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Role of tranexamic acid in blood loss control and blood transfusion management of patients undergoing multilevel spine surgery

A meta-analysis

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Abstract

Background: This study aimed to explore the role of tranexamic acid (TXA) in blood loss control and blood transfusion management of patients undergoing multilevel spine surgery.

Methods: In this meta-analysis, a comprehensive search of literatures was performed from PubMed, Embase, Cochrane Library, and Web of Science from inception to June 23rd, 2020. Weighed mean difference (WMD) was used as the effect size for measurement data, and risk ratio for enumeration data. Publication bias was assessed by Begg test.

Results: Totally 23 studies (11 randomized controlled trials and 12 cohort studies) involving 1621 participants were enrolled in this meta-analysis. The results showed that the administration of TXA can significantly decrease the intraoperative [WMD: –215.655, 95% CI: (–307.462, –123.847), $P < .001$], postoperative [WMD: –69.213, 95%CI: (–104.443, –33.983), $P = .001$] and total [WMD: –284.388, 95%CI: (–437.66, –131.116), $P < .001$] volumes of blood loss of patients undergoing multilevel spine surgery. It can also significantly reduce the intraoperative [WMD: –333.775, 95%CI: (–540.45, –127.099), $P = .002$] and postoperative [WMD: –114.661, 95%CI: (–219.58, –9.742), $P = .032$] volumes of transfusion. In addition, TXA was found to significantly increase the preoperative [WMD: 0.213, 95%CI: (0.037, 0.389), $P = .018$] and postoperative [WMD: 0.433, 95%CI: (0.244, 0.622), $P < .001$] hemoglobin levels as well as the preoperative platelet count [WMD: 14.069, 95%CI: (0.122, 28.015), $P = .048$].

Conclusion: The administration of TXA can effectively reduce blood loss and transfusion, and improve hemoglobin levels and preoperative platelet count in patients undergoing multilevel spine surgery.

Abbreviations: RR = risk ratio, TXA = tranexamic acid, WMD = weighed mean difference.

Keywords: blood loss, blood transfusion, multilevel spine surgery, tranexamic acid

1. Introduction

Tranexamic acid (TXA) is a synthetic lysine analogue that acts as an effective inhibitor of fibrinolysis.[1] By reversibly blocking the lysine binding sites of plasminogen, TXA can prevent its activation to plasmin and therefore stop the lysis of polymerized fibrin.[2] Recently, TXA has shown its effectiveness in reducing perioperative blood loss in many surgeries, such as cardiac surgery,[3] oral surgery,[4] and urological surgery,[5,6] without significant increases in adverse events. In addition, TXA can also effectively reduce blood loss and transfusion requirements during orthopedic surgery, most commonly in knee and hip joint replacement.[7–9]

Spine surgery, especially multilevel spine surgery, is associated with large blood loss and requires blood transfusion in most cases. Extensive blood loss can lead to adverse effects, such as pulmonary or cerebral edema, shock, etc.[10] It has been proven that both low-dose and high-dose administration of TXA can effectively control blood loss and decrease blood transfusion in multilevel spine surgery.[11–13] However, Farrokhi et al found that the low-dose administration of TXA before surgery did not have a significant effect on the management of blood loss and transfusion requirements in patients undergoing multilevel spine surgery.[14] Furthermore, Colimina et al discovered that TXA did not significantly reduce transfusion requirements, but significantly reduced perioperative blood loss in major spinal surgery.[15]

Although a lot of studies have demonstrated the role of TXA in multilevel spinal surgery, there still exists inconsistency. Thus, a meta-analysis was performed to figure out the role of TXA in blood loss control and blood transfusion management of patients undergoing multilevel spine surgery.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

In a study such as meta-analysis, the Institutional Review Board's approval or the informed consent are not required. Our study was performed documented according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Attachment 1). The supplementary material describes the methods of this study in detail.

