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Is intravenous tranexamic acid effective and safe during hip fracture surgery? An updated meta-analysis of randomized controlled trials

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Abstract

Introduction The efficacy and safety of intravenous (IV) tranexamic acid (TXA) during hip fracture surgery remain controversial. This meta-analysis aimed to assess the efficacy of IV-TXA administration during hip fracture surgery for reducing the transfusion requirement and blood loss as well as its safety regarding the risk of thrombolysis.

Materials and methods PubMed, EMBASE, Web of Science, and the Cochrane Library Database were systematically searched for randomized controlled trials (RCTs) that focused on the efficacy and safety of IV-TXA in patients during hip fracture surgery. The primary outcome was the transfusion requirement. Secondary outcomes included total blood loss (TBL), deep vein thrombosis (DVT), and total thromboembolic events (TTEs). Risk ratio (RR), risk difference (RD), and mean difference (MD) for dichotomous and continuous data outcomes were determined from the meta-analysis. Data were analyzed using Rev Man 5.3.

Results Altogether, 11 RCTs were included (total sample size 892 patients). IV-TXA significantly reduced the transfusion requirement [RR 0.60, 95% confidence interval (CI) 0.38–0.93, $P=0.02$] and TBL (MD 326.64 ml, 95% CI −462.23 to −191.06, $P<0.00001$) vs. cosntrol group. IV-TXA caused no increased risk of DVT (RD 0.02, 95% CI −0.01 to 0.04, $P=0.13$) or TTEs (RD 0.02, 95% CI −0.01 to 0.05, $P=0.12$).

Conclusion Available evidence indicates that IV-TXA efficaciously reduces TBL and transfusion requirements during hip fracture surgery without significantly increasing the risk of TTEs including DVT.

Keywords Hip fracture · Meta-analysis · Thromboembolism · Tranexamic acid · Transfusion

Introduction

Hip fracture is common, with the reported lifetime prevalence of 20% for women and 10% for men in the United States [1]. A national epidemiological study in China reported a higher incidence among older people [2]. Despite recent advances in the techniques and instrumentation of orthopedic procedures, however, hip fracture surgery is still commonly associated with substantial blood loss, subsequent acute anemia, and the need for transfusion [3]. Postoperative anemia could lead to increased impairment of functional ability, longer length of hospital stay, and increased mortality [4, 5]. In addition, blood transfusions may increase the risk of anaphylaxis, transfusion-related acute lung injury, and virus transmission [6]. Therefore, reducing the perioperative blood loss and transfusion requirement during the treatment of hip fractures is a vital issue.

Tranexamic acid (TXA) is an analog of the amino acid lysine, which can competitively inhibit plasminogen

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activation and plasmin binding to fibrin, thereby achieving the effect of anti-fibrinolysis [7]. Recently, numerous studies have proved that intravenous (IV) TXA could reduce perioperative blood loss and transfusion requirements without increasing the risk of thrombosis during joint arthroplasty [8–10]. However, concern about preoperative vascular endothelial damage, which is an etiologic factor in thrombosis, hindered the wide adoption of TXA use in patients undergoing hip fracture surgery [11].

Although the scientific rationale and supporting evidence suggest that IV-TXA may be useful for hemostasis during hip fracture surgery, studies of TXA and hip fracture surgery have so far provided variable assessments of efficacy in reducing blood loss and the thromboembolic risk with no clear consensus because of the small sample sizes and lack of published articles. The purpose of the present meta-analysis of randomized controlled trials (RCTs) was, therefore, to address these limitations with evidence and examine the available literature regarding the potential risks and benefits of IV-TXA use during hip fracture surgery.

Materials and methods

Literature search

Before May 2018, two independent reviewers searched electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science. The keywords used included "randomized controlled trial," "tranexamic acid," and "hip fracture." We further screened the reference lists for citations of additional eligible studies. No limitations were placed on language or publication type.

Study selection criteria

We retrieved all RCTs that compared the efficacy and safety of IV-TXA use in hip fracture patients with those of controls and that reported adequate data on targeted outcomes. Studies were excluded if (1) their quality was too low, (2) studies with other types of fracture were included, or (3) the outcomes information was insufficient even after contacting the authors. After exclusion of duplicates, one reviewer screened the titles and abstracts to discard the articles that were clearly ineligible. We then obtained the full texts of the remaining references and reviewed them to assess whether the studies should be included based on the predefined selection criteria. Disagreements were resolved by discussion.

