estimate is uncertain. The evidence quality is graded using the GRADEpro Version 3.6 software.

2.6. Data analysis

We perform the meta-analysis with the Stata 11.0 software (StataCorp, College Station, TX). Statistical heterogeneity is tested depending on the value of P and I^2 using the standard χ^2 test. When there is no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .05$), a fixed-effects model is adopted; otherwise, a random-effect model is used. Continuous outcomes (total blood loss, hemoglobin decline, and length of hospital stay) are expressed as the weighted mean differences (WMD) and 95% confidence intervals (CIs). Dichotomous outcomes (transfusion rates and postoperative complications) are expressed as the risk differences (RD) with 95% CI.

3. Results

3.1. Search result

A total of 211 relevant articles are identified according to the initial search. After reading the titles and abstracts, 207 studies are excluded from the present meta-analysis. No additional articles are obtained after the reference review. Finally, 4 RCTs[16–19] which were published between 2015 and 2017 are included in the present meta-analysis. These studies involve 254 participants in the TXA groups and 260 participants in the control groups. The search process proceeds as presented in Figure 1.

3.2. Study characteristics

The sample size ranges from 77 to 200 and the average age ranges from 67 to 81. In the included studies, the experimental groups received local administration of TXA in the area of the perioperative blood loss and the control groups received a placebo or nothing. The characteristics of the included studies are shown in Table 1.

3.3. Risk of bias

The Cochrane Handbook for the Systematic Review of Interventions is consulted to assess the risk of bias for the RCTs. All RCTs use the correct methods to generate the random sequence, and the concealment of the 3 articles is achieved using closed envelopes. Three RCTs apply blinding for the participants and study personnel, and only one study applies blinding for the assessors. Low risk of bias due to incomplete outcome data or selective outcome reporting is

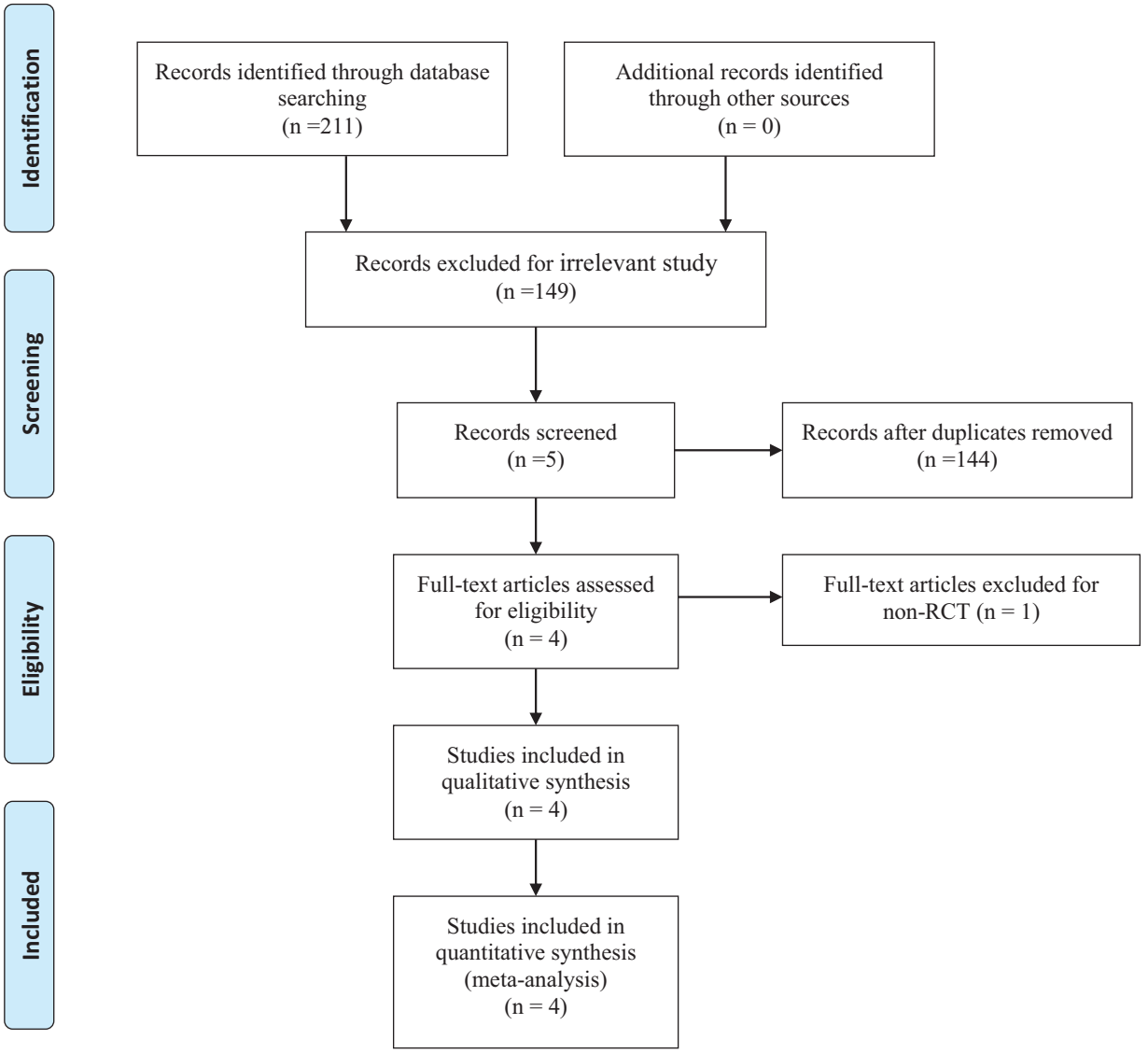


Figure 1. Search results and the selection procedure.

detected. The methodological qualities of the included studies are presented in Table 2. Judgments regarding each risk of bias item are presented as percentages across all the included studies in Table 3.