2.1. Search strategies

Literatures were retrieved from PubMed, Embase, Cochrane Library, and Web of Science from inception to June 23rd, 2020. The index words for searching literatures were as follows: "tranexamic acid" OR "TXA" AND "major spine surgery" OR "scoliosis" OR "multiple-level" OR "multiple levels" OR "complex spine surgery".

2.2. Eligibility criteria

Inclusion criteria:

1. randomized controlled trials (RCTs) or cohort studies;
2. studies involving patients who underwent multilevel spine surgery;
3. patients treated with TXA as the TXA group, and patients treated with placebo or without TXA as the control group;
4. English literatures.

Exclusion criteria:

1. meta-analysis, reviews, case reports, conference abstracts, reporting guidelines, or animal studies;
2. patients undergoing single-level spine surgery;
3. patients with abnormalities in bleeding dialysis and prothrombin time, partial thromboplastin time, or platelet counts;
4. patients with a history of hemorrhagic disease or thromboembolism;
5. patients with severe heart or respiratory disease, and renal or liver dysfunction;
6. patients allergic to TXA.

2.3. Data extraction and methodological quality appraisal

Two researchers (Yibo Zhao, Chunyang Xi) reviewed the identified literatures and extracted the research data according to inclusion and exclusion criteria. If a discrepancy existed, a third party (Wenxiao Xu) would participate in the extraction of data. The items were extracted below, including the first author, country, year of publication, study design, age, dosage, as well as medication method (Table 1).

The quality of 12 literatures of cohort studies was assessed using the revised Newcastle-Ottawa Scale. The scale was divided into 10 points, where <5 was defined as low or moderate quality and ≥5 was defined as high quality. The quality of 11 literatures of RCT studies was evaluated by the modified Jadad scale. The scale was divided into 7 points, where <4 was defined as low or moderate quality and ≥4 was defined as high quality.

2.4. Statistical analysis

Heterogeneity test was conducted for each indicator and measured by I^2 statistics. If $I^2 \geq 50\%$, the random effects model was applied; if $I^2 < 50\%$, the fixed effects model was used. Sensitivity analysis was performed for all models and publication bias was detected by Begg test for model study with ≥9 combined literatures. The subgroup analysis was performed by dosage (low-dose/high-dose) and medication method (sustained/intermittent) when there is high heterogeneity. The Stata 15.0 software (Stata Corporation, College Station, TX) was used for statistical analysis. Weighed mean difference (WMD) was used as the effect size for measurement data, and risk ratio (RR) for enumeration data. $P < .05$ was considered statistically significant.

3. Results

3.1. Literature search and study characteristics

Initially, 468 potential literatures were identified through database search, leaving 352 literatures after removing duplicates. These literatures were then screened by researchers through reading the titles and abstracts, after which full-text screening was performed for the remaining 68 literatures. Finally, 23 literatures were enrolled for this meta-analysis. The flow chart of literature search is shown in Figure 1.

A total of 1621 participants (TXA group: n=852, control group: n=769) were enrolled in 23 studies, including 11 RCTs (TXA group: n=349, control group: n=345)[11,14–23] and 12 cohort studies (TXA group: n=503, control group: n=424).[10,12,13,24–32] According to Newcastle-Ottawa Scale, 12 cohort studies were all of high quality; according to Jadad scale, 6 of 11 RCTs were evaluated as high quality, while 5 as low or moderate quality. The basic characteristics and specific indicators of enrolled studies are summarized in Table 1.

3.2. Meta-analysis outcomes

3.2.1. Intraoperative volume of blood loss. The intraoperative volume of blood loss was analyzed in 15 studies (n=1067), including 6 RCTs (n=384) [WMD: –171.812, 95%CI: (–324.976, –18.647)] and 9 cohort studies (n=683) [WMD: –257.953, 95%CI: (–443.196, –72.71)]. The results showed that the intraoperative volume of blood loss in the TXA group (n=574) was significantly lower than that in the control group (n=493) [WMD: –215.655, 95%CI: (–307.462, –123.847), $P < .001$] (Table 2, Fig. 2A).

