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SYSTEMATIC REVIEW

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Intravenous versus topical tranexamic acid in spinal surgery: a systematic review and meta-analysis

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Abstract

Background The administration of tranexamic acid (TXA) during spinal surgery has been shown to reduce blood loss. However, the efficacy and safety of intravenous TXA (ivTXA) and topical TXA (tTXA) are poorly documented. The present meta-analysis aimed to compare the efficacy and safety of ivTXA and tTXA administration in spinal surgery.

Methods Potentially relevant academic articles were identified from PubMed, Ovid, Cochrane Library, CNKI database, and Wanfang Data from the date of inception until March 1, 2024. Randomized controlled trials (RCTs) and nonrandomized controlled trials (non-RCTs) were included in our meta-analysis if they compared the efficacy and safety of ivTXA versus tTXA administration during spinal surgery. Secondary sources were identified from the references of the included literature. The meta-analysis was performed in accordance with the guidelines of the Cochrane Reviewer's Handbook and the PRISMA statement. Data were summarized using RevMan 5.3 software from Denmark.

Results Four RCTs and one non-RCT met our inclusion criteria. The pooled outcomes demonstrated that ivTXA groups compared with tTXA groups had significantly less amount of total blood loss [weighted mean difference (WMD)=-159.55, 95% CI (-181.91,-137.19), $P<0.00001$], hidden blood loss [WMD=-132.27, 95% CI (-159.81, -104.72), $P<0.00001$], intraoperative blood loss [WMD=-86.22, 95% CI (-99.13, -73.31), $P<0.00001$, $I^2=96\%$], and more high postoperative hemoglobin level [WMD = 8.96, 95% CI (5.18, 12.75), $P<0.00001$, $I^2=29\%$], and less transfusion rate [risk ratio (RR) = 1.11, 95% CI (0.81,1.52), $P=0.50$, $I^2=94\%$]. The pooled results showed no significant difference in thromboembolic events (deep venous thrombosis and pulmonary embolism) between the two groups.

Conclusion Our meta-analysis demonstrated that ivTXA was more effective than tTXA in inducing hemostatic effect during spinal surgery. However, the risk of a thrombotic event was not different between the two administration methods of TXA. More high quality RCTs are needed to further confirm our conclusions.

Keywords Tranexamic acid, Intravenous, Topical, Spinal surgery

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Introduction

Severe perioperative blood loss is still one of the most frequent complications in spinal surgery. In particular, spinal surgery with prolonged operative time is common and often requires allogeneic blood transfusion [1, 2]. A large amount of perioperative blood loss will prolong the hospitalization of patients and cause some complications, Such as anemia, intravascular hemolysis, organ damage, and even increased mortality [3, 4]. Therefore, reduction of perioperative blood loss is crucial for patients undergoing spinal surgery [5–7].

Many measures are available to reduce perioperative blood loss during spinal surgery, such as controlled hypotension; regional anesthesia; autologous blood transfusion; and various intravenous (IV), intramuscular, and oral medications [4]. However, there is another hemostatic technique that is not currently included in these measures. Tranexamic acid (TXA) is a common hemostatic drug that competitively inhibits plasminogen, plasmin, and tissue plasminogen activator at lysine binding sites [8]. This drug is widely used in hip or knee replacement, gynecological surgery, and cardiac surgery and exerts a significant hemostatic effect [9–11]. A previous meta-analysis showed that topical administration of TXA can significantly reduce perioperative blood loss in spinal surgery [12–14]. TXA can be administered through various routes, including IV, oral, topical, or the combination of IV and topical.

However, it remains controversial whether the intravenous or topical administration route of TXA is more efficient and safe in spinal surgeries [15]. Therefore, we conducted a meta-analysis to compare the efficacy and safety of IV versus topical TXA in patients who underwent spinal surgery.

Materials and methods

The meta-analysis was performed in accordance with the guidelines of the PRISMA statement.

Literature search

Electronic literature search was conducted using PubMed, Ovid, Cochrane library database, CNKI database, and Wanfang Data from the date of inception to March 1 2024. In addition, we searched for references of the included literatures for potentially relevant studies. Articles published in Chinese or English were searched. The key words including "tranexamic acid," "antifibrinolytic" "fibrinolysis" "inhibitor", "TXA", "Cyklokapron", "Lysteda", "Transamin", or "Exacyl" "intravenous," "topical," "spinal," and "surgery" were used in combination with the Boolean operators AND or OR. The search process was conducted as shown in Fig. 1.

