



# Effect of intravenous tranexamic acid on perioperative bleeding and transfusion in spine surgery: systematic review and meta-analysis of randomized controlled trials

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**Background:** This study aimed to systematically review the literature investigating the effect of intravenous (IV) tranexamic acid (TXA) on the perioperative blood loss and amount of transfused blood in patients who underwent spine surgery under general anesthesia.

**Methods:** MEDLINE, EMBASE, and CENTRAL databases were searched for studies published up to June 2017. Randomized controlled trials comparing the intervention of tranexamic acid use with a placebo in corrective spine fusion surgery were included. Outcome measures included intraoperative and postoperative blood loss and perioperative blood transfusion volume. We also conducted subgroup analyses according to the dose of administration of intervention drug.

**Results:** In total, 12 studies involving 875 patients were included in the final analysis. Blood loss decreased in patients treated with perioperative IV TXA by a mean volume of 189.58 ml intraoperatively (95% confidence interval [CI]: 135.82 to 243.34 ml,  $P < 0.001$ ;  $I^2 = 74\%$ ), 121.04 ml postoperatively (95% CI: 84.92 to 157.17 ml,  $P < 0.001$ ;  $I^2 = 0\%$ ), and 285.97 ml in total (95% CI: 190.70 to 381.23 ml,  $P < 0.001$ ;  $I^2 = 0\%$ ). Perioperative transfusion volume also decreased by 162.10 ml in patients who received IV TXA (95% CI: 31.77 to 292.44 ml,  $P = 0.010$ ;  $I^2 = 47\%$ ).

**Conclusions:** Blood loss was reduced in patients who were administered TXA during spine surgery. Additionally, the perioperative volume of blood transfusion decreased in patients who received TXA. Further research is required to confirm the optimal dosage and timing of TXA usage.

**Keywords:** Anesthesia; Blood transfusion; Hemorrhage; Spine; Tranexamic acid.

## INTRODUCTION

Spine surgery is associated with significant blood loss due to the large amount of cut bone, soft tissue dissection, and prolonged operation time [1-3]. Surgical bleeding may require allogenic blood transfusions and the risk of serious ad-

verse transfusion reactions may increase [4,5]. Besides, transfusions can cause damage to vital organs and coagulopathy. Another concern regarding perioperative bleeding during spine surgery is the risk of spinal epidural hematoma formation, which might lead to spinal cord or cauda equina compression [6,7]. Therefore, controlling perioperative bleeding

and reducing exposure to allogeneic blood have become important for spine surgeons.

Several techniques have been used to reduce bleeding, and consequently, reduce the frequency of exposure to allogeneic transfusions: controlled hypotension, regional anesthesia, autologous blood transfusion, intraoperative blood salvage, and administration of various medications [8]. Tranexamic acid (TXA) is a synthetic antifibrinolytic drug derivative of a lysine-binding site of plasminogen; it inhibits plasminogen from binding to fibrin and suppresses fibrinolysis [9]. More studies have focused on the administration of TXA for reducing blood loss and need for transfusion in major orthopedic surgery [10–12], and cardiac surgery [13].

However, the evidence on the efficacy of this agent in spine surgery is not sufficient.

The aim of this meta-analysis is to clarify the effect of TXA on perioperative blood loss and the volume of perioperative transfused blood.

## MATERIALS AND METHODS

### Study design

This meta-analysis was performed according to the recommendations of the PRISMA [14] and the Cochrane Collaboration [15]. The protocol was registered in PROSPERO (<https://www.crd.york.ac.uk/prospero>, CeRD42017060238).

### Information sources and search strategy

MEDLINE, EMBASE, and Cochrane Central were used to search articles without restriction to year of publication. Primary investigation was performed to confirm search keywords and strategies.

We searched MEDLINE, EMBASE, and Cochrane Central using the terms (“tranexamic acid” AND (“bleeding” OR “transfusion”)). Broad search terms had been used to achieve higher sensitivity. The language of the article was limited to English only. The last search was in June 2017. We manually checked the references of review articles to find any additional relevant studies.

### Study selection and eligibility criteria

Two authors (DL and SL) searched for the articles using the following databases. The selection of data was carried out according to the criteria set out in the protocol. Three investigators (DL, KK, and WYL) performed the selection or exclusion of studies. Primary selection was performed based on the article title and abstract by three investigators. Secondary selection was performed independently using the full-text. Studies for final assessment were selected based on agreement among the investigators. If needed, a third-party investigator (SL) participated and the final decision was made based on the majority.

Studies were included in the meta-analysis if they satisfied the following criteria: (1) patients underwent spine surgery under general anesthesia; (2) systemic intravenous administration of TXA was used during surgery as interventions; (3) results of the control group were reported; (4) outcomes including intraoperative, postoperative, and total blood loss (primary outcomes) were reported; (5) reported outcomes included the amount of allogeneic blood transfusions (secondary outcome).

Articles were excluded for the reasons below: (1) oral, intramuscular, or topical TXA administration; (2) did not report appropriate outcomes or outcome measurements as mentioned; (3) underwent epidural anesthesia combined with general anesthesia; (4) non-randomized controlled trials; (5) non-human studies; (6) articles not in English.

