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REVIEW

A systematic review of tranexamic acid usage in patients undergoing femoral fracture surgery

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Background: Patients undergoing femoral fracture surgery frequently require blood transfusion. Tranexamic acid (TXA) has been widely used to decrease transfusion rate in joint replacement surgery. Therefore, we conducted a systematic review to evaluate the efficacy and safety of TXA usage in femoral fracture surgery.

Materials and methods: Studies involving TXA usage in femoral fracture surgery were searched through four electronic databases. The end points included total blood loss, postoperative hemoglobin decline, transfusion rate, thromboembolic events, 90-day mortality, and operative time. The present study was performed following Cochrane Reviewers' Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was carried out by using Stata 14.0 software.

Results: Eleven studies concerning intravenous (IV) application of TXA and three studies concerning topical administration of TXA were included. Twelve studies were randomized controlled trials (RCTs), and one was a retrospective cohort study. Regarding IV TXA, our paper indicated that the IV TXA group had less total blood loss (weighted mean difference [WMD] = –319.282, P = 0.000), lower postoperative hemoglobin decline (WMD = –1.14, P = 0.000) and lower transfusion rate (risk difference [RD] = –0.172, P = 0.000). No significant differences were found in thromboembolic events (RD = 0.008, P = 0.507), 90-day mortality (RD = 0.009, P = 0.732) and operative time (WMD = –2.227, P = 0.103). Regarding topical TXA, no significant differences were found in the transfusion rate (RD = –0.098, P = 0.129), postoperative hemoglobin decline (WMD = –1.137, P = 0.231), thromboembolic events (RD = –0.017, P = 0.660) and operative time (WMD = –4.842, P = 0.136).

Conclusion: Our meta-analysis demonstrated that both IV and topical application of TXA reduced transfusion rate in femoral fracture surgery. However, still further studies are needed to identify the optimal route of administration, TXA dosage and timing. In addition, high-quality RCTs with a large sample size are required to figure out the safety of TXA application, especially in the elderly, before its wide recommendation.

Keywords: femoral fracture, tranexamic acid, systematic review

Introduction

Femoral fracture is a common type of fractures, especially in the elderly. Femoral fracture surgery frequently results in a significant blood loss, which could lead to severe anemia and subsequent need for transfusion, prolonged hospital stay, high hospital cost and a detrimental effect on long-term mortality.[1,2] Blood transfusion could correct anemia, but it could cause complications such as infections, hemolytic reaction, cardiovascular dysfunction and even death.[2–5] Therefore, it is a significant issue to reduce perioperative blood loss following surgeries for femoral fractures.

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Tranexamic acid (TXA) is a synthetic amino acid analog, which acts as a competitive inhibitor of plasminogen and finally interferes with fibrinolysis.[6] TXA has been reported to be an easily accessible and cost-effective treatment that could reduce the amount of blood loss and subsequent need for blood transfusion, and it has been successfully used in gynecological and obstetric, spinal and thoracic surgeries.[7–9] In addition, numerous studies have proved that TXA could decrease blood loss and transfusion rates without increasing the rate of thrombotic events in hip and knee arthroplasty.[10–13] However, there is limited data on the efficacy and safety of TXA usage in femoral fracture surgery; whether TXA should be used in femoral fracture surgery remains controversial. So, we performed this meta-analysis to investigate the efficacy and safety of TXA usage following surgeries for femoral fractures.

Materials and methods

Literature search

Electronic databases were searched before January 20, 2018 by two independent investigators, including Cochrane Library, Embase, Medline and Web of Science. The references of the included literatures were also checked for potentially relevant studies. Only English studies were included. The key words including "tranexamic acid", "fracture", "hemiarthroplasty", "total hip arthroplasty", "total hip replacement", "nail", "screw" and "open reduction internal fixation" were used. They were combined with Boolean operators. The searched results are shown in Figure 1.

Inclusion and exclusion criteria

Trials were eligible for inclusion if they met the following criteria: 1) studies involved the comparison of the efficacy and safety of TXA usage in femoral fracture surgery and 2) studies included at least one of the outcome measures. Studies were excluded if 1) case reports and publications only included an abstract; 2) they included other types of fractures; 3) they were not published in English and 4) there was duplicate publication.

Data extraction

The following data were independently extracted from each of the included studies by two investigators: first author