Quality assessment of included studies

Based on the criteria in the Cochrane Handbook for Systematic Reviews of Interventions [12], two reviewers independently assessed study quality and risk of bias, including assessment of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Each study was judged to be at low, high, or unclear risk of bias in each domain. Likelihood of bias was scored using the modified Jadad scale [13]. Studies scoring ≥ 4 from a possible total of eight were considered of high quality. Discrepancies were resolved by consensus and a third reviewer was consulted if necessary.

Outcome measures

We compared the use of IV-TXA and controls in terms of hemostatic effect and safety. Primary outcome was the proportion of patients transfused with allogenic blood. Secondary outcomes included total blood loss (TBL), deep vein thrombosis (DVT), and total thromboembolic events (TTEs).

The following data were extracted from the included trials: general information (authors, publication year, study location); participants (number, age, sex ratio, body mass index, preoperative hemoglobin level, American Society of Anesthesiologists grade, fracture type, surgical management, anesthesia, transfusion trigger, DVT prophylaxis); TXA dose and route of administration; outcome measures. All data were extracted on an intention-to-treat basis. Missing data were obtained from the corresponding authors of the studies when possible.

Statistical analysis

The meta-analysis was performed according to the PRISMA statement [14], and statistical analysis was performed using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) with a significance threshold of $P < 0.05$. For dichotomous data, the risk ratio (RR) or risk difference (RD) was estimated with a 95% confidence interval (95% CI). The RD was calculated if a zero number of events was reported for an outcome within an individual trial. For continuous data, mean differences (MDs) and 95% CIs were calculated. The χ^2 test and I^2 statistic were used to test for the presence of statistical heterogeneity, which was defined as present when $P < 0.10$ or $I^2 > 50\%$. When heterogeneity was absent, a meta-analysis was performed using a fixed-effects model. Otherwise, a random-effects model was selected. If $P > 0.10$ but $I^2 < 50\%$, heterogeneity was considered absent, and a fixed-effects model was used. Publication bias was tested using the transfusion requirement. If the funnel plot was symmetrical, there was a low potential for publication bias and vice versa.

Results

Search results

Our initial search strategy identified 200 potentially relevant citations (Fig. 1). After the process of finding duplicates, 71 studies were excluded. Scanning the titles and abstracts resulted in 115 studies being excluded from the analysis. Three more studies were excluded after the full texts were carefully read for eligibility (one was not an RCT [15], and two had insufficient data [16, 17]). Finally, 11 RCTs [18–28] involving 892 patients were pooled to form the current meta-analysis.

Study characteristics and quality assessment

Of the 11 studies, 5 administered a single preoperative dose of IV-TXA [18, 20, 21, 23, 26], 4 administered two doses of IV-TXA (one preoperatively, one later) [22, 25, 27, 28], and another 2 administered a preoperative dose combined with IV-TXA infusion [19, 24]. Sample sizes of the included trials ranged from 18 to 69, and the mean age of the participants ranged from 44.4 to 82.2 years. Further details of the study characteristics are presented in Tables 1 and 2.

Table 3 summarizes the methodological quality and the risk of bias of the included studies. All 11 trials were relatively well designed, and the modified Jadad scores were ≥4. Randomization was performed in all 11 trials, and the method was mentioned in all but two trials [18, 19]. Allocation concealment was reported in 6 of the 11 RCTs and details of blinding were clearly reported in 10 studies. One study did not report postoperative TTEs or complications [20]. A funnel plot (Fig. 2) showed the trials to be generally symmetrical around the pooled RR, indicating a low risk of publication bias.

Meta-analysis of the transfusion requirement

All 11 studies [18–28] (892 patients) reported the number of patients who required allogeneic blood transfusion. Transfusion requirements were reported in 158 of 441 patients (35.8%) in the TXA group, compared with 242 of 451 patients (53.7%) in the control group. Pooling the data showed that patients in the TXA group had a lower risk of transfusion requirement than patients in the control