3.4. Outcomes for meta-analysis

3.4.1. Total blood loss. Four articles[16–19] reported the total blood loss after internal fixation. The pooled results of the studies showed that administration of TXA could significantly reduce

Table 1

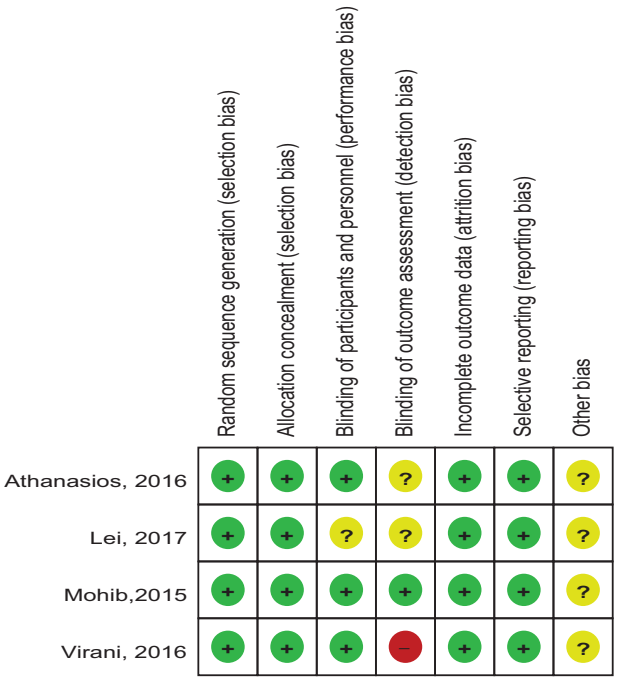
Cohort characteristics.

Studies	Locate	Cases (T/C)	Mean age (T/C)	Female patients (T/C)	Surgical procedure	Anesthesia method	TXA intervention	Transfusion trigger	Follow-up
Mohib, 2015	Pakistan	50/50	69/70	29/26	DHS	Spinal anesthesia	T: local administration of 3 g TXA; C: none	Hemoglobin <7 g/dL	2 mo
Virani, 2016	India	67/70	67/69	67/70	PFNA	Spinal anesthesia	T: intramuscular infiltration of 2 g TXA; C: none	Hemoglobin <7 g/dL	1 mo
Athanasios, 2016	Greece	100/100	81/81	73/79	PFNA	Spinal anesthesia	T: local administration of 3 g TXA; C: none	Hemoglobin <8 g/dL	24 mo
Lei, 2017	China	37/40	78/79	32/33	PFNA	Spinal anesthesia	T: intravenous administration of g TXA; C: normal saline	Hemoglobin <9 g/dL	1 mo

C = control group, g = gram, NS = not stated, RCT = randomized controlled trial, T = TXA group.

Table 2

Methodological quality of the randomized controlled trials.



total blood loss (WMD = −131.49, 95% CI, −163.63 to −99.35, $P = .00$; Fig. 2). There was no significant heterogeneity among the studies ($\chi^2 = 5.99$, $df = 3$, $I^2 = 49.9\%$, $P = .11$) and a fixed-effects model was used.

3.4.2. Hemoglobin decline. Four articles[16–19] with 514 participants provided the outcome of hemoglobin decline after internal fixation. There was no significant heterogeneity between studies ($\chi^2 = 1.63$, $df = 3$, $I^2 = 0\%$, $P = .652$). The pooled results of the studies showed that administration of TXA could significantly decrease the postoperative hemoglobin decline (WMD = −0.31, 95% CI, −0.44 to −0.19, $P = .00$; Fig. 3).

3.4.3. Transfusion rates. Transfusion rates were shown in 4 studies.[16–19] There was no significant heterogeneity among these studies ($\chi^2 = 5.29$, $df = 3$, $I^2 = 43.3\%$, $P = .15$) and a fixed-effects model was adopted. There was significant difference in transfusion rates between groups (RD = −1.11, 95% CI, −0.19 to −0.04, $P = .00$; Fig. 4).

3.4.4. Length of hospital stay. Four articles[16–19] showed the length of hospital stay between groups. A random-effects model was used ($\chi^2 = 23.48$, $df = 3$, $I^2 = 87.2\%$, $P = .00$). No significant difference in the length of hospital stay was found between the groups (WMD = −0.23, 95% CI, −0.56 to 0.09, $P = .16$; Fig. 5).

3.4.5. Deep venous thrombosis. Four studies[16–19] reported the incidence of deep venous thrombosis (DVT) between groups. A fixed-effects model was used ($\chi^2 = 1.46$, $df = 3$, $I^2 = 0\%$, $P = .69$). No significant difference in the incidence of DVT was found between the groups (RD = 0.004, 95% CI, −0.02 to 0.03, $P = .70$; Fig. 6).

