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Efficacy and safety of topical versus intravenous tranexamic acid in spinal surgery: a systematic review and meta-analysis

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Abstract

Background The relative efficacies of topical and intravenous tranexamic acid (TXA) in spinal surgery remain controversial. This meta-analysis aimed to compare the efficacy and safety of topical versus intravenous TXA in spinal surgery, with a particular focus on the impacts on intraoperative blood loss (IBL) and associated outcomes.

Methods We searched the PubMed, EMBASE, Medline, and Cochrane Library databases to identify all literature related to topical and intravenous TXA in spinal surgery. Six trials met the inclusion criteria. The IBL, postoperative drainage volume, total blood loss, postoperative hematological variables, postoperative blood transfusions, and complications were analyzed.

Results The meta-analysis of randomized controlled trials indicated that IBL and total blood loss were markedly higher in the group receiving topical TXA compared to the intravenous TXA group. Conversely, data from retrospective studies did not show significant differences between the two groups. Hemoglobin levels on postoperative days 1 and 3 were significantly lower in the topical TXA group than in the intravenous TXA group. No significant differences were observed between the topical and intravenous TXA groups regarding other postoperative hematological parameters, drainage volume, transfusion rates, and complications.

Conclusions The current evidence suggests that topical TXA does not significantly reduce postoperative blood loss in spinal surgery compared with intravenous TXA, but has good safety and does not increase the associated risks. There is a need for high-quality studies that explore the effects of topical TXA in spinal surgery.

Keywords Tranexamic acid, Hemoglobin, Spinal surgery, Blood loss, Complications

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Introduction

With the continuous development of society, science, economy, and medical care, the number of operations has rapidly increased in recent years, and the number of patients who require spinal surgery for various diseases is also increasing [1, 2]. Especially in multi-segment, thoracic, and lumbar spinal surgery, the surgical incisions are deep and long and there are many muscle tissues to be peeled off, leaving large wounds and causing bleeding [3]. Heavy bleeding causes anemia, which delays wound healing or causes non-union, increases the probability of infection, and leads to increased surgical complications and perioperative mortality [4]. Therefore, it is important to reduce the bleeding caused by surgery. Various methods used clinically to reduce perioperative bleeding include improving surgical methods and techniques, shortening the operation time, autologous blood transfusion, and applying hemostatic drugs [5–7]; however, these methods cannot completely alleviate perioperative bleeding, and a large number of patients still need blood transfusions. Blood transfusion not only increases the incidences of infectious diseases and adverse reactions, but also increases medical costs and wastes blood resources [8–10]. The concept of Enhanced Recovery After Surgery is currently being advocated and includes the administration of hemostatic drugs to reduce perioperative bleeding, reduce complications, and shorten the length of hospital stay [11].

Tranexamic acid (TXA) is an antifibrinolytic type of hemostatic drug [12]. TXA achieves antifibrinolytic and hemostatic effects by binding to the lysine-binding site of plasminogen to competitively inhibit plasminogen adsorption on fibrin and activation of plasminogen, so that plasmin is not degraded by plasmin [4, 13]. TXA has been shown to reduce perioperative bleeding and the need for allogeneic blood transfusions [14, 15]. Itcan be administered orally, intravenously, or topically to achieve hemostasis [16–18]. Although intravenous TXA is commonly used, it has drawbacks, including a delayed onset of action (approximately 15 minutes) and an increased risk of venous thrombosis due to its antifibrinolytic effect [19, 20]. Topical TXA, however, has demonstrated promising results in surgeries such as hip and knee replacements and thoracic procedures, offering potential advantages over intravenous administration [21–24]. One study recommended topical TXA over intravenous TXA because high-dose intravenous TXA increases the incidence of postoperative venous thrombosis and pulmonary embolism, especially in patients with a history of embolism [25]. Compared with intravenous TXA, topical TXA directly aggregates at the site of action to directly and effectively exert a hemostatic effect, reduce systemic absorption, reduce the systemic effect of TXA, and eliminate the risk of venous thrombosis and cardiovascular and cerebrovascular diseases caused by intravenous TXA infusion [26, 27].