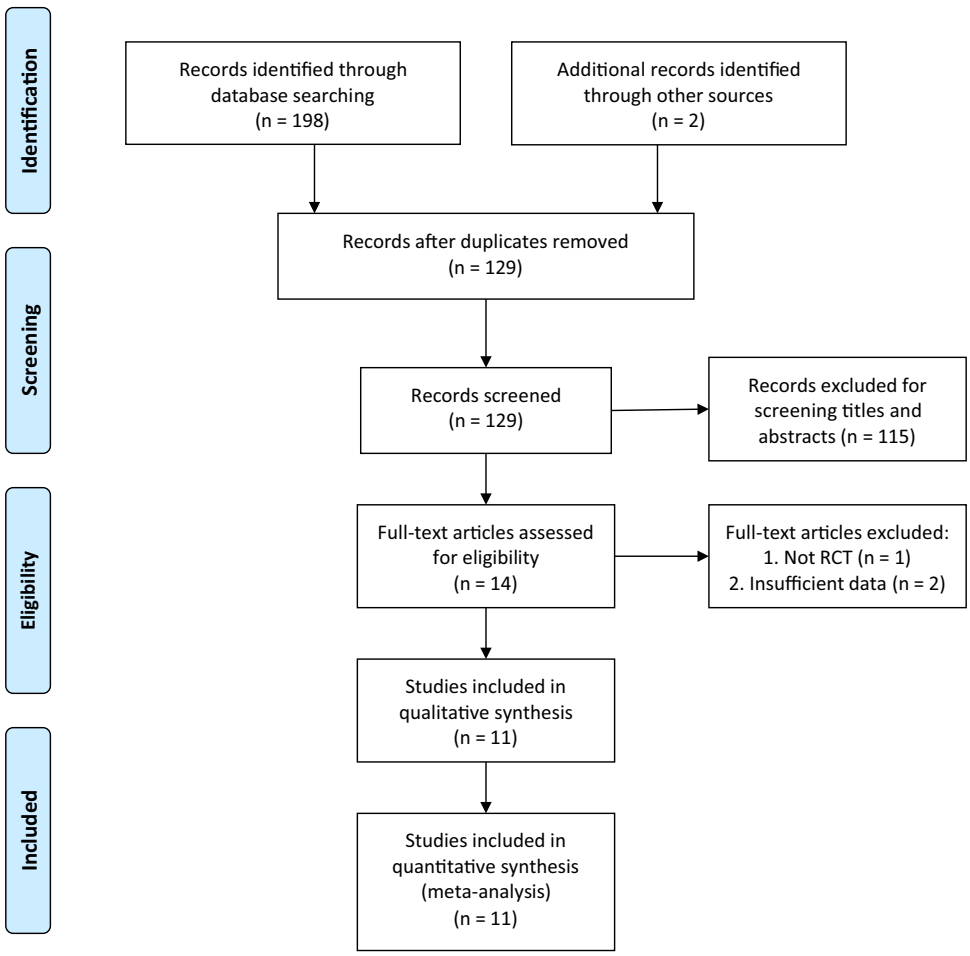

Fig. 1 PRISMA flow diagram of search and study selection

Table 1 Characteristics of included trials showing general patient information

Study	Country	Patients (T/C)	Age (years, T/C)	Gender (M/F)	BMI (kg/m^2, T/C)	Pre-Hb (g/dl, T/C)	ASA grade (3 or 4, T/C)	Follow-up (months)
Baruah [18]	India	30/30	57.7/55.3	49/11	25.8/26.2	10.0/10.0	NR	NR
Emara [19]	Egypt	20/20	56.5/56.0	26/14	NR	13.3/13.2	NR	1
Haghighi [20]	Iran	18/20	65.1/66.2	31/7	25.4/25.5	12.0/12.4	3/5	NR
Lei [21]	China	37/40	77.8/79.2	12/65	23.8/23.3	10.9/11.2	18/19	1
Mohib [22]	Pakistan	50/50	69.0/70.0	45/55	NR	11.5/11.3	NR	NR
Sadeghi [23]	Iran	32/35	51.8/44.4	41/26	22.7/22.9	11.1/11.5	NR	1.5
Tengberg [24]	Denmark	33/39	79.8/75.0	21/51	22.6/23.0	11.9/12.9	5/12	3
Tian [25]	China	50/50	77.7/79.3	33/67	24.2/22.9	NR	12/18	1
Vijay [26]	India	45/45	48.8/49.3	20/70	NR	10.5/10.9	0/0	NR
Watts [27]	USA	69/69	81.0/82.2	43/95	25.1/25.1	12.2/12.5	64/65	6
Zufferey [28]	France	57/53	81.0/82.0	14/96	25.0/24.0	11.7/11.4	19/20	12

ASA American Society of Anesthesiologists, *BMI* body mass index, *C* control group, *F* female, *T* tranexamic acid group, *M* male, *NR* not reported, *Pre-Hb* preoperative hemoglobin

group (RR 0.60, 95% CI 0.38–0.93, $P=0.02$). As there was significant heterogeneity of the pooled data ($P<0.00001$, $I^2=94\%$), a random-effects model was used (Fig. 3).

