Systematic Review and Meta-Analysis

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Tranexamic acid can reduce blood loss in patients undergoing intertrochanteric fracture surgery

A meta-analysis

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Abstract

Background: This meta-analysis aimed to assess whether administration tranexamic acid (TXA) could reduce blood loss and transfusion requirements in patients undergoing intertrochanteric fracture surgery.

Methods: We performed an electronic search of PubMed (1950–October 2018), EMBASE (1974–October 2018), the Cochrane Library (October 2018 Issue 3), the Google database (1950–October 2018), and the Chinese Wanfang database (1950–October 2018). Studies were included in accordance with Population, Intervention, Comparison, Outcomes, and Setting (PICOS) including criteria. Intertrochanteric fracture patients prepared for surgery were selected. Administration with TXA and the placebo or no interventions were considered as an intervention and comparators, respectively. Measures related to total blood loss, blood loss in drainage, hemoglobin on postoperative day were analyzed. A fixed/random-effects model was used according to the heterogeneity assessed by the I^2 statistic. Data analysis was performed using Stata 12.0 software.

Results: A total of five RCTs with 584 patients (TXA group = 289, control group = 298) were included in the meta-analysis. Based on the results, administration of TXA was associated with a reduction in total blood loss, blood loss in drainage, need for transfusion, length of hospital stay, and occurrence of hematoma ($P < .05$). Administration of TXA increased the hemoglobin level at 3 days after surgery ($P < .05$). There were no significant differences between the two groups in terms of the occurrence of deep venous thrombosis, pulmonary embolism, or infection ($P > .05$).

Conclusion: Administration of TXA is associated with reduced total blood loss, postoperative hemoglobin decline, and transfusion requirements in patients with intertrochanteric fractures. Additional high-quality RCTs should be conducted in the future.

Abbreviations: CI = confidence interval, DHS = dynamic hip screw, DVT = deep vein thrombosis, PE = pulmonary embolism, PFNA = proximal femoral nail antirotation, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, RR = relative risk, TXA = tranexamic acid, WMD = weighted mean difference.

Keywords: Intertrochanteric fracture surgery, meta-analysis, tranexamic acid

1. Introduction

Hip fractures are common and have become a major burden for health care systems.[1] As the main type, intertrochanteric fracture accounts for half of hip fractures.[2] Internal fixation with dynamic hip screw (DHS) or proximal femoral nail antirotation (PFNA) is frequently performed for the treatment of intertrochanteric fractures.[3,4] However, those surgical procedures are associated with substantial perioperative blood loss, which would increase the risk of cardio-cerebrovascular events.[5] Several factors, including perioperative anemia, are associated with functional outcomes and mortality rate.

Numerous methods and techniques have been applied to minimize blood loss, such as antifibrinolytic agent administration, autologous donation, and blood pressure control. Autologous blood transfusion increases the risk of infection and cardiovascular load, resulting in financial burden and potentially life-threatening effects.[6]

One alternative, tranexamic acid (TXA), is becoming increasingly popular for use in hip fractures.[7] TXA is a synthetic analog of an amino acid that can inhibit plasminogen from dissolving clots, thereby reducing blood loss and transfusion requirements.[8,9] It is reported that administration of TXA can help to reduce blood loss in knee and spinal surgeries,[10,11] and recent studies have focused on TXA for reducing perioperative blood loss in patients with intertrochanteric fractures. However, the use of TXA in reducing blood loss in intertrochanteric fracture surgery remains controversial.

Thus, we undertook a further meta-analysis to evaluate whether TXA is superior to placebo with respect to: (1) total blood loss, blood loss in drainage, hemoglobin on postoperative day 3; (2) length of hospital stay, need for transfusion; (3) occurrence of deep vein thrombosis (DVT), pulmonary embolism (PE), infection and hematoma in intertrochanteric fracture surgery. We hypothesized that TXA results in less blood loss and incidence of blood loss transfusion, but provide similar

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complication rates than placebo in intertrochanteric fracture surgery.

2. Materials and methods

This systematic review is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[12] This meta-analysis was registered in Research Registry (reviewregistry622).

2.1. Search strategies

The following databases were searched in October 2017 without restrictions on language or publication type: PubMed (1950–October 2018), EMBASE (1974–October 2018), the Cochrane Library (October 2018 Issue 3), the Google database (1950–October 2018), and the Chinese Wanfang database (1950–October 2018). The following MeSH terms and their combinations were used in the search: "tranexamic acid" OR "antifibrinolytic" OR "anti-fibrinolytic agent" AND "intertrochanteric fracture" [MeSH terms]. The reference lists of related review articles and original studies were searched for any relevant studies, including RCTs involving adult humans. There was no restriction on language or publication date. When multiple reports describing the same sample were published, the most recent or most complete report was used. Ethics approval is not required because the data will not include individual patient data.

2.2. Inclusion criteria and study selection

Patients: patients prepared for intertrochanteric fracture surgery. Intervention: use of TXA as an intervention group. Comparison: placebo. Outcomes: total blood loss, blood loss in drainage, hemoglobin on postoperative day 3, length of hospital stay, need for transfusion, occurrence of deep vein thrombosis (DVT), pulmonary embolism (PE), infection and hematoma. Study design: RCT.

Two independent reviewers screened the titles and abstracts of the identified studies after removing duplicates from the search results. Any disagreements about the inclusion or exclusion of a study were solved by discussion or consultation with an expert. The reliability of the study selection was determined by Cohen's kappa test, and the acceptable threshold value was set at 0.61.[6,7]

2.3. Data abstraction and quality assessment

A specific extraction was conducted to collect data in a pre-generated standard Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) file. The items extracted from relevant studies were as follows: first author and publication year; sample size; mean age of the TXA and control groups; type of fracture; TXA dose and administration method and follow-up. Outcomes, such as total blood loss, blood loss in drainage, hemoglobin on postoperative day 3, length of hospital stay, need for transfusion, and occurrence of DVT, PE, infection and hematoma, were abstracted and recorded in the spreadsheet. Data in other formats (i.e., median, interquartile range, and mean ±95% confidence interval [CI]) were converted to the mean± standard deviation (SD) according to the Cochrane Handbook.[13] If the data were not reported numerically, we extracted them from the published figures using "GetData Graph Digitizer" software. All data were extracted by two independent reviewers, and disagreements were resolved by discussion. There was no process for obtaining and confirming data from investigators.

The quality of all included trials was independently assessed by two reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://www.cochrane-handbook.org/).[13] A total of 7 domains were used to assess overall quality: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other biases. Each domain was measured as low bias, unclear bias or high bias.

2.4. Outcome measures and statistical analysis

Continuous outcomes (total blood loss, blood loss in drainage, hemoglobin on postoperative day 3, and length of hospital stay) were expressed as weighted mean differences (WMD) with 95% CIs. Dichotomous outcomes (need for transfusion, occurrence of DVT, PE, infection, and hematoma) were expressed as risk ratio (RRs) with 95% CIs. Statistical significance was set at $P < .05$ to summarize the findings across the trials. Variables in the meta-analysis were calculated using Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was evaluated using the chi-square test and the I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was adopted; otherwise, a random-effects model was chosen. Publication bias was tested and visually assessed using funnel plots and quantitatively assessed using Begg's test. We considered there to be no publication bias if the funnel plot was symmetrical and the P-value was >0.05.

