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The effect of tranexamic acid in open reduction and internal fixation of pelvic and acetabular fracture

A systematic review and meta-analysis

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Abstract

Background: Pelvic bone fractures may cause extensive bleeding; however, the efficacy of tranexamic acid (TXA) usage in pelvic fracture surgery remains unclear. In this systematic review and meta-analysis, we aimed to evaluate the efficacy of TXA in open reduction and internal fixation surgery for pelvic and acetabular fracture.

Methods: MEDLINE, Embase, and Cochrane Library databases were systematically searched for studies published before April 22, 2020, that investigated the effect of TXA in the treatment of pelvic and acetabular fracture with open reduction and internal fixation. A pooled analysis was used to identify the differences between a TXA usage group and a control group in terms of estimated blood loss (EBL), transfusion rates, and postoperative complications.

Results: We included 6 studies involving 764 patients, comprising 293 patients who received TXA (TXA group) and 471 patients who did not (control group). The pooled analysis showed no differences in EBL between the groups (mean difference –64.67, 95% confidence interval [CI] –185.27 to –55.93, $P = .29$). The study period transfusion rate showed no significant difference between the groups (odds ratio [OR] 0.77, 95% CI 0.19–3.14, $P = .71$, $I^2 = 82\%$), nor in venous thromboembolism incidence (OR 1.53, 95% CI 0.44–5.25, $P = .50$, $I^2 = 0\%$) or postoperative infection rates (OR 1.15, 95% CI 0.13–9.98, $P = .90$, $I^2 = 48\%$).

Conclusions: Despite several studies having recommended TXA administration in orthopedic surgery, our study did not find TXA usage to be more effective than not using TXA in pelvic and acetabular fracture surgery, especially in terms of EBL reduction, transfusion rates, and the risk of postoperative complications.

Abbreviations: CI = confidence interval, EBL = estimated blood loss, Hb = hemoglobin, MD = mean difference, MINORS = Methodological Index for Nonrandomized Studies, OR = odds ratio, ORIF = open reduction and internal fixation, pRBC = red blood cell pack, RCT = randomized controlled trial, TXA = tranexamic acid, VTE = venous thromboembolism.

Keywords: acetabular fracture, blood loss, complication, pelvic bone fracture, tranexamic acid, transfusion, TXA

1. Introduction

A pelvic bone fracture is a serious injury resulting from major trauma such as a motor vehicle accident or a major fall. Pelvic and acetabular fracture may cause extensive bleeding not only from the fracture site, but from major blood vessels or organs located near to the injured site. Hypovolemic shock has been reported to be one of the main causes of mortality in trauma patients with pelvic bone fracture.[1]

Bleeding and hypovolemic shock are among the most serious complications after major surgeries. Several recent studies have reported that tranexamic acid (trans-4-aminomethyl-cyclohexane-1-carboxylic acid, TXA) can reduce bleeding during various surgeries and reduce the postoperative mortality rate.[2] Several orthopedic studies have recommended the use of TXA to safely reduce blood loss during major orthopedic surgeries, including arthroplasty or hip fracture surgeries.[3,4]

To date, however, the efficacy of TXA in pelvic and acetabular fracture surgery remains unclear. Few large, high-quality, prospective studies have investigated the efficacy of TXA in pelvic fracture, particularly fractures requiring reduction and internal fixation, and studies that have investigated this issue have

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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comprised small participant numbers. To our knowledge, no qualitative synthesis of this topic has been undertaken. Therefore, we undertook a systematic review and meta-analysis to clarify the efficacy of TXA in pelvic and acetabular fracture that required open reduction and internal fixation (ORIF) surgery. We aimed to investigate the effect of TXA following surgical fixation of pelvic and acetabular fracture in terms of estimated blood loss (EBL), transfusion rates, and postoperative complications.

2. Materials and Methods

This study was performed in accordance with Cochrane Review and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[5,6] Institutional review board approval is not necessary for this type of study.