### Risk of bias in individual studies

Four authors (DL, KK, WYL, and SJC) reviewed the articles independently to assess the risk of bias using the “risk of bias” tool provided in the Review Manager ver. 5.3 software (The Cochrane Collaboration, UK) according to the Cochrane guidelines [16]. If necessary, a third-party review author (SL) was included to resolve disagreements. Quality assessments of the studies were based on Cochrane’s assessment of risk of bias. The following seven domains to assess the risk of bias were used in each trial: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The methodology for each trial was graded as “high,” “low,” or “unclear,” to reflect

a high risk of bias, low risk of bias, or uncertainty of bias, respectively.

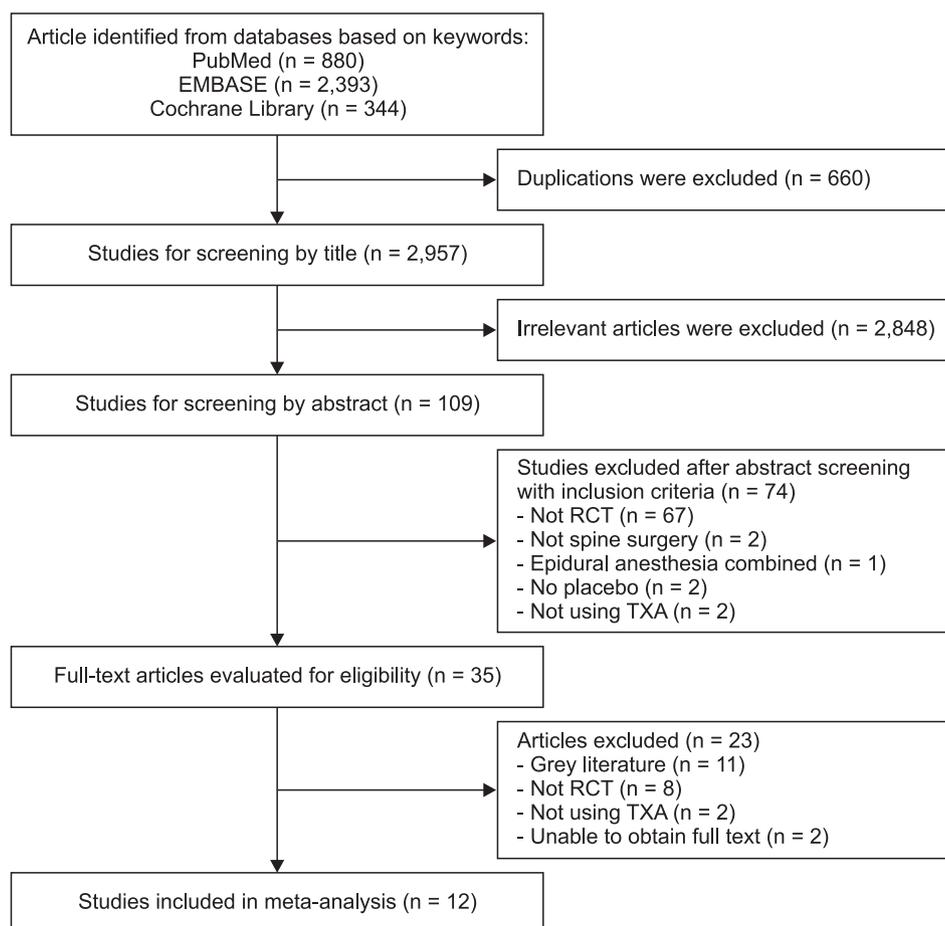
## Data collection process and extracted items

The initial database search to find potentially relevant articles was completed by two authors (DL and KK). Three investigators (DL, KK, and WYL) performed the selection or exclusion of studies according to the criteria set in the protocol. Primary selection was performed based on article title and abstract. Secondary selection was done independently using the full-text. Studies for final assessment were selected by the agreement among three investigators. If needed, a third-party investigator (SL) took part and decided if the study should have been included.

The data were collected by three authors (DL, KK, and SJC) and rechecked by another investigator (SL) to ensure the accuracy. References and data for each included study were carefully cross-checked to ensure that no duplicate

data were present and that integrity of the meta-analysis was maintained. In case of insufficient data, authors of each article were contacted and asked to provide information and clarification. If the data were available as a median and range (minimum–maximum), the conversion to mean and standard deviation (SD) was performed by the methods proposed by Hozo et al. [17].

The general characteristics, treatment or intervention types, and outcomes were collected for each study. General characteristics included study design, publication year, first author, and subject age. TXA dose regimen and timing, type of surgery, and anesthesia methods were recorded for the included studies. The measured outcomes included primary and secondary outcomes, as previously described. For assessing the reliability of agreement between four raters, we used Fleiss' kappa analysis.



**Fig. 1.** Flow diagram for selection of relevant studies in meta-analysis. RCT: randomized controlled trial, TXA: tranexamic acid.