Study selection and eligibility criteria

Studies were considered eligible on the basis of the following inclusion criteria: (1) the patient underwent spinal surgery; (2) the control group was administered tTXA and the experimental group was administered ivTXA; (3) the primary outcome measures should include one of the following outcomes: amount of total blood loss, blood transfusion, postoperative Hb level, length of hospital stay, transfusion rate, the secondary outcomes should include thrombosis complications, such as deep vein thrombosis (DVT) or pulmonary embolism; and (4) study designs were RCTs and non-RCTs.

Further, studies were excluded on the basis of the following exclusion criteria: (1) study design did not provide sufficient data and had incomplete data; (2) the study was a case report, review, commentary, et al.; and (3) the patient had received other measures to reduce blood loss and had a history of thromboembolic events (deep venous thrombosis (DVT) or pulmonary embolism (PE).

Data extraction

Two researchers independently extracted data from the included literature. The following general characteristics of each study were extracted: first author name, year of publication, sample size, age, patient type, study design, and intervening measures. Two researchers discussed the discrepancy in data and finalized the following endpoints: total blood loss (TBL), hidden blood loss (HBL), intraoperative blood loss (IBL), postoperative blood loss (PBL), postoperative Hb decline, transfusion rate, and thromboembolic events.

Quality assessment

On the basis of whether the study was a randomized or nonrandomized trial, the quality of RCTs was independently assessed by two researchers according to the method reported in Cochrane Handbook for Systematic Review of Interventions (Fig. 2). Retrospective controlled trials were assessed using a nonrandomized methodological indicators (MINORS) form [16]. Any disagreement was resolved by consensus or discussion with another investigator.

Data analysis and statistical methods

The meta-analysis was performed using RevMan 5.3 software for statistical analysis. We used the weighted mean difference (WMD) with a 95% confidence interval (CI) to describe continuous results, while risk ratio (RR) with a 95% CI was calculated as summary statistics to describe dichotomous data. Statistical heterogeneity was assessed using the values of P and I^2. The random-effect model was used if $P<0.1$ and $I^2>50\%$; otherwise, the fixed-effect model was used for analysis. When necessary, we will conduct subgroup analysis according to autologous and