2.1. Literature search

Based on these guidelines, we searched MEDLINE, Embase, and the Cochrane Library databases for comparative studies that had investigated the effect of TXA in the treatment of pelvic bone fracture with ORIF. We searched for studies published up to April 22, 2020, using an a priori search strategy. Following PICO framework, these articles will be included in this meta-analysis: 1. Population: the pelvic bone fracture; 2. Intervention: ORIF surgery for osteosynthesis; 3. Comparator: administration TXA or not; 4. Outcomes: EBL, transfusion rates, and other postoperative complications. The search terms included synonyms and related terms for TXA and pelvic bone fracture as follows: ("tranexamic acid" OR "antifibrinolytic" OR "anti-fibrinolytic") AND ("pelvis" OR "pelvic" OR "acetabulum" OR "acetabular"). There were no restrictions on language, publication year, and type of publication. After the initial electronic search, relevant studies and their bibliographies were also manually searched.

2.2. Study selection

From the study titles and abstracts, 2 board-certified orthopedic surgeons specialized in hip and pelvic surgery independently selected the studies for full-text review. If a title and an abstract did not provide sufficient data to enable a decision, the full article was reviewed.

In this study, we excluded nonoriginal research articles, such as biomechanical or cadaveric studies, technical notes, letters to the editor, expert opinions, review articles, meta-analyses, and case reports; however, we considered conference abstracts for inclusion when they met appropriate study protocols, following the suggestion of a previous study.[7]

Studies were included in the systematic review if they directly compared a TXA group with a control group and if the study reported complete data or if the required data (means, standard deviations, sample sizes, and percentages) could be extracted or calculated. We excluded the following studies: those conducted involving patients who had been treated and managed conservatively; those in which ORIF had not been performed, such as closed reduction and fixation; and duplicate studies based on the same patients that had been published in another study.

At each stage of the literature search, kappa values were calculated to determine interreviewer agreement concerning study selection. Agreement between reviewers was correlated with kappa values a priori: $\kappa = 1$, corresponding to perfect agreement; $1.0 > \kappa \geq 0.8$, almost perfect agreement; $0.8 > \kappa \geq 0.6$, substantial agreement; $0.6 > \kappa \geq 0.4$, moderate agreement; $0.4 > \kappa \geq 0.2$, fair agreement; and $\kappa < 0.2$, slight agreement.

2.3. Data extraction

We used a standardized form to extract the following information and variables for the qualitative data synthesis: study design, the number of patients included in each group, the type of pelvic bone fracture included in the study, the use of TXA, the TXA regimen, and study details such as outcomes measured, the definition of EBL, the investigated period for transfusion, and the indications for transfusion in each study.

For the pooled analysis, the following data were extracted and compared from the included studies: mean EBL, transfusion rates, and venous thromboembolism (VTE) and postoperative infection complication rates.

If the required data had not been described in the article, we attempted to calculate it from the full-text review and, in cases where this information could still not be obtained, the study authors were contacted. Two investigators independently extracted the data and resolved disagreements through discussion.

2.4. Risk of bias assessment

The methodological quality of the included studies was assessed using the methodological index for nonrandomized studies (MINORS),[8] which is a validated tool for assessing the qualities of randomized controlled trials (RCTs) and nonrandomized studies. According to the MINORS checklist, the maximum MINORS score for comparative studies is 24. Two independent reviewers performed a quality assessment and resolved disagreements through discussion.

2.5. Data synthesis and statistical analysis

The outcomes for this meta-analysis were comparisons of mean EBL, transfusion rates, the number of red blood cell packs (pRBC) transfused, and VTE and postoperative infection complication rates.