Meta-analysis of TBL

Six studies [18, 19, 21, 23–25] reported usable data for TBL (202 and 214 patients in the TXA and control groups, respectively). Pooling the data showed that TXA administration significantly reduced the TBL by a mean of 326.64 ml compared with the control group (95% CI −462.23 to −191.06, $P<0.00001$). As there was significant heterogeneity of the pooled data ($P<0.00001$, $I^2=95\%$), the random-effects model was used (Fig. 4).

Meta-analysis of DVT incidence

Ten studies [18, 19, 21–28] reported data on DVTs, which occurred in 16 of 423 patients (3.8%) in the TXA group compared with 8 of 431 patients (1.9%) in the control group. The overall incidence of DVT was 2.8%. Given the presence of significant heterogeneity among studies ($P=0.66$, $I^2=0$), a fixed-effects meta-analysis model was used. Pooling the data showed that the risk of DVT was similar in the two groups (RD 0.02, 95% CI −0.01 to 0.04, $P=0.13$) (Fig. 5).

Meta-analysis of the TTEs incidence

Ten studies [18, 19, 21–28] reported data on TTEs, which occurred in 26 of 423 patients (6.1%) in the TXA group, compared with 16 of 431 patients (3.7%) in the control group. The total incidence of TTEs was 4.9%. Given the presence of significant heterogeneity among studies ($P=0.15$, $I^2=32\%$), a fixed-effects meta-analysis model was used. Pooling the data showed that the risk of TTEs was similar in the two groups (RD 0.02, 95% CI −0.01 to 0.05, $P=0.12$) (Fig. 6).

Discussion

Preoperative and postoperative anemia was highly prevalent in patients undergoing hip fracture surgery, being reported in 44 ± 9% and 87 ± 10%, respectively [29]. Perioperative anemia was associated with a blood transfusion rate of 44 ± 15%, which could increase the risk of anaphylaxis, immunosuppression, infectious disease, and transfusion reactions, leading to postoperative infections, poorer physical functioning and recovery, and increased length of hospital stay and mortality [6]. Although the application of TXA provides new ideas for reducing blood loss and the transfusion rate, its safety and efficacy have not been widely addressed.

Although several RCTs reported that IV-TXA use in hip fracture surgery was clinically effective in reducing blood loss and transfusion requirements without increasing the incidence of thromboembolic events [18, 21–28], the sample sizes of the studies were small. Lee et al. [30] conducted a comparative study that included 84 cases in the TXA group and 271 in the control group. They found that patients given IV-TXA (a bolus of 1 g on induction) had a lower transfusion rate (6% vs 19%) and less blood loss, but the study was performed retrospectively. A systematic review and meta-analysis on the efficacy and safety of TXA in hip fracture surgery by Farrow et al. [31] that included 770 patients found that the application of TXA resulted in a 46% lower risk of transfusion requirement and higher postoperative hemoglobin level, although the incidence of

Table 2 Characteristics of included trials showing general surgical information

Study	Fracture type	Surgical management	Anesthesia	Intervention	Control	Transfusion trigger	DVT prophylaxis	DVT screen
Baruah [18]	Trochanteric (AO type 31A1 or 31A2.1)	DHS	Spinal	15 mg/kg IV TXA before surgery	NS	Hb < 8.5 g/dl or Hct < 27%	NR	Ultrasound
Emara [19]	Hip	HHA	General	10 mg/kg IV TXA before skin incision, 5 mg/kg/h infusion until surgery completion	NS	NR	LMWH	Clinical and ultrasound
Haghighi [20]	Proximal femoral shaft	IMN	General	15 mg/kg IV TXA before skin incision	NS	based on allowable blood loss	NR	NR
Lei [21]	Intertrochanteric (AO type 31A1, 31A2, or 31A3)	PFNA	NR	1 g IV TXA before surgery	NS	Hb < 9 g/dl	NR	Ultrasound
Mohib [22]	Intertrochanteric	DHS	NR	2 doses of 15 mg/kg IV TXA before surgery and 3 h later	NS	Hb < 7 g/dl	LMWH	Clinical
Sadeghi [23]	Extra-capsular or intra-capsular	Plating and nailing, or HHA	Spinal	15 mg/kg IV TXA before skin incision	NS	Case by case Hb between 8 g/dl and 10 g/dl	NR	Clinical
Tengberg [24]	Extra-capsular (AO type 31A2.2 to 31A3)	short IMN	Epidural	1 g IV TXA before surgery, 3 g post-operative 24-h infusion	Placebo	Hb < 9.67 g/dl	LMWH	Clinical
Tian [25]	Intertrochanteric (AO type 31A1, 31A2, or 31A3)	PFNA	NR	2 doses of 10 mg/kg IV TXA 10 min preoperatively and 5 h postoperatively	no TXA	Hb < 9 g/dl	LMWH	Ultrasound
Vijay [26]	Hip and femoral	ORIF, HHA, or THA	Combined spinal epidural	10 mg/kg IV TXA before skin incision	NS	Hb loss > 25%	NR	Clinical
Watts [27]	Femoral neck (AO 31B)	HHA or THA	General	2 doses of 15 mg/kg IV TXA just before incision and at wound closure	NS	Hb < 7 g/dl or Hb < 8 g/dl (with systemic symptoms)	LMWH	Ultrasound
Zufferey [28]	Cervical, trochanteric, transtrochanteric, or subtrochanteric	HHA, THA, DHS, or IMN	General	2 doses of 15 mg/kg IV TXA at skin incision and 3 h later	NS	Hb < 10 g/dl (at risk patients) or Hb < 9 g/dl	Fondaparinux	Clinical and ultrasound