A number of unresolved issues regarding the potential risk of thrombosis, rare epileptogenic adverse effects, and contraindications to systemic TXA in patients with coagulopathy or renal impairment necessitate the use of topical TXA for bleeding management in spinal surgery. In addition, the fact that excessive fibrinolysis due to acute wasting coagulopathy caused by surgical trauma is concentrated in the surgical incision has aroused interest in exploring whether topical application of TXA may improve the current standard of treatment for hemostasis. The topical route of administration delivers hemostatic drugs directly to the wound during or at the end of surgery. Compared with non-TXA group, both topical and intravenous TXA significantly reduced the postoperative blood loss, blood transfusion rate, and postoperative hospital stay, but these variables did not differ between the topical and intravenous TXA groups [28]. However, intravenous TXA significantly reduced intraoperative bleeding compared with topical TXA [28]. Weissmann et al. retrospectively analyzed patients undergoing posterior fusion surgery and found no significant difference between the topical and intravenous TXA groups [29]. Wang et al. found that the total blood loss and intraoperative blood loss were significantly greater in the topical TXA group than the intravenous TXA group [30]. These previous findings suggest that both intravenous and topical TXA reduce f blood loss and transfusion rate during spinal surgery, while the best way to use TXA in spinal surgery is still debatable. Therefore, we performed a meta-analysis of existing studies to assess the effectiveness and safety of intravenous versus topical TXA in spinal surgery.

Methods

The study adheres to the standards outlined in the Cochrane Handbook for Systematic Reviews [31] and follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [32]. The protocol for this meta-analysis has been registered on PROSPERO (No: CRD 42023463198).

Inclusion criteria

Study type: randomized controlled trial (RCT) or non-RCT. Participants: Spinal surgery patients. Intervention and control: topical TXA vs. intravenous TXA. Outcomes: blood loss, postoperative hematological variables at 1 and 3 days after surgery, transfusions, and complications.

Search strategy

A comprehensive search was performed in PubMed, EMBASE, Medline, and the Cochrane Central Register of

Controlled Trials from their inception to September 01, 2023. The keywords used were: "Intravenous and topical and tranexamic acid and (cervical or lumb* or thora* or spin*)".

Study selection

Two researchers (CXX and GPC) independently screened the literature. They initially reviewed titles and abstracts, followed by a full-text review for those meeting the criteria. Disagreements were resolved by a senior researcher (HL).

Data collection process

Data extracted from the included studies encompassed: author and year, study design, country, sample size, participant details, TXA treatment specifics, age, and outcomes.

Assessment of risk of bias and quality of evidence

Two researchers (HL and CXX) independently assessed trial quality using the Cochrane risk-of-bias criteria [33] and the Newcastle–Ottawa scale for retrospective studies [34].

Data synthesis

Meta-analysis was conducted using Stata (version 17; StataCorp, 2021). Heterogeneity was assessed with the Q test and I^2 statistic. Random effect models were used. Dichotomous outcomes were measured using odds ratios (OR) with 95% confidence intervals (CI), and continuous outcomes were analyzed using standard mean difference (SMD).

Sensitivity analyses

We performed a sensitivity analysis by excluding individual trial.

Results

An initial total of 203 studies were identified. On the basis of the titles and abstracts, 87 duplicates were removed and 94 irrelevant studies were excluded. After the full text of 22 articles was read, a further 17 articles were excluded (3 meetings, 9 trials without results, and 5 studies that compared intravenous plus topical TXA with a control). An additional study was extracted from the reference list of a previous review. Finally, six studies (5 RCTs and 1 retrospective study) with a total of 518 patients were included in our study. The study by Arun-Kumar et al. was divided into three groups, and the group that received local TXA before the skin incision was excluded from our study [35]. Figure 1 shows the screening process, and Table 1 summarizes the characteristics of the included studies.

Intraoperative blood loss

Six studies (5 RCTs and 1 retrospective study) assessed the intraoperative blood loss (IBL) [28–30, 35–37]. Meta-analysis of the RCTs showed that IBL was significantly greater in the topical TXA group than the intravenous TXA group SMD 1.16, 95% CI 0.38 to 1.94, $I^2 = 93.0\%$, $P = 0.004$; Table 2). In the retrospective study, there was no significant difference in IBL between the topical TXA and intravenous TXA groups (SMD – 0.26, 95% CI – 0.78 to 0.27, $P = 0.335$; Table 2).

Total blood loss

Three studies (2 RCTs and 1 retrospective study) reported the total blood loss (TBL) [29, 30, 36]. Analysis of the RCTs using a random-effects model showed that TBL was significantly greater in the topical TXA group than the intravenous TXA group (SMD 0.52, 95% CI 0.05 to 0.99, $I^2 = 72.1\%$, $P = 0.03$; Table 2). In the retrospective study, there was no significant difference in TBL between groups (SMD – 0.25, 95% CI -0.78 to 0.27, $P = 0.335$; Table 2).

