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SPINE

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

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- *Purpose*: This study aimed to assess the effects of topical tranexamic acid (tTXA) in spinal surgery to provide reliable clinical evidence for its usefulness.
- *Methods*: The PubMed, EMBASE, Medline, and Cochrane Central Register of Controlled Trials databases were comprehensively searched to identify randomized controlled trials and non-randomized controlled trials evaluating the effect of tTXA on blood loss during spine surgery. The observation indexes were intraoperative blood loss, total blood loss, output and duration of postoperative drainage, postoperative hematological variables, length of postoperative hospital stay, blood transfusion rate, and complication rate.
- *Results*: A total of 21 studies involving 1774 patients were included. Our results showed that the use of tTXA during spinal surgery significantly reduced the total blood loss, postoperative drainage volume, postoperative transfusion rate, duration of postoperative drainage, and postoperative hospital stay, and increased the serum hemoglobin concentration, thereby providing better clinical outcomes for surgical patients. However, tTXA had no effect on intraoperative blood loss and associated complications.
- *Conclusion*: On the basis of the available evidence, the present results provide strong clinical evidence of the clinical value of tTXA in spinal surgery and provide an important reference for future research and clinical decision-making.

Keywords: blood loss; hematological parameters; spinal surgery; tranexamic acid

Introduction

Spinal surgery necessitates the peeling of soft tissues such as muscles from around the vertebral bodies, while fusion surgery also necessitates the opening of the laminae and removal of the intervertebral discs from the affected spaces. Therefore, spinal surgeries cause a lot of bleeding and it is critical to address this intra- and post-operative bleeding.

Tranexamic acid (TXA) is a synthetic lysine derivative that competitively inhibits plasminogen adsorption on

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fibrin and activation of plasminogen by binding to the lysine binding site of plasminogen so that fibrin is not degraded by plasmin, thus achieving anti-fibrinolytic and hemostatic effects (1, 2). In recent years, many studies have reported that the use of TXA reduces perioperative bleeding and allogeneic blood transfusion and can be administered orally, intravenously, or topically to achieve hemostasis (3, 4, 5). Clinically, an intravenous drip is usually used. However, administering TXA via the intravenous route has certain disadvantages: if the onset of action is not timely, the drug may gather in the surgical and traumatic areas and have a hemostatic effect after a period of time, which may even increase the incidence of venous thrombosis due to its antifibrinolytic effect in blood vessels (6, 7, 8); intravenous TXA is also associated with rare systemic adverse effects, such as visual disturbances, orthostatic symptoms, headache, and myoclonus (9). Therefore, it may be better to use topical TXA (tTXA) than intravenous TXA, and the advantages of tTXA have been demonstrated in other types of surgery such as hip replacement, knee replacement, and thoracic surgery (10, 11, 12).

Studies have produced inconsistent results on whether tTXA reduces the amount of bleeding during spinal surgery. Some randomized controlled trials (RCTs) and non-RCTs claim that tTXA reduces blood loss (13,14, 15). However, tTXA has also been shown to have no significant effect on reducing blood loss (16). In addition, there is no consensus on the amount of postoperative bleeding, potential risk of thrombosis, and optimal dose of tTXA.

Meta-analysis is an effective way to summarize published high-quality comparative cohort studies. High-quality RCTs are still considered the most reliable type of comparative study. However, previous meta-analyses of studies evaluating tTXA in spinal surgery have had statistical methodological limitations as they combined results from RCTs and non-RCTs, which could lead to heterogeneity, methodological differences, bias, confounding, and problems with the interpretation of results, and thus did not truly reflect the outcome measures (17, 18, 19, 20, 21). Therefore, to resolve the controversy regarding the effectiveness of tTXA, we conducted the present analysis to comprehensively evaluate the efficacy and safety of tTXA in spinal surgery.

Methods

The study conforms to the principles outlined in the Handbook of the Cochrane Collaboration (22), along with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (23). The protocol for this meta-analysis was registered on PROSPERO (registration no. CRD 42023461986).

Inclusion criteria

Study type: RCTs or non-RCTs. Study population: patients underwent cervical, thoracic, or lumbar spinal surgeries irrespective of the anterior or posterior approach. Intervention and control: topical TXA (without intravenous TXA) in the treatment group, without TXA used in the control group. Outcome index: intraoperative blood loss (IBL), output and duration of postoperative drainage, total blood loss (TBL), postoperative hospital stay, postoperative blood parameters, postoperative blood transfusions, and complications.