**Table 1.** Characteristics of the Included Studies

Source	Study type	Surgery	Interventions (no. of patients)	Outcome measures
Neillipovitz et al. 2001 [1]	Randomized study	Posterior spinal fusion	Loading 10 mg/kg over 15 min after final patient positioning + maintenance 1 mg/kg/h infusion until skin closure (22) Placebo (18)	IBL and transfusion
Peters et al. 2015 [24]	Randomized study	Posterior spinal fusion for adult spinal deformity	Loading 10 mg/kg over 15 min before skin incision + maintenance 1 mg/kg/h infusion for the duration of the surgery (19) Placebo (13)	IBL, postoperative and perioperative blood loss, and transfusion
Elwatidy et al. 2008 [18]	Randomized study	Anterior cervical discectomy with or without fixation, laminectomy and discectomy, laminectomy with pedicle screw fixation, inter-segmental decompression, laminectomy and excision of spinal tumor	Loading 2 g for adults, 30 mg/kg for children over 20 min after induction of anesthesia + maintenance 100 mg/h for adults, 1 mg/kg/h for children until 5 h after operation (32) Placebo (32)	IBL, postoperative and perioperative blood loss, and transfusion
Farrokhi et al. 2011 [23]	Randomized study	Posterior thoracic or lumbar instrumented spinal fusion	Loading 10 mg/kg over 10 min at the initiation of induction of anesthesia + maintenance 1 mg/kg/h during surgery (38) Placebo (38)	IBL and transfusion
Colomina et al. 2009 [21]	Randomized study	Instrumented surgery involving the thoracic/lumbar spine by a posterior midline approach	Loading 10 mg/kg over 20 min before surgical incision + maintenance 2 mg/kg/h until surgical wound closure (44) Placebo (51)	IBL, perioperative blood loss, and transfusion
Taghaddomi et al. 2009 [22]	Randomized study	Lumbar disc resection	Loading 15 mg/kg over 20–30 min before skin incision + maintenance 0.1 mg/kg/min during the operation (40) Placebo (40)	IBL
Verma et al. 2014 [26]	Randomized study	Posterior spinal arthrodesis of adolescent idiopathic scoliosis	Loading 10 mg/kg over 15 min + maintenance 1 mg/kg/h (36) Placebo (47)	IBL, postoperative and perioperative blood loss
Sethna et al. 2005 [2]	Randomized study	Scoliosis surgery	Loading 100 mg/kg over 15 min after induction of the anesthesia + maintenance 10 mg/kg/h until skin closure (23) Placebo (21)	IBL and transfusion
Wong et al. 2008 [3]	Randomized study	Posterior thoracic/lumbar instrumented spinal fusion	Loading 10 mg/kg after anesthetic induction + maintenance 1 mg/kg/h until skin closure (73) Placebo (74)	IBL, postoperative and perioperative blood loss, and transfusion
Shi et al. 2017 [25]	Randomized study	Posterior lumbar decompression interbody fusion	Loading 30 mg/kg over 15 min before skin incision + maintenance 2 mg/kg/h until skin closure (50) Placebo (46)	IBL, postoperative and perioperative blood loss
Raksakietisak et al. 2015 [19]	Randomized study	Surgery with instrumentation or laminectomy more than or equal to 3 levels of thoracolumbar spine	Loading 15 mg/kg over 20 min before induction of anesthesia + second dose of 15 mg/kg administered 3 h after the first dose (39) Placebo (39)	IBL, postoperative and perioperative blood loss
Xu et al. 2012 [20]	Randomized study	Idiopathic scoliosis surgery	Loading 20 mg/kg bolus at skin incision + maintenance 10 mg/kg/h during operation (20) Placebo (20)	IBL, postoperative blood loss, and transfusion

IBL: intraoperative blood loss.

## Statistical analysis

Meta-analysis on the data, including effects and outcomes of treatments, was performed using the Mantel-Haenszel method and Review Manager software (RevMan version 5.3, The Cochrane Collaboration, UK). For continuous data, such as blood loss and transfusion volume, mean  $\pm$  SD was used to calculate the weighted mean difference and 95% confidence interval (CI). Heterogeneity was analyzed via the value of  $I^2$  and the result of the chi-squared test. We regarded a level of 10% significance ( $P < 0.1$ ) in the chi-square statistic or an  $I^2 > 50\%$  for considerable heterogeneity and proceeded to sub-group analysis. If any heterogeneity was observed, the causes of heterogeneity were first analyzed and then subjected to sub-group treatment. We used R software (version 3.4.0, R Foundation for Statistical Computing, Austria) for analysis the publication bias and drawing the funnel plot.