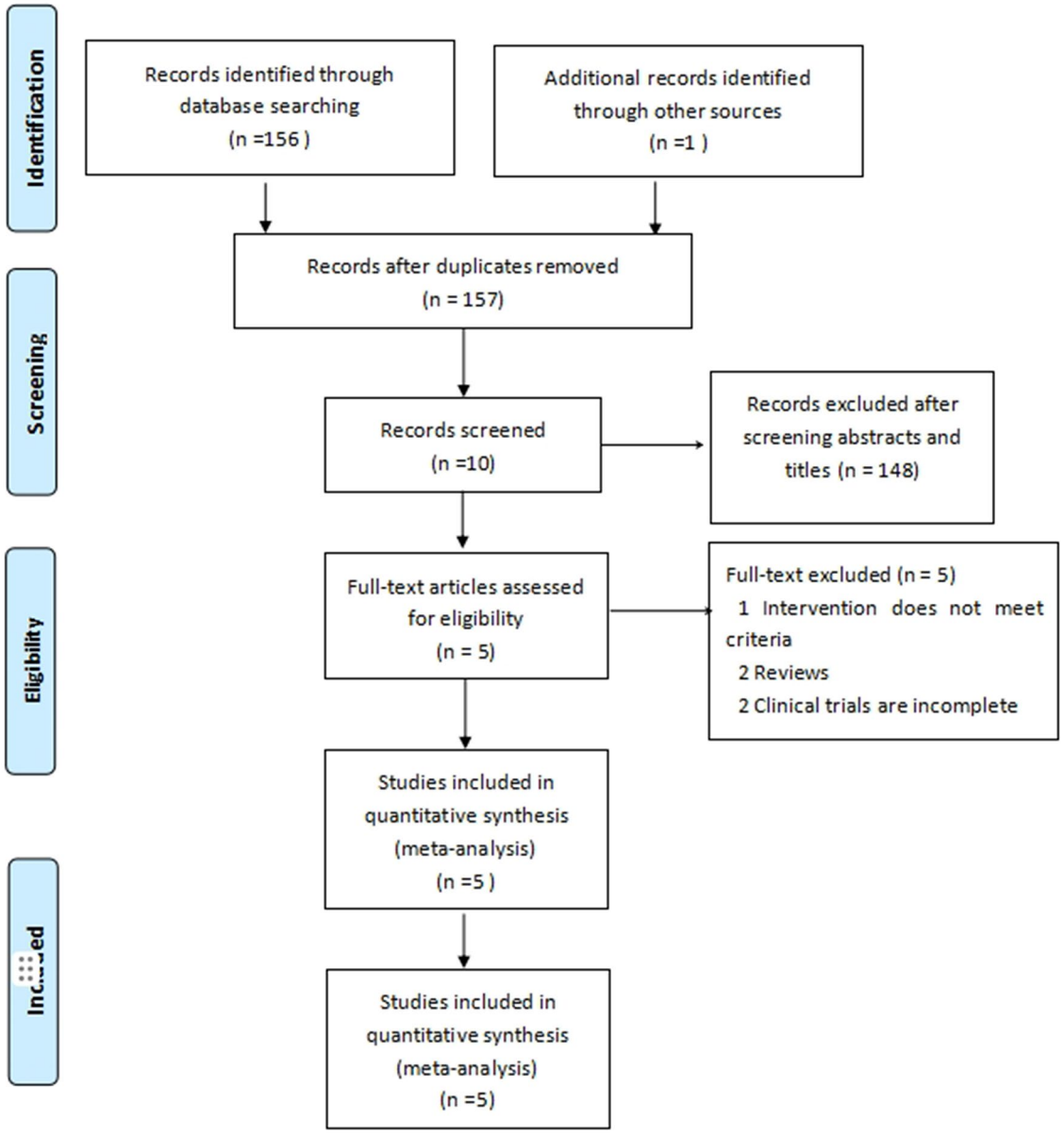

Fig. 1 Flowchart of the literature screening

allogeneic blood transfusion routes, research design and the quality of studies.

Results

Search result

The literature included only RCTs and non-RCTs that compared ivTXA administration to tTXA administration in spinal surgery. According to the search strategy, there were 157 potentially relevant studies at the initial stage. By scanning the title and abstract of each literature, 148 irrelevant studies were excluded. After full-text articles were assessed for eligibility, we excluded four studies including one study with unsuitable intervention, two review articles, and one prospective quasi-experimental study. Finally, the data of five studies [17–21] were pooled to perform this meta-analysis, including four RCTs [17–20] and one non-RCT [21]. The characteristics of all the included literature are shown in Table 1.

Study characteristics and quality appraisal

Demographic characteristics and the literature type of the included studies are summarized in Table 1. The quality of the included RCTs is shown in Fig. 2. There was significant difference in baseline characteristics between the two groups of patients. The study of Ou et al. [19]. was a non-RCT, and the MINORS score was 18. The methodological quality appraisal is shown in Table 2.