Postoperative drainage

Four studies (3 RCTs and 1 retrospective study) reported the postoperative drainage volume [28, 29, 35, 36]. In the RCTs, there was no significant difference in total postoperative drainage between the topical TXA and intravenous TXA groups (SMD 0.54, 95% CI -0.06 to 1.14, $I^2 = 81.6\%$, $P = 0.077$; Table 2). The conclusions of the retrospective study were consistent with those of the RCTs.

Postoperative hematological variables at 1 and 3 days after surgery

One RCT reported the hemoglobin (Hb) concentration on postoperative day 1 [35], two RCTs reported Hb concentrations on postoperative day 3 [28, 35], one RCT reported the hematocrit value (HCT) on postoperative day 1 [35], three RCTs reported the HCT on postoperative day 3 [28, 30, 35], and one RCT reported the postoperative D-dimer concentrations [30]. The Hb concentration on postoperative day 1 was significantly lower in the topical TXA group than the intravenous TXA group (SMD – 1.214, 95% CI -1.807 to -0.621, $P < 0.001$; Table 2). There was no significant difference in Hb levels between the two groups on postoperative day 3 (SMD – 2.30, 95% CI -5.94 to 1.33, $I^2 = 97.8\%$, $P = 0.215$; Table 2). There was no significant difference in the HCT between the two groups on postoperative day 1 (SMD – 0.38, 95% CI -0.93 to 0.17, $P = 0.174$; Table 2). However, the HCT on postoperative day 3 was significantly lower in the topical TXA group than the intravenous TXA group (SMD – 0.77, 95% CI -1.44 to -0.09, $I^2 = 84.7\%$, $P = 0.027$; Table 2). There was no difference between the two groups