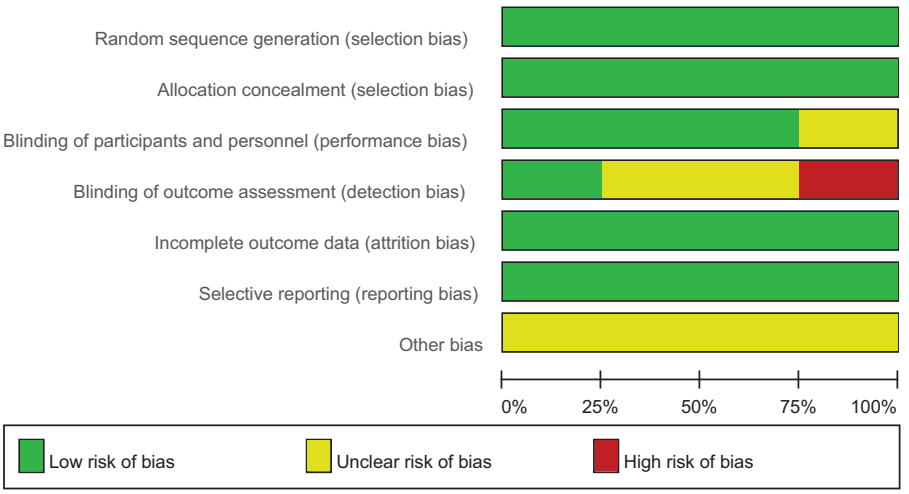
3.4.6. Pulmonary embolism. Pulmonary embolism (PE) was reported in 4 articles.[16–19] A fixed-effects model was used ($\chi^2 = 0.73$, $df = 3$, $I^2 = 0\%$, $P = .866$). No significant difference was found in the incidence of PE between the groups (RD = 0.00, 95% CI, −0.03 to −0.03, $P = .976$; Fig. 7).

3.4.7. Infection. Infection was reported in 4 articles.[16–19] A fixed-effects model was used ($\chi^2 = -0.01$, $df = 3$, $I^2 = 29.5\%$, $P = .235$). There was no significant difference regarding the incidence of infection between the groups (RD = −0.01, 95% CI, −0.04 to −0.02, $P = .426$; Fig. 8).

3.4.8. Publication bias. The publication bias is evaluated with a funnel plot diagram. The funnel plot diagrams for total blood loss and transfusion rates are symmetrical, indicating a low risk of publication bias (Figs. 9 and 10). However, publication bias could not be excluded completely, as the reliability of this kind of assessment is weak, especially when a low number of studies are included.

Table 3

Risk of bias.



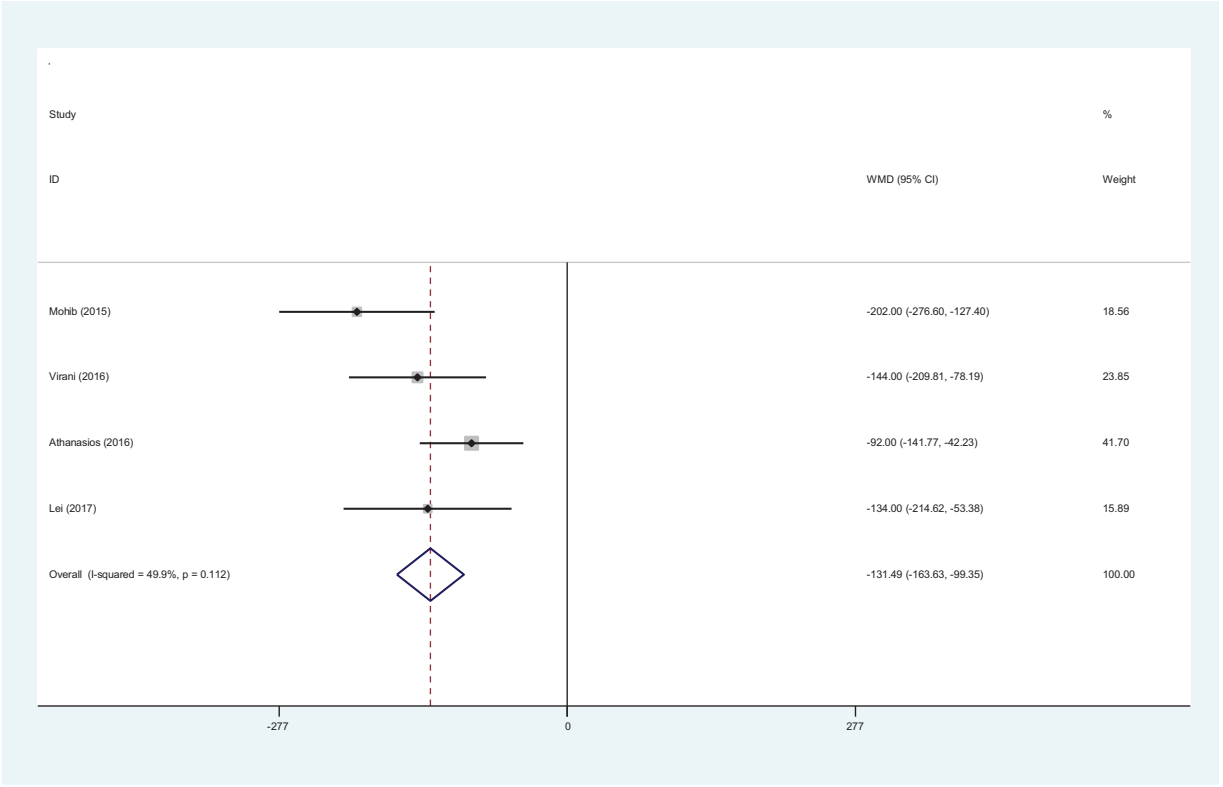


Figure 2. Forest plot diagram showing effect of TXA on reducing total blood loss.