For all comparisons, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as dichotomous data, and continuous data were analyzed using mean differences (MDs) with 95% CIs. Heterogeneity was assessed using the I^2 statistic, in which 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively. Forest plots were used to show the outcomes, the pooled estimate of effects, and the overall summary effect of each study. Statistical significance was set at a P value of <.05. All data were pooled using a random-effect model, which has previously been recommended to avoid overestimation of study results, particularly in the medical field.[9] We did not perform the test for publication bias since this test is typically recommended only when at least 10 studies have been included in the meta-analysis, in accordance with the Cochrane Library guideline.[6] Statistical analyses were performed using Review Manager (RevMan; version 5.3) and R (version 3.4.3) software.

3. Results

3.1. Study identification

Details concerning the studies identified and the selection process are summarized in Figure 1. An initial electronic literature search yielded 254 articles. After removing 70 duplicates and including 2 additional publications that had been identified through a manual search, 186 studies were screened. Of these, 171 were excluded after screening the titles and abstracts and 9 were excluded after a full-text review. Finally, 6 studies were eligible for qualitative and quantitative data synthesis. There was substantial agreement between reviewers concerning study selection at the title review ($\kappa = 0.796$) and abstract review ($\kappa = 0.788$) stages, and agreement was perfect at the full-text review stage ($\kappa = 1.0$).

3.2. Study characteristics and qualitative synthesis

Of the 6 included studies, 2 were RCTs,[10,11] and 4 were retrospective comparative studies.[12–15] In total, 764 patients were