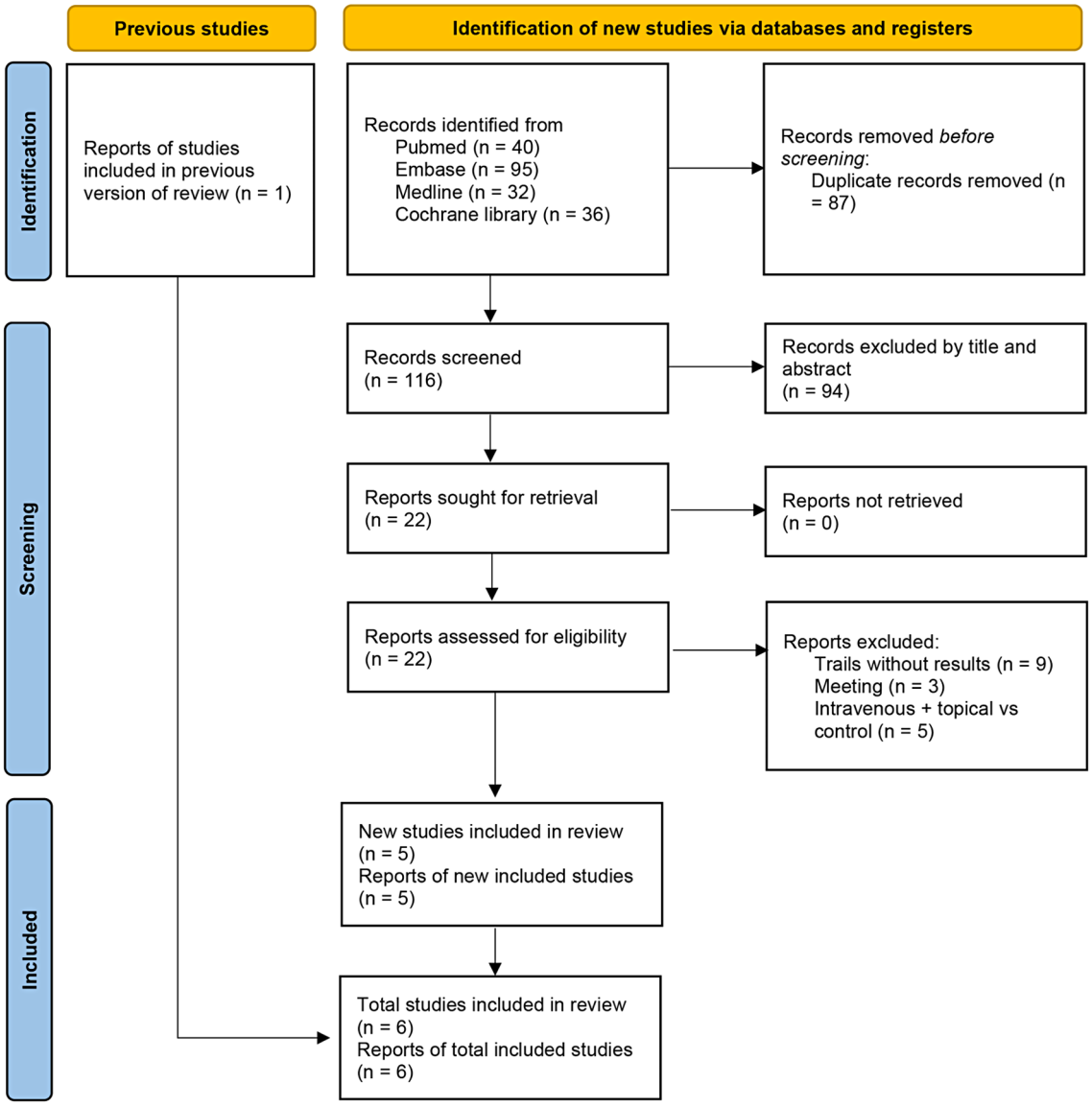

Fig. 1 Flow diagram for search and selection of included studies

in the D-dimer concentration (SMD – 0.052, 95% CI -0.41 to 0.30, $P = 0.775$; Table 2).

Postoperative blood transfusions

Postoperative blood transfusions were reported in four RCTs [28, 30, 35, 36]. Data from Wang et al. were excluded due to the absence of events [30]. The pooled analysis revealed no significant difference in transfusions rates between topical and intravenous TXA groups (OR: 0.89, 95% CI: 0.48 to 1.69, $I^2 = 0\%$, $P = 0.727$; Table 2).

Complications

Four RCTs reported complications [28, 30, 36, 37]. Mu et al. and Wang et al. reported no related adverse reaction events in either group [28, 30]. The pooled results showed no significant difference in postoperative complications between the topical and intravenous TXA groups (OR: 0.86, 95% CI: 0.31 to 2.42, $I^2 = 0\%$, $P = 0.781$; Table 2).

Sensitivity analysis

The remaining studies were pooled when any individual study was excluded, and no single study significantly affected the results.

Publication bias

Publication bias was not assessed due to fewer than 10 trials.

Discussion

We conducted a meta-analysis of six studies with a total of 518 patients who received either topical or intravenous TXA administration in spinal surgery. The five included

Table 1 Characteristics of included studies

Study	Country	Date range	Participants	Treatment		Design	No. of subject	Age		Sex (Male/Female)		BMI		Risk of bias assessment tool (RCTs) or NOS (observational)	Outcomes
				tTXA	ivTXA			tTXA	ivTXA	tTXA	ivTXA	tTXA	ivTXA		
Arun-Kumar 2021	India	2017.10-2018.08	Lumbar fusion	1 g TXA + 100 mL NS rinsed	1 g ivTXA	RCT	52	51.9 + 2.8	50.3 + 3.2	13/13	12/14	25.6 + 2.1	25.8 + 2.3	High	IBL, postoperative drainage, blood transfusion, length of hospital stay, hematological parameters
El-Sharkawi 2016	Egypt	2011–2014	Spinal deformities	Sponges soaked with TXA	ivTXA	RCT	60	17 + 4		34/49		49 + 6		Unclear	IBL, complication
Li 2020	China	2015.12-2019.12	Lumbar fusion	2 g TXA + 20 mL NS into injected in the incision	15 mg/kg ivTXA	RCT	140	65.61 + 4.81	66.67 + 3.27	25/45	24/46	22.24 + 2.78	23.95 + 3.25	High	IBL, TBL, postoperative drainage, hemoglobin drop, transfusion rate, complication

Table 1 (continued)

Study	Country	Date range	Participants	Treatment		Design	No. of subject	Age		Sex (Male/Female)		BMI		Risk of bias assessment tool (RCTs) or NOS (observational)	Outcomes
				tTXA	ivTXA			tTXA	ivTXA	tTXA	ivTXA	tTXA	ivTXA		
Mu 2019	China	2015.09-2017.08	Lumbar degenerative disease	Sponge soaked 1 g TXA	15 mg/kg ivTXA	RCT	84	51.77 + 8.13	54.20 + 7.37	22/17	27/18	24.72 + 1.82	24.83 + 1.95	Low	IBL, postoperative drainage, blood transfusion, time for drainage remove, HB, HCT, complication