3. Results

3.1. Search results and general characteristics

In the initial search, 386 studies were identified from electronic databases (PubMed = 112, EMBASE = 108, Web of Science = 60, Cochrane Library = 50, Google database = 56). All papers were then inputted into Endnote X7 (Thomson Reuters Corp., USA) software for the removal of duplicate papers. A total of 308 papers were reviewed, and 303 were removed according to the inclusion criteria at the abstract and title levels. Ultimately, 5 clinical studies with 584 patients (TXA group = 289, control group = 298) were included in the meta-analysis.[14–19] The search and selection processes are illustrated in Figure 1. The general characteristics of the included patients are shown in Table 1. All of the included studies were published in or after the year 2015. One study used DHS as internal fixation, and the remainder used PFNA. The sample size ranged from 35 to 100. The follow-up period ranged from 35 days to 2 months.

3.2. Quality assessment

The quality assessment for the included studies is presented in Figures 2 and 3. Only one study did not state the random sequence generation. Two studies did not describe the allocation concealment. One study did not include the blinding of the participants and outcome assessment. Other risks of bias were all low. The overall kappa value was 0.827, which indicated acceptable consistency.

4. Results of the meta-analysis

4.1. Need for transfusion

Four studies mentioned the need for transfusion, and the pooled results indicated that administration of TXA was associated with

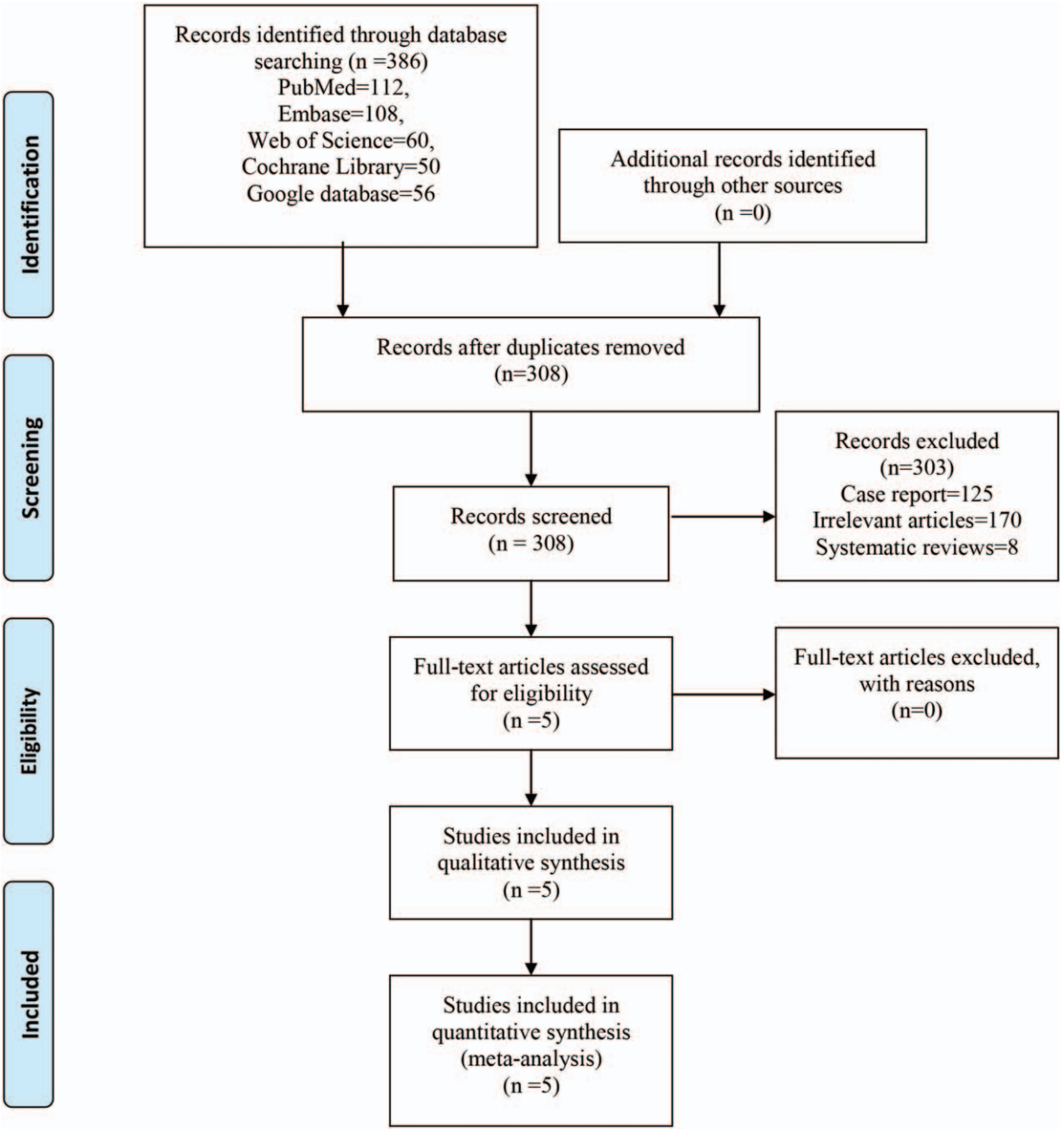

Figure 1. PRISMA flow chart of retrieved studies.

Table 1

The general characteristic of the included studies.

Author	Language	Publication status	No. of patients (T:C)	Mean age (year, T:C)	Internal fixation	Type of fracture	Intervention	Control	Concomitant thromboprophylaxis	Follow-up
Mohib 2015	English	Published	50/50	29/26	DHS	A1, A2, A3	3 g TXA intra-articular	Placebo	Enoxaparin 40 mg subcutaneously once a day	2 months
Virani 2016	English	Published	67/70	67/70	PFNA	NS	2 g TXA intramuscular	Saline	LMWH to all patients 12 hours after surgery and for 30 days	1 month
Drakos 2016	English	Published	100/100	73/79	PFNA	A1, A2, A3	3 g TXA intra-articular	Control	LMWH to all patients 12 hours after surgery and for 30 days	2 months
Lei 2017	Chinese	Published	37/40	32/33	PFNA	A1, A2, A3	1 g TXA iv	Saline	NS	1 month
Wang 2017	Chinese	Published	35/35	73/74	PFNA	NS	1 g TXA iv	Saline	Oral aspirin 100 mg, twice a day for 35 days	35 days

DHS = dynamic hip screw, iv = intravenous, LMWH = low molecular weight heparin, NS = not stated, PFNA = proximal femoral nail antirotation, TXA = tranexamic acid.