The heterogeneity test after merging studies showed statistically significant difference ($I^2 = 87.8\%$), so subgroup analysis was performed based on dosage and medication method. The results showed that the intraoperative volumes of blood loss both in the low-dose and high-dose TXA groups were significantly lower than those in the control groups [low-dose group: WMD: –154.073, 95%CI: (–249.593, –58.553), $P = .002$; high-dose group: WMD: –340.82, 95%CI: (–527.02, –154.62), $P < .001$] (Table 2, Fig. 2B). In addition, the intraoperative volume of blood loss was significantly lower in the TXA group than that in the control group in terms of sustained medication [WMD: –240.443, 95%CI: (–377.298, –103.589), $P = .001$], while there was no significant difference between the 2 groups when medicated intermittently [WMD: –147.104, 95%CI: (–382.480, 88.271), $P = .221$] (Table 2, Fig. 2C).

3.2.2. Postoperative volume of blood loss. A total of 6 studies (n=453) were enrolled, including 3 RCTs (n=188) [WMD: –74.568, 95%CI: (–132.614, –16.522)] and 3 cohort studies (n=265) [WMD: –63.995, 95%CI: (–134.972, 6.981)], to investigate the postoperative volume of blood loss. It was shown that the

Table 1

Extracted data of included literatures.