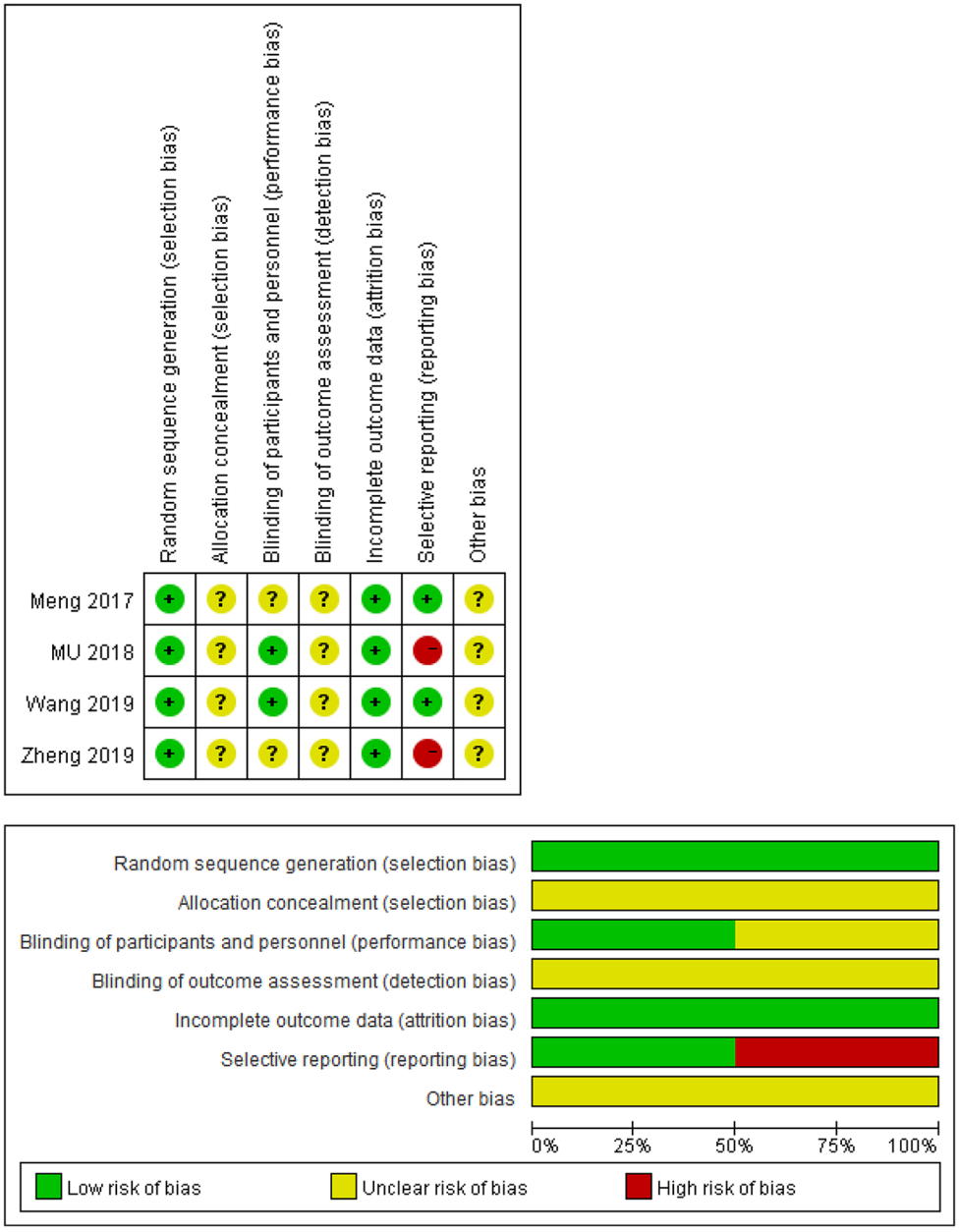

Fig. 2 Risk of bias summary of randomized controlled trials

Outcomes measure

Blood loss (measured in milliliter)

Three studies compared TBL. The pooled result demonstrated that IV administration of TXA led to lower TBL than topical administration of TXA in spinal surgery [WMD=-159.55, 95% CI (-181.91, -137.19), $P<0.00001$, $I^2=0\%$, Fig. 3a]. Two studies provided data on HBL, and the pooled result showed a significant difference between the ivTXA group and the tTXA group [WMD=-132.27, 95% CI (-159.81, -104.72), $P<0.00001$, $I^2=21\%$, Fig. 3b]. Four studies reported data on IBL, and the pooled result again showed a significant difference between the ivTXA group and the tTXA group [WMD=-86.22, 95% CI (-99.13, -73.31), $P<0.00001$, $I^2=96\%$, Fig. 3c]. *S*ubgroup analysis and sensitivity analysis were performed to explore the source of heterogeneity We considered that the sources of heterogeneity of the data of intraoperative blood loss include different surgical methods and different intraoperative use of tranexamic acid. However, due to the lack of sufficient data, we did not conduct subgroup analysis.