Exclusion criteria

Case reports, reviews, or republished studies; outcome indicators do not include the abovementioned main indicators and those with incomplete data; studies lacking a control group; patients with a past medical history of coagulopathy, bleeding disorders, blood clots, and motor disease; articles with no original data, statistical errors, vague data, or diagnosis and treatment that do not meet the requirements.

Search strategy

To identify the published articles on spine surgery and tTXA delivery, an exhaustive literature search of PubMed, EMBASE, Web of Science (Medline), and the Cochrane Central Register of Controlled Trials was performed from the inception dates to September 01, 2023, using the keywords ‘Intravenous’, ‘topical’, ‘intrawound’, ‘tranexamic acid’, ‘TXA’, and ‘spinal’. No language restrictions were applied during the search.

Study selection

Two researchers individually screened the retrieved literature strictly against inclusion and exclusion criteria. If two researchers do not agree during the literature screening process, it will be left to the senior researcher.

Data collection process

Data on relevant outcome measures were extracted from the literature that met the inclusion criteria, including: author year, study design type, country, sample size, participants, TXA treatment, age, outcomes, etc.

Assessment of risk of bias and quality of evidence

Two researchers independently assessed the quality of all included trials based on Cochrane risk-of-bias criteria (24). The Newcastle–Ottawa scale was used to evaluate the literature quality of the retrospective studies (25).

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Statistical analysis

The meta-analysis was performed using Stata (version 17; StataCorp, 2021) software. The heterogeneity was assessed by using the *Q* test and I^2 value calculation. Given the clinical heterogeneity, the random effects model was used. The odds ratio (OR) and its associated 95% CI were used to assess dichotomous outcomes. Continuous outcomes were analyzed using mean, S.D., and sample size to provide a standard mean difference (SMD) or mean difference (MD) between the tTXA and control groups. A *P*-value less than 0.05 suggested that the difference was statistically significant.

Sensitivity analyses

We performed a sensitivity analysis by excluding the largest trial; excluding cluster randomized or quasi-randomized trials; excluding trials with high risk of bias; using random-effect models.

Results

Our comprehensive search using the abovementioned search strategy identified 419 articles. Fourteen of these articles met the inclusion and exclusion criteria and were included (5, 13, 14, 15, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35), and a further seven studies were identified from previous meta-analyses (36, 37, 38, 39, 40, 41, 42), resulting in a total of 21 studies included in our meta-analysis (Table 1). The included studies comprised 14 RCTs and seven non-RCTs, with a total of 1774 patients. As the study by Saberi *et al.* (35) compared patients with segmental fusion and two-segment fusion, we divided the study into two studies. The studies by Arun-Kumar *et al.* (27), Chen *et al.* (28), Liang *et al.* (38), and Zheng *et al.* (42) had two treatment groups, which we combined to create a single pairwise comparison, as recommended by the Cochrane Handbook. In the RCTs, the percentages of women in the intervention and control groups were 33–69% and 29–60%, respectively; in the non-RCTs, the percentages of men in the exposure and non-exposure groups were 35–80% and 20–55%, respectively. In the RCTs, the mean age was 35.6–69 years in the TXA group and 32.7–66 years in the control group. In the non-RCTs that reported the patients' ages, the mean age was 51.1–66.1 years in the TXA group and 53.5–66.3 years in the control group. The literature screening process is shown in Fig. 1. The basic characteristics of the included studies are shown in Tables 1 and 2.

Intraoperative blood loss

In total, 11 RCTs and six non-RCTs had sufficient data to analyze the IBL (5, 14, 15, 26, 27, 28, 29, 30, 31, 32, 33, 34, 36, 38, 39, 41, 42). Using a random-effects model, there was no statistically significant difference in IBL between the tTXA and control groups in the RCTs (MD: −28.08, 95% CI: −56.85 to 0.69, $I^2 = 80.9\%$, $P = 0.056$; Table 3). The combined analysis of the non-RCTs also showed no difference in IBL between the two groups (MD: −73.32, 95% CI: −150.77 to 4.13, $I^2 = 94.2\%$, $P = 0.064$; Table 3).