DHS dynamic hip screw, *Hb* hemoglobin, *Hct* hematocrit, *HHA* hip hemiarthroplasty, *IMN* intramedullary nail, *IV* intravenous, *LMWH* low molecular weight heparin, *NR* not reported, *NS* normal saline, *ORIF* open reduction internal fixation, *PFNA* proximal femoral nail anti-rotation, *THA* total hip arthroplasty, *TXA* tranexamic acid

Table 3 Quality assessment of selected studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias	Jadad score (0–8)
Baruah [18]	Unclear	Unclear	Low	Low	Low	Low	4
Emara [19]	Unclear	Unclear	Low	Low	Low	Low	6
Haghighi [20]	Low	Unclear	Low	Low	High	Low	5
Lei [21]	Low	Unclear	Low	Low	Low	Low	6
Mohib [22]	Low	Low	Low	Low	Low	Low	7
Sadeghi [23]	Low	Low	Low	Low	Low	Low	7
Tengberg [24]	Low	Low	Low	Low	Low	Low	8
Tian [25]	Low	Unclear	Unclear	Low	Low	Low	4
Vijay [26]	Low	Low	Low	Low	Low	Low	6
Watts [27]	Low	Low	Low	Low	Low	Low	8
Zufferey [28]	Low	Low	Low	Low	Low	Low	8

Low low risk of bias, *High* high risk of bias, *Unclear* unclear risk of bias, lack of information or uncertainty over the potential bias

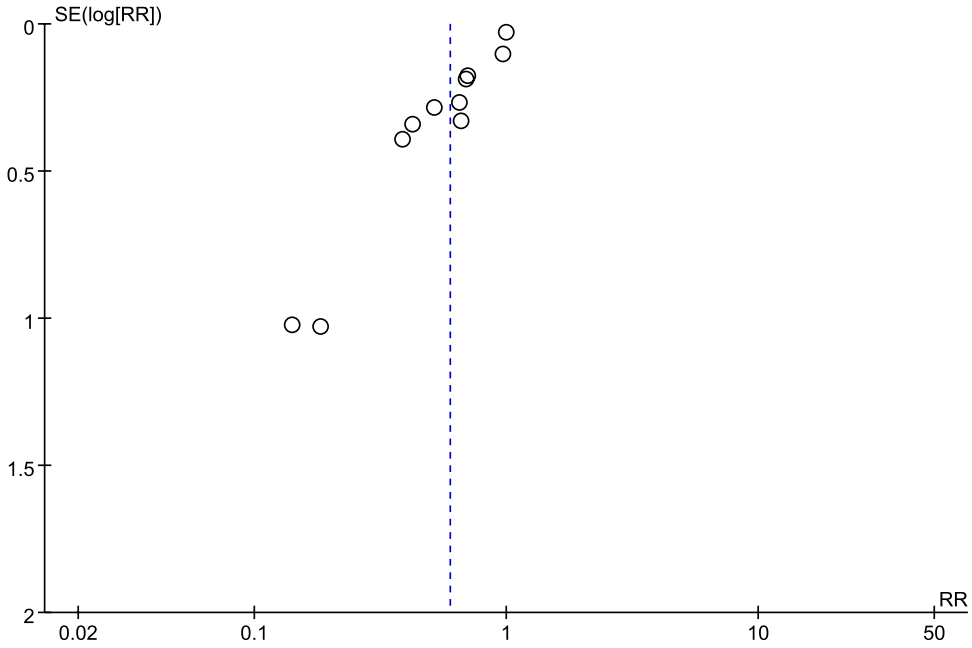

Fig. 2 Funnel plot of transfusion requirement demonstrates minimal publication bias