Table 1 Characteristics of included studies

Study	Operation	No.I vs. T	Mean age (years) I VS T	Study design	TXA intervention	transfusion criteria	Outcome measures
Meng [17]	Posterior Lumbar surgery	40/40	61 0.1 ± 5.8/62.3 ± 5.4	RCT	I:15 mg/kg TXA IV T:15 min interval for topical administration in the wound, unlimited dose	Hb < 7 g/dl	③④⑥⑦
MU [19]	PLIF	45/39	54.20 ± 7.37/51.77 ± 8.13	RCT	I:15 mg/kg in 100 mL of normal saline T:1 g TXA dissolved in 50mL of normal saline	Hb < 7 g/dl	①②③④⑤⑥⑦
Ou [19]	PLF	59/59	64.0 ± 5.1/64.2 ± 5.14.6	CCT	I:15 mg/kg TXA T:1.0 g TXA in 10 mL of normal saline	Hb < 9 g/dl	①③⑤⑥⑦
Wang [18]	percutaneous pedicle screw fixation	61/62	45.53 ± 8.18/45.72 ± 9.96	RCT	I:15 mg/kg TXA IV T:3 g topical TXA	NR	①②③④⑥⑦
Zheng [21]	multi-segment, thoracolumbar posterior internal fusion	24/24	55.3 ± 7.3/57.2 ± 5.7	RCT	I:1%TXA Sodium Chloride Injection T:1% TXA Sodium Chloride Injection 100 ml	NR	④⑦

① total blood loss, ② hidden blood loss, ③ intraoperative blood loss, ④ postoperative blood loss, ⑤ postoperative hemoglobin level, ⑥ transfusion rate, ⑦ thromboembolic events

I: intravenous group; T: topical group; Hb: hemoglobin; IV: intravenous injection, RCT: randomized controlled trial; CCT: case control trial, NR: no report, PLIF: posterior lumbar interbody fusion, PLF: posterior lumbar fusion

Table 2 Quality assessment for non-randomized trials

Quality assessment for non-randomized trials	Ou 2018 CCT
A clearly stated aim	2
Inclusion of consecutive patients	2
Prospective data collection	0
Endpoints appropriate to the aim of the study	2
Unbiased assessment of the study endpoint	2
A follow-up period appropriate to the aims of study	2
Less than 5% loss to follow-up	2
Prospective calculation of the sample size	0
An adequate control group	2
Contemporary groups	0
Baseline equivalence of groups	2
Adequate statistical analyses	2
Total socre	18

Postoperative hemoglobin level

Two studies reported the outcomes of postoperative hemoglobin (HB) level. The pooled result demonstrated a significant difference in postoperative HB level between the ivTXA group and the tTXA group [WMD = 8.96, 95% CI (5.18, 12.75), $P < 0.00001$, $I^2 = 29\%$, Fig. 4].

Transfusion rate

Four studies reported the outcomes of transfusion rate. The pooled result showed no significant difference in the transfusion rate between the two groups [RR = 1.12, 95% CI (0.80, 1.56), $P = 0.51$, $I^2 = 95\%$, Fig. 5]. The source of heterogeneity in our pool-analysis of the four included studies is mainly the study of ou et al. [19]. When we excluded the study of ou et al [19], we found no obvious heterogeneity, which is mainly caused by the inconsistent of indications of blood transfusion in the four studies. Mu et al. [18] considered that hemoglobin (Hgb) level below 70 g/L and red blood cell count below 3.0×10^2/L were the indications of blood transfusion. The criteria for blood transfusion in the study of Ou et al [19] were that the postoperative red blood cell count was less than 3.0×10^2/L, and the hemoglobin (HGB) level of less than 90 g/L.

Thrombotic events (DVT and PE)

Five studies reported the outcomes of thrombotic events. The pooled result indicated no significant difference between the two groups [RR = 1.00, 95% CI (0.98, 1.02), $P = 0.68$, $I^2 = 0\%$, Fig. 6].

Discussion

This is the first meta-analysis of the efficacy and safety of IV and topical administration of TXA in spinal surgery. The present meta-analysis demonstrated that the ivTXA group had a lower volume of TBL, HBL, IBL, and PBL in spinal surgery. The meta-analysis also showed no significant differences in thrombotic events and transfusion rate between the ivTXA group and the tTXA group in spinal surgery. Our meta-analysis showed that intravenous and topical administration of TXA without an increased risk of complications (DVT and PE) in spinal surgery was similar to the results observed for primary total hip arthroplasty (THA) [16].