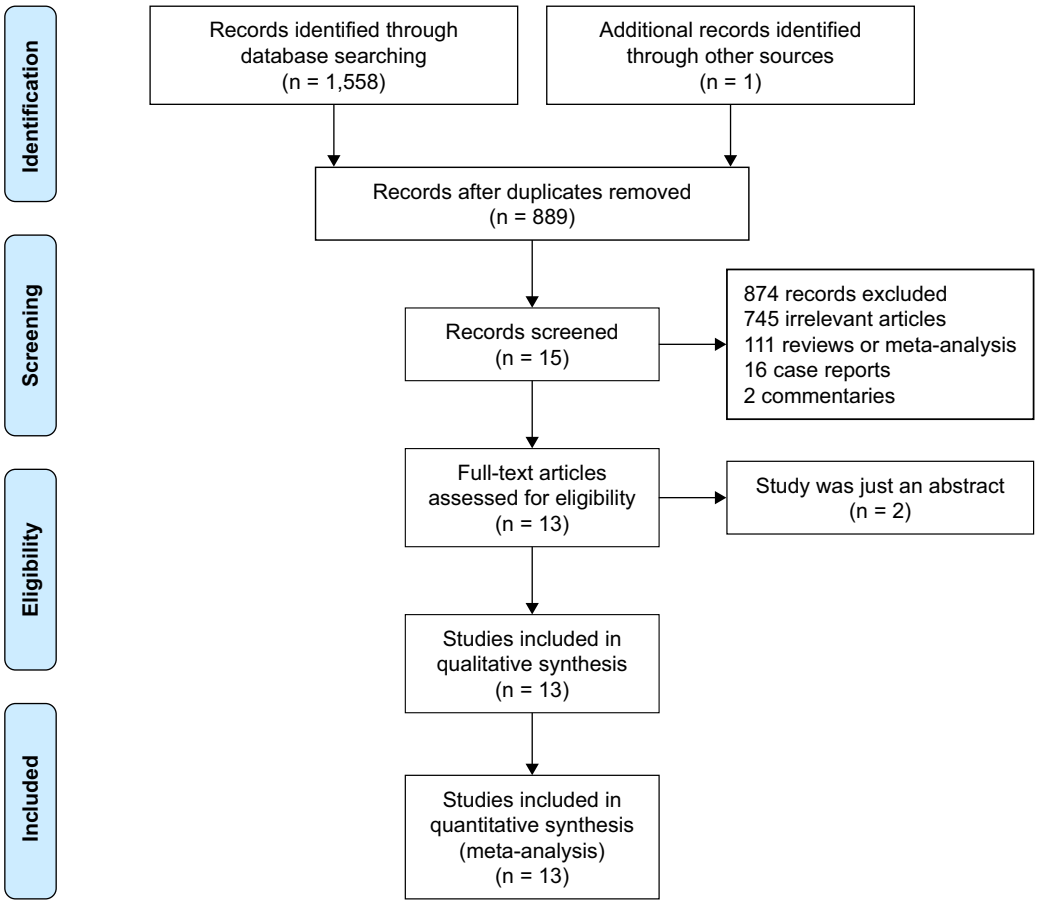

Figure 1 PRISMA flow diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

names, published year, sample size, mean age, anesthesia methods, fracture type, surgical management, intervention, control, thromboprophylaxis, transfusion criteria and follow-up. Disagreement was resolved by consulting the reviewer. The end points included total blood loss, postoperative hemoglobin decline, transfusion rate, thromboembolic events, 90-day mortality and operative time.

Quality assessment

Two investigators independently assessed the quality of the randomized controlled trials (RCTs) according to the methods of the 12-item scale.[14] Each item was scored "Yes", "Unclear" or "No". A trial with a score of more than 7 "Yes" was considered as of high quality, more than 4 but no more than 7 was considered as of moderate quality and no more than 4 was considered as of low quality. The Methodological Index for Non-Randomized Studies (MINORS) criteria was used to assess non-RCTs and was scored from 0 to 24.[15] Agreement on the outcome was assessed by the means of a kappa test. Any different opinions were resolved by a third reviewer.

Data analysis and statistical methods

The meta-analysis was conducted using Stata 14.0 software. For continuous outcomes, a weighted mean difference (WMD) and 95% CI were used. For dichotomous data, the risk difference (RD) with 95% CI was calculated as the summary statistics. Statistical heterogeneity was assessed using the value of P and I^2. If P was >0.1 and I^2 was $<50\%$, the fixed-effects model was used; otherwise, the random-effects model was used to do analysis. Random-effects models were used to reduce heterogeneity. The assessment of publication bias and meta-regression could not be conducted because the most frequent outcome (transfusion rate) just included nine studies, and tests for them are generally performed only when at least 10 studies are involved. Owing to the limited information, subgroup analyses were just conducted on mean age (<65 years, ≥ 65 years). In addition, sensitivity analyses were conducted to insure the accuracy of the outcomes.

Ethical approval

All analyses were based on previous published studies; thus, no ethical approval and patient consent were required.

Results

Search result

A total of 1,559 potentially relevant references were founded. After the process of finding duplicates, 670 studies were excluded. By scanning the titles and abstracts, 874 studies were excluded from the analysis. After full texts carefully read for eligibility, two studies were excluded, because they were just an abstract.[16,17] Finally, 12 RCTs[18–21,23–30] and 1 retrospective cohort study[22] were included. The characteristics of all included studies are shown in Tables 1 and 2.

Study quality

The quality of RCTs is shown in Table 3. The value of weighted kappa for the agreement on these studies between reviewers was excellent ($\kappa = 0.72$). Ten studies[18–21,23,25,26,28–30] were of high quality, and two studies were of moderate quality.[24,27] The randomization methods were explicitly introduced in nine studies.[18–20,23,25,26,28–30] Randomization allocation was concealed adequately in six studies.[19,20,23,25,26,30] Nine RCTs provided the information of double blinding.[18–21,23,25,26,28,30] None of them reported a binding of outcome assessment. However, all of the included studies were reported with complete outcome data. The quality of the cohort study is shown in Figure 2.

Total blood loss (mL)

Intravenous (IV) administration of TXA

Four studies[18,24,26,29] compared total blood loss. The data of them were pooled to do analysis. There was a significant heterogeneity between the studies ($P < 0.1$, $I^2 = 81.9\%$). Therefore, the random-effects model was used. The pooled results manifested that the IV TXA group had a significant decrease in total blood loss (WMD = −319.282, 95% CI: −475.229 to −163.336, $P = 0.000$; Figure 3).

Postoperative hemoglobin decline (g/dL)

IV administration of TXA

Seven articles[18,20–24,28] reported the outcome of postoperative hemoglobin decline. A significant heterogeneity was detected between the studies ($P < 0.1$, $I^2 = 75.4\%$). Therefore, the random-effects model was used to do analysis. The pooled results demonstrated that the IV TXA group had a lower postoperative hemoglobin decline (WMD = −1.144, 95% CI: −1.727 to −0.561, $P = 0.000$; Figure 4).

Topical administration of TXA

Two articles[21,27] reported the outcomes of postoperative hemoglobin decline. A significant heterogeneity was detected between the studies ($P < 0.1$, $I^2 = 92.0\%$); Therefore, the random-effects model was used to do the analysis. It showed no significant difference in postoperative hemoglobin decline between the topical TXA group and the control group (WMD = −1.137, 95% CI: −2.999 to 0.725, $P = 0.231$; Figure 4).