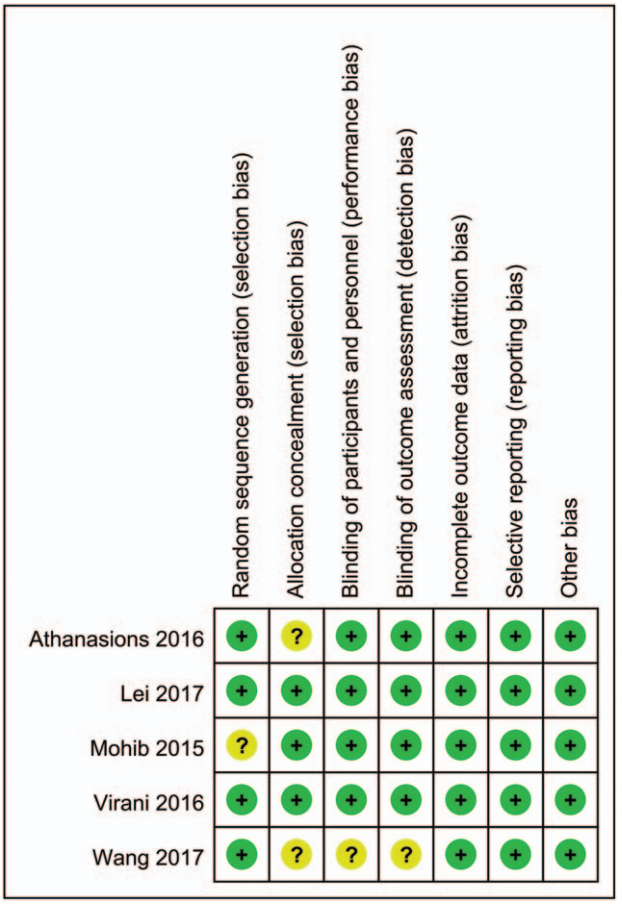

Figure 2. The risk of bias summary; + denotes low risk of bias; − denotes high risk of bias; ? denotes unclear risk of bias.

a reduction in the need for transfusion by 17.5% (20.7% vs 38.2%, RR = 0.55, 95% CI 0.41, 0.74, $P = .000$, Fig. 4).

4.2. Total blood loss

Four studies used total blood loss to assess clinical outcomes. The pooled results indicated that TXA administration can significantly decrease total blood loss (WMD = −114.89, 95% CI −221.01, −8.78, $P = .012$, Fig. 5).

4.3. Blood loss in drainage

Blood loss in drainage was reported in three studies. Based on the pooled results, administration of TXA can decrease blood loss in drainage, with a statistically significant difference (WMD = −51.96, 95% CI −96.48, −9.23, $P = .017$, Fig. 6).

4.4. Hemoglobin on postoperative day 3

Hemoglobin on postoperative day 3 was reported in five studies, and the pooled results indicated that TXA administration can increase hemoglobin values on postoperative day 3 (WMD = 5.86, 95% CI 1.39, 10.34, $P = .010$, Fig. 7).

4.5. Length of hospital stay

Four studies showed the length of hospital stay, with no heterogeneity ($I^2 = 0.0\%$, $P = .450$). The pooled results showed that TXA administration can decrease the length of hospital stay (WMD = −0.63, 95% CI −1.07, −0.20, $P = .005$, Fig. 8).

4.6. Occurrence of DVT, PE, infection and hematoma

The occurrence of DVT was reported in four studies, and according to the pooled results, there was no significant difference between the TXA and control groups with regard to the occurrence of DVT (RR = 0.81, 95% CI 0.24, 2.75, $P = .739$, Fig. 9). The occurrence of PE was reported in four studies, with the pooled results showing no significant difference between the TXA and control groups with regard to the occurrence of PE (RR = 0.64, 95% CI 0.25, 1.62, $P = .346$, Fig. 10).

The occurrence of infection was reported in three studies; the pooled results indicated that there was no significant difference between the TXA and control groups regarding the occurrence of infection (RR = 0.22, 95% CI 0.05, 1.00, $P = .052$, Fig. 11). The occurrence of hematoma was reported in four studies, and the pooled results showed that administration of TXA can decrease hematoma occurrence (RR = 0.34, 95% CI 0.15, 0.78, $P = .011$, Fig. 12).

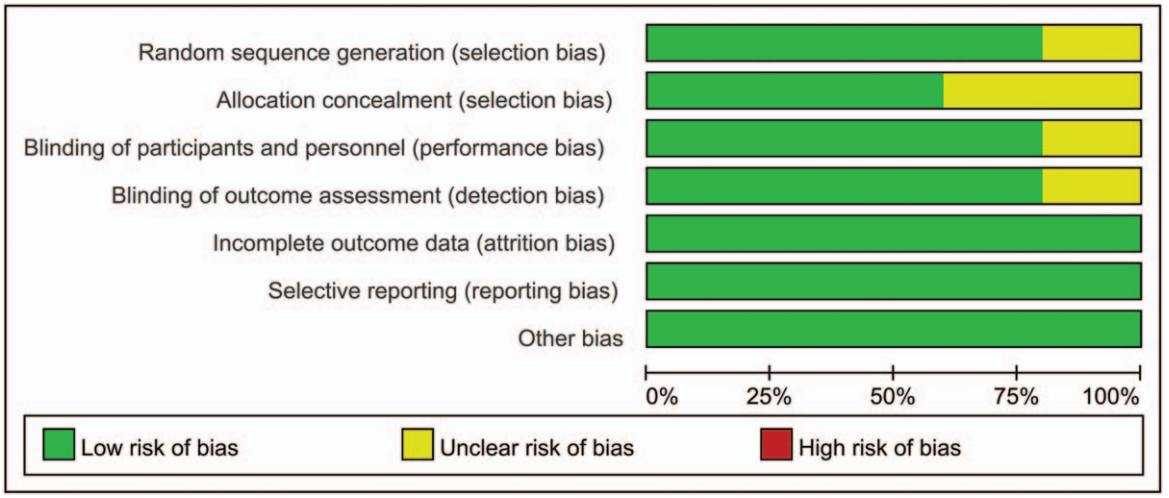

Figure 3. Risk of bias graph of the included studies.