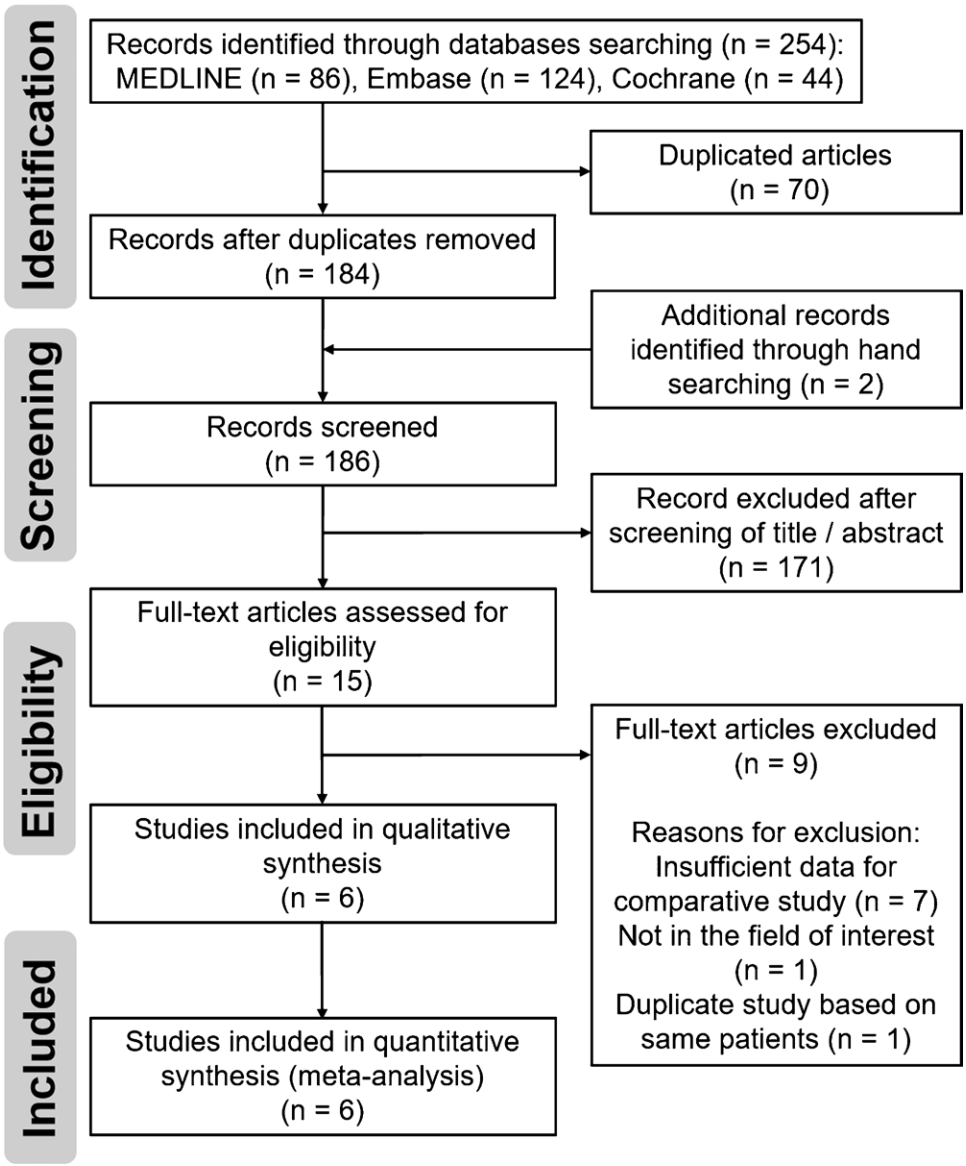

Figure 1. PRISMA flow diagram for the identification and selection of studies included in the meta-analysis. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-analyses.

involved in the studies selected, including 293 patients who had received TXA (TXA group) and 471 patients who had not (control group). All the included studies involved acetabular fracture and/or pelvis fracture. In 5 studies, intravenous (IV) TXA[10–14] administration had been undertaken, and 1 study involved a topical TXA application.[15] Demographic data and study characteristics, including the TXA regimen for each study, are shown in Table 1.

Several outcome measures had been included in each of the studies, such as EBL, transfusion rates, the number of pRBC transfused, operation times, the rate of blood loss, changes in hemoglobin (Hb) and hematocrit levels, drain output, and postoperative complications. Two studies used formula by Nadler et al to calculate EBL,[11,15] and 1 study used EBL as reported in anesthesia records.[12] Four studies evaluated the transfusion profile over the whole study period,[10,11,14,15] and we extracted intraoperative transfusion-related data from 3 studies[11–13] and postoperative transfusion-related data from 3 studies.[11,13,15] Three studies reported the indications for pRBC transfusion, the Hb level <7 or 8 g/dL, or symptomatic anemia.[10,11,15] Additional study details are shown in Table 2.

3.3. Risk of bias assessment

The mean MINORS score for the methodological quality assessment was 19.5/24 (range, 18–24; Table 1). Of the 8 main evaluation parameters, 4 of 6 studies received a point deduction for their retrospective study design,[10–13] and all but 1 study[10] received a point deduction as they did not provide clear information concerning blind evaluation of the study endpoint. One study received a point deduction for a 5% loss to follow-up compared with the initially included number of patients.[11] Four studies received a point deduction due to the lack of a prospective calculation of the study size.[12–15] There were no further point deductions in the other criteria domains.

3.4. Quantitative synthesis

3.4.1. Estimated blood loss. All 6 studies compared EBL between both TXA and control groups. A pooled analysis showed no differences in terms of EBL between the 2 groups (mean difference [MD] = –64.67, 95% CI –185.27 to –55.93, P = .29). The heterogeneity was considered moderate (I^2 = 70%). A forest plot is shown in Figure 2.

Table 1

Study design, demographic data, study characteristics, and the MINORS scores for the included studies.

Author (year)	Study design	No. of patients		Fracture type included	Usage of TXA	TXA regimen	MINORS score
		TXA	Control				
Atchison et al (2019)[12]	RCS	128	284	Acetabular	IV	Intraoperative, no details available	18
Criner et al (2016)[13]	RCS	33	53	Acetabular	IV	No details available	18
Harris et al (2015)[14]	RCS	12	12	Pelvis/acetabular/femur	IV	Intraoperative, 1 g q3h	18
Kashyap et al (2019)[15]	RCS	31	30	Acetabular	Topical	Intraoperative, 3 g mixed with 100 mL N/S	18
Lack et al (2017)[10]	RCT	42	46	Acetabular	IV	Preoperative, 10 mg/kg within 30 min of surgery Intraoperatively, 10 mg/kg during a 4 h infusion	24
Spitler et al (2019)[11]	RCT	47	46	Pelvis/acetabular/femur	IV	Preoperative, 15 mg/kg immediately prior to surgery Intraoperatively, 15 mg/kg 3 h postoperatively	21

IV = intravenous, MINORS = methodological index for nonrandomized studies, No. = number, N/S = normal saline, RCS = retrospective comparative study, RCT = randomized controlled trial, TXA = tranexamic acid.