Table 1 The characteristics of studies regarding IV TXA

Study ID	No I vs C	Mean age (years): I vs C	Anesthesia	Fracture type	Surgical management	Intervention	Control	Thromboprophylaxis	Transfusion criteria	Follow-up
Sadeghi and Mehr-Aein (2007)[18]	32/35	51.8/44.4	Spinal anesthesia	Intracapsular, extracapsular fractures	Hemiarthroplasty, plating, nailing	15 mg/kg before surgery	Normal saline	NR	NR	NR
Zufferey et al (2010)[19]	57/53	81/82	General anesthesia	Cervical only, trochanteric, transtrochanteric fractures	Total hip arthroplasty, hemiarthroplasty, dynamic hip screw, intramedullary nail	15 mg/kg before surgery, a second 15 mg/kg 3 h later	Placebo	Fondaparinux	Hb <9 g/dL	1 year
Vijay et al (2013)[20]	45/45	48.8/49.3	Combined spinal epidural anesthesia	Hip and femoral fractures	Open reduction internal fixation, hemiarthroplasty, total hip replacement	A bolus of 500 mg TXA through 50 mL syringe during 10 min, ~15 min before incision and a continuous infusion of 1 mg/kg/h dissolved in 1 L of saline until the end of surgery	Normal saline	NR	A reduction in hemoglobin exceeding 25% of preoperative level	NR
Emara et al (2014)[21]	20/20	56.5/56	General anesthesia	Hip fracture	Hemiarthroplasty	20 mg/kg in 20 mL normal saline before skin incision, 500 mg TXA in 250 mL normal saline with rate of 80 mL/h until the end of surgery	Normal saline	Low-molecular-weight heparin	NR	4 weeks
Mohib et al (2015)[23]	50/50	69.0/70	NR	Intertrochanteric fracture	NR	10 mg/kg before surgery, a second 10 mg/kg 3 h later	Placebo	Enoxaparin	Hb <7 g/dL	NR
Tengberg et al (2016)[26]	33/39	79.8/75.0	Epidural anesthesia	Trochanteric fracture	Intramedullary nail	1 g just prior to surgery, 3 g postoperatively	Placebo	Low-molecular-weight heparin	Hb <9.67 g/dL	90 days
Haghighi et al (2017)[28]	18/20	65.1/66.1	General anesthesia	Femoral fracture	Intramedullary nail	15 mg/kg before incision	Normal saline	NR	NR	NR
Baruah et al (2016)[24]	30/30	57.7/55.3	Spinal anesthesia	Trochanteric fracture	Dynamic hip screw plate fixation	A single dose of TXA (15 mg/kg) 15 min prior to surgery	Normal saline	NR	Hb <8.5 g/dL Hematocrit level <27%	NR
Watts et al (2017)[30]	69/69	81.0/82.2	General anesthesia	Femoral neck fracture	Hemi or total hip arthroplasty	2 doses of 15 mg/kg, 1 dose just before incision and the second dose at wound closure	Normal saline	Low-molecular-weight heparin	Hb <8.0 g/dL	6 months
Lei et al (2017)[29]	37/40	77.8/79.2	NR	Intertrochanteric fracture	Proximal femoral nail antirotation	1 g after anesthesia, but before surgery	Normal saline	NR	Hb <9 g/dL	30 days
Lee et al (2015)[22,*]	84/187	86/85	General anesthesia ± block, spinal anesthesia	Hip fracture	Hemiarthroplasty	A bolus of 1 g TXA intravenously on induction	NR	Tinzaparin	NR	NR

Note: All studies were RCTs except Lee et al (2015),[22] which was an observational cohort study. *Observational cohort study.
Abbreviations: IV, intravenous; TXA, tranexamic acid; I, intravenous TXA group; C, control group; NR, no report; RCT, randomized controlled trial.

Table 2 The characteristics of studies regarding topical TXA

Study ID	No T vs C	Mean age (years): T vs C	Anesthesia	Fracture type	Surgical management	Intervention	Control	Thromboprophylaxis	Transfusion criteria	Follow-up
Emara et al (2014)[21]	20/20	55/56	General anesthesia	Hip fracture	Hemiarthroplasty	100 mL normal saline with 1.5 g of TXA was purred into the surgical field and left for 5 min before suction	Normal saline	Low-molecular-weight heparin	NR	4 weeks
Drakos et al (2016)[25]	100/100	81/80.7	Spinal anesthesia	Intertrochanteric fracture	Intramedullary nail	Subfascial administration of 3 g of TXA around the fracture site at the end of the surgical procedure	NR	Low-molecular-weight heparin	Hb <8 g/dL or hematocrit <25%	12 months
Virani et al (2016)[27]	67/70	67/69.1	NR	Peritrochanteric fracture	Dynamic hip screw and barrel plate	Subfascial and intramuscular infiltration of 2 g TXA before wound closure	NR	NR	NR	NR

Abbreviations: TXA, tranexamic acid; T, topical TXA group; C, control group; NR, no report.

Table 3 Study quality

RCTs	Randomized adequately[a]	Allocation concealed	Patient blinded	Care provider blinded	Outcome assessor blinded	Acceptable dropout rate[b]	ITT analysis[c]	Avoided selective reporting	Similar baseline	Similar or avoided cofactor	Patient compliance	Similar timing	Quality[d]
Sadeghi and Mehr-Aein (2007)[18]	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	High
Zufferey et al (2010)[19]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Emara et al (2014)[21]	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Mohib et al (2015)[23]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Tengberg et al (2016)[26]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Unclear	Yes	Unclear	High
Haghighi et al (2017)[28]	Yes	Unclear	Yes	Yes	No	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	High
Watts et al (2017)[30]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	High
Baruah et al (2016)[24]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Moderate
Vijay et al (2013)[20]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Drakos et al (2016)[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Virani et al (2016)[27]	Unclear	Unclear	Yes	No	No	Yes	No	Yes	Yes	Unclear	Yes	Yes	Moderate
Lei et al (2017)[29]	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High

Notes: [a]Only if the method of sequence made was explicitly introduced could get a "Yes". [b]Dropout rate <20% could get a "Yes", otherwise "No". [c]ITT = intention-to-treat, only if all randomized participants were analyzed in the group they were allocated to could receive a "Yes". [d]"Yes" items more than seven means "High", more than four but no more than seven means "Moderate" and no more than four means "Low".
Abbreviation: RCT, randomized controlled trial.

Methodological items for non-randomized studies	Lee et al (2015)[22]
1. A clearly stated aim	2
2. Inclusion of consecutive patients	2
3. Prospective collection of data	1
4. End points appropriate to the aim of the study	2
5. Unbiased assessment of the study end point	2
6. Follow-up period appropriate to the aim of the study	1
7. Loss to follow-up <5%	2
8. Prospective calculation of the study size	0
9. An adequate control group	2
10. Contemporary groups	2
11. Baseline equivalence of groups	2
12. Adequate statistical analyses	2
Total	20

Figure 2 The MINORS criteria.
Abbreviation: MINORS, Methodological Index for Non-Randomized Studies.

Transfusion rate

IV administration of TXA

Ten studies[18–23,26,28–30] involved the comparison of transfusion rate. No significant heterogeneity was detected between the studies ($P > 0.1$, $I^2 = 3.8\%$). Therefore, the fixed-effects model was used to do the analysis. The results showed that the IV TXA group had a lower transfusion rate (RD = –0.172, 95% CI: –0.224 to –0.121, $P = 0.000$; Figure 5).

Topical administration of TXA

Three studies[21,25,27] involved the comparison of transfusion rate. There was a significant heterogeneity between the studies ($P > 0.1$, $I^2 = 54.5\%$). Therefore, the random-effects model was used to do the analysis. It showed no significant difference in the transfusion rate between the two groups (RD = –0.098, 95% CI: –0.225 to 0.029, $P = 0.129$; Figure 5).