Total blood loss

Three RCTs and four non-RCTs reported the TBL (5, 26, 28, 29, 31, 32, 41). The analysis of the RCTs showed that tTXA significantly reduced the TBL (MD: −182.27, 95% CI: −284.54 to −80.01, $I^2 = 76.1\%$, $P < 0.001$; Table 3). In the non-RCTs, tTXA was also effective in reducing the TBL relative to the control group (MD: −214.75, 95% CI: −304.91 to −124.59, $I^2 = 63.1\%$, $P < 0.001$; Table 3).

Postoperative drainage volume

In total,16 studies reported the postoperative drainage volume, including ten RCTs and six non-RCTs (5, 13, 15, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42). tTXA significantly reduced the postoperative drainage volume compared with controls in both the RCTs (MD: −128.83, 95% CI: −171.18 to −86.48, $I^2 = 95.8\%$, $P < 0.001$; Table 3) and non-RCTs (MD: −117.36, 95% CI: −155.23 to −79.49, $I^2 = 83.0\%$, $P < 0.001$; Table 3).

Duration of postoperative drainage

Four RCTs and five non-RCTs described the duration of postoperative drainage (5, 13, 28, 29, 31, 32, 33, 38, 39). As the units of measurement varied between studies, we used the SMD as the statistical effect size. Meta-analysis showed that tTXA significantly reduced the duration of postoperative drainage in the RCTs (SMD: −0.77, 95% CI: −1.01 to −0.52, $I^2 = 0\%$, $P < 0.001$; Table 3) and non-RCTs (SMD: −2.0, 95% CI: −3.18 to −0.82, $I^2 = 96.2\%$, $P = 0.001$; Table 3).

Postoperative hospital stay

Mu *et al.* (39) and Shen *et al.* (31) both mentioned the length of hospital stay, but neither specified whether they evaluated the total length of hospital stay or the length of postoperative hospital stay; therefore, these two studies were excluded from the analysis of postoperative hospital stay. Three RCTs and three non-RCTs reported the length of postoperative hospital stay (14, 15, 28, 29, 33, 41). In the RCTs, tTXA reduced the length of postoperative hospital stay (MD: −1.04, 95% CI: −1.76 to −0.32, $I^2 = 90.5\%$, $P = 0.005$; Table 3). However, in the non-RCTs, tTXA did not shorten the postoperative hospital stay (MD: −0.99, 95% CI: −2.18 to 0.21, $I^2 = 94.9\%$, $P = 0.106$; Table 3).

Table 1 Characteristics of the population included in the studies.