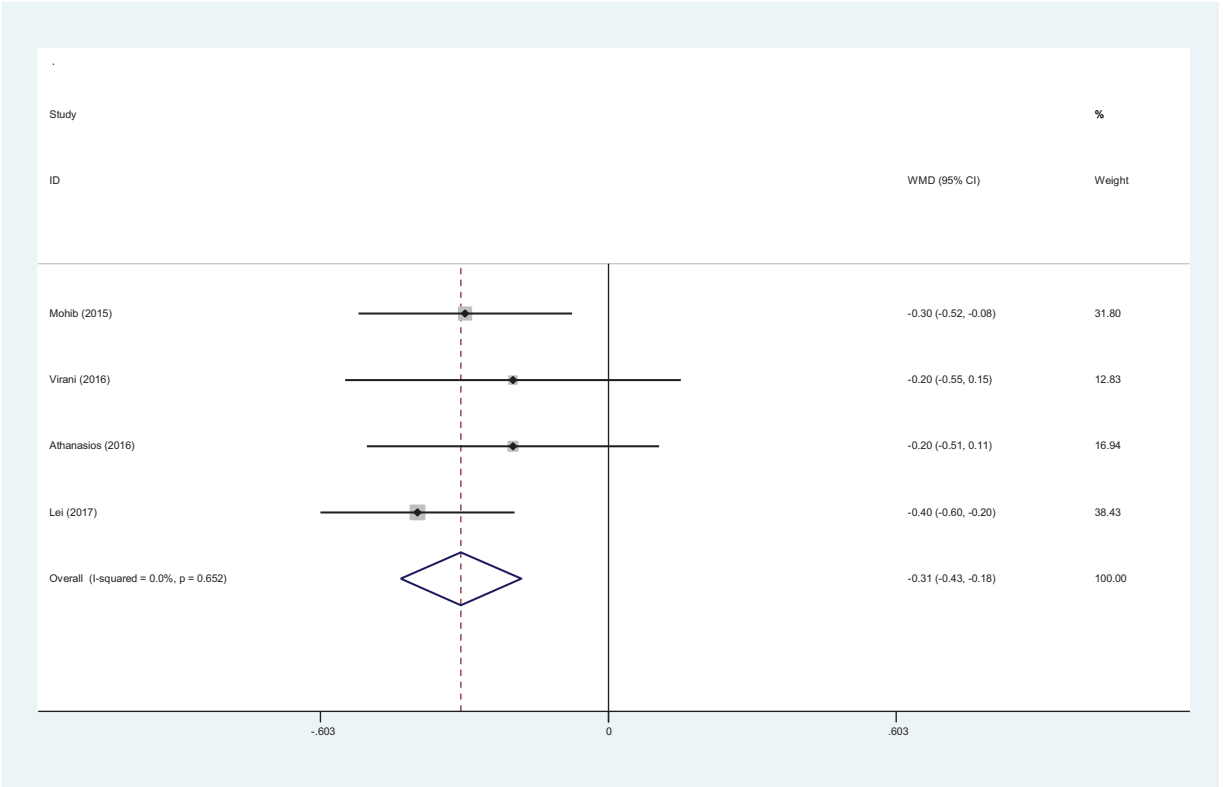


Figure 3. Forest plot diagram showing effect of TXA on reducing hemoglobin decline.