Table 2

Summary of the study details.

Author (year)	Outcomes measured	Definition of EBL	Investigated period for transfusion	Indication for transfusion
Atchison et al (2019)[12]	EBL, OR of transfusion rate	Intraoperative EBL as reported in the anesthesia records	Intraoperative	N/A
Criner et al (2016)[13]	EBL, number of pRBC transfused, operation time, rate of blood loss, VTE	N/A	Intraoperative Postoperative	N/A
Harris et al (2015)[14]	EBL, transfusion rate, number of pRBC transfused, Hb change, complications (revision d/t bleeding, infection, VTE, death)	N/A (only included >600 mL EBL)	Overall study period (within 4 d of surgery)	N/A
Kashyap et al (2019)[15]	EBL, transfusion rate, postop drain output, postop Hb level, complications (infection, VTE, nerve injection)	Calculated from the formula by Good et al[16] and Nadler et al[17]	Overall study period Postoperative	Hb <8 g/dL
Lack et al (2017)[10]	EBL, transfusion rate, number of pRBC transfused, VTE	N/A	Overall study period	Hb <7 g/dL or symptomatic anemia
Spitler et al (2019)[11]	EBL, transfusion rate, number of pRBC transfused, Hct change, VTE	Calculated from the formula by Nadler et al[25]	Overall study period Intraoperative Postoperative	Hb <8 g/dL in healthy patients, <9 g/dL in significant cardiac or pulmonary disease, or symptomatic anemia

EBL = estimated blood loss, Hb = hemoglobin, Hct = hematocrit, N/A = not available, OR = odds ratio, postop = postoperative, pRBC = pack red blood cell, VTE = venous thromboembolism.

3.4.2. Transfusion rate. Four studies[10,11,14,15] reported transfusion rates. Over the study period, transfusion rates did not differ significantly between the groups (OR 0.77, 95% CI 0.19–3.14, P = .71, I^2 = 82%). In a subgroup analysis, we attempted to perform a pooled analysis for the intraoperative and postoperative transfusion rates; however, only 1 study[11] had reported the intraoperative transfusion rate. Therefore, we were unable to perform a synthetic analysis of the intraoperative period. Two studies[11,15] had investigated postoperative transfusion rates. The postoperative transfusion rate was statistically higher in the control group than in the TXA group (OR 0.26, 95% CI 0.07–0.92, P = .04). The heterogeneity was considered to be moderate (I^2 = 63%). Details are shown in Figure 3.

3.4.3. Complication rate: VTE and postoperative infection. Five studies[10,11,13–15] reported VTE incidence rates and 2 studies[14,15] reported postoperative infection rates as a comparison of complications between the TXA and control groups. A pooled analysis showed no difference between the groups in both VTE incidence (OR 1.53, 95% CI 0.44–5.25, P = .50, I^2 = 0%) and postoperative infection rates (OR 1.15, 95% CI 0.13–9.98, P = .90, I^2 = 48%). A forest plot with details is shown in Figure 4.