Table 1 (continued)

Study	Country	Date range	Participants	Treatment		Design	No. of subject	Age		Sex (Male/Female)		BMI		Risk of bias assessment tool (RCTs) or NOS (observational)	Outcomes
				tTXA	ivTXA			tTXA	ivTXA	tTXA	ivTXA	tTXA	ivTXA		
Wang 2019	China	2017.01-	Thoracolumbar fracture	3 g TXA + NS rinsed	15 mg/kg ivTXA	RCT	122	45.72 + 9.96	45.43 + 8.18	37/24	34/27	21.37 + 2.17	21.26 + 2.26	Low	TBL, HBL, IBL, HCT, complications
Weissmann 2020	USA	2009–2016	Spinal deformities	6 g TXA + 3 L NS rinsed	20 mg/kg ivTXA + continuous infusion of 1 mg/kg/h	Retrospective cohort	60	14.7 + 3.71	14.59 + 2.07	7/16	4/33	NA	NA	NOS (8)	IBL, TBL, postoperative drainage, transfusion rates, time for drainage remove, complication

RCT, randomized controlled trial; TXA tranexamic acid; tTXA, topical TXA; ivTXA, intravenous TXA; NS, normal saline; IBL, intraoperative blood loss; TBL, total blood loss; NOS, Newcastle–Ottawa Scale; HBL, hidden blood loss; HB, hemoglobin; HCT, hematocrit

Table 2 Pooled effect size and heterogeneity tests outcomes including IBL, TBL, postoperative drainage, postoperative hematological variables, postoperative blood transfusions, and complication using the random-effects model

Outcome	Study type	No. of studies	Effect size (95% CI)	I^2 (%)	*p*-Heterogeneity	*p*-value
IBL	RCT	5	1.16 (0.38, 1.94)	93	< 0.0001	0.004
	non-RCT	1	-0.26 (-0.78, 0.27)	NA	NA	0.335
TBL	RCT	2	0.52 (0.05, 0.99)	72.1	0.058	0.03
	non-RCT	1	-0.25 (-0.78, 0.27)	NA	NA	0.341
Postoperative drainage	RCT	3	0.54 (-0.06, 1.14)	81.6	0.004	0.077
	non-RCT	1	-0.07 (-0.59, 0.45)	NA	NA	0.792
HB postoperative 1 day	RCT	1	-1.214 (-1.807, -0.621)	NA	NA	0
	non-RCT	0	NA	NA	NA	NA
HB postoperative 3 days	RCT	2	-2.301 (-5.937, 1.334)	97.8	< 0.0001	0.215
	non-RCT	0	NA	NA	NA	NA
HCT postoperative 1 day	RCT	1	-0.381 (-0.929, 0.168)	NA	NA	0.174
	non-RCT	0	NA	NA	NA	NA
HCT postoperative 3 day	RCT	3	-0.766 (-1.443, -0.088)	84.7	0.001	0.027
	non-RCT	0	NA	NA	NA	NA
Postoperative blood transfusions	RCT	4	0.892 (0.470, 1.693)	0	0.859	0.727
	non-RCT	0	NA	NA	NA	NA
Complications	RCT	4	0.864 (0.309, 2.417)	0	0.492	0.781
	non-RCT	0	NA	NA	NA	NA

RCT, randomised controlled trial; NA, lack of sufficient number of studies; IBL, intraoperative blood loss; TBL, total blood loss; HB, hemoglobin; HCT, hematocrit

RCTs had a high quality of evidence. An analysis of the data from these five RCTs found that topical TXA did not significantly reduce IBL and TBL during spinal surgery compared with intravenous TXA. However, this relates to the timing of topical application rather than the method of drug use. In the studies we included, topical application of TXA was performed at the end of surgery. This timing may not effectively prevent intraoperative bleeding. In contrast, intravenous TXA is usually administered before the start of surgery, thus providing suppression of the systemic fibrinolytic system throughout the operation. Therefore, the inability of topical TXA to reduce intraoperative blood loss may be due to its timing of use. To better assess the efficacy of topical TXA, we recommend injecting it locally before the start of surgery and using TXA-soaked gauzes intraoperatively for local hemostasis. Such methods might more effectively reduce bleeding in surrounding tissues during surgery. By administering the drug in advance and maintaining its application during surgery, local fibrinolytic activity can be better suppressed, thereby reducing intraoperative bleeding. Our review included only one retrospective study. Retrospective studies are often subject to a number of limitations, such as selection bias, information bias, and confounding bias, which makes the quality of the evidence relatively low. Therefore, the conclusions of a retrospective study may not be sufficiently credible and are susceptible to bias and statistical uncertainty. Although the findings of this retrospective study differed from the findings of the RCTs and concluded that the total and intraoperative blood loss was similar in the topical and intravenous TXA groups, this conclusion needs to be interpreted with caution due to the low level of evidence and small sample size of the retrospective study. As RCTs have a higher quality and quantity of evidence, their results are considered more reliable. The conclusions of retrospective studies may be valuable, but need to be interpreted with caution as their methodological limitations may result in less stable conclusions. Overall, there is a need for more high-quality RCTs to fully assess the effect of topical TXA on blood loss in spinal surgery to improve our understanding and guide clinical practice.