thromboembolic events was similar in the TXA and control groups. However, non-RCTs and studies with topical use of TXA were included. Finally, an RCT conducted by Emara et al. [19] reported an opposite result regarding the DVT incidence. Thus, whether IV-TXA should be used during hip fracture surgery remained controversial due to the limited data—which prompted us to perform the present meta-analysis to evaluate updated, more comprehensive evidence regarding the use of IV-TXA during hip fracture surgery.

The current study has several advantages over the meta-analysis previously published by Zhang et al. [32]. First, our meta-analysis had more stringent inclusion criteria. Three studies on the treatment of intertrochanteric fractures that were included in the meta-analysis by Zhang et al. [32] were excluded in ours because of the low methodological quality (modified Jadad scores < 4). Second, more high-quality RCTs [21, 25, 27] were published since Zhang et al.'s report and had positive conclusions that supported the application of IV-TXA during hip fracture surgery.

There is a dynamic balance between the formation and dissolution of blood clots during the perioperative period. TXA can reduce the dissolution of blood clots by inhibiting fibrinolytic activity, thereby reducing local bleeding but also increasing the risk of thrombosis to some degree. Although many surgeons are hesitant to use TXA in high-risk patients, basic science has shown that TXA inhibits fibrinolysis only at sites of active thrombogenesis, with no effect on systemic blood vessels [33]. In accordance with most studies [31, 32],