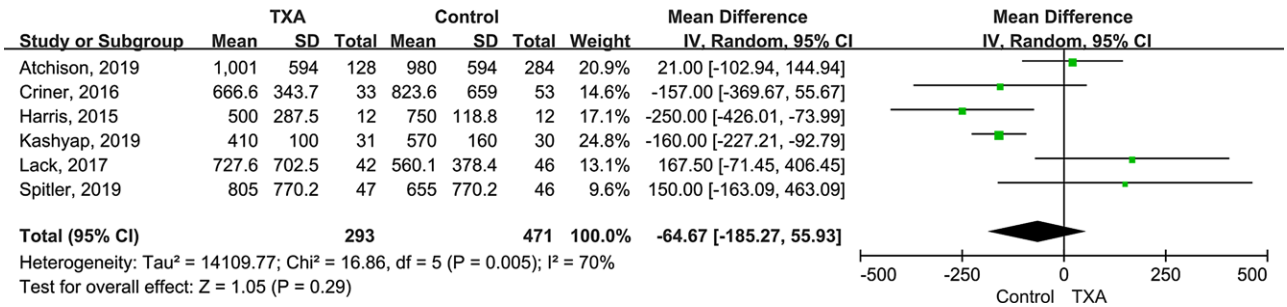

Figure 2. Forest plot showing the EBL between the TXA and control groups. CI = confidence interval, EBL = estimated blood loss, SD = standard deviation, TXA = tranexamic acid.

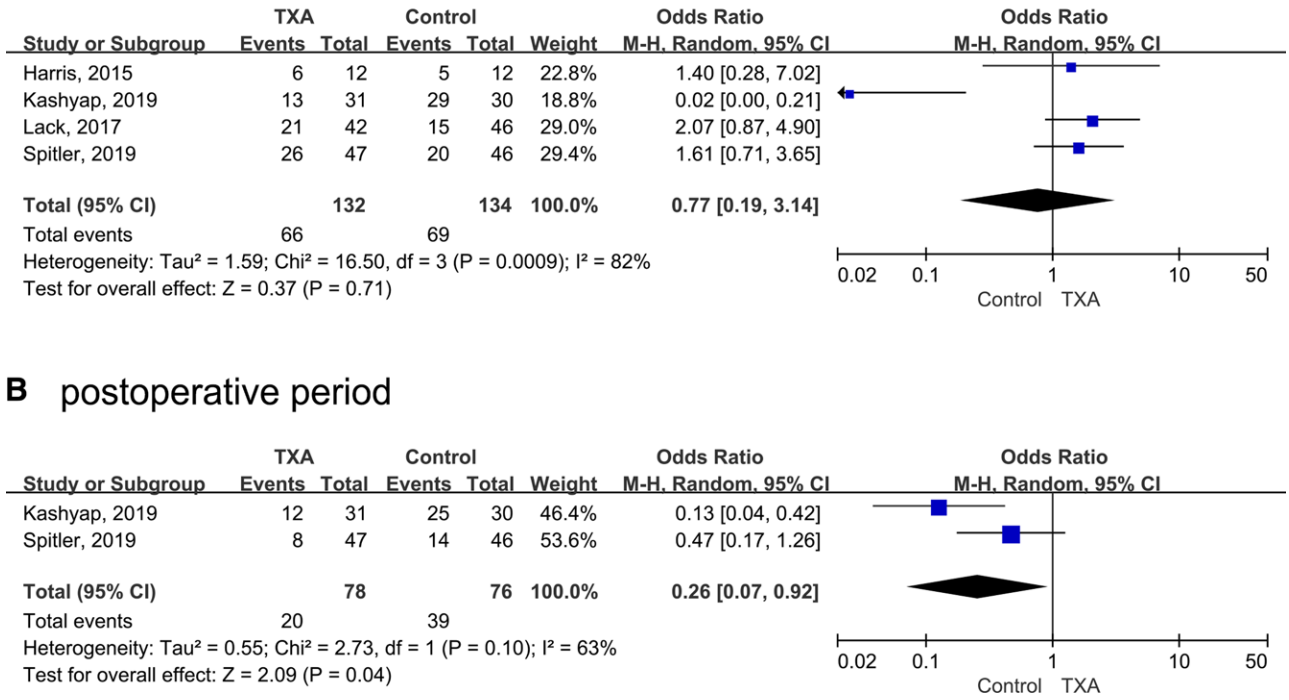

Figure 3. Forest plot showing the transfusion rate between the TXA and control groups in overall study period (A) and postoperative period (B). CI = confidence interval, TXA = tranexamic acid.