Author	Year	Country	Design	Group	Total	Age, yr	Levels fused	Dosage	Medication	Score	Dosage and dose of tranexamic acid in surgery
Neilipovitz[16]	2001	Canada	RCT	TXA	22	14.1 ± 2.1	14 (8–17)	LD	Sustained	3	Initial dose of 10 mg/kg and a maintenance infusion of 1 mg/kg/h
				Placebo	18	13.7 ± 2.5	15 (7–18)				
Sethna[17]	2005	USA	RCT	TXA	23	13.6 ± 1.8	14 (9–16)	HD	Sustained	4	Receive 100 mg/kg before incision followed by an infusion of 10 mg/kg/h during surgery
				Placebo	21	14.0 ± 2.0	13 (7–18)				
Shapiro[24]	2007	USA	Cohort	TXA	20	13.9 (10.8–17)	14.7 (13–16)	HD	Intermittent	7	TXA dose of 100 mg/kg intravenously over 15 min after induction of anesthesia before incision followed by an infusion of 10 mg/kg/h during surgery until skin closure
				Control	36	14.0 (9.6–18)	14.3 (13–16)				
Baldus[25]	2010	USA	Cohort	TXA	20	54.6 ± 10	7.6 ± 4.0	LD	Sustained	8	Intravenous loading dosage of 10 mg/kg and a maintenance dosage of 0.5 mg/kg/h
				Control	10	55.2 ± 11	7.5 ± 3.0				
Endres[26]	2011	Germany	Cohort	TXA	46	67 ± 10.5		HD	Intermittent	7	Receive 1 g TXA intravenously preoperatively (60 min before surgery), 6 h and 12 h after surgery
				Control	51	69 ± 9.8					
Farrokhi[14]	2011	Iran	RCT	TXA	38	45.5 ± 11.6		LD	Sustained	3	Dosage of 10 mg/kg at initiation of induction of anesthesia and a maintenance dosage of 1 mg/kg/h
				Placebo	38	51.4 ± 11.6					
Yagi[27]	2012	Japan	Cohort	TXA	43	15.2 ± 2.9	12.1 ± 1.4	HD	Sustained	6	Loading TXA dose of 1 g followed immediately by a maintenance dose of 100 mg/h
				Control	63	15.5 ± 3.0	12.2 ± 1.3				
Wang[18]	2013	China	RCT	TXA	30	63.1 ± 4.0		LD	Intermittent	4	Receive a dosage of 15 mg/kg intravenously over 15 min before skin incision
				Placebo	30	62.0 ± 4.6					
Halanski[19]	2014	USA	RCT	TXA	22	13.2 (12.4–14.1)	10.5 (8.8–12.1)*	HD	Sustained	7	Loading dose of 100 mg/kg, which was to be given once over 30 min at the beginning of the operative procedure and a maintenance infusion of 10 mg/kg/h
				Control	25	13.9 (13.1–14.6)	10.4 (9.0–11.8)				
da Rocha[28]	2015	Brazil	Cohort	TXA	21	18.0 ± 4.4	9.4 ± 2.2	HD	Sustained	6	Receive 100 mg/kg within 30 min before skin incision and a maintenance infusion of 30 mg/kg/h
				Control	19	21.6 ± 8.0	9.2 ± 2.3				
Ng[29]	2015	China	Cohort	TXA	55	15.16 ± 2.61	13.51 ± 1.62	HD	Sustained	7	Initial dose of 100 mg/kg and a maintenance infusion of 10 mg/kg/h
				Control	35	15.31 ± 2.97	12.14 ± 2.79				
Peters[20]	2015	USA	RCT	TXA	19	60	11	LD	Sustained	6	Loading dose of 10 mg/kg, followed by a maintenance dose of 1/mg/kg/h
				Placebo	13	43	13				
Raksakietisak[21]	2015	Thailand	RCT	TXA	39	52.6 ± 12.8		LD	Intermittent	7	Dosage of 15 mg/kg over 20 min before induction of anesthesia; 15 mg/kg 3 h later
				Placebo	39	53.1 ± 11.7					
Xie[12]	2015	China	Cohort	TXA	26	18.9 ± 9.0	13 ± 3	HD	Sustained	8	Loading dose at 100 mg/kg within 20 min before skin incision, followed by a continuous infusion of 10 mg/kg/h until skin closure
				Control	33	18.6 ± 7.7	12 ± 4				
Choi[10]	2017	Korea	Cohort	TXA	89	53.15 ± 24.75	9.38 ± 2.91	LD	Sustained	8	Loading dosage of 10 mg/kg and maintenance dose of 1 mg/kg/h
				Control	43	59.40 ± 21.91	9.81 ± 3.54				
Colomina[15]	2017	Spain	RCT	TXA	44	59.2 (20–75)	5.5 (4–9)	LD	Sustained	3	Infusion of 10 mg/kg TXA and maintenance dose of 2 mg/kg/h
				Placebo	51	50.8 (18–75)	6 (3–11)				
Jones[30]	2017	USA	Cohort	TXA	18	16.1 ± 3.1	10.5 ± 2.2	LD	Sustained	7	Loading dosage of 10 mg/kg and maintenance dose of 1 mg/kg/h
				Control	18	15.2 ± 3.4	9.6 ± 2.0				
Yu[31]	2017	China	Cohort	TXA	73	64.40 ± 9.13		LD	Sustained	7	Receive a dose of 15 mg/kg of TXA and maintenance dose of 100 mg/h
				Control	46	63.70 ± 8.85					
Shakeri[22]	2018	Iran	RCT	TXA	25	50.52 ± 6.51		LD	Intermittent	3	Receive single TXA dose of 15 mg/kg intravenously
				Placebo	25	49.12 ± 9.12					
Carabini[11]	2018	USA	RCT	TXA	31	65 (62–69)	10 (9–16)	LD	Sustained	6	Loading dosage of 10 mg/kg and maintenance dose of 1 mg/kg/h
				Placebo	30	68 (62–72)	15.5 (10–16)				

(*continued*)

Table 1

(continued).

Author	Year	Country	Design	Group	Total	Age, yr	Levels fused	Dosage	Medication	Score	Dosage and dose of tranexamic acid in surgery
Goobie[23]	2018	USA	RCT	TXA	56	14.9 ± 2.0	10 (5–13)	HD	Sustained	3	Loading dosage of 50 mg/kg and maintenance dose of 10 mg/kg/h
				Placebo	55	14.7 ± 1.8	9 (5–13)				
Xue[32]	2018	China	Cohort	TXA	20	53.41 ± 7.93	4.18 ± 1.01	LD	Sustained	8	Receive an intravenous infusion of 15 mg/kg 15 min before surgery and maintenance dose of 1 mg/kg/h
				Control	22	55.10 ± 8.43	4.25 ± 1.12				
Pernik[13]	2019	USA	Cohort	TXA	71	66.5 ± 9.70	9.2 ± 3.41	LD	Sustained	6	Loading dosage of 10 mg/kg and maintenance dose of 1 mg/kg/h
				Control	48	69.2 ± 9.10	8.1 ± 2.78				

HD = high-dose (>15 mg/kg), LD = low-dose (≤15 mg/kg), RCT = randomized controlled trial, TXA = tranexamic acid.