				Participants, *n*		Age		BMI	
Study	**Country**	**Time period**	**Design**	**TXA**	**Control**	**TXA**	**Control**	**TXA**	**Control**
Arun kumar *et al.* (27)	India	2017.10–2018.08	RCT		26		50.8 ± 3.4		27.6 ± 1.4
Cohort 1				26		51.9 ± 2.8		25.6 ± 2.1	
Cohort 2				26		48.0 ± 2.3		26.1 ± 1.9	
El-sharkawi *et al.* (36)	Egypt	2011–2014	RCT	31	23	17 ± 4		49 ± 6	
Chen *et al.* (28)	China	2018.07–2021.07	RCS		45		65.12 ± 8.72		21.37 ± 2.27
Cohort 1				44		64.43 ± 8.68		22.14 ± 1.90	
Cohort 2				44		63.82 ± 9.43		21.44 ± 2.18	
Emrah *et al.* (13)	Turkey	2019.01–2020.08	RCS	26	26	63.0 (59.0–68.3)	63.5 (53.5–67.0)	29.6 (27.2–31.4)	30.0 (28.4–33.8)
Farzanegan *et al.* (14)	Iran	NA	RCT	54	54	51.39 ± 12.77	54.8 ± 14.04	26.57 ± 4.18	26.56 ± 5.44
Jiang *et al.* (26)	China	2020.07–2021.03	RCT	45	45	58.9 ± 10.7	59.7 ± 12.5	23.0 ± 1.2	23.3 ± 1.4
Khadivi *et al.* (15)	Iran	2018–2020	RCS	48	40	51.1 ± 11.0	53.5 ± 13.7	28.3 ± 5.3	28.6 ± 5.7
Krohn *et al.* (37)	Norway	NA	RCT	16	14	NA	NA	NA	NA
Liang *et al.* (38)	China	2013.05–2015.12	RCT	30	30	51.13 ± 10.72	53.83 ± 11.23	26.2 ± 4.41	24.9 ± 5.3
Liang *et al.* (29)	China	2015.12–2017.12	RCS		20		67.9 ± 5.33		25.35 ± 3.6
Cohort 1				20		66.1 ± 8.8		24.87 ± 3.46	
Cohort 2				20		59.75 ± 6.95		26.06 ± 2.74	
Mallepally *et al.* (30)	India	2017.11–2018.10	RCS	175	75	55.3 ± 12.8	56.9 ± 13.4	24.4 ± 2.31	24.3 ± 2.09
Mu *et al.* (39)	China	2015.09–2017.08	RCT	39	42	51.77 ± 8.13	52.57 ± 6.73	24.72 ± 1.82	23.93 ± 1.35
Ren *et al.* (5)	China	2014.09–2016.09	RCCS	50	50	55.2 ± 13.0	58.7 ± 12.9	25.7 ± 2.8	25.1 ± 3.1
Saberi *et al.* (35)	Iran	NA	RCT	25	25			NA	NA
Study 1						35.6 ± 9.73	32.72 ± 8.31		
Study 2						49.96 ± 4	46.68 ± 5.36		
Shen *et al.* (31)	China	2017.10–2019.05	RCT	39	37	38.85 ± 4.17	39.41 ± 6.51	26.3 ± 2.32	25.63 ± 2.43
Shi *et al.* (32)	China	2018.12–2019.12	RCS	60	60	64.77 ± 7.22	66.33 ± 6.78	24.36 ± 3.43	24.53 ± 3.18
Sudprasert *et al.* (33)	Thailand	2015.05–2016.09	RCT	29	28	52 (33.5–55.5)	51.5 (33.5–58.0)	22.2 ± 3.3	22.3 ± 3.2
Wood *et al.* (40)	USA	NA	RCT	12	17	69 (62–72)	66 (50–73)	NA	NA
Xu *et al.* (34)	China	2013.11–2016.10	RCT	40	40	53.1 ± 12	57.4 ± 10.7	25.6 ± 2.8	24.9 ± 3.9
Xu *et al.* (41)	China	2013.11–2017.04	RCT	30	30	49.6 ± 12.8	50.6 ± 16.2	25.3 ± 3.0	25.7 ± 3.0
Zheng *et al.* (42)	China	2017.10–2018.10	RCT		24		54.6 ± 10.0		NA
Cohort 1				24		56.2 ± 6.6		NA	
Cohort 2				24		57.2 ± 5.7		NA	

NA, not applicable; RCCS, retrospective case-control study; RCS, retrospective cohort study; RCT, randomized controlled trial.

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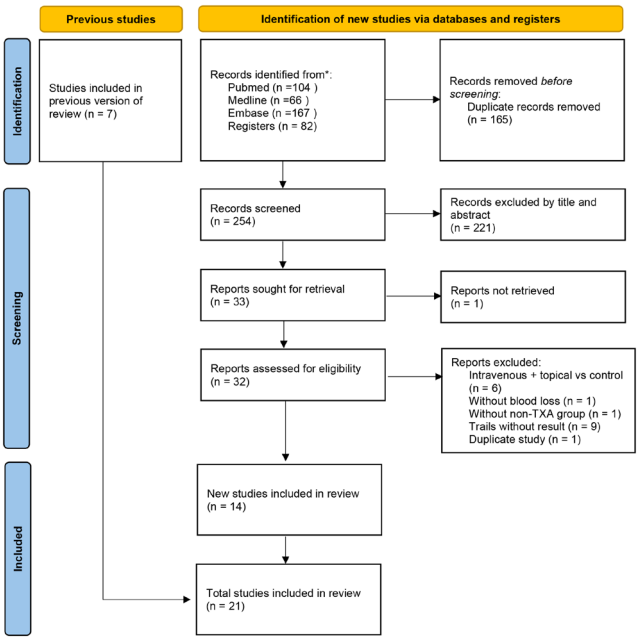

Figure 1

Flow diagram for search and selection of included studies.