Thromboembolic events

IV administration of TXA

Nine studies[19–24,26,29,30] reported thromboembolic events. No significant heterogeneity was detected ($P > 0.1$, $I^2 = 9.0\%$), so the fixed-effects model was performed. It showed no significant difference in the rate of thromboembolic events between the two groups (RD = 0.008, 95% CI: –0.017 to 0.034, $P = 0.507$; Figure 6).

Topical administration of TXA

Two studies[21,25] reported thromboembolic events. No significant heterogeneity was detected ($P > 0.1$, $I^2 = 0\%$), so the fixed-effects model was performed. There was no significant difference in the rate of thromboembolic events between the two groups (RD = –0.017, 95% CI: –0.091 to 0.058, $P = 0.66$; Figure 6).

90-day mortality

IV administration of TXA

Five studies[18,22,26,29,30] reported 90-day mortality. No significant heterogeneity was detected ($P > 0.1$, $I^2 = 17\%$), so the fixed-effects model was performed. It showed no significant

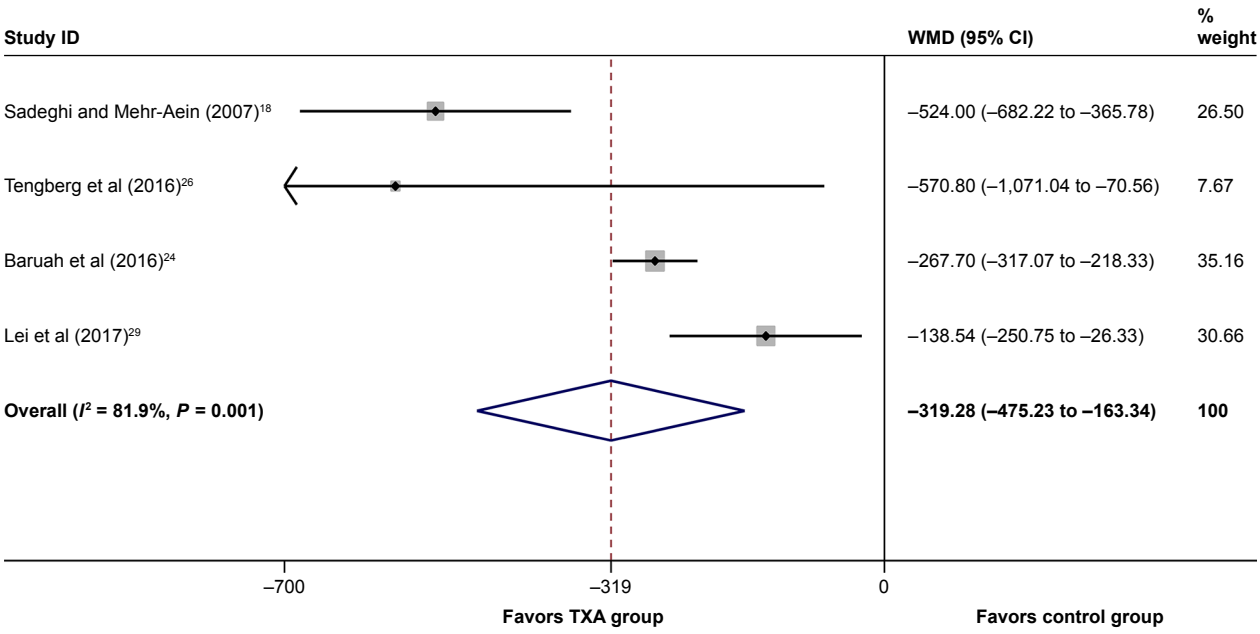

Figure 3 Forest plot for total blood loss.
Note: Weights are from random-effects analysis.
Abbreviations: TXA, tranexamic acid; WMD, weighted mean difference; CI, confidence interval.