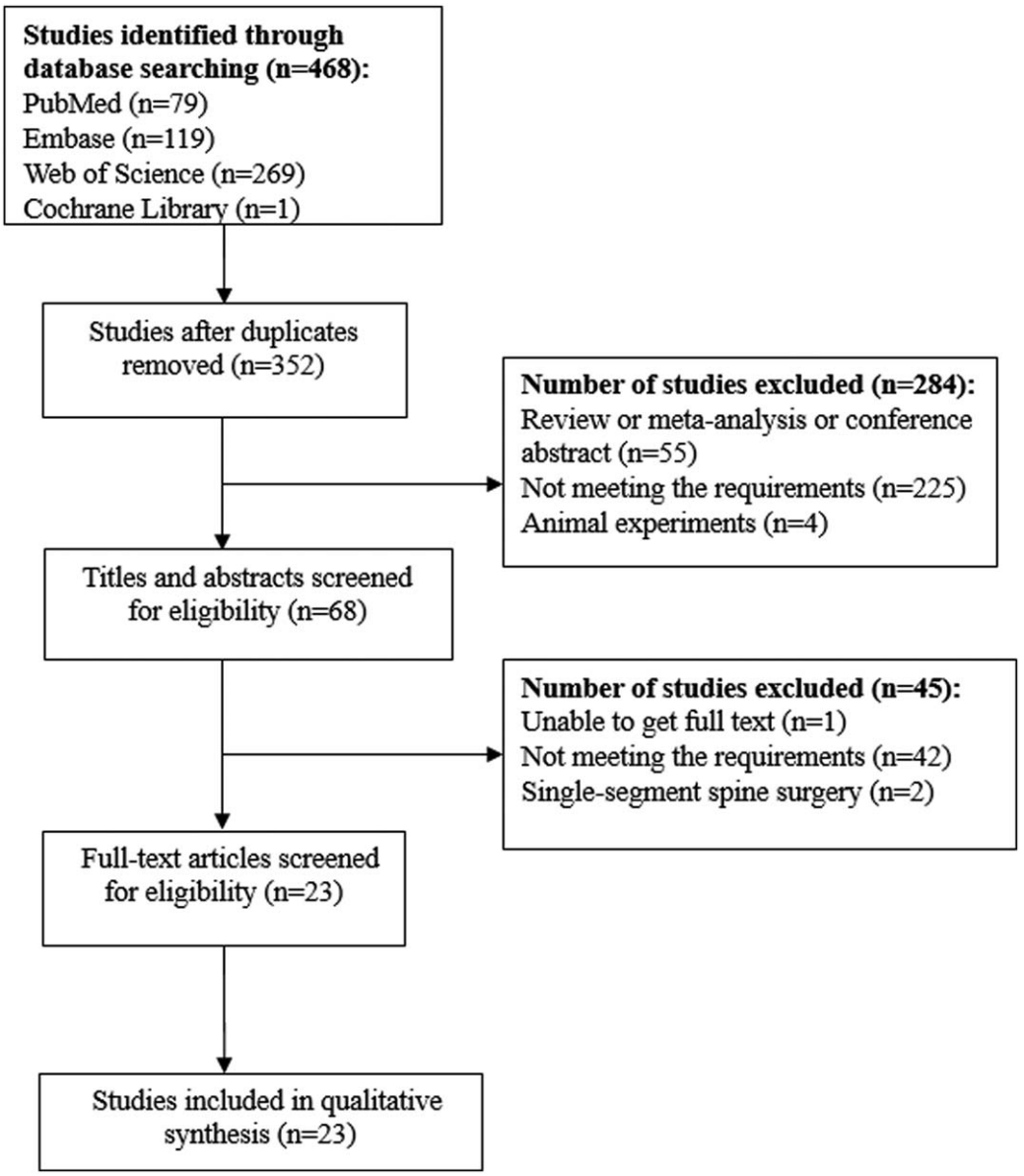

Figure 1. The flow chart of literature search.