Hematological variables at 1 and 3 days after surgery

The details of the hematological test results are shown in Table 3. The pooled results showed that the hemoglobin concentration on postoperative days 1 and 3 and the hematocrit (HCT) value on postoperative day 3 were significantly higher in the tTXA group than the control group in both the RCTs and non-RCTs. The HCT value on postoperative day 1 did not significantly differ between the two groups in the RCTs. In the non-RCTs, the HCT values were higher in the tTXA group than the control group. There were no significant differences between the two groups in the platelet count (PT) on postoperative days 1 and 3.

Postoperative blood transfusions

In total, six RCTs and five non-RCTs reported comparisons of postoperative blood transfusions (5, 13, 15, 27, 28, 29, 31, 34, 38, 39, 41). Among the non-RCTs, the studies by Chen *et al.* (28) and Ren *et al.* (5) did not have any postoperative blood transfusion events in either group, and were thus excluded from the statistical calculations. In the RCTs, the transfusion rate was significantly reduced in the tTXA group compared with the control group (OR: 0.34, 95% CI: 0.21 to 0.57, $I^2 = 0\%$, $P < 0.001$; Table 2). Similarly, in the non-RCTs, the postoperative transfusion rate was significantly reduced in the tTXA group compared with the control group (OR: 0.36, 95% CI: 0.16 to 0.83, $I^2 = 0\%$, $P = 0.017$; Table 3).

Complications

A total of 13 studies reported the occurrence of related complications (5, 13, 14, 26, 28, 29, 31, 32, 33, 34, 38, 41, 42). Eleven of these studies reported no complications in either group and were excluded from the statistical calculations (5, 13, 26, 28, 29, 31, 33, 34, 38, 41, 42), leaving only one RCT and one non-RCT (14, 32). There was no difference in the incidence of complications between the two groups (Table 3).

Sensitivity analysis

The remaining studies were combined when any individual study was excluded. No individual study had a significant impact on the results.

Risk of bias

The funnel plots of IBL (Fig. 2A), postoperative drainage volume (Fig. 2B) and postoperative blood transfusions (Fig. 2C) indicated a certain deviation, showing that small sample sizes or publication bias may be the leading cause of bias. As for other outcomes, fewer than 10 trials were included, and no publication bias assessment was performed by funnel plots.

Discussion

We conducted a comprehensive literature search that retrieved 419 articles, of which 21 studies (14 RCTs and 7 non-RCTs) with 1774 patients were included in this systematic review and meta-analysis. According to the available evidence, the use of tTXA in spinal surgery effectively reduces the TBL, postoperative drainage volume, duration of postoperative drainage, and postoperative blood transfusion rate, without affecting the PT and related complications. However, the RCTs showed that tTXA reduced the length of hospital stay after surgery, while the non-RCTs showed no difference in the length of postoperative hospital stay between the tTXA and control groups; this inconsistency may be due to insufficient testing power. Furthermore, tTXA had no significant effect on intraoperative bleeding. As tTXA was used near the end of surgery in most studies, the tTXA would theoretically have a limited effect on the IBL. The main effect of tTXA is to reduce the postoperative drainage volume, which ultimately achieves the purpose of reducing the TBL. The study by Arun-Kumar *et al.* (27) included four groups: preoperative intravenous TXA, preoperative local infiltration of TXA in the paravertebral muscles at the incision, tTXA before closing the incision, and control. Their results suggest that local infiltration of the paravertebral muscles with TXA before surgery significantly reduces the IBL (27). However, more research is needed to further demonstrate the efficacy and safety of preoperative tTXA at the incision site. In addition, the postoperative hemoglobin and

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Table 2 Indications for tranexamic use, dosage, and outcomes reported in the included studies.