The amount of blood loss during spinal fusion surgery ranged from 650 to 2,839 mL, and the proportion of blood transfusion required was 50–81%. There is currently no effective strategy to reduce blood loss [22]. TXA has been recommended as an essential drug by WHO in 2011, and it is currently widely used in clinical treatment

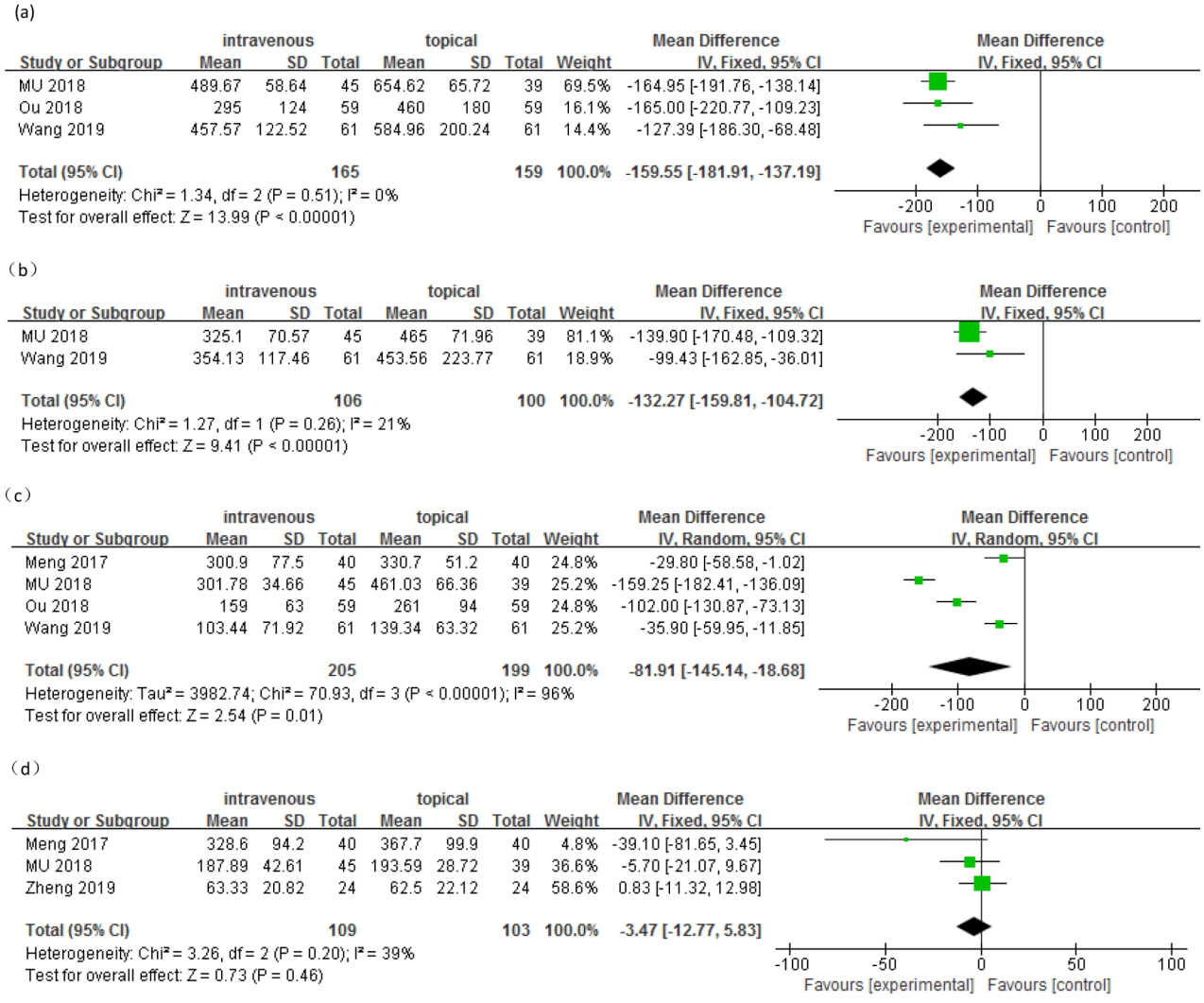

Fig. 3 (**a**) Forest plot of total blood loss; (**b**) Forest plot of hidden blood loss; (**c**) Forest plot of intraoperative blood loss; and (**d**) Forest plot of postoperative blood loss