## RESULTS

### Study selection and characteristics

In the initial database search, a total of 3,617 articles were identified from PubMed ( $n = 880$ ), EMBASE ( $n = 2,393$ ), and Cochrane Library ( $n = 344$ ) (Fig. 1). After excluding 660 duplications, three authors independently reviewed and excluded 2,957 irrelevant articles based on the title of the article. We excluded 2,848 articles based on the exclusion criteria. The remaining 109 studies were evaluated for eligibility by abstract, and 74 were excluded for the following reasons: no randomized controlled trial (RCT) ( $n = 67$ ); not spine surgery ( $n = 2$ ); epidural anesthesia was combined with general anesthesia ( $n = 1$ ); no appropriate placebo group ( $n = 2$ ); and no TXA use as an intervention ( $n = 2$ ). Finally, we conducted a full-text review of the remaining 35 studies and included

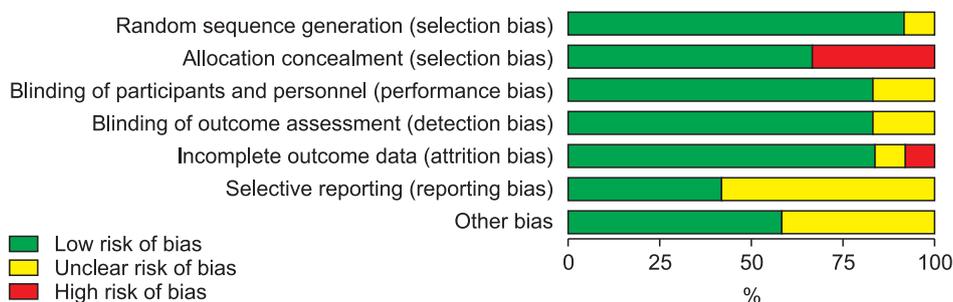
12 papers in the meta-analysis. A total of 23 studies were excluded because of grey literature ( $n = 23$ ), non-RCT studies ( $n = 8$ ), studies not using systemic TXA ( $n = 2$ ), and documents in which the full text could not be obtained ( $n = 2$ ).

Table 1 shows the characteristics of the 12 studies included in our final analysis. Every study was a randomized controlled trial. There was a total of 875 participants (436 in TXA group, 439 in control group) from these studies, ranging from 4 to 86 years old. The number of participants in each study ranged from 40 to 147. There were no significant differences in patients' characteristics between the intervention and control groups, such as age, gender, height, weight, American Society of Anesthesiologists grading, and preoperative hemoglobin. Various types of surgeries were performed, including lumbar disc resection, idiopathic scoliosis surgery, posterior spinal fusion surgery, anterior cervical discectomy, and excision of spinal tumors after laminectomy. The extent of spinal surgeries varied, but no study differences were reported between groups in terms of the level of surgery. In all studies, general anesthesia was performed, but the anesthetic methods varied.

TXA was administered by intravenous (IV) in every study, although different dosages (ranging from 10–100 mg/kg) and delivery timings (ranging from bolus dose to 30-min infusion) were used. The loading dose of TXA was administered immediately after the anesthesia induction and maintenance infusion continued throughout the surgery in 10 studies. Maintenance infusion was continued until 5 h after operation in one study [18]. In another study [19], TXA was administered as the second bolus dose 3 h after the first loading dose.

### Quality assessment for included studies (risk of bias within studies)

The methodological quality of all included studies was esti-



**Fig. 2.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

mated to have less bias-based error or uncertainty (Fig. 2).

Most studies reported detailed information regarding the randomization techniques that were used, such as manual random number selection or computer-generated random number table; Xu et al. [20] did not specify a randomization method. Allocation concealment was high in 4 studies [1,2,20,21] and low in the others. The studies by Taghaddomi et al. [22] and Xu et al. [20] were rated as unclear to blinding of the participants and the outcome assessor. The risk of incomplete outcome data was high in the study by Colomina et al. [21] because the dropout rate was over 20%, and the study by Xu et al. [20] had an unclear evaluation process. Some studies except Colomina et al. [21], Farrokhi et al. [23], Peters et al. [24], Raksakietisak et al. [19], Shi et al. [25], and Verma et al. [26] have no information about in the Web-based study registration site (e.g., www.clinicaltrials.gov). We could not evaluate the selective reporting bias of papers without study

records, thus rated them as ‘unclear’. Five of the studies [18,20,22,24,25] did not have a detailed description about sample size calculation, indicating a potential bias. The methodological domain assessment for each study is shown in Fig. 3.

## Effects on blood loss and transfusion volume

### Intraoperative blood loss

A total of 13 studies (n = 875; 436 TXA group and 439 control group) reported detailed data on intraoperative blood loss. Perioperative IV TXA administration was shown to significantly reduce intraoperative blood loss by a mean volume of 189.58 ml, ranging from 135.82 to 243.34 ml compared with the results of the control patients (95% CI; P < 0.001, I<sup>2</sup> = 74%) (Fig. 4).

### Postoperative blood loss

A total of 6 studies (n = 500; 249 TXA group and 251 control group) showed data on postoperative blood loss. Perioperative IV TXA administration significantly reduced postoperative blood loss by a mean volume of 121.04 ml, ranging from 84.92 to 157.17 ml compared with the results of the control patients (95% CI; P < 0.001, I<sup>2</sup> = 0%) (Fig. 5).

### Total blood loss

A total of 8 studies (n = 635; 315 TXA group and 320 control group) provided data on total blood loss. Perioperative IV TXA administration significantly reduced total blood loss by a mean volume of 285.97 ml, ranging from 190.70 to 381.23 ml compared with the results of the control patients (95% CI; P < 0.001, I<sup>2</sup> = 0%) (Fig. 6).