Study	Indication	Treatment with TXA	Outcomes
Arun kumar *et al.* (27)	Lumbar surgery		IBL, volume of drainage, blood transfusion, postoperative hospital stay, and hematological parameters
Cohort 1		1 g TXA soaked into wound	
Cohort 2		1 g TXA injected into paraspinal muscles before surgery	
El-sharkawi *et al.* (36)	Spinal deformities	TXA soaked with sponge	IBL
Chen *et al.* (28)	Degenerative cervical myelopathy		IBL, volume and length of drainage, postoperative hospital stay, hematological parameters, postoperative complications, and blood transfusion
Cohort 1		1g TXA soaked with sponge	
Cohort 2		1 g of TXA injected into wound.	
Emrah *et al.* (13)	Thoracolumbar fusion	1 g TXA soaked into wound	Volume and length of drainage, blood transfusion, complications, and postoperative hospital stay
Farzanegan *et al.* (14)	Lumbar surgery	3 g TXA for washing and soaking	IBL, complications, length of hospitalization
Jiang *et al.* (26)	Lumbar surgery	TXA injected into muscle	IBL, TBL, hematological parameters, complications
Khadivi *et al.* (15)	Cervical surgery	3 g TXA for irrigation	IBL, volume of drainage, blood transfusion, length of hospital stay
Krohn *et al.* (37)	Lumbar surgery	0.5 g TXA soaked into wound	Volume of drainage
Liang *et al.* (38)	Lumbar surgery	2g TXA soaked with sponge	IBL, volume and length of drainage, blood transfusion, complications, and hematological parameters
Liang *et al.* (29)	Lumbar surgery		IBL, TBL, volume and length of drainage, blood transfusion, complications, and hematological parameters
Cohort 1		1 g of TXA injected into wound	
Cohort 2		1g TXA soaked with sponge	
Mallepally *et al.* (30)	Lumbar surgery	1 g TXA soaked into wound	IBL, volume and length of drainage, hematological parameters
Mu *et al.* (39)	Lumbar surgery	1g TXA soaked with sponge	IBL, volume and length of drainage, blood tranfusion, hospital stay, and hematological parameters
Ren *et al.* (5)	Lumbar surgery	1 g TXA soaked into wound	Volume and length of drainage, blood transfusion, length of hospital stay, complications
Saberi *et al.* (35)*	Spine trauma and degenerative diseases	0.25 g TXA soaked into wound	Volume of drainage
Shen *et al.* (31)	Thoracolumbar fracture	1 g TXA soaked into wound	TBL, IBL, volume and length of drainage, hematological parameters, hospital stay, blood transfusion, complications
Shi *et al.* (32)	Lumbar surgery	1 g TXA soaked into wound	IBL, TBL, volume and length of drainage, complications, hematological parameters
Sudprasert *et al.* (33)	Thoracolumbar trauma	1 g TXA soaked into wound	IBL, volume and length of drainage, complications
Wood *et al.* (40)	Thoracolumbar stenosis	3 g TXA soaked into wound	Volume of drainage
Xu *et al.* (34)	Spinal degenerative diseases	1 g TXA soaked into wound	IBL, volume of drainage, blood transfusion, complications
Xu *et al.* (41)	Patients with lumbar degenerative disease	1 g TXA soaked into wound	IBL, TBL, volume of drainage, blood transfusion, length of hospital stay, complications
Zheng *et al.* (42)	Thoracolumbar fusion		IBL, hematological parameters, complications
Cohort 1		0.5 g TXA soaked into wound	
Cohort 2		1 g TXA soaked into wound	

*Parameters were the same for both studies.
IBL, intraoperative blood loss; TBL, total blood loss; TXA, tranexamic acid.

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Table 3 Pooled effect size and heterogeneity tests outcomes including IBL, TBL, postoperative drainage, duration of postoperative drainage, postoperative hospital stay, postoperative hematological variables, postoperative blood transfusions, and complications using the random-effects model.