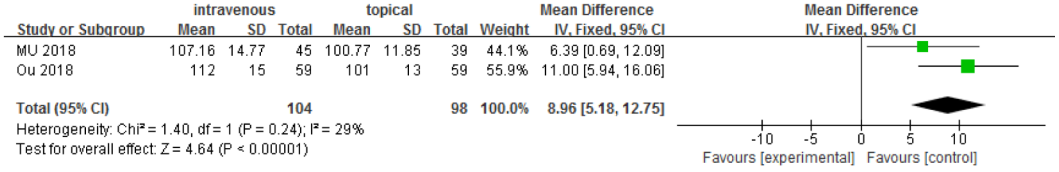

Fig. 4 Forest plot of postoperative HB decline

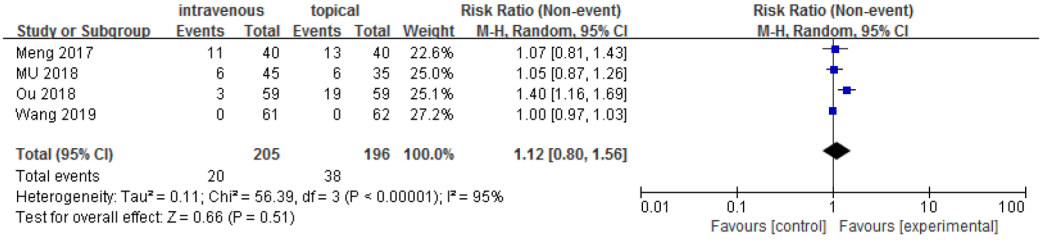

Fig. 5 Forest plot of transfusion rates

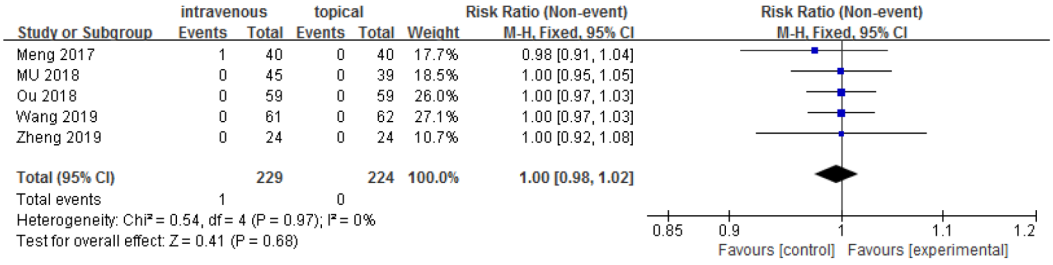

Fig. 6 Forest plot of thromboembolic events

to reduce blood loss [23]. TXA has been successfully used in spinal surgery to reduce blood loss [22]. TXA can significantly reduce perioperative bleeding, reduce the need for transfusions, and rarely increases the risk of thrombosis during orthopedic surgeries [24–27]. Topical TXA can reduce HBL in the posterior lumbar interbody fusion (PLIF) as reported by Ren et al [28]. A recent meta-analysis assessed the efficacy and safety of tTXA in terms of TBL; drainage volume; postoperative HB level; and the risk of complications, including hematoma, DVT, and PE, in spinal surgeries [29]. Yang et al. [30] also conducted a meta-analysis of 581 patients in 9 studies and demonstrated that perioperative ivTXA administration in patients undergoing spinal surgery can reduce blood loss, Similarly, the percentage of spinal surgery patients who required allogeneic blood transfusion was significantly decreased.