### Transfusion volume

A total of 5 studies (n = 320; 160 TXA group and 160 control group) reported the total volume of transfused allogeneic blood cells. Perioperative IV TXA administration was shown to significantly reduce volume of transfused blood cells by a mean volume of 162.10 ml, ranging from 31.77 to 292.44 ml compared with the results of the control patients (95% CI; P = 0.010, I<sup>2</sup> = 47%) (Fig. 7).

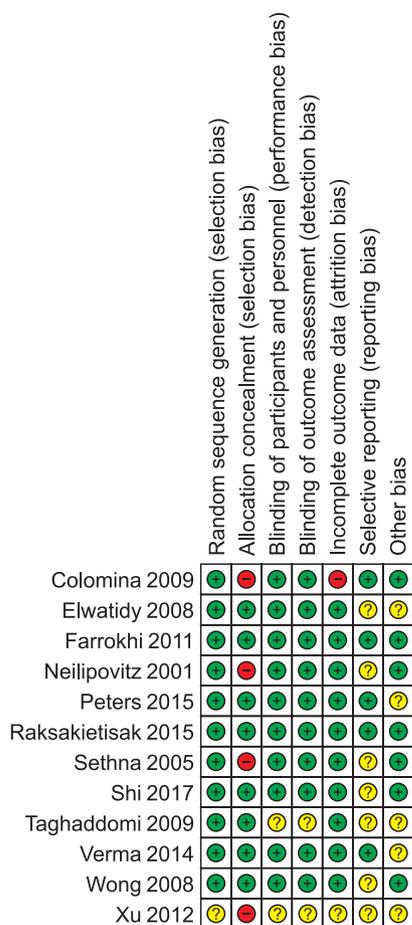
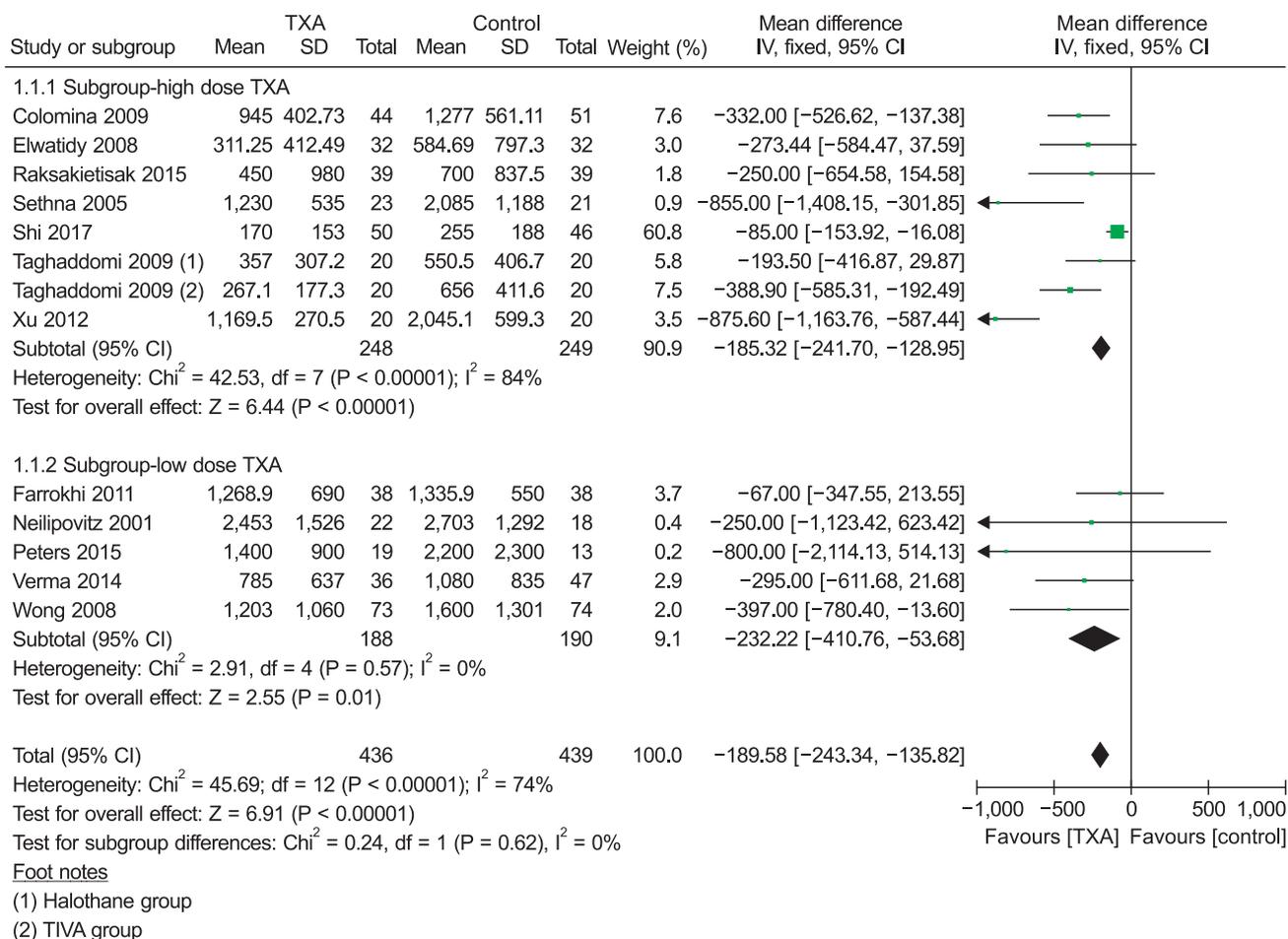
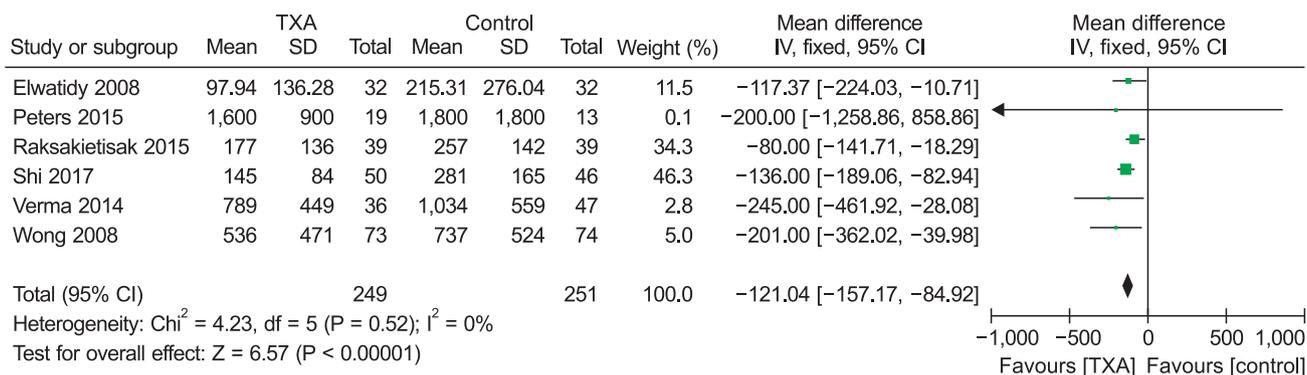


Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



**Fig. 4.** Forest plot diagram showing the effect of tranexamic acid (TXA) on intraoperative blood loss. SD: standard deviation, IV: intravenous, CI: confidence interval, TIVA: total intravenous anesthesia.

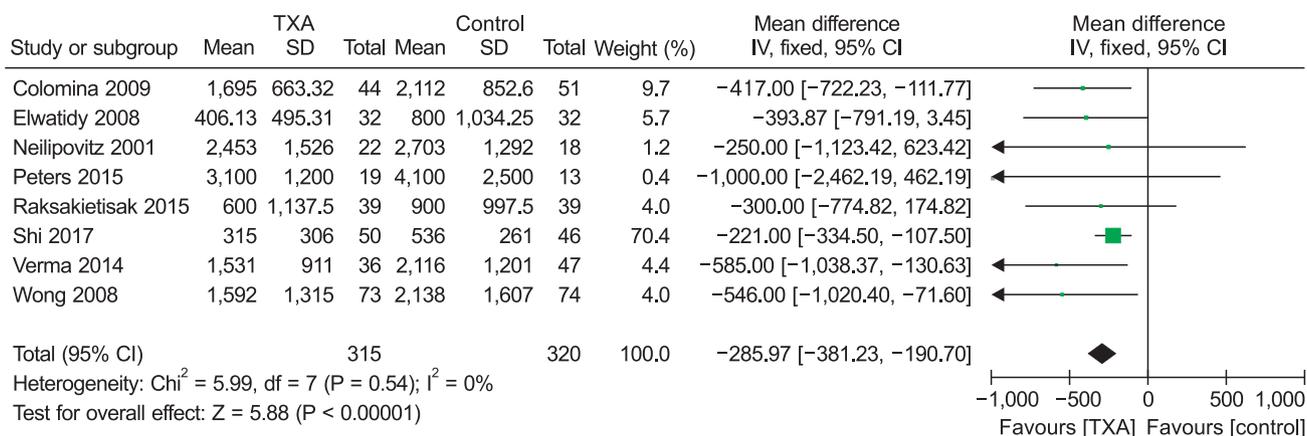


**Fig. 5.** Forest plot diagram showing the effect of tranexamic acid (TXA) on postoperative blood loss. SD: standard deviation, IV: intravenous, CI: confidence interval.