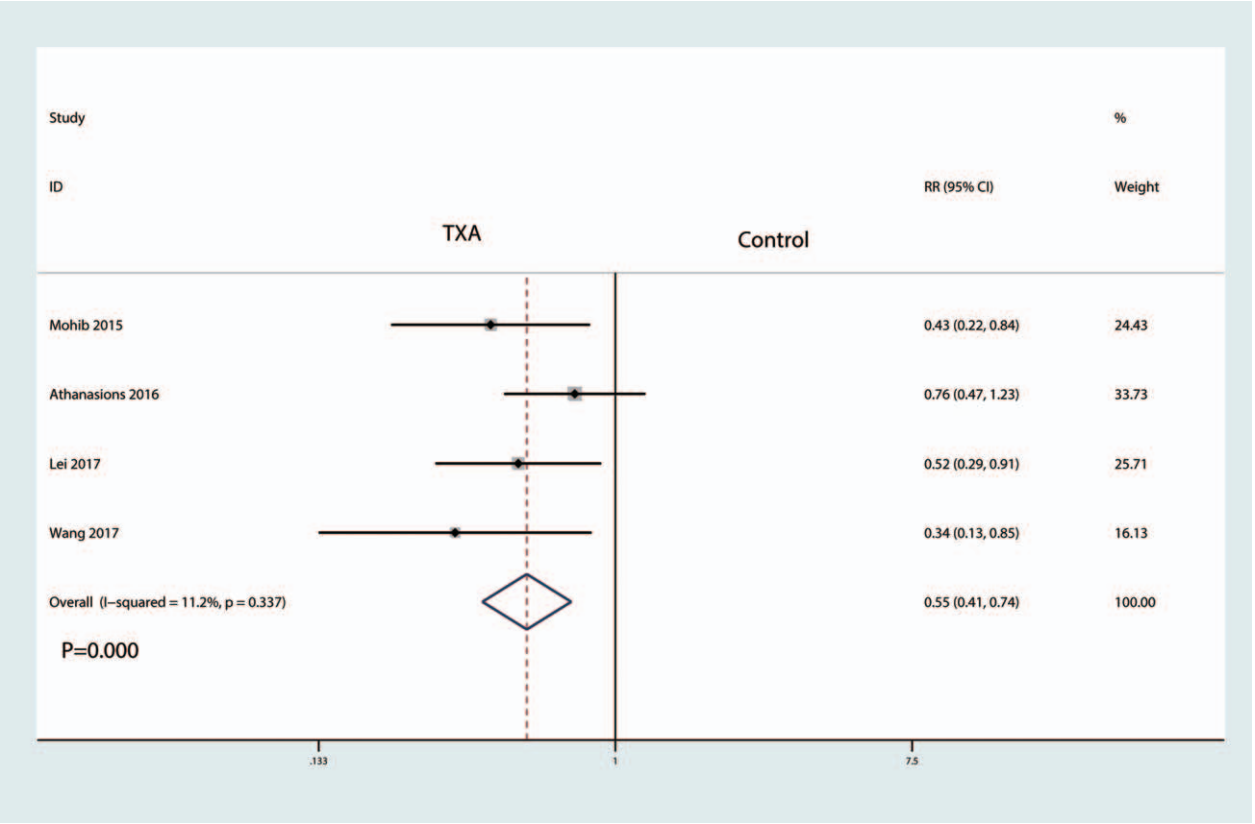

Figure 4. Forest plot comparing the need for transfusion between the two groups.

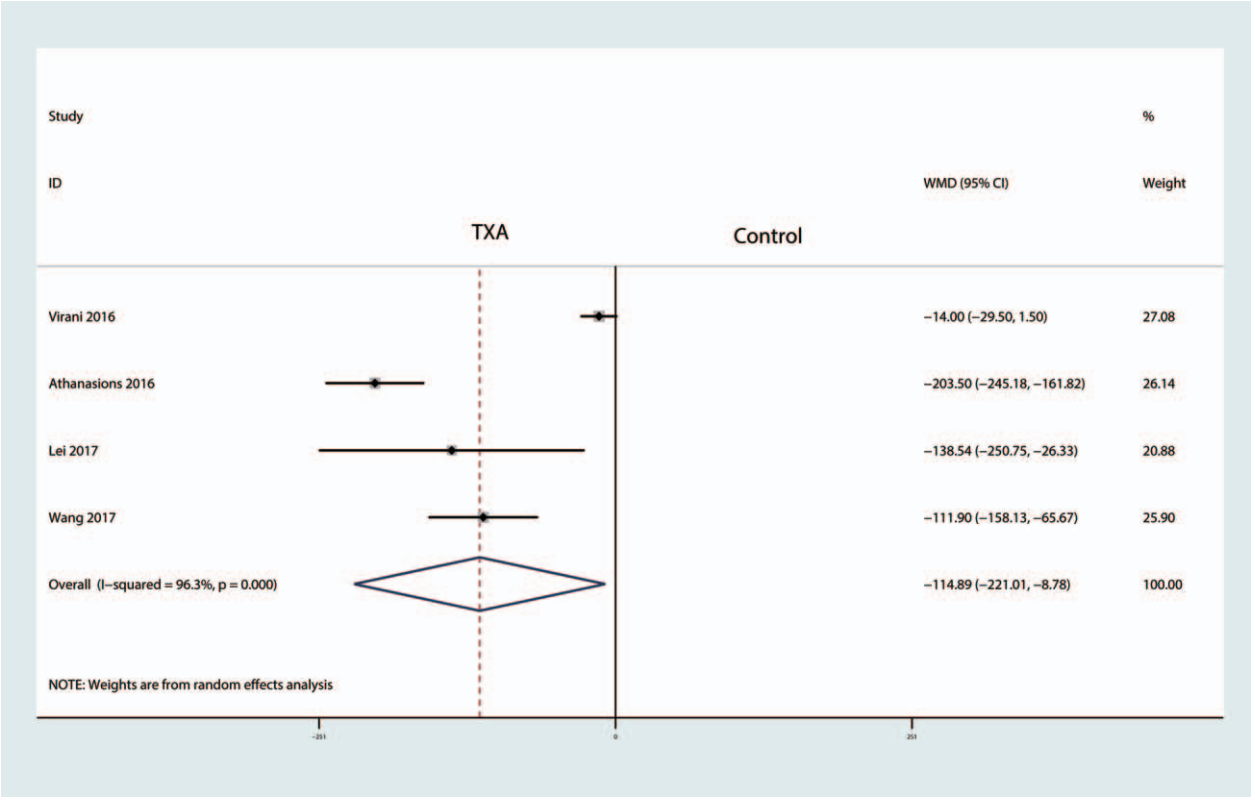

Figure 5. Forest plot comparing total blood loss between the two groups.

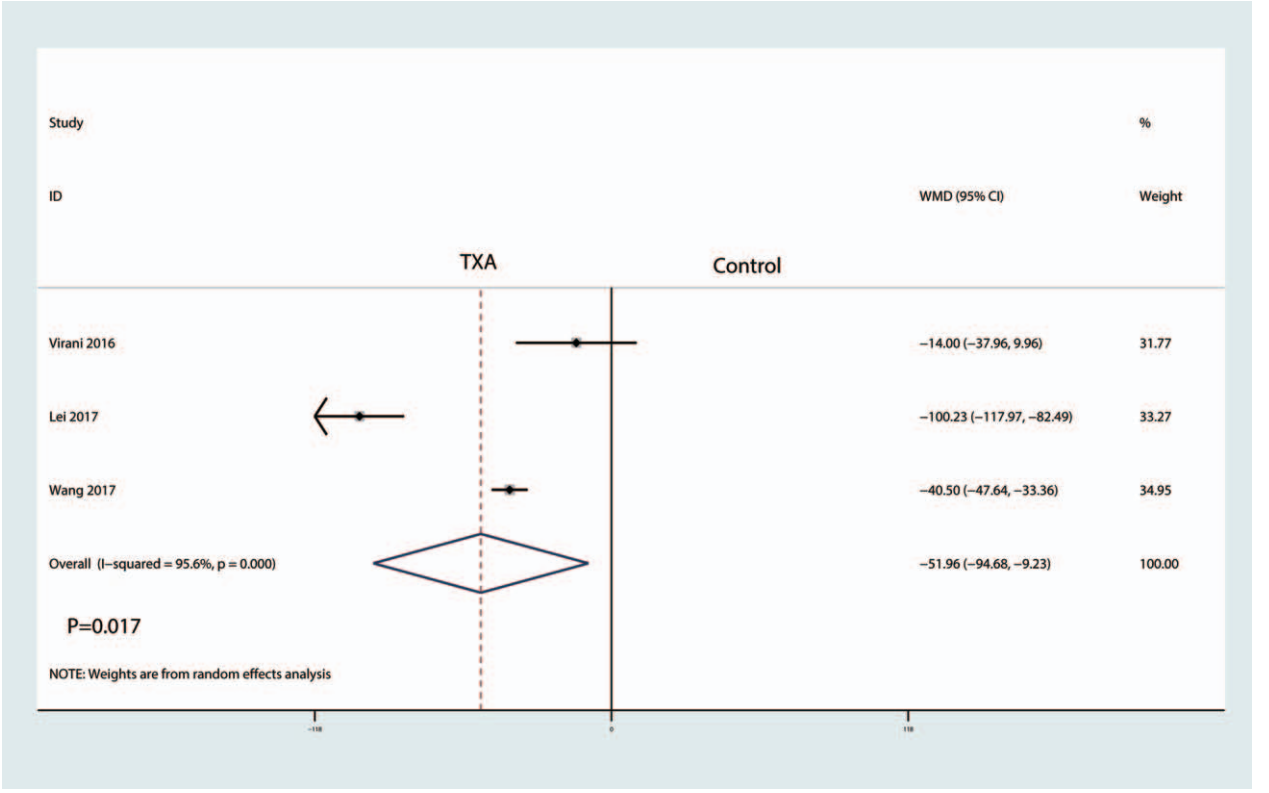

Figure 6. Forest plot comparing blood loss in drainage between the two groups.