Outcome/study type	Studies, *n*	Effect size (95% CI)	I^2 (%)	*P*-heterogeneity	*P*
IBL					
RCT	11	−28.08 (−56.85, 0.69)	80.9	<0.001	0.056
Non-RCT	6	−73.32 (−150.77, 4.13)	94.2	<0.001	0.064
TBL					
RCT	3	−182.27 (−284.54, −80.01)	76.1	0.015	<0.001
Non-RCT	4	−214.75 (−304.91, −124.59)	63.1	0.043	<0.001
Postoperative drainage					
RCT	10	−128.83 (−171.18, −86.48)	95.8	<0.001	<0.001
Non-RCT	6	−117.36 (−155.23, −79.49)	83.0	<0.001	<0.001
Duration of postoperative drainage					
RCT	4	−0.77 (−1.01, −0.52)	0	0.449	<0.001
Non-RCT	5	−2.0 (−3.18, −0.82)	96.2	<0.001	0.001
Postoperative hospital stay					
RCT	5	−1.04 (−1.76, −0.32)	90.5	<0.001	0.005
Non-RCT	3	−0.99 (−2.18, 0.21)	94.9	<0.001	0.106
HB postoperative 1 day					
RCT	5	0.57 (0.04, 1.11)	83.9	<0.0001	0.036
Non-RCT	3	0.62 (0.37, 0.86)	0	0.718	<0.001
HB postoperative 3 days					
RCT	6	0.54 (0.35, 0.73)	0	0.578	<0.001
Non-RCT	2	0.52 (0.22, 0.82)	0	0.684	0.001
HCT postoperative 1 day					
RCT	4	−0.86 (−8.50, 6.78)	99.5	<0.0001	0.825
Non-RCT	2	2.14 (0.86, 3.42)	0	0.503	0.001
HCT postoperative 3 day					
RCT	5	1.56 (0.27, 2.86)	89.2	<0.0001	0.018
Non-RCT	2	2.81 (1.72, 3.90)	0	0.962	<0.001
PT postoperative 1 day					
RCT	1	−0.33 (−0.66, 0.002)	NA	NA	0.052
Non-RCT	1	−0.24 (−0.52, 0.04)	NA	NA	0.092
PT postoperative 3 day					
RCT	2	0.24 (−0.63, 1.11)	88.2	0.004	0.586
Non-RCT	1	−0.11 (−0.33, 0.11)	NA	NA	0.321
Postoperative blood transfusions					
RCT	6	0.34 (0.21, 0.57)	0	0.593	<0.0001
Non-RCT	3	0.36 (0.16, 0.83)	0	0.406	0.017
Complications					
RCT	1	0.57 (0.22, 1.48)	NA	NA	0.247
Non-RCT	1	0.79 (0.20, 3.08)	NA	NA	0.729

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

HCT values were higher in the tTXA group than in the control group, which further supports the safety of topical use. tTXA avoids the systemic adverse effects caused by intravenous TXA administration under the premise of effective hemostasis, especially in high-risk patients. However, it is important to note that long-term infiltration of TXA in local tissues may lead to damage to fibroblasts, which may delay wound healing. In vitro experiments showed that 100 mg/mL of TXA has no significant effect on fibroblast viability, proliferation, and apoptosis. However, long-term exposure to high concentrations of TXA (> 25 mg/mL) leads to dose- and time-dependent cytotoxicity, affecting fibroblast viability, proliferation, apoptosis, collagen synthesis, adhesion, and migration (43). Thus, the toxic effects of TXA may also impair the ability of fibroblasts to repair when TXA is used topically as a hemostatic agent during surgery. In our study, tTXA did not affect the PT and did not increase the associated risks of thrombosis or wound infection. Overall, the present results show that the use

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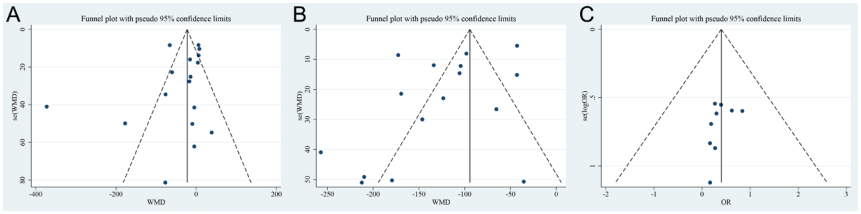

Figure 2

Funnel plot of the included studies in this meta-analysis for intraoperative blood loss (A), postoperative drainage volume (B), and postoperative blood transfusions (C).

of TXA in spinal surgery did not increase the risks of thrombosis or wound infection and may reduce the TBL and transfusion rate, which has important clinical value in specific settings. However, larger RCTs are needed to validate these results.