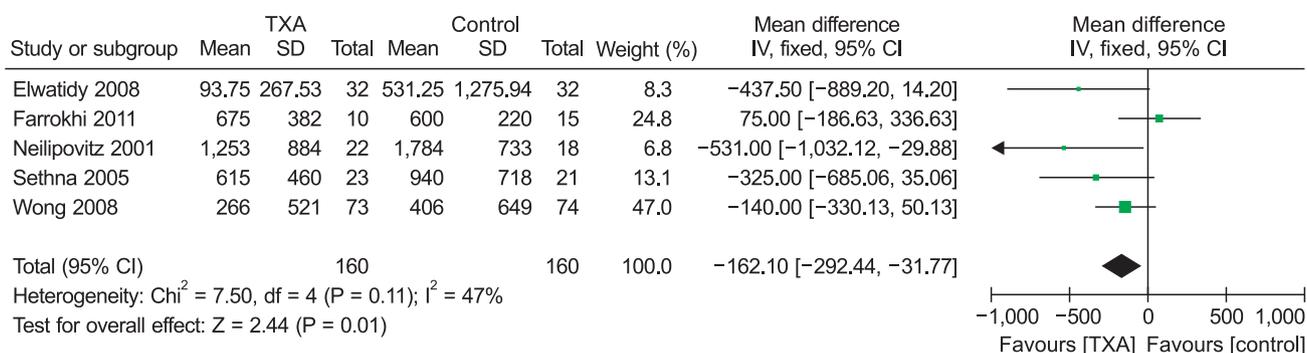
## Heterogeneity and subgroup analysis

Although most outcomes were favorable for the intervention, subgroup analysis was planned due to high heterogeneity. Subgroup analysis was performed on intraoperative

bleeding ( $I^2 = 73\%$ ) which has high heterogeneity. The subgroup analysis was designed to follow domains based on heterogeneity data: anesthesia type (total intravenous anesthesia [TIVA] technique or inhalation anesthetics), IV TXA dosing regimen and timing, type and range of spine surgery,



**Fig. 6.** Forest plot diagram showing the effect of tranexamic acid (TXA) on total perioperative blood loss. SD: standard deviation, IV: intravenous, CI: confidence interval.



**Fig. 7.** Forest plot diagram showing the effect of tranexamic acid (TXA) on transfusion volume. SD: standard deviation, IV: intravenous, CI: confidence interval.

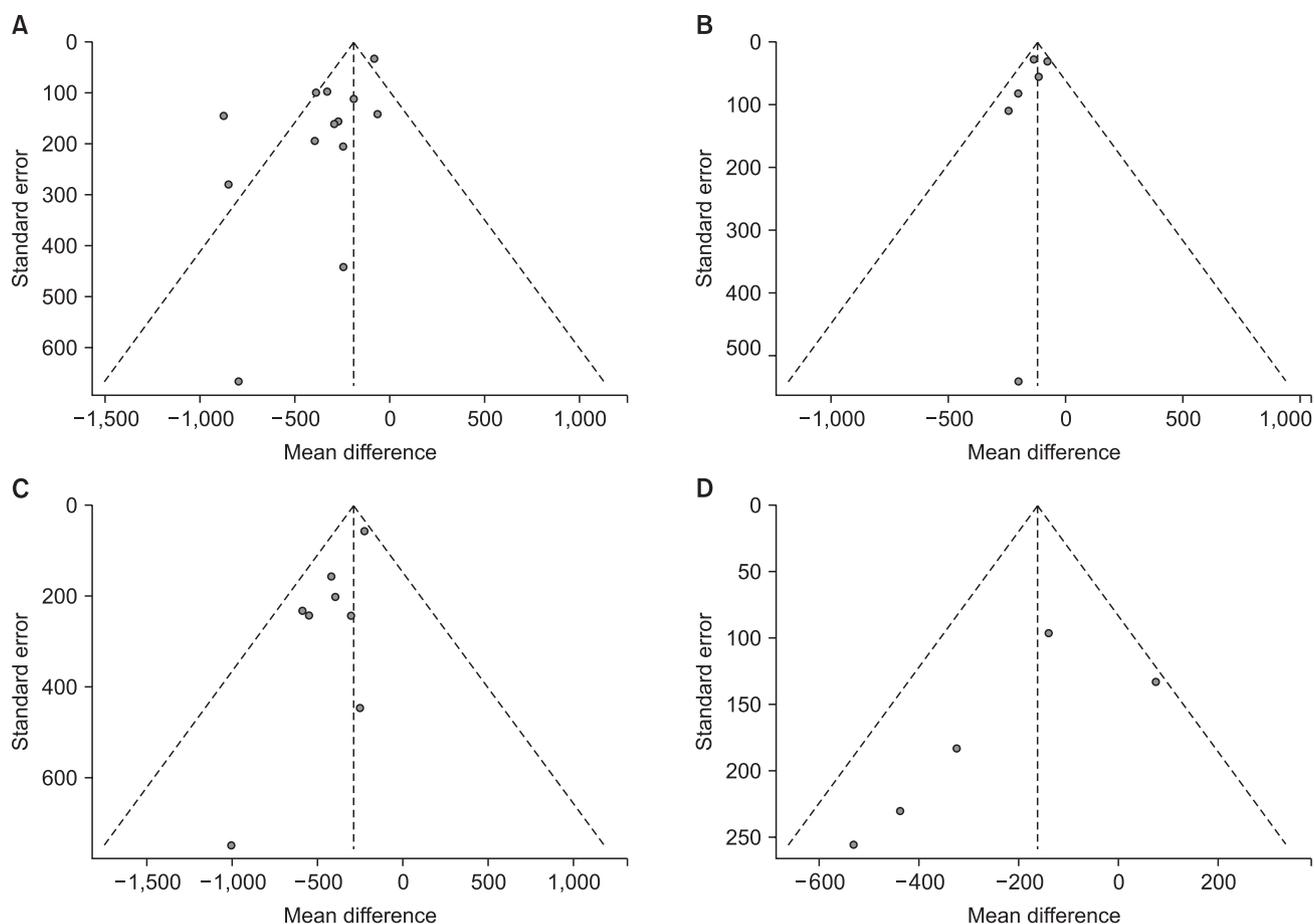
and transfusion triggers. However, due to insufficient data and ununified reporting criteria, subgroup analysis was conducted on the TXA dosing regimen. Low dose group (loading 10 mg/kg and maintenance 1 mg/kg/h) includes Neilipovitz et al. [1], Wong et al. [3], Farrokhi et al. [23], Peters et al. [24], and Verma et al. [26]. High dose group (higher dosage than low dose group) includes Sethna et al. [2], Elwatidy et al. [18], Raksakietisak et al. [19], Xu et al. [20], Colomina et al. [21], Taghaddomi et al. [22], and Shi et al. [25]. Subgroup analysis showed that high dose of intravenous TXA significantly reduces intraoperative blood loss by a mean volume of 185.32 ml, ranging from 128.95 to 241.70 ml (95% CI;  $P < 0.001$ ,  $I^2 = 84\%$ ). Low dose of intravenous TXA reduces intraoperative blood loss by a mean volume of 189.69 ml, ranging from 53.68 to 410.76 ml (95% CI;  $P = 0.570$ ;  $I^2 = 0\%$ ), but not significant results. The funnel plot analysis of publication bias was performed using the collected outcomes (Fig. 8). The asymmetrical property of the resulting plot shows the presence of