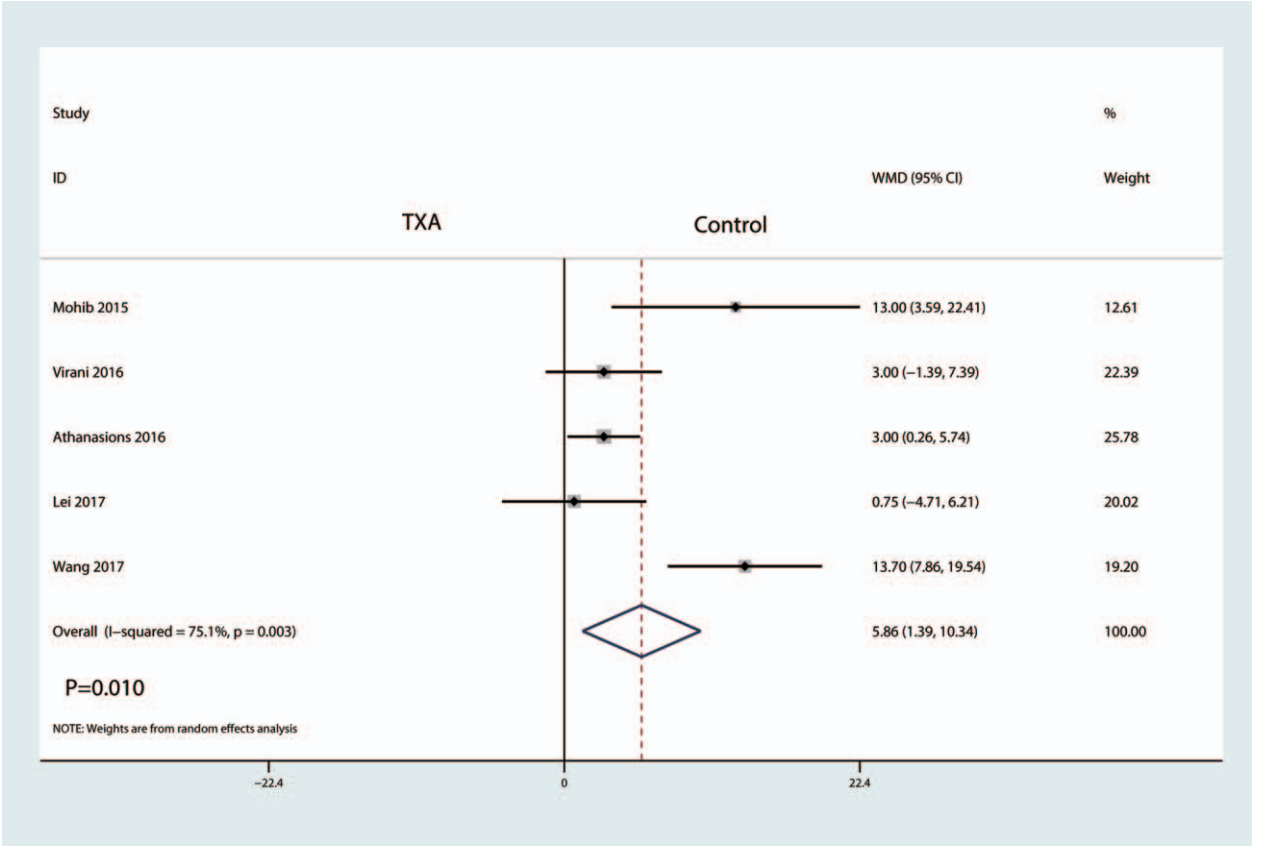

Figure 7. Forest plot comparing the hemoglobin level on postoperative day 3 between the two groups.

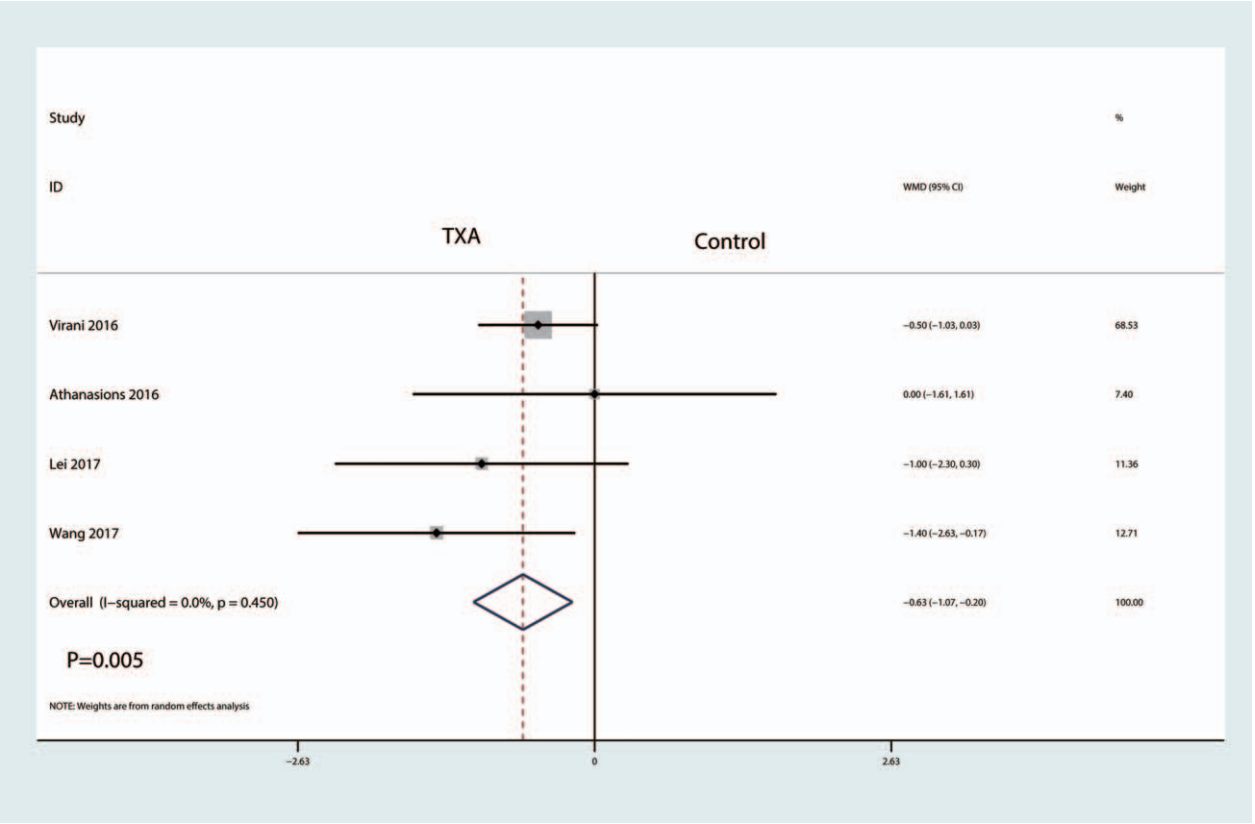

Figure 8. Forest plot comparing the length of hospital stay between the two groups.