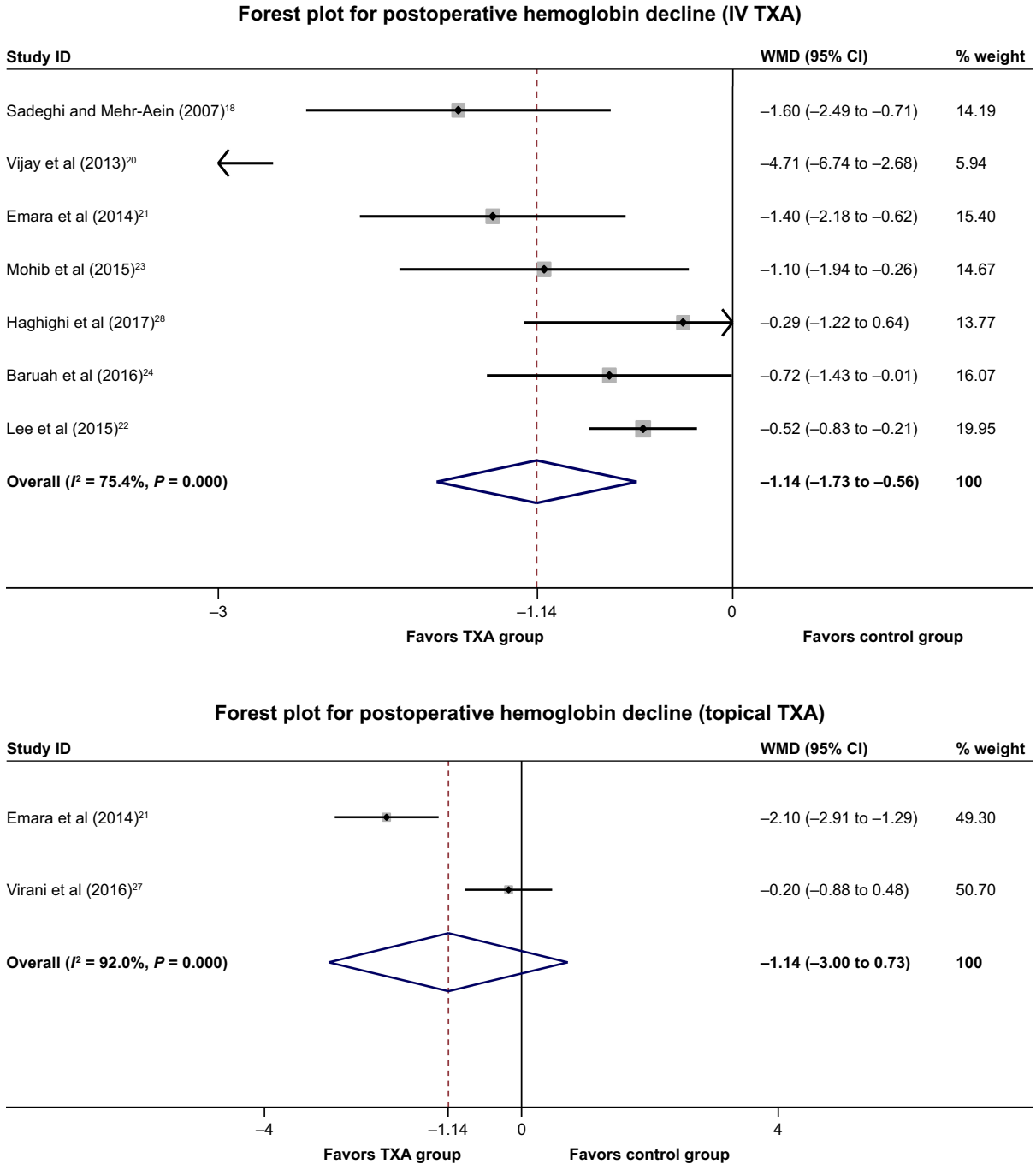

Figure 4 Forest plot for postoperative hemoglobin decline.
Note: Weights are from random-effects analysis.
Abbreviations: IV, intravenous; TXA, tranexamic acid; WMD, weighted mean difference; CI, confidence interval.

difference in 90-day mortality between the groups (RD = 0.009, 95% CI: –0.040 to 0.058, $P = 0.732$; Figure 7).

Topical administration of TXA

Only one study[25] reported outcome of mortality. The rate was 13% (13 patients) in the TXA group and 14% (14 patients) in the control group ($P > 0.05$) during the first 12 months after surgery.

Operative time (min)

IV administration of TXA

The operative time was reported in seven studies.[19–21,23,28–30] There was no significant heterogeneity between the two groups ($P > 0.1$, $I^2 = 0.0\%$); therefore, the fixed-effects model was used. The result manifested that no significant difference was detected. (WMD = –2.227, 95% CI: –4.904 to 0.450, $P = 0.103$; Figure 8).

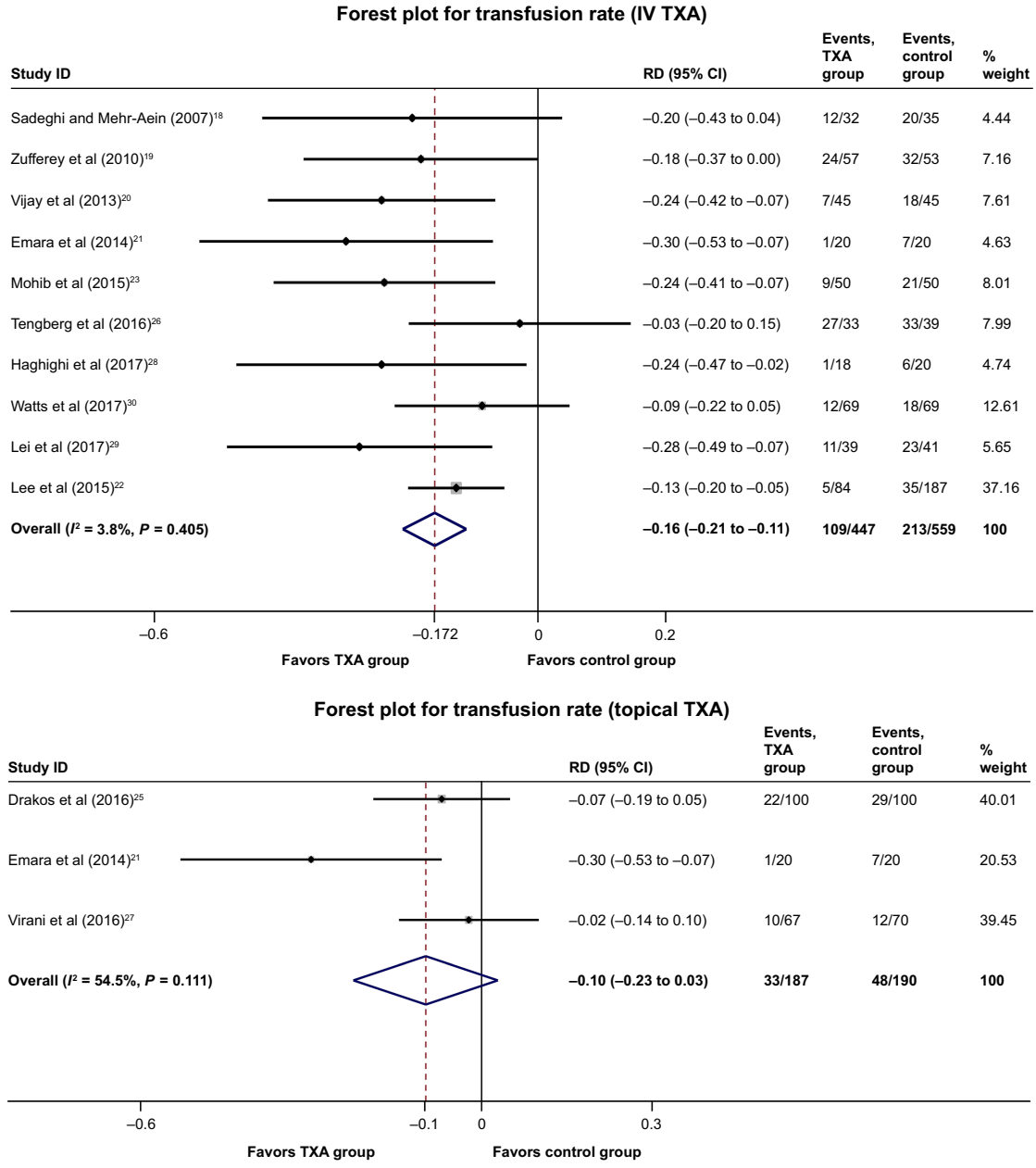

Figure 5 Forest plot for transfusion rate.
Note: Weights are from random-effects analysis.
Abbreviations: IV, intravenous; TXA, tranexamic acid; RD, risk difference; CI, confidence interval.

Topical administration of TXA

The operative time was reported in two studies.[21,25] There was a significant heterogeneity between the studies ($P < 0.1$, $I^2 = 74.0\%$). Therefore, the random-effects model was used. The result manifested that no significant difference was detected (WMD = –4.842, 95% CI: –11.214 to 1.530, $P = 0.136$; Figure 8).