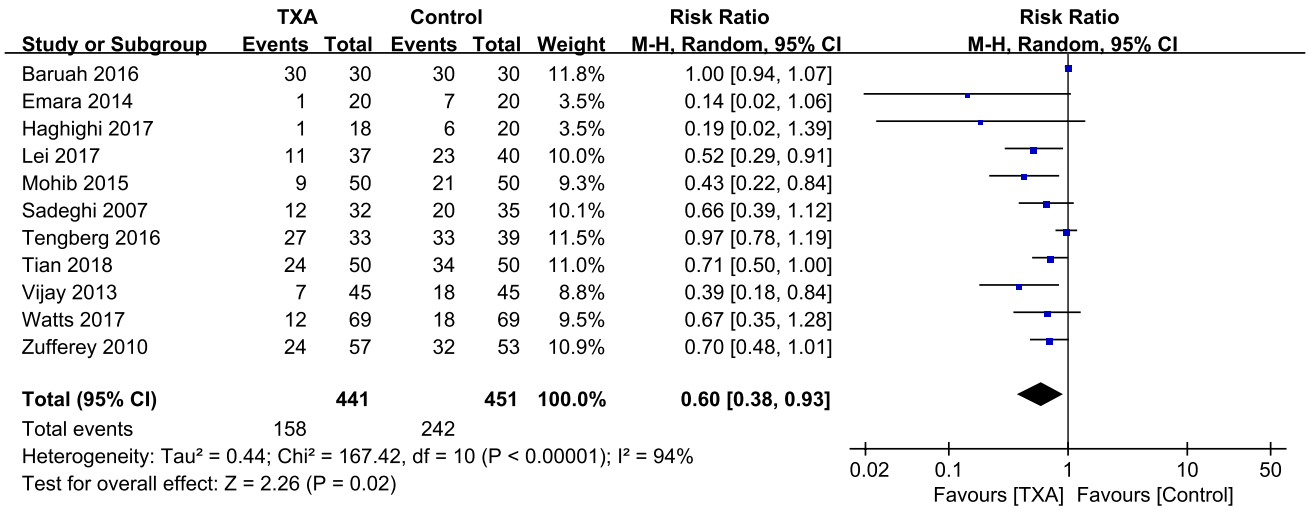

Fig. 3 Forest plot of TXA versus control for transfusion requirement

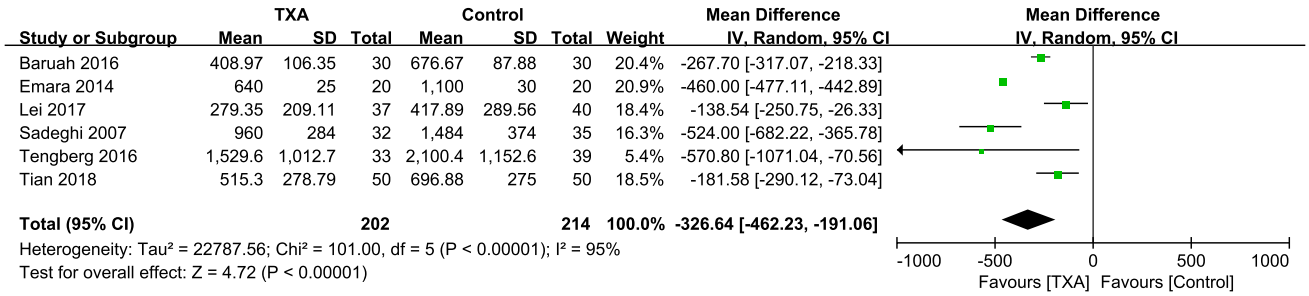

Fig. 4 Forest plot of TXA versus control for total blood loss

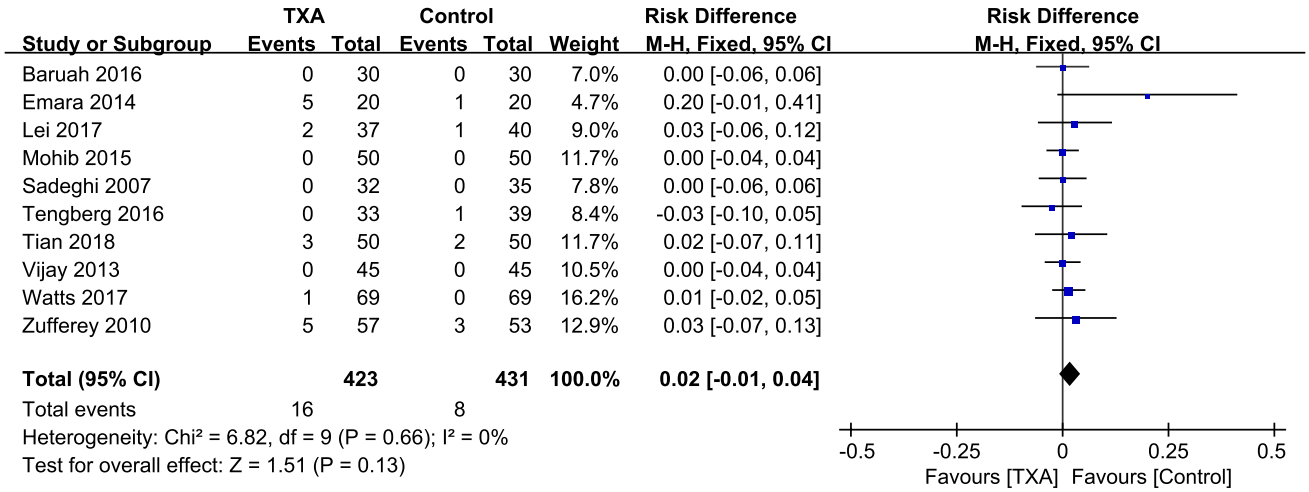

Fig. 5 Forest plot of TXA versus control for the incidence of DVT

our meta-analysis indicated no significant difference in the incidence of TTEs, including DVT, between the two groups. Many patients undergoing hip fracture surgery are at high risk of DVT because of their advanced age, multiple comorbid conditions, surgical delay, and immobilization during the early rehabilitation period [34]. In fact, these patients