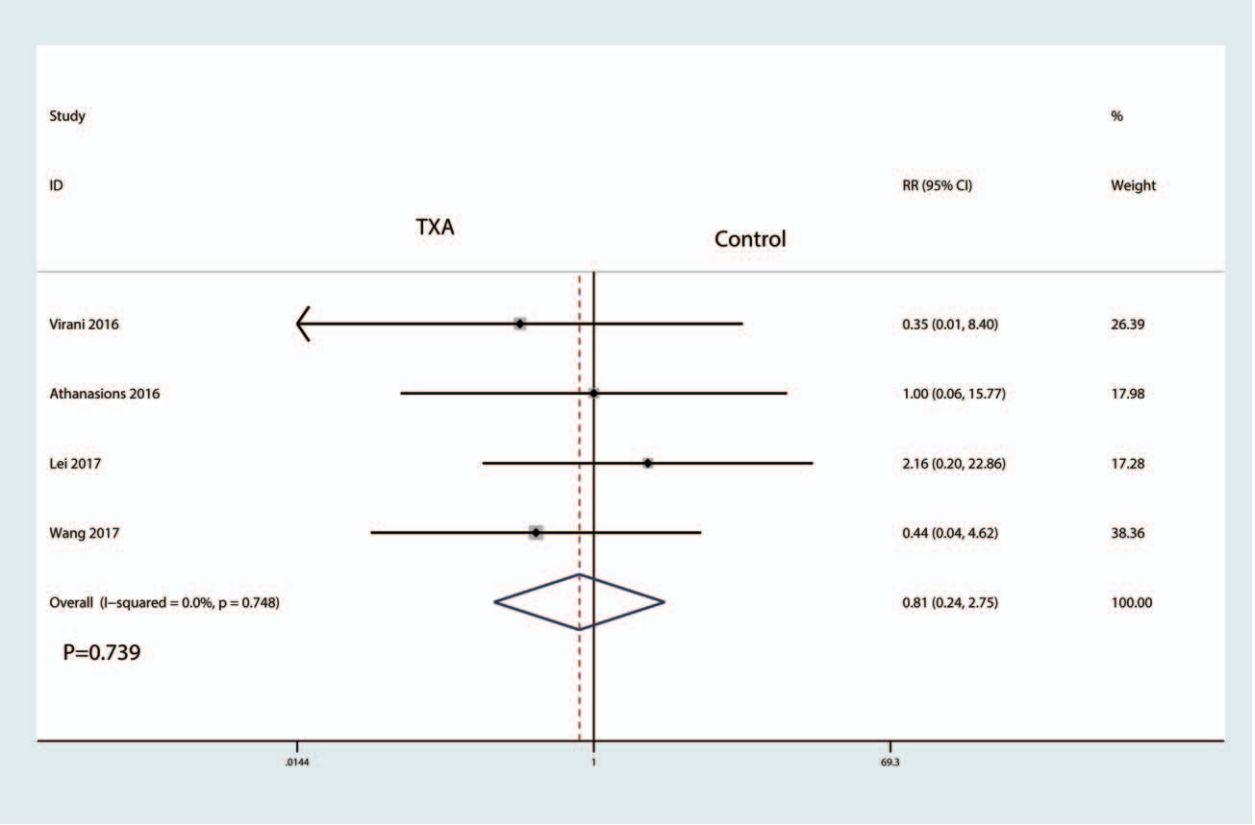

Figure 9. Forest plot comparing the occurrence of DVT between the two groups. DVT = deep vein thrombosis.

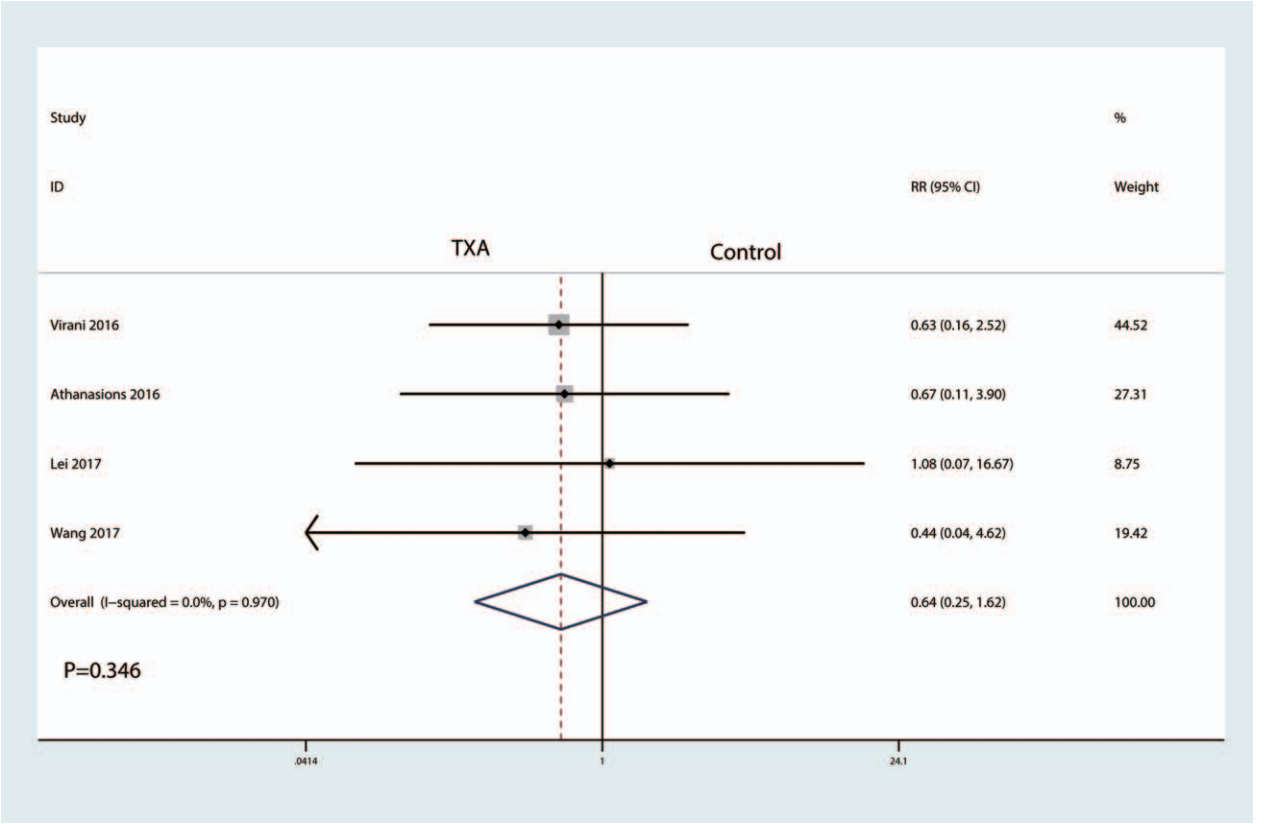

Figure 10. Forest plot comparing the occurrence of PE between the two groups. PE = pulmonary embolism.