4. Discussion

The main finding of this study was that the administration of TXA did not significantly reduce EBL, transfusion rates, and the risk of postoperative complications including VTE and infection in pelvic and acetabular fracture surgeries.

One RCT involving pelvic trauma compared intravenous administration of TXA with a double-blinded placebo.[18] That study reported significant differences in Hb levels in the first 72 hours after admission and in hematocrit levels 48 hours after admission. Based on these results, it was concluded that TXA could reduce the amount of blood loss in pelvic injury. This conclusion was contrary to our findings, as we did not find any superiority concerning TXA usage. However, the RCT did not evaluate the severity of pelvic injury, even in terms of the presence or absence of fracture. Moreover, details concerning the surgical procedures were not clearly provided; therefore, the RCT could not fully reflect the efficacy of TXA in pelvic and acetabular fracture surgeries.

We found no difference in transfusion rates between the TXA and control groups throughout the period of our meta-analysis. However, in the postoperative period, there was a statistically lower transfusion rate in the TXA group. We consider that a further extended study with larger patient numbers should be undertaken, because the pooled result concerning the transfusion rate throughout the overall study period showed high heterogeneity at >80%, which indicated low reliability of the study results, yet even this result suggests no evidence of superior efficacy using TXA. In terms of the postoperative period, our results showed a statistically significant difference between the 2 groups. However, only 2 studies evaluated the postoperative period; therefore, it is difficult to conclude that TXA usage had reduced the postoperative transfusion rate. Further high-quality, large scale studies are required to confirm these findings.

It remains unclear whether TXA usage is associated with a risk of developing VTE. Theoretically, TXA inhibits fibrinolysis through hindering plasmin from binding to fibrin and the activation of plasminogen.[19,20] In a case–control study that used British General Practice Research Database data, women who were taking TXA had a 3-fold higher risk of developing a deep vein thrombosis.[21] In contrast, several orthopedic studies have reported the safety of TXA and that TXA was not associated with an increased risk of VTE.[22,23] Baskaran et al[22] reported no significant increased risk in VTE following TXA administration for hip fracture surgery in all 8 studies included in their meta-analysis. Our study findings showed no additional VTE risk in relation to TXA administration compared with the control group, which accords with the results of previous studies.

Regarding postoperative infection risk, some previous studies.[24,25] have reported that TXA could help to reduce the risk of postoperative infection following orthopedic surgeries, and have suggested that TXA is likely to be linked to a reduction in blood loss, a lower need for allogeneic blood transfusion, and fewer issues related to immunomodulation associated with blood transfusion. In our pooled results, no difference was found in postoperative infection rates between the groups, nor in terms of blood loss or transfusion rates. However, further extended studies are needed to confirm our findings.

This study had several limitations. First, the number of included studies was relatively small, and >50% of the studies were retrospective in design. Pelvic fractures are frequently accompanied with massive internal or external bleeding that can sometimes be life-threatening; however, the incidence of these events is relatively low but, due to the characteristics of possible subsequent complications, RCTs or retrospective cohort studies are challenging to undertake. Therefore, our inclusion criteria included conference abstracts, following the suggestion of a previous study,[7] which we considered could strengthen the precision of our results in this meta-analysis. Second, we could not fully assess the subgroup data, particularly in terms of intraoperative or postoperative transfusion-related variables, and further