Sensitivity analysis

As fewer studies were concerning topical TXA, so we just made sensitivity analysis in outcomes of studies that involved IV TXA usage. All the outcomes kept stable after the exclusion of each study once a time, and it showed some result when using a random effect.

Subgroup analysis

Owing to the lack of related studies, subgroup analysis was just conducted on postoperative hemoglobin decline, transfusion rates and thromboembolic events. Concerning postoperative hemoglobin decline, subgroup analysis showed no significant difference between the mean age <65 years group (WMD = –1.740, 95% CI: –2.767 to –0.713, $P = 0.001$) and

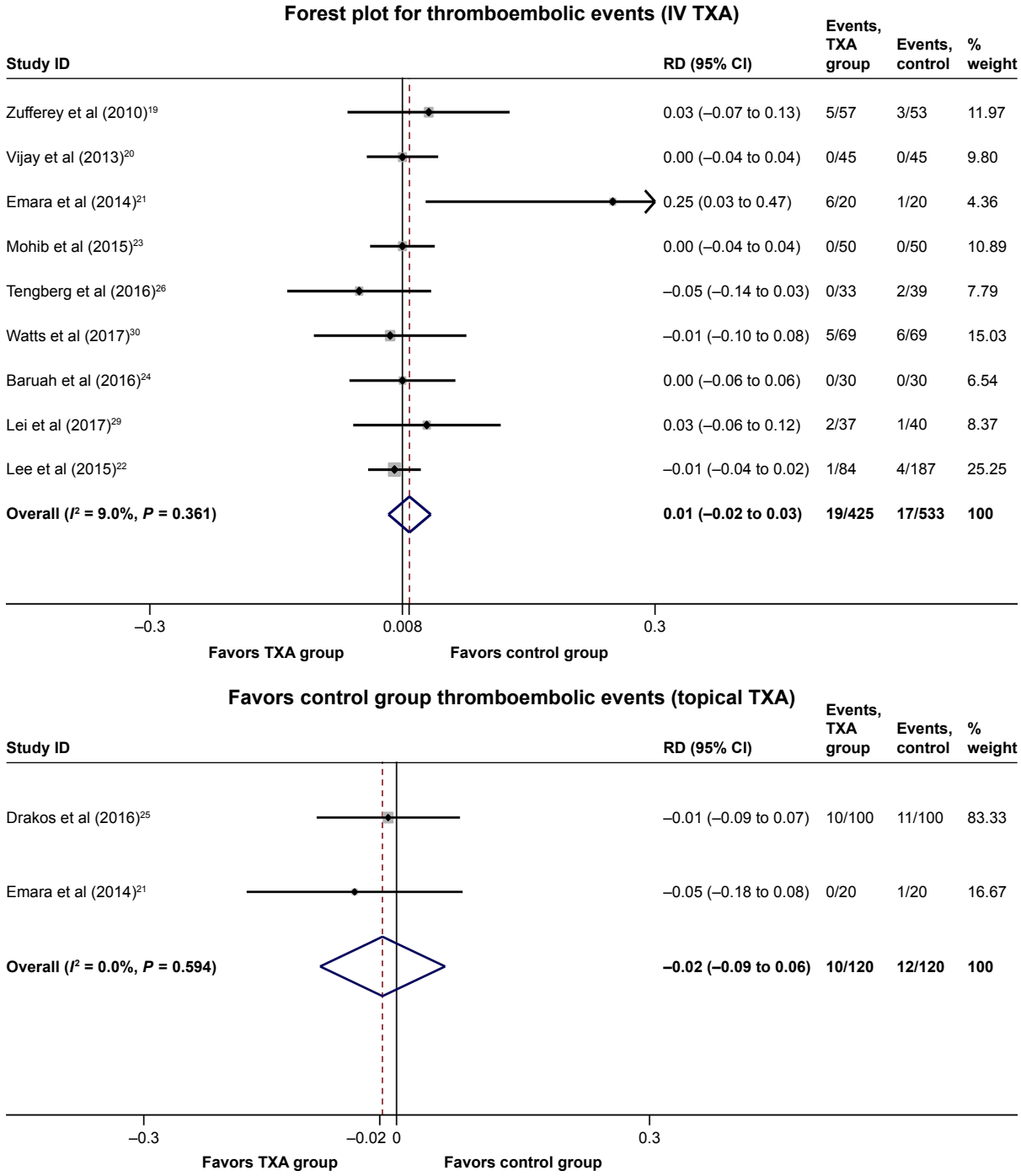

Figure 6 Forest plot for thromboembolic events.
Abbreviations: IV, intravenous; TXA, tranexamic acid; RD, risk difference.

mean age >65 years group (WMD = –0.565, 95% CI: –0.844 to –0.285, $P = 0.000$). Concerning transfusion rates, subgroup analysis showed no significant difference regarding mean age <65 years (RD = –0.239, 95% CI: –0.363 to –0.116, $P = 0.000$) and mean age >65 years (RD = –0.155, 95% CI: –0.211 to –0.099, $P = 0.000$). Regarding thromboembolic events, subgroup analysis showed no significant difference regarding mean age <65 years (RD = 0.053, 95% CI: –0.002 to 0.108, $P = 0.061$) and mean age >65 years (RD = –0.003, 95% CI: –0.031 to 0.025, $P = 0.832$).

Discussion

The most important findings of our meta-analysis were that TXA reduced transfusion rate without increasing thromboembolic events in femoral fracture surgery. Although no significant differences were found in the transfusion