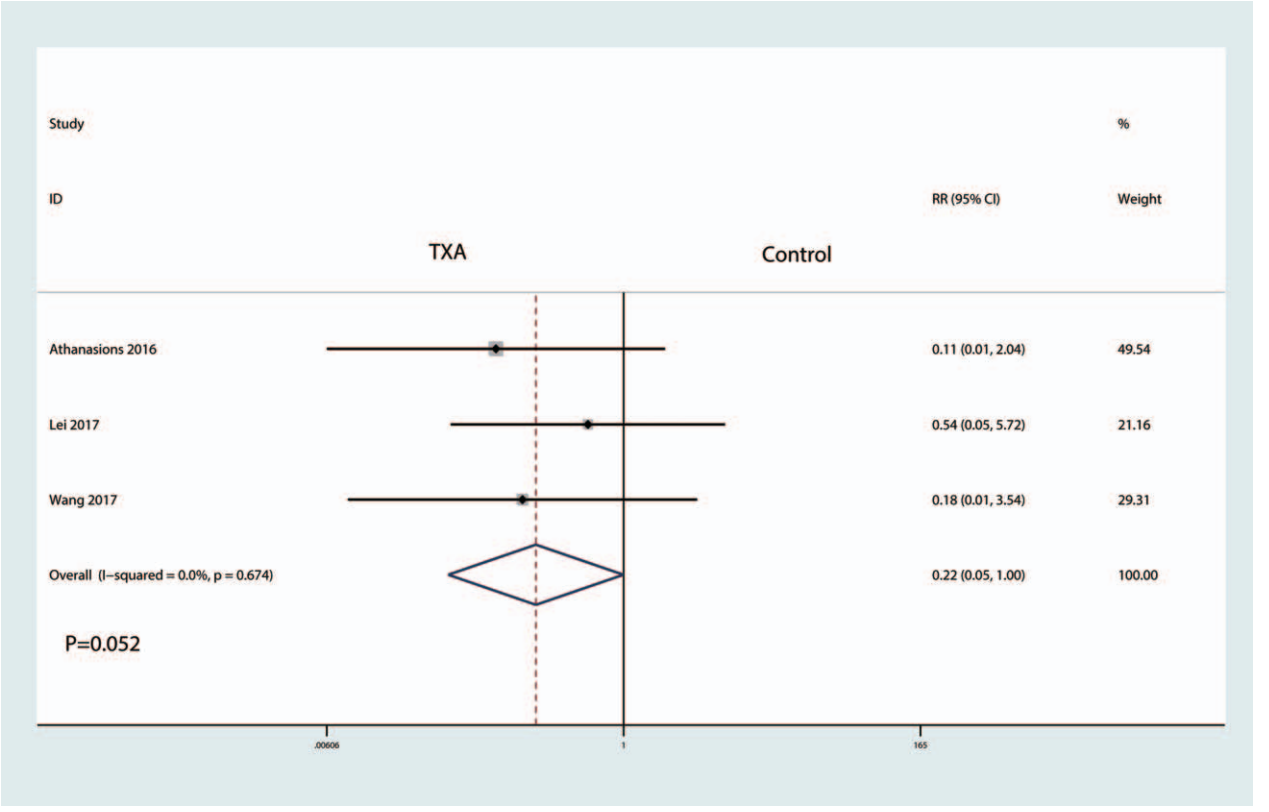

Figure 11. Forest plot comparing the occurrence of infection between the two groups.

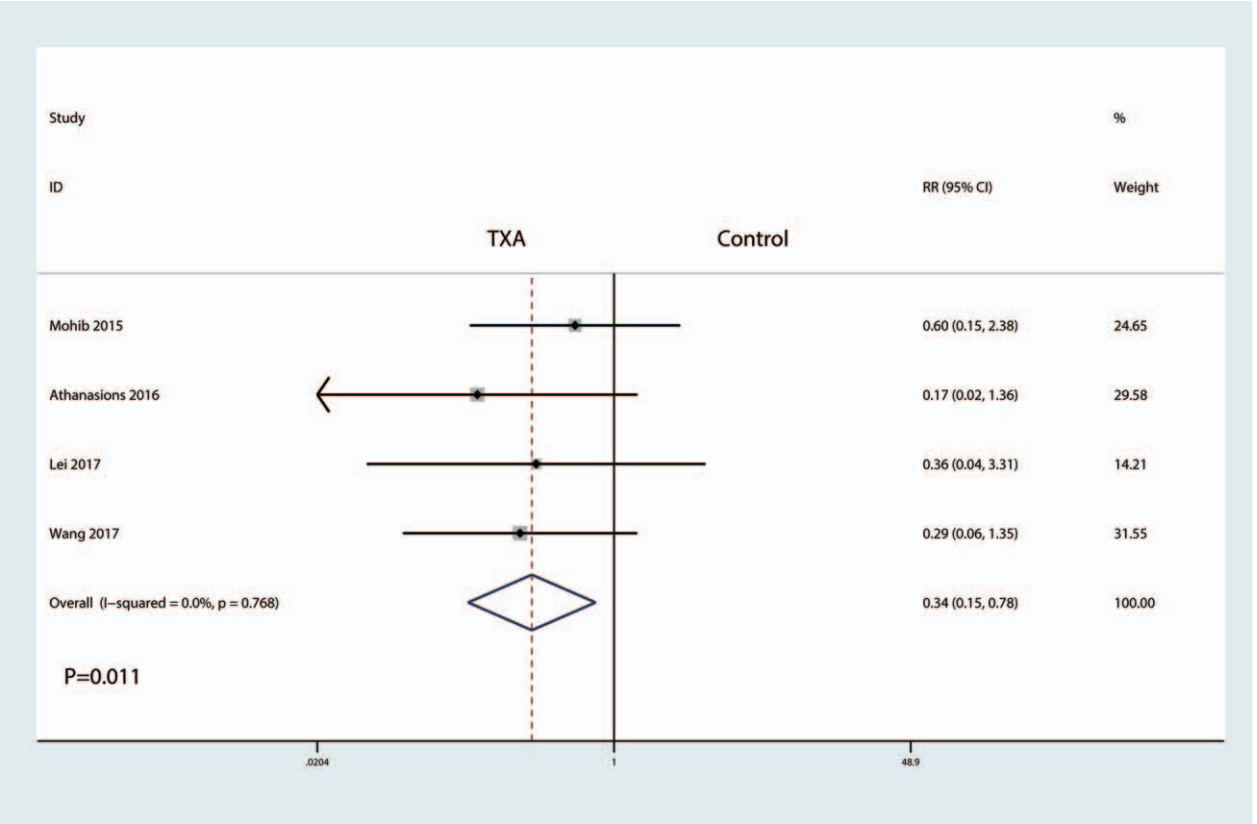

Figure 12. Forest plot comparing the occurrence of hematoma between the two groups.

4.7. Subgroup analysis

As the included studies utilized topical and intravenous TXA, subgroup analysis was performed to assess the two administration method with regard to the need for transfusion. The results are shown in Figure 13. The final results indicated that intravenous TXA can decrease the need for transfusion by 27.2% (RR = 0.62, 95% CI 0.42, 0.91, $P = .016$), whereas topical TXA decreased the need for transfusion by 12.7% (RR = 0.45, 95% CI 0.28, 0.73, $P = .001$).

5. Discussion

This is the first meta-analysis to compare the efficacy and safety of TXA for blood loss control in patients undergoing intertrochanteric fracture surgery. The pooled results indicated that administration of TXA can decrease total blood loss, blood loss in drainage, the need for transfusion and the occurrence of hematoma. Furthermore, administration of TXA was associated with an increase in the hemoglobin level at 3 days after surgery. There was no significant difference between the occurrence of DVT, PE, and infection. A major strength of the current meta-analysis was that we comprehensively searched electronic databases.