In our meta-analysis, compared to tTXA, ivTXA more effectively reduced TBL, HBL, IBL, and PBL. Operation time and visible surgical field are directly affected by IBL. It is quite challenging for an orthopedist to perform spine surgery. In the current meta-analysis, significant heterogeneity in IBL was detected between the two groups. This may be due to the small sample size of the included studies and performance of different spinal surgeries. Therefore, the volume of IBL was also very different. The dosages of TXA should be determined according to the type of spinal surgery, the patient's conditions (e.g., weight, renal function) and other factors. Besides, the relevant dose-re sponse analysis should be performed to identify the optimal TXA dose in spinal surgery. Four studies [17–20] compared the two methods of TXA administration and reported that ivTXA administration led to less IBL than topical TXA administration. In the study of Ren et al [28], 50 patients received topical administrations of TXA in PLIF surgery. In the tTXA group, because the postoperative HB level showed a slight decrease, TBL was significantly reduced at the perioperative stage. In a recent RCT, similar results were observed with ivTXA in patients undergoing posterior fusion because of thoracolumbar fracture dislocation [29]. In the current meta-analysis, the pooled results showed the ivTXA group had a higher postoperative HB level. This finding was consistent with the results of Mu et al. [18] and Ou et al. [19] we considered that the ivTXA has a better effect than the tTXA on blood loss reduction. When a blood vessel is damaged during surgery, the formation of a blood clot activates the fibrinolytic system of the human body to release a large amount of plasmin to decompose the clot. The iv TXA during surgery can increase speed and efficaciousness by inhibiting the decomposition of the blood clot compared with tTXA after the fibrinolytic system has been activated.

Although the present meta-analysis showed no significant difference in the blood transfusion rate between the two groups, the ivTXA group had a lower transfusion rate. Postoperative HB levels and clinical symptoms of anemia are indications of blood transfusion. However, the indications for transfusion are different for each study, which may lead to incomparability. Several studies have shown that topical or ivTXA administration during joint replacement had a significant reduction in transfusion rates [31, 32]. In the present meta-analysis, Wang et al. [20] reported no blood transfusion in both groups, because of absence of clinical symptoms of anemia during the operation.

Thromboembolic events are life threatening for patients undergoing spinal surgery. The potential high risk of clinical application of TXA is a huge concern. Previous studies have focused on other surgeries such as heart, hip, and knee replacements. tTXA is easier to administer than ivTXA. tTXA can provide the maximum drug concentration in the surgical incision with little or no systemic exposure of TXA. In general, tTXA is more safer than ivTXA, with fewer complications, including venous thrombosis, renal impairment, and convulsive seizures. However, the present meta-analysis showed no significant difference between the tTXA group and the ivTXA group in spinal surgeries. This outcome was consistent with the results of Mu et al. [18], Ou et al. [19], and Wang et al. [20]. Zhang et al. [16] conducted a meta-analysis of 964 patients in 7 studies and demonstrated no significant difference between the tTXA group and the ivTXA group in hip replacement. Therefore, it can be concluded that the different administration methods of TXA did not increase the risk of thrombotic events.

The present meta-analysis had the following limitations: (1) all the included studies were from China, resulting in publication bias, (2) the number of studies included in the meta-analysis was the small sample size and the inclusion of a non-RCT may affect the reliability of present conclusions, (3) the dose and timing of TXA administration in the included studies were not of the same standard; thus, it was impossible to perform subgroup analysis, and (4) the differences in surgical procedures and postoperative measures and techniques may lead to different postoperative results, which will significantly affect the credibility of the outcome.Therefore, We recommend future research as follows.(1)The most appropriate time and dose of TXA in spinal surgery still need to be further determined. (2) The tTXA in spinal surgery has less effect on the systemic fibrinolytic system than ivTXA, However, its efficacy needs further study.(3) relevant research should be further exploring the application of TXA in spinal surgery for patients with severe cardiopulmonary disease. (4) High quality large-scale sample randomized controlled trials are needed in the future to verify our conclusions.

Conclusion

Our meta-analysis revealed that ivTXA was more effective than tTXA during spinal surgery and resulted in reduced TBL, IBL, HBL, and PBL and higher postoperative HB level. However, there was no significant difference in transfusion rate and thromboembolic events between the two administration methods of TXA. More high quality RCTs are needed to further confirm our conclusions.

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Author contributions
BD, XP and XDL designed the study and developed the retrieval strategy. XZL and XLY searched and screened the summaries and titles. DB drafted the article. All authors read and approved the final draft.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This is a meta-analysis, There is no relevant problems exist.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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