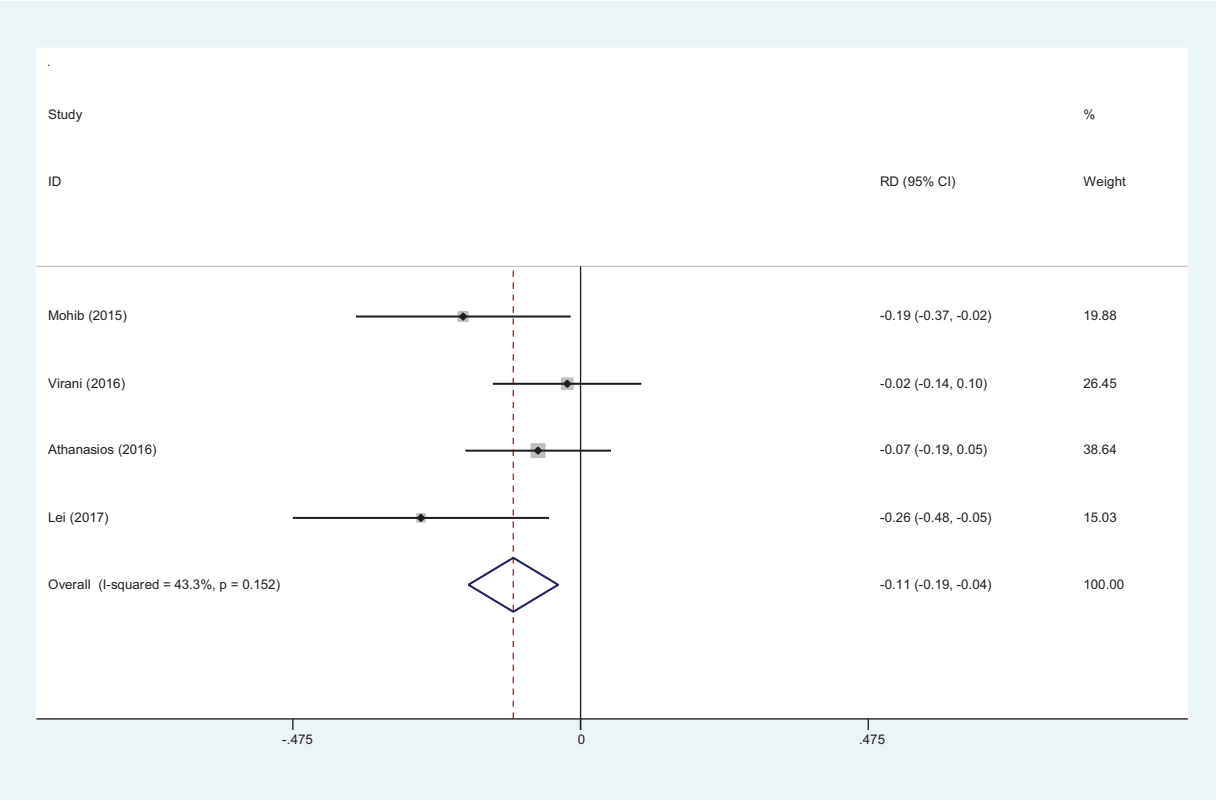


Figure 4. Forest plot diagram showing effect of TXA on reducing transfusion rate.

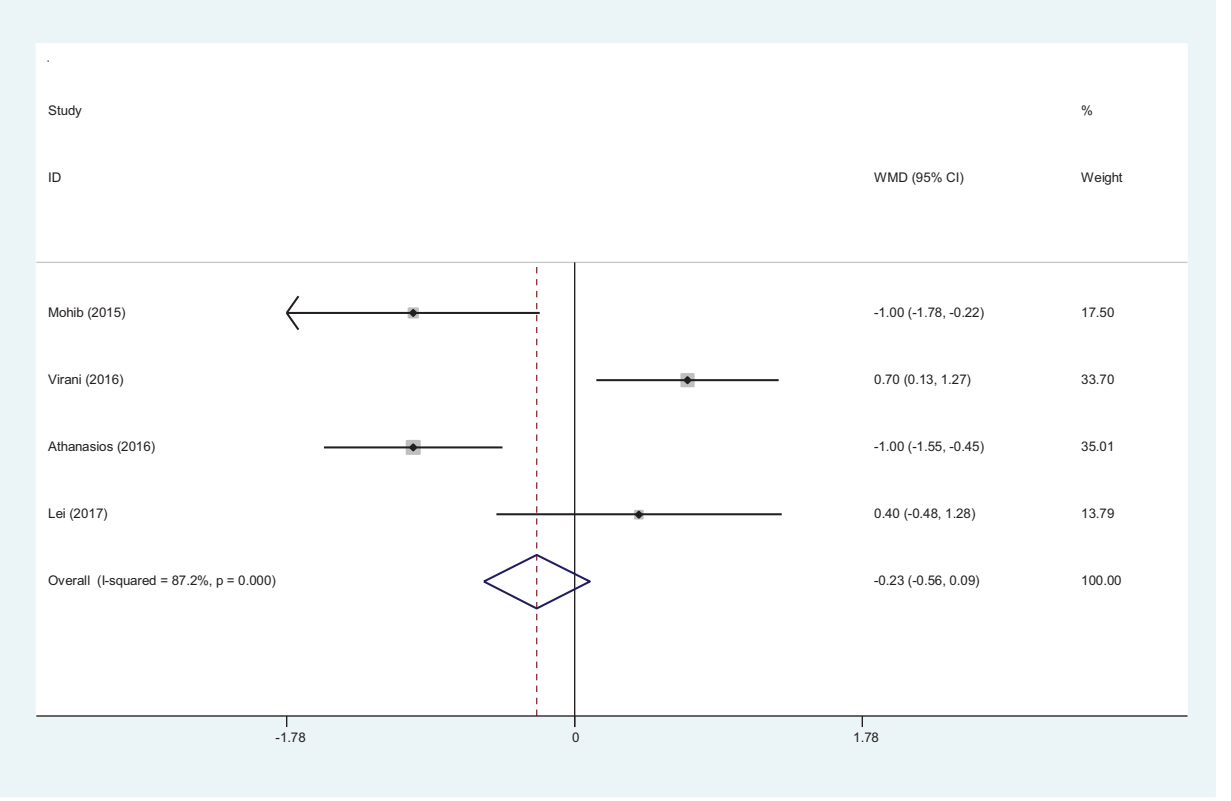


Figure 5. Forest plot diagram showing effect of TXA on the length of hospital stay.