Because intertrochanteric fracture surgery may result in substantial blood loss in elderly patients, it is important to identify the optimal blood management to control blood loss during surgery. Previous studies have shown that TXA is associated with a reduction in total blood loss in total knee arthroplasty, total hip arthroplasty, and cardiac surgery.[20–23] However, it has remained unclear whether TXA decreases blood loss in patients undergoing intertrochanteric fracture surgery. The results of the current meta-analysis indicated that administration of TXA is linked to a reduction in total blood loss and drainage in patients undergoing intertrochanteric fracture surgery. Indeed, TXA administration was associated with a reduction in the need for transfusion by 17.5% in patients undergoing intertrochanteric fracture surgery. Zhang et al[24] reported that intravenous TXA can decrease total blood loss by 277 ml and hidden blood loss by 246 ml in hip fracture surgery. TXA reportedly blocks the lysine-binding sites on plasminogen to inhibit plasminogen activation and decrease total blood loss.[25] Four of the studies in our meta-analysis describe the use of PFNA but only one the use of DHS for fixation of intertrochanteric fractures. Because the number of studies included was limited, we did not perform subgroup analysis for DHS or PFNA. Future studies should focus on the efficacy of TXA for reducing blood loss in intertrochanteric fracture surgery with DHS versus PFNA.

We also compared the length of hospital stay between TXA and control groups, and the results indicated that administration of TXA can decrease the length of hospital stay in intertrochanteric fracture surgery. A shorter length of hospital stay typically results in lower patient costs and higher patient satisfaction. However, pre-existing co-morbidities as well as the fracture pattern, quality of reduction achieved, stability of fixation, and quality of bone all contribute to postoperative mobility and the possibility of an early discharge. Thus, all of these factors influence the length of hospital stay. In addition, Boese et al[26] reported that epsilon-aminocaproic acid and TXA can decrease the length of hospital stay.

Moreover, we compared the occurrence of DVT and PE, which are major safety concerns for TXA administration. The results

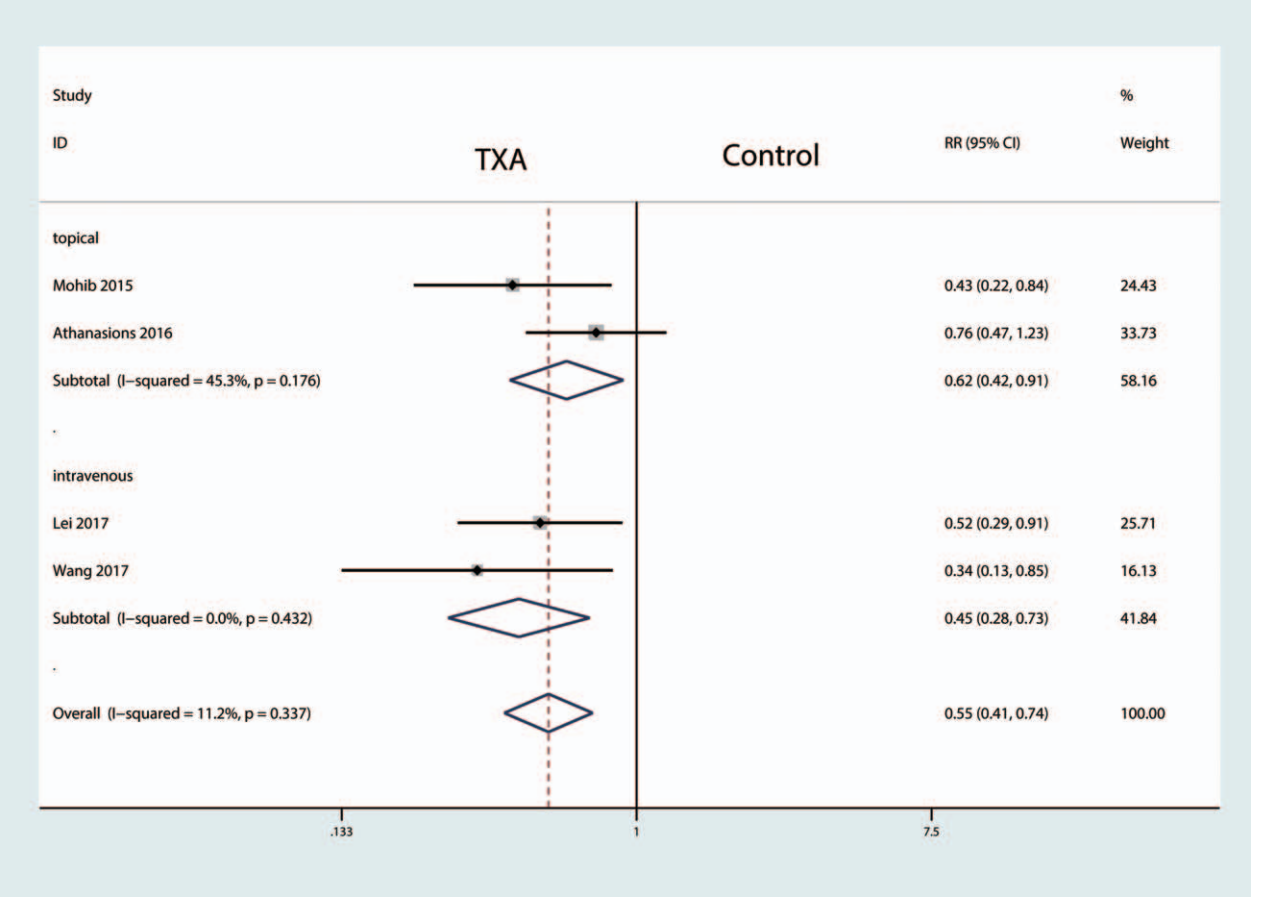

Figure 13. Subgroup analysis of the need for transfusion.

show that TXA administration was not associated with an increase in the occurrence of DVT or PE. Astedt et al[27] treated 16 patients with TXA, intravenously or orally, and found that intravenous TXA did not suppress fibrinolytic activity in vessel walls, and Li et al[28] showed that neither intravenous nor topical TXA increases the occurrence of DVT or PE. In fact, any TXA administration route is reportedly safe for reducing total blood loss in hip fracture surgery. An important finding of our meta-analysis is that administration of TXA can decrease the occurrence of hematoma.

A major strength of this meta-analysis was that our meta-analysis was registered in the researchregistry. To increase the robustness of this meta-analysis, we applied subgroup analysis to increase the strength of our meta-analysis.

This meta-analysis has several potential limitations. Only 5 RCTs compared TXA and placebo for blood loss management after intertrochanteric fracture surgery; thus, the sample analyzed was insufficient. Furthermore, as there is no consensus regarding the optional dose and time to apply TXA, further research should be conducted to find the most effective dose of TXA. Finally, because the follow-up in the trials was of a short duration, a long-term follow-up study should be undertaken to observe the long-term effects of TXA on the occurrence of DVT.

Our meta-analysis of currently available evidence indicates that compared with placebo, administration of TXA is effective at reducing both blood loss and transfusion rates, without sacrificing safety, in intertrochanteric fracture surgery. However, studies with more patients and better-designed RCTs are still needed to establish the optimal regimen of TXA in intertrochanteric fracture surgery.

Author contributions

Formal analysis: Wenming Jiang.
Resources: Wenming Jiang.
Software: Wenming Jiang.
Supervision: Wenming Jiang, Liyong Shang.
Validation: Liyong Shang.
Visualization: Liyong Shang.

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