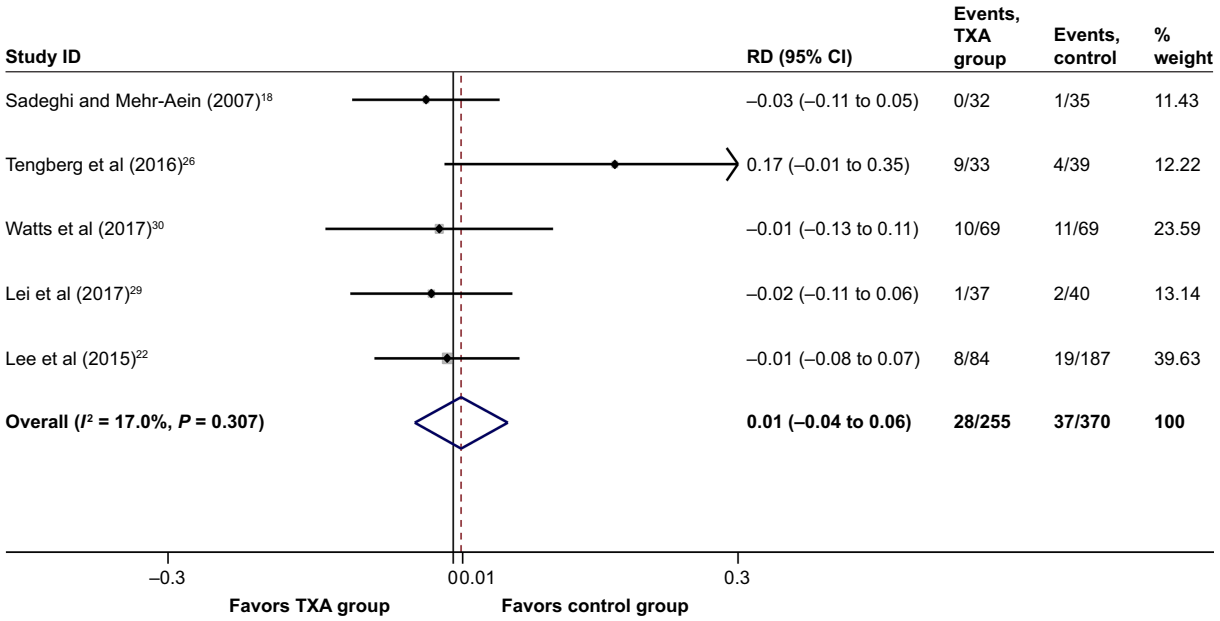

Figure 7 Forest plot for 90 days mortality.
Abbreviations: RD, risk difference; TXA, tranexamic acid.

rate regarding topical TXA, the topical group had a lower transfusion rate compared with the control group. However, a significant heterogeneity was detected in some outcomes. The limited data concerning TXA usage may be contributed to it. The differences in clinical measures should also be taken into consideration.

There were limited studies focusing on TXA usage in femoral fracture surgery. Such reasons include older age, female gender, lower admission hemoglobin, higher American Society of Anesthesiologists grade, frailty and greater co-existing comorbidities. Patients suffering from femoral fractures were more susceptible to thromboembolic events comparing with patients undergoing elective joint replacement.[31] Therefore, there is still clinical uncertainty regarding TXA application in femoral fracture patients. However, the potential benefits of TXA in significantly decreasing blood loss and transfusion rates are overwhelming. In addition, TXA could bring improved functional recovery, shorter length of hospital stay and lower cost.[18] Therefore, the potential benefits of TXA in femoral fracture patients may outweigh the risk of it.

Regarding the hemostatic efficacy of IV TXA, all included studies were in favor of its application in femoral fracture surgery. Although some studies found no significant difference in the transfusion rate and/or blood loss, there was a lower transfusion rate and/or blood loss in the TXA group. It is almost a consensus that TXA could reduce blood loss and transfusion rate. Further research on the safety of its usage especially whether it could induce increased thromboembolic events should be carried out. Zufferey et al[19] found a three-fold increased risk in vascular events at 6 weeks with IV TXA usage in hip fracture surgery ($P = 0.10$), but the incidence rate of vascular events between the IV group and the control group was not statistically significant. Emara et al[21] used thromboelastogram as a monitor for coagulation (significant decrease in r and k and significant increase in maximum amplitude and α-angle), which favored relative hypercoagulable state in the IV TXA group, and they found a statistically significant increase in the incidence of thromboembolic events in the form of deep vein thrombosis (DVT) in the IV TXA group ($P < 0.05$). However, most included studies proved its safety.[20,22–24,30]

At present, the common methods of IV TXA usages are preoperative dose of 1 g or 10–15 mg/kg (sometimes, second dose was added after 3 or 6 h) or combined use of continuous infusion for >8 h. Lanoiselée et al[32] pointed out that TXA plasma concentrations were maintained for >10 mg/L during surgery and for a minimum of 3 h with a preoperative TXA dose of 1 g in hip arthroplasty. However, keeping TXA concentrations above this threshold up to 16 h could not reduce blood loss more effectively. Zufferey et al[33] also reported that a continuous infusion of 1 g TXA after a preoperative bolus of TXA in hip replacement did not achieve any further reduction in blood loss. Piolanti et al[34] divided 80 patients who underwent primary unilateral minimally invasive TXA into two groups: one group received two IV doses of 10 mg/kg of TXA and the other group received two doses of 20 mg/kg. They found that a dose of 10 or 20 mg/kg provides statistically similar results in blood loss sparing, and they pointed that the use of two 10 mg/kg doses could be considered more