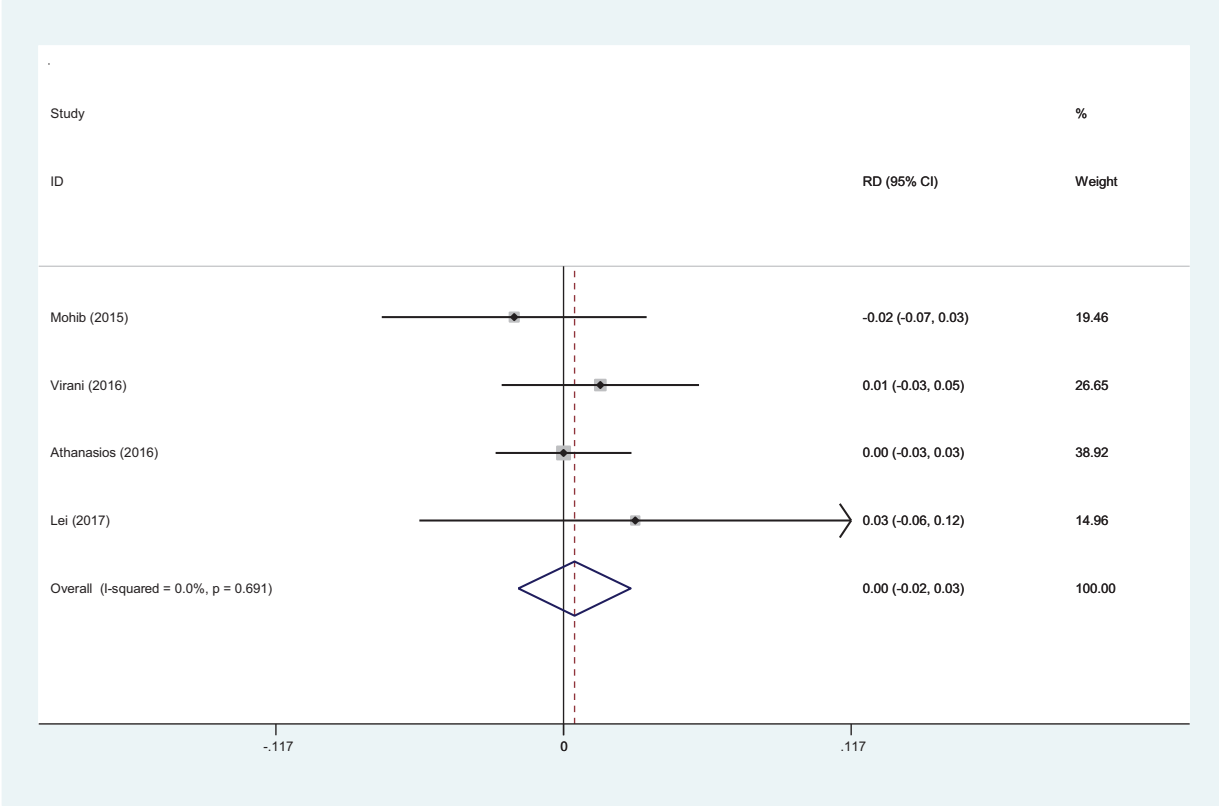


Figure 6. Forest plot diagram showing effect of TXA on the risk of DVT.

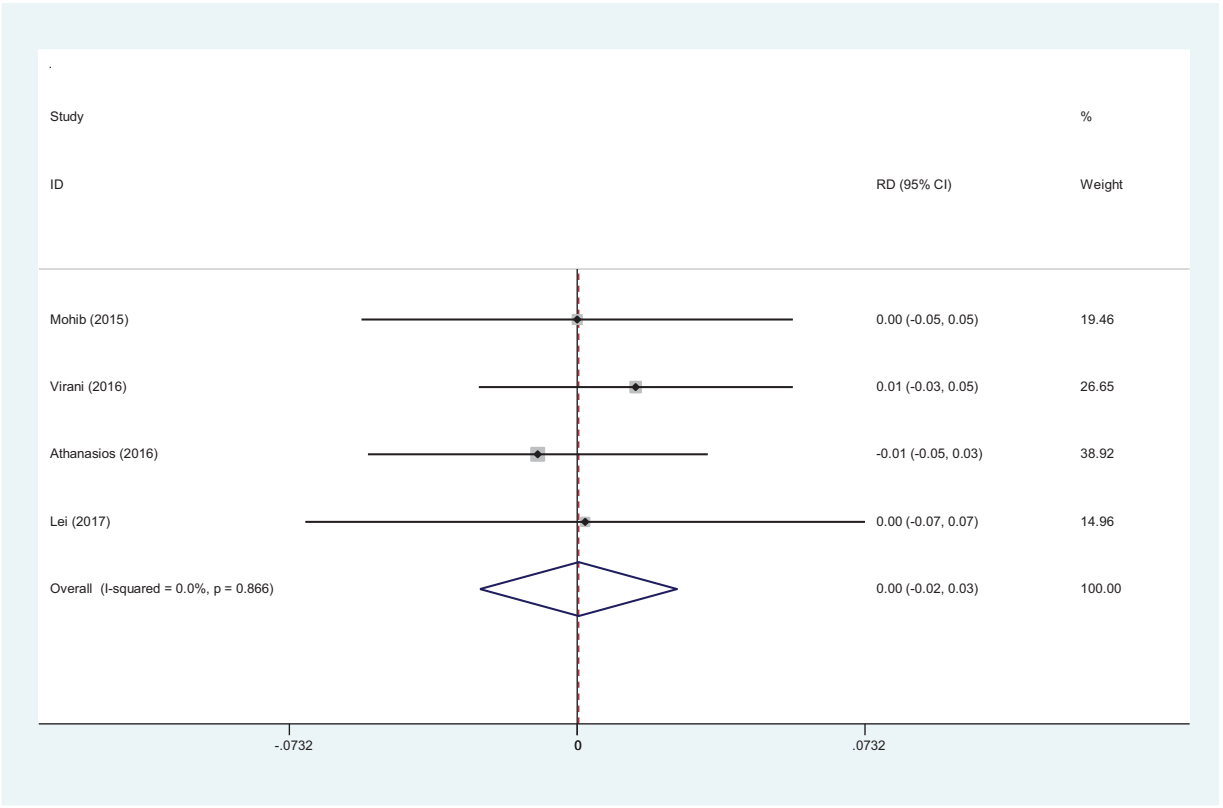


Figure 7. Forest plot diagram showing effect of TXA on the risk of PE.