Our meta-analysis showed no significant difference in total postoperative drainage between the topical and intravenous TXA groups in the RCTs. This result was also validated in the retrospective study. In terms of postoperative blood variables, we found that the Hb concentration was significantly lower in the topical TXA group than the intravenous TXA group on postoperative day 1. However, this difference was no longer significant on postoperative day 3. In contrast, the HCT significantly differed between groups on postoperative day 3 but not on postoperative day 1. This may reflect differences between the two groups in blood recovery in the days after surgery. Although the Hb concentration significantly differed between the two groups on postoperative day 1, further research is needed to determine whether this finding has practical implications for clinical outcomes. Finally, our analysis did not find a significant difference between the topical and intravenous TXA groups in the incidences of blood transfusion and complications. Overall, the current findings suggest that topical TXA has a poor effect on blood preservation compared with intravenous TXA. This is consistent with the conclusions of Cao et al. [38].

Xiong et al. analyzed eight RCTs on nondeformity spinal surgery, finding no differences between topical and intravenous TXA in blood loss, HCT, Hb, fibrinogen, prothrombin time, partial thromboplastin time, drainage volume, or transfusion rate [39]. Our study included two studies of patients with spinal deformities. The large degree of trauma and bleeding in surgery for spinal deformities may be the reason for the different conclusions of these two studies. However, another important factor is that the studies included by Xiong et al. were all published by Chinese scholars [39]; therefore, there may have been publication bias. Although topical TXA is less effective than intravenous TXA in the hem sparing effect, studies have shown that topical TXA has a high efficacy in reducing blood loss and drainage volume compared with patients who did not receive TXA, and enables a rapid recovery with a high safety profile in spinal surgery [40].

Limitations

Our study has several limitations. First, it included only six studies (5 RCTs and 1 retrospective study), each with a small sample size, which may limit the statistical power and generalizability. Second, high heterogeneity was observed in the analyses of IBL, TBL, and day 3 Hb values, likely due to variations in patient populations, surgical techniques, TXA doses, or other factors. Third, publication bias could not be assessed due to fewer than 10 studies. Fourth, differences in TXA administration methods (e.g., injection [36], irrigation [29, 35], soaked sponges [37]) and doses across studies may impact the consistency and interpretation of the results. Considering that only six studies were included, we were limited in our ability to conduct subgroup analyses based on the dosage and use of TXA to explore the impact of different doses and use on bleeding control. Therefore, future research should further investigate the optimal dosage and administration methods of TXA to enhance its effectiveness in spinal surgery. Fifth, participant differences across studies may introduce heterogeneity, bias, and limit generalization, impacting the interpretation and applicability of pooled results. This requires carefully statistical analysis to ensure confidence and clinical utility. Varying TXA doses can affect outcomes, needing careful consideration. Due to the small number of studies, subpopulation analysis was not possible. Future research focusing on consistent TXA doses or regimens may provide more robust conclusions.

Conclusions

On the basis of the current evidence, topical TXA was not found to significantly reduce postoperative blood loss compared with intravenous TXA. However, the safety of topical TXA was confirmed without increasing the associated risk of blood clots. Although topical TXA does not achieve the same efficacy as intravenous TXA, it still reduces bleeding compared with no TXA. However, heterogeneity was observed between studies, with outcomes varying across study types. Future research should explore the effects of TXA in diverse populations and surgical procedures to better understand its role and applicability in spinal surgery.

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Author contributions
HL and CXX conceptualized the study; HL, CXX, GPC and LWZ performed the selection, data extraction, and risk of bias assessment; HL performed the statistical analysis and drafted the manuscript; PW and CXX provided critical appraisal of the manuscript. YWS helped revised the manuscript.All authors reviewed and agreed on the final version of the manuscript.

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

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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