A meta-analysis of three RCTs and one non-RCT published in 2018 found that tTXA significantly reduces the TBL, postoperative drainage, and length of hospital stay but found no significant differences between tTXA and controls in postoperative transfusion and complication rates (20). In addition, meta-analyses of six studies (18) and 13 studies (19) consistently showed that tTXA significantly reduces the postoperative drainage volume and drainage time, negative blood loss, TBL, and length of hospital stay without increasing the risks of associated complications or IBL. However, it is worth noting that these meta-analyses had duplicate inclusions of the two studies by Ren *et al.* (5, 44). Given that the two studies had the same data and authorship and a similar study span and writing style, the repeated publication may have artificially increased the effectiveness of tTXA. Therefore, the meta-analysis by Yerneni *et al.* (21) included only one of the studies by Ren *et al.* (5). In addition, Fatima *et al.* (17) conducted a meta-analysis of the efficacy of TXA in surgical patients with spinal deformities, as such patients have greater surgical trauma and blood loss than those undergoing general spinal surgery. Their findings suggest that tTXA reduces postoperative bleeding, drainage, operative time, length of hospital stay, and transfusion needs and maintains postoperative hemoglobin levels (17). However, compared with the control group, tTXA does not appear to affect the IBL and the occurrence of complications (17). It is important to note that these meta-analyses included patients who received intravenous TXA, which may have influenced the assessment of the results to some extent. Furthermore, the results of RCTs and non-RCTs were combined in the abovementioned meta-analyses, and there was statistical uncertainty. Bao *et al.* (45) conducted a meta-analysis of relevant RCTs published from 2016 to 2019. However, although they claimed that their meta-analysis analyzed patients undergoing spinal surgery, the included articles were actually inconsistent with spinal surgery; therefore, the article has been retracted. The meta-analysis by Hui *et al.* (19) included the largest number of articles, covering a total of 13 studies. Our study differed in that we pooled a total of 21 studies and comprehensively analyzed the effects of TXA from all aspects, including blood loss, hematological variables, drainage time, and complications. Our study is therefore the most comprehensive study to date to evaluate the effects of tTXA in spinal surgery. Although our findings are broadly consistent with previous meta-analyses, our study has some methodological and analytical advantages that further support the use of tTXA in spinal surgery.

Strengths and limitations

This meta-analysis included 21 studies with a total of 1774 participants. This large overall sample size substantially enhanced the statistical power of our data analysis and provided more reliable estimates than a single study. One of the clear advantages of our study is the comparison of RCTs with non-RCTs. This approach ensures that the potential risk of bias is effectively reduced when assessing the effects of TXA. The separate analysis of these two types of studies further strengthened the confidence in the conclusions, especially when both analyses yielded similar results, providing readers with clearer and more convincing conclusions.

Our study also had certain limitations. First, most of the results were obtained under conditions of high heterogeneity. This high heterogeneity suggests that there may be significant differences between studies, possibly due to different patient populations, surgical procedures, TXA doses, methods of TXA use, publication bias, or other unknown factors. Second, there were differences in the dose and method of use of TXA in different studies. For example, Wood *et al.* (40) injected 3 g of TXA around the wound, Liang *et al.* (29) used 2 g of TXA, and other studies used 1 g of TXA. In addition, some studies applied tTXA by irrigation, while others used soaked sponges, and some used local injection. This means that our analysis may be affected by multiple TXA doses and regimens, which may affect the consistency and interpretability of the results. Third, there were differences between the participants in the different studies, which may have introduced limitations in terms of heterogeneity, bias, and generalization. These differences may affect the interpretation and applicability of the results of pooled analyses, and therefore require more rigorous statistical analysis and interpretation to ensure confidence and clinical utility. In addition, the criteria for postoperative drainage removal and blood transfusion varied across studies. Despite these limitations, our study provides strong evidence for the role of tTXA in spinal surgery. However, more research is needed to confirm our findings and address these limitations.

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Conclusion

This meta-analysis provides strong evidence to support the clinical use of tTXA in spinal surgery to reduce bleeding and transfusion rates and shorten the postoperative hospital stay. These results have important implications for guiding the clinical practice and future research direction of spinal surgery. However, to gain a more complete picture of the efficacy and safety of tTXA, we encourage the performance of more RCTs and further exploration of best practices for the dose and application method.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Author contribution statement
HL conceived the study. XY developed the research protocol. GC and YR performed the literature search. XZ and CX screened titles and abstracts, and reviewed full texts. LW performed data abstraction. HL prepared the first manuscript draft. All authors contributed to final edits and revisions prior to submission.

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