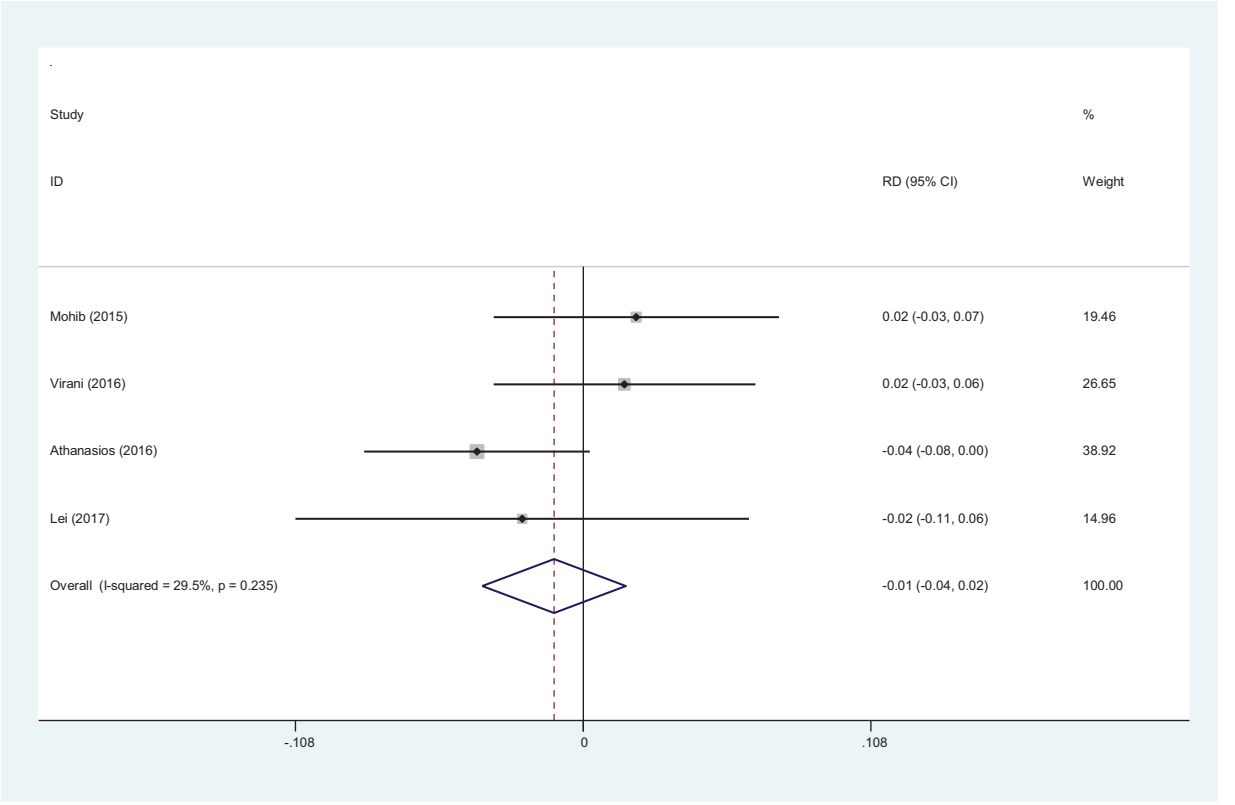


Figure 8. Forest plot diagram showing effect of TXA on the risk of infection.

3.4.9. Quality of the evidence. The main outcomes of this meta-analysis are evaluated using the GRADE system. The evidence quality for each outcome is high, which means further research is very unlikely to change our confidence in the estimate of effect (Table 4).

4. Discussion

To the best of our knowledge, this is the first meta-analysis from RCTs to evaluate the efficacy and safety of the administration of TXA in patients with intertrochanteric fractures. The most important finding of the present meta-analysis is that the application of TXA could significantly reduce the total blood loss, hemoglobin decline, and transfusion requirements. In addition, no increased risk of the thrombotic events, such as DVT or PE, is identified. The main outcomes of this meta-analysis are evaluated using the GRADE system. The evidence quality for each outcome is high, which means that further research is unlikely to change confidence in the effect estimate.

TXA, which acts as an antifibrinolytic agent, is established in reducing peri- and postoperative blood loss, and is widely used in

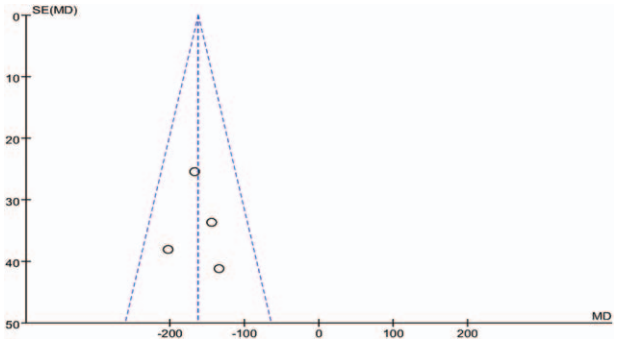


Figure 9. Funnel plot of total blood loss.