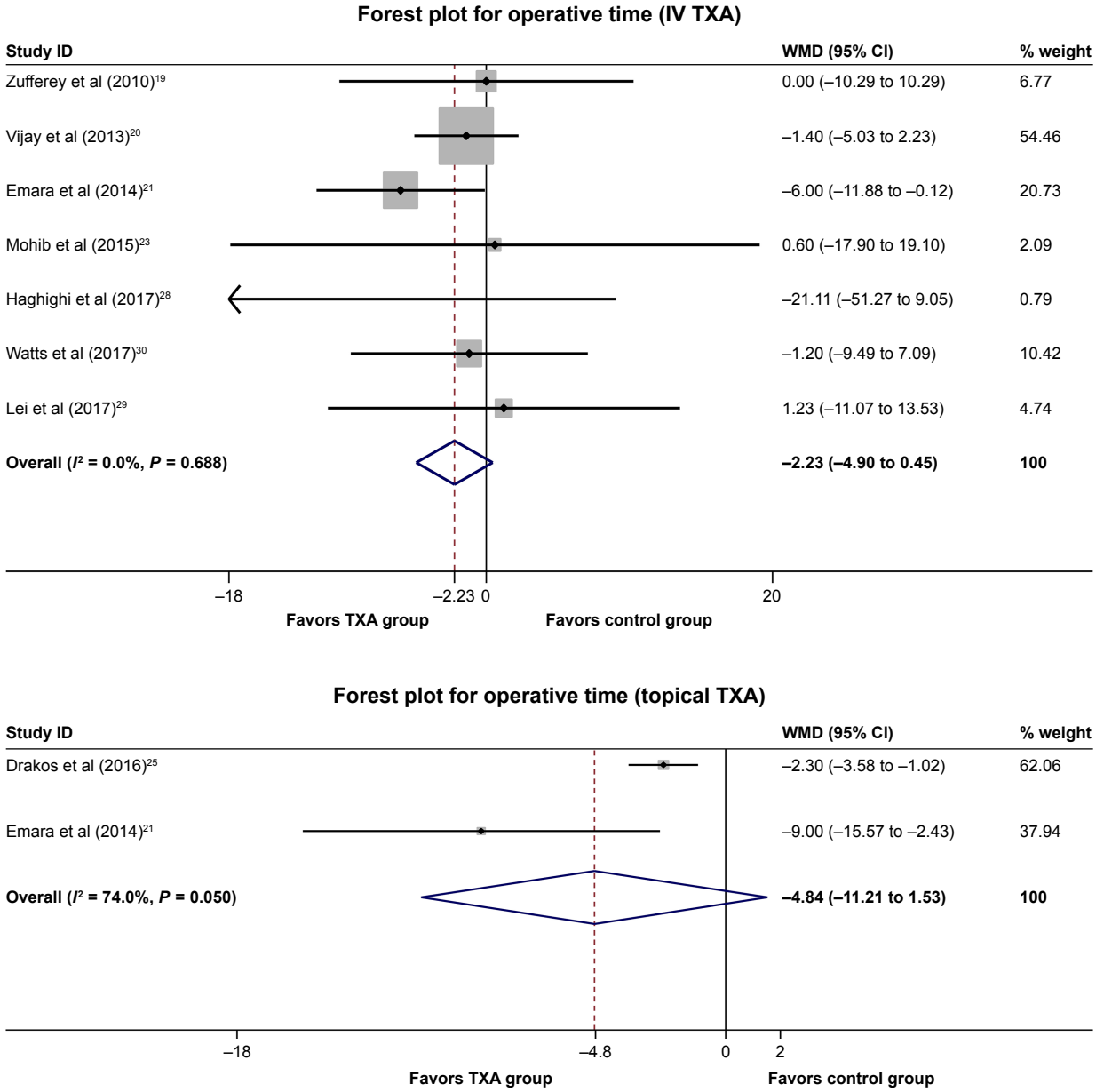

Figure 8 Forest plot for operative time.
Note: Weights are from random-effects analysis.
Abbreviations: IV, intravenous; TXA, tranexamic acid; WMD, weighted mean difference; CI, confidence interval.

advisable in order to reduce the potential thromboembolic risks. In the trial of Sun et al,[35] 180 patients who underwent primary unilateral total knee arthroplasty were randomized into four groups. In group A, TXA (30 mg/kg) was infused 15 min before tourniquet inflation. In group B, TXA (15 mg/kg) was infused 15 min before tourniquet inflation and 3 h postoperatively. As for group C, TXA (10 mg/kg) was infused 15 min before tourniquet inflation and 3 and 6 h postoperatively. In all, 250 mL of normal saline without TXA was infused 15 min before tourniquet inflation in group D. They concluded that the preoperative dose and an additional dose of TXA were superior to a single preoperative dose of TXA in reducing blood loss and one additional dose was comparable to two additional doses of TXA in reducing blood loss.

Owing to a lack of systemic absorption, topical usage should be taken into consideration. Although no significant differences were found in our meta-analysis, the topical group had a lower transfusion rate. Drakos et al[25] reported that topical TXA used around the fracture site in elderly patients undergoing surgery of intertrochanteric fractures was safe and cost-effective, and a significant reduction in blood loss and transfused blood units and health care cost could be achieved. In addition, Emara et al[21] demonstrated that topical TXA as an effective way to decrease blood and transfusion

rates was safer comparing with IV TXA. However, Virani et al[27] considered that TXA does not play a significant role in reducing postoperative blood loss and blood transfusion when used locally in pertrochanteric fracture surgery.

Blocking the lysine-binding sites on plasminogen to inhibit the activation of plasminogen and finally interfering with fibrinolysis is the mechanism of TXA. TXA itself does not increase the synthesis of fibrin, so TXA in theory does not lead to a high coagulation state after surgery and certainly not an increase in thromboembolic events. Benoni and Fredin[36] also suggested that TXA does not affect the risk of DVT because it inhibits fibrinolysis in the wound, not in circulation. The Clinical Randomisation of an Antifibrinolytic in Significant Haemarrhage-2 study included 20,000 patients; most of them suffered from significant hemorrhage. It showed that TXA safely reduced the risk of death in bleeding trauma patients.[37] A large sample size study carried out by Poeran et al[38] involving 872,416 patients showed no increased risk of complications, including thromboembolic events and renal failure, with TXA usage in joint replacement surgery.

The key aspects for future research are as follows. 1) High-quality RCTs regarding different TXA dosages and timing still are needed to acquire a better application. 2) The thrombotic risk is of vital importance to its recommendation, so large and high-quality studies should focus on the safety of TXA application, especially in the elderly. 3) The use of topical TXA is a new challenge in controlling intraoperative blood loss among the major orthopedic surgery. RCTs with a larger sample size and a longer follow-up time are necessary to precisely compare IV and topical administrations of TXA. 4) Early surgery has been reported with a lower risk of death and lower rates of postoperative pneumonia and pressure sores among elderly patients with hip fracture.[39] In femoral fractures frequently accompanied by a high initial blood loss, early TXA may decrease the incidence rate of preoperative anemia and then bring an earlier surgery. 5) Most previous studies have excluded patients with significant cardiorespiratory comorbidities and preoperative anemia, which are prevalent features in the elderly fracture population, so whether TXA is safe in these patients needs further research. 6) Combined IV and local TXA has proved efficacy and safety in joint replacement; this kind of TXA administration may be also useful in femoral fracture surgery.

The limitations of this study are as follows. 1) Significant heterogeneity was found in the outcomes of total blood loss and postoperative hemoglobin decline. The differences in TXA dosage, duration, time of administration and number of administered times, fracture type, surgical measurements and transfusion criteria may be contributed to it. As the included studies showed different TXA dosages and timing still, therefore, it was impossible to make subgroup analysis of them across studies. 2) There were very few studies involving topical TXA, so it is hard to make further analysis of it. 3) The publication bias exists.

Conclusion

Our meta-analysis demonstrated that both IV and topical application of TXA reduced transfusion rate in femoral fracture surgery. However, still further studies are needed to identify the optimal route of administration, TXA dosage and timing still. In addition, high-quality RCTs with a large sample size are required to figure out the safety of TXA application, especially in the elderly, before its wide recommendation.

Data sharing statement

All data are fully available without restriction.

Author contributions

J Wang and P Zhang made substantial contributions to conception and design. P Chen and J Bai took acquisition of data and interpretation of data; J He and Y Liang performed statistical analysis. P Zhang drafted the article. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors read and approved all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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