publication bias.

## DISCUSSION

Significant blood loss both during and after spine surgery is crucial and contributes to the increased need for allogeneic blood transfusions, which may lead to an increased risk of developing moderate to severe complications. Thus, several techniques regarding the administration of TXA have been used.

There are studies comparing the use of drugs such as TXA, Epsilon-aminocaproic acid (EACA), and aprotinin in addition to TXA to reduce blood loss. There is a study showing that EACA was also effective in reducing bleeding [27]. Although aprotinin and TXA are both effective to reduce blood loss, TXA is a better option for clinical use [28]. TXA has been reported as effective in reducing blood loss and transfusions for various surgeries, regardless of age. One study that inves-



**Fig. 8.** Funnel plot to assess publication bias. (A) Intraoperative blood loss, (B) postoperative blood loss, (C) total blood loss, (D) transfusion volume.

tigated scoliosis correctional surgery revealed better results when used with other blood conservation methods [27]. In idiopathic scoliosis surgery, similar results have been shown in both adults and children [29]. As the dosage of TXA among the included studies differed by up to 10-fold, further studies are needed to establish a better regimen with optimal dosage and administration timing.

A previous meta-analysis has reported the effectiveness of several antifibrinolytic agents to reduce blood loss and transfusion rates in spine surgeries [30]. The use of TXA has been shown to reducing bleeding in many different types of surgery and a previous meta-analysis by Yang et al. [11]. Also showed that the use of TXA may contribute to reduce blood loss in spine surgery. However, there was a limit to include non-RCT studies, which can be a risk of inconclusive findings [30], and there is a limit as the results of the latest studies of the last five years have not been included [11]. Therefore, our study reflects recent research results and reduces methodologic quality and bias-based errors by including only RCTs.

As a result, we confirmed that the administration of perioperative TXA is significantly effective to reduce blood loss and the amount of transfused blood.

As surgical procedures are quite different according to the types of surgeries, the amount of bleeding can vary. Unlike other surgeries, it was difficult to bind the results to a unified standard because spine surgery was performed at various levels, and thus, variation of the blood loss was large. In addition, transfusion triggers and the criteria for measuring postoperative blood loss were different or not specified. This fragmentation may result in reduced accuracy of the results in this analysis. For this reason, the subgroup analysis was carried out only according to the TXA dosing, unlike the plan.

Further studies with uniformity of the outcome measures, which is lacking in the subgroup analysis of this paper, will help to draw better conclusions about the effectiveness of TXA.

In summary, perioperative administration of TXA significantly reduces intraoperative blood loss and postoperative

blood loss in patients who underwent spine surgery. Thus, the volume of transfused blood was reduced by using TXA perioperatively. Reduced total blood loss by TXA administration may improve postoperative outcomes. Given the heterogeneity and small number of studies, further research with an increased number of subjects and an accurate study control is needed to establish a stronger basis for the dosage and administration timing of TXA in patients undergoing spine surgery.

In summary, perioperative administration of TXA significantly reduces intraoperative, postoperative, and total blood loss and transfusion volumes for patients undergoing spine surgery. Additional studies are needed to assure optimal dosage and timing of TXA usage.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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