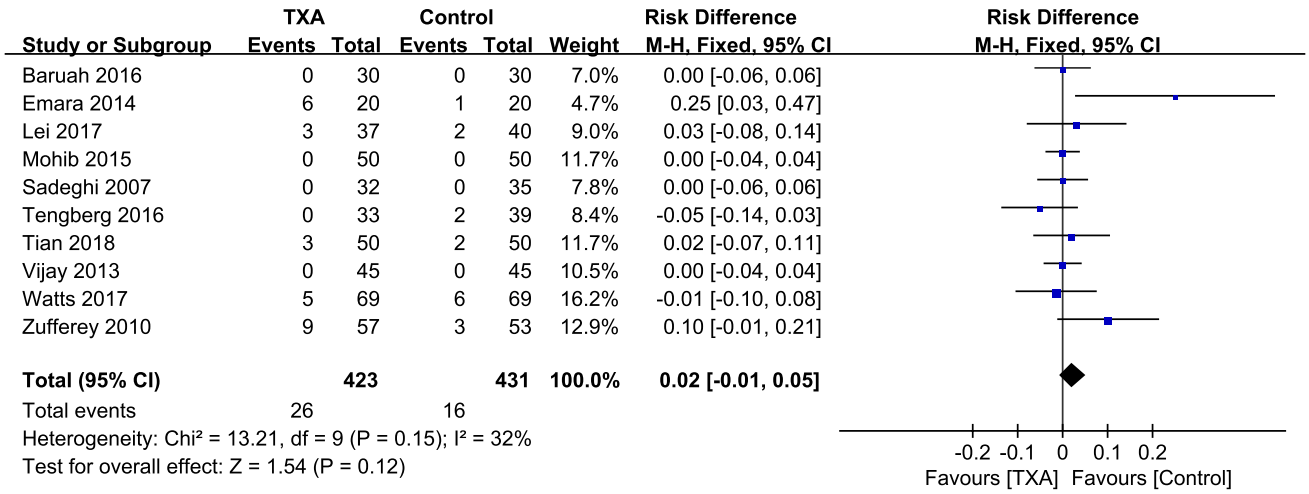

Fig. 6 Forest plot of TXA versus control for the incidence of total thromboembolic events

are liable to develop a DVT preoperatively [35]. The value of anticoagulation remains contentious, however, and the associated adverse events (i.e., bleeding, wound hematoma) may well outweigh the intended benefits because of trauma-induced hyperfibrinolysis [36]. Therefore, anticoagulation and reduced postoperative bleeding require careful balancing during hip fracture surgery.

Several studies that evaluated patients with TXA reported that they tended to require less total transfusion of blood products than the control group, but the difference between the groups failed to reach statistical significance [24, 27, 28]. After pooling the data of the included studies in the current meta-analysis, the transfusion rate was lower in the TXA group, which was consistent with previous findings [31, 32]. It also supports our conclusion that IV-TXA use could be beneficial for reducing transfusion requirements. Various transfusion triggers, however, were utilized among the included studies. Blood transfusion thresholds varied from a hemoglobin level of < 7 [22] to < 10 g/dl [23, 28], which could have led to underrepresentation of the required allogenic blood transfusions between the TXA and control groups.

We observed trends in our meta-analysis suggesting that, during hip fracture surgery, the use of IV-TXA could lead to less TBL. Despite statistical significance, the mean TBL varied from 279.35 [21] to 1529.6 ml [24] in the TXA group and from 417.89 [21] to 2100.4 ml [24] in the control group. Sources of heterogeneity included sample size variation, diverse patient characteristics, different inclusion and exclusion criteria, different modes of anesthesia, and varied outcome measurement protocols. Baruah et al. [18], Emara et al. [19], and Sadeghi et al. [23] directly measured blood loss, which included the perioperative suction drain volume, swab weights, and postoperative indwelling drain volume. In contrast, Lei et al. [21], Tengberg et al. [24], and Tian et al. [25] calculated blood loss using the Nadler formula [37], preoperative and postoperative hematocrit or hemoglobin levels, and the number of transfusions required, respectively.

There are several limitations in the current study. First, there was substantial heterogeneity in the meta-analyses of several outcomes and the sources of heterogeneity were due not only to varying blood management and outcome measurements but to different fracture configurations and fracture management protocols. Second, most of the included studies reported preoperative-only or preoperative plus postoperative IV-TXA, and the total dose ranged from 10 mg/kg to 1–4 g, so the optimal timing and dosage of IV-TXA are still unclear. Third, many of the included studies had short follow-up periods and so lack long-term results concerning the safety of IV-TXA administration during hip fracture surgery. Finally, the number of studies included and the sample size were relatively small compared with a similar meta-analysis of joint arthroplasty [38]. These limitations highlight the need for careful, scientifically designed RCTs in the future to confirm our conclusions.

Conclusions

This updated meta-analysis of the available evidence indicates that IV-TXA efficaciously reduces TBL and transfusion requirements in patients undergoing hip fracture surgery without significantly increasing the risk of TTEs including DVT. The data are limited, however, and we concluded that, in future, we need some large, high-quality RCTs to provide more robust data on the use of IV-TXA during hip fracture surgery.

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Compliance with ethical standards

Conflict of interest None of the authors has financial or personal relationships with other people or organizations that could inappropriately influence this work.

Ethical approval Because this study was a literature review, ethical approval was not obtained.

Informed consent Not applicable.

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