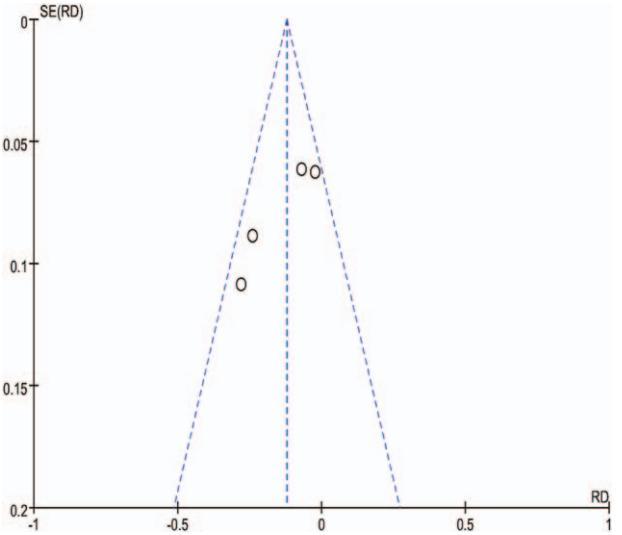


Figure 10. Funnel plot of transfusion rate.

Table 4

The GRADE evidence quality for main outcome.

Quality assessment							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TXA groups	Control groups	Absolute	Quality	Importance
Total blood loss (follow-up 1–24 mo; better indicated by lower values)											
4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	254	260	WMD = −131.49, 95% CI, −163.63 to −99.35, $P = .00$	High	Critical
Hemoglobin decline (follow-up 1–24 mo; better indicated by lower values)											
4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	254	260	WMD = −0.31, 95% CI, −0.44 to −0.19, $P = .00$	High	Critical
Transfusion rates (follow-up 1–24 mo)											
4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	52/254 (20.5%)	85/260 (32.7%)	RD = −1.11, 95% CI, −0.19 to −0.04, $P = .00$	High	Critical

surgical procedures.[20,21] Numerous published studies have reported improved outcomes in hip surgeries. Watts et al[22] showed that intravenous TXA administration safely reduced blood loss and total blood product consumption for patients undergoing hip arthroplasty with femoral neck fractures. Wang et al[23] reported that topical TXA was associated with a reduced hemoglobin decline, volume of drainage, and total blood loss after total hip arthroplasty, and that it was not related to adverse effects or complications such as wound infection, DVT, or PE. However, blood loss in intertrochanteric fractures is different from that in elective total hip arthroplasties, the fibrinolytic system is activated after the injury and continues to increase during surgery. Therefore, the surgeries are associated with substantial total blood loss. It is important to evaluate the effectiveness of TXA in intertrochanteric fractures separately from total hip arthroplasty. No systemic review and meta-analysis has been performed regarding this issue. Thus, there is a requirement for an evidence base to help orthopedists make clinical decisions. The present meta-analysis indicates that the application of TXA is effective in reducing blood loss and postoperative hemoglobin decline in patients with intertrochanteric fractures.

With the aging population, the occurrence of intertrochanteric fractures is increasing, and internal fixation with DHS or PFNA is a popular treatment. It is reported that these surgical procedures are associated with a substantial blood loss ranging from 378 to 1,013 mL.[24] Allogenic blood transfusions are frequently required, but they have several potential adverse effects. Intertrochanteric fractures commonly occur in the elderly population, and some of them are more likely to suffer cardiac insufficiency. Thus, it is important to minimize perioperative blood loss to promote quick recovery and decrease the risk of postoperative complications. However, the application of TXA in the setting of intertrochanteric fractures after internal fixation has been limited with few published studies. Thus, there is a lack of reliable evidence for the use of TXA in patients with intertrochanteric fractures. Meta-analysis is performed as a major statistical method in the present study. Pooling the results of published studies that provide stronger evidence can strengthen the statistical power and enlarge the sample size. Four RCTs show the outcomes of transfusion rates. The present meta-analysis reveals that in hip fracture surgeries, the requirement for allogeneic blood transfusion was significantly reduced in patients receiving TXA, as 20.5% patients in TXA groups versus 32.7% in control groups. The funnel plot diagrams of total blood loss and transfusion rates are symmetrical, indicating a low risk of publication bias. However, publication bias could not be excluded completely, as the reliability of this kind of assessment is weak, especially when a low number of studies are included. All included studies are from middle- and low-income countries. In fact, developing countries also report the effect of TXA in reducing blood loss in hip fractures; however, we have excluded the femoral neck fractures from hip fractures, and only included patients with intertrochanteric fractures. Therefore, only 4 RCTs are included. No commercial bias is found. More RCTs are still needed for further investigation.

Hemostatic efficacy is not the only concern when assessing the efficacy of TXA in surgeries. DVT has been considered a common postoperative complication which may develop to PE after major orthopedic surgery.[25] TXA is an antifibrinolytic agent; theoretically, it can increase the risk of thrombotic events. The overall incidence of DVT is 4/254 in the TXA groups compared with 3/260 in the control groups. No significant difference is

observed in terms of thrombotic events which aligns with the previous articles. More high-quality RCTs with long-term follow-ups are still required to assess the safety of TXA.

There are several limitations in this meta-analysis: only 4 RCTs are included in the present study and the sample size in each trial is small; range of motion is an important outcomes which is not analyzed in the meta-analysis; different modes of administration, such as oral and intravenous, are not discussed, therefore more RCTs are needed; the follow-up period is short, which leads to an underestimation of complications; and publication bias that existed in the meta-analysis also influences the results.

Despite the limitations above, it is the first meta-analysis from RCTs to assess the efficacy and safety of local TXA in patients with intertrochanteric fractures. More high-quality RCTs are required in future studies to assess the optimal dose and mode of TXA, as well as potential adverse effects.

5. Conclusions

Local administration of TXA is associated with a reduced total blood loss, postoperative hemoglobin decline, and transfusion requirements in patients with intertrochanteric fractures. High-quality RCTs are still required for further investigation.

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