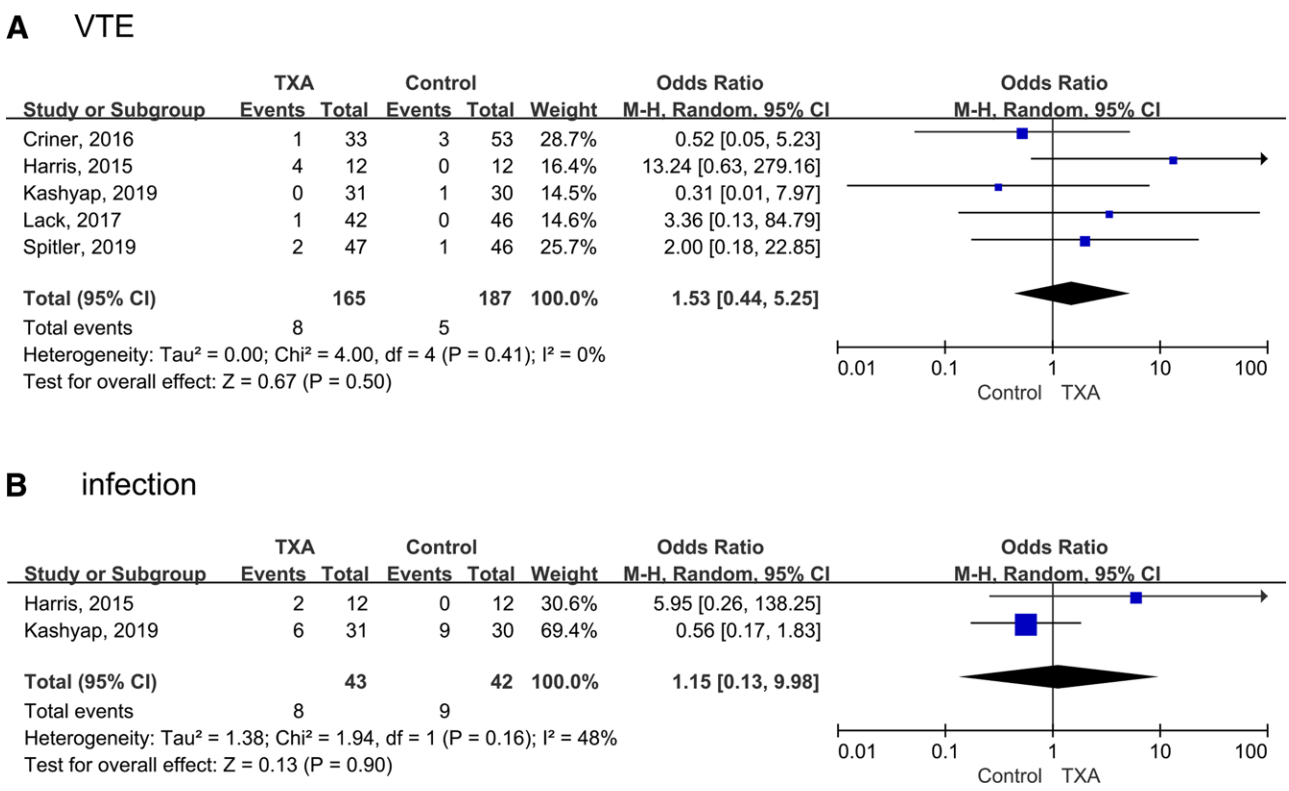

Figure 4. Forest plot showing the incidence of postoperative VTE (A) and infection (B) between the TXA and control groups. CI = confidence interval, TXA = tranexamic acid, VTE = venous thromboembolism.

high-quality studies are required to more precisely verify the effect of TXA usage in ORIF surgery for pelvic bone fractures.

In conclusion, despite several studies having recommended TXA administration in orthopedic surgery, we did not find TXA usage to be superior in pelvic fracture surgery, especially in terms of reduction in EBL, transfusion rates, and the risk of postoperative complications.

Author contributions

CH Kim, SJ Lee: designed the meta-analysis, wrote the first draft and revise manuscript
J Hwang : extracted the data
PW Yoon: reviewed the articles
CH Kim, J Hwang: performed the meta-analysis
KS Yoon: supervision
All authors have read and approved the final draft.

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