Table 2

Results of various indicators.

Indicator	WMD/RR (95%CI)	P	I^2
Intraoperative volume of blood loss			
Overall	−215.655 (−307.462, −123.847)	<.001	87.8
Design			
RCT	−171.812 (−324.976, −18.647)	.025	90.0
Cohort	−257.953 (−443.196, −72.71)	.006	87.1
Dosage			
Low-dose	−154.073 (−249.593, −58.553)	.002	86.4
High-dose	−340.82 (−527.02, −154.62)	<.001	70.1
Medication			
Sustained	−240.443 (−377.298, −103.589)	0.001	81.5
Intermittent	−147.104 (−382.480, 88.271)	.221	97.8
Postoperative volume of blood loss			
Overall	−69.213 (−104.443, −33.983)	.001	94.0
Design			
RCT	−74.568 (−132.614, −16.522)	.012	97.0
Cohort	−63.995 (−134.972, 6.981)	.077	87.7
Dosage			
Low-dose	−60.677 (−99.985, −21.368)	.002	95.8
High-dose	−105.359 (−140.835, −69.883)	<.001	0.0
Medication			
Sustained	−63.995 (−134.972, 6.981)	.077	87.7
Intermittent	−74.568 (−132.614, −16.522)	.012	97.0
Total volume of blood loss			
Overall	−284.388 (−437.66, −131.116)	<.001	84.0
Design			
RCT	−423.441 (−921.121, 74.240)	.095	67.6
Cohort	−463.585 (−864.829, −62.341)	.024	88.2
Dosage			
Low-dose	−127.008 (−199.314, −54.702)	.001	51.0
High-dose	−1094.84 (−1845.04, −344.650)	.004	87.7
Medication			
Sustained	−373.105 (−731.656, −14.553)	.041	85.6
Intermittent	−641.682 (−1500, 214.693)	.142	85.3
Intraoperative rate of transfusion			
Overall	0.879 (0.767, 1.007)	.063	49.4
Design			
RCT	0.789 (0.289, 2.149)	.642	71.1
Cohort	0.902 (0.798, 1.019)	.097	27.3
Postoperative rate of transfusion			
Overall	0.901 (0.746, 1.087)	.276	0.0
Design			
RCT	0.878 (0.488, 1.579)	.663	37.3
Cohort	0.905 (0.746, 1.098)	.312	0.0
Perioperative volume of transfusion			
Overall	−217.042 (−579.274, 145.191)	.240	66.3
Dosage			
Low-dose	−188.766 (−777.636, 400.103)	.530	77.3
High-dose	−325.000 (−685.062, 35.062)	.077	NA
Intraoperative volume of transfusion			
Overall	−333.775 (−540.45, −127.099)	.002	65.1
Design			
RCT	−553.000 (−1100, 40.760)	.068	NA
Cohort	−314.092 (−532.783, −95.401)	.005	68.6
Dosage			
Low-dose	−251.078 (−705.689, 203.532)	.279	66.3
High-dose	−410.235 (−722.993, −97.476)	.010	72.3
Medication			
Sustained	−310.733 (−551.999, −69.467)	.012	63.4
Intermittent	−443.000 (−694.548, −191.452)	.001	NA
Postoperative volume of transfusion			
Overall	−114.661 (−219.58, −9.742)	.032	0.0
Preoperative hemoglobin			

(*continued*)

Table 2

(continued).

Indicator	WMD/RR (95%CI)	*P*	I^2
Overall	0.213 (0.037, 0.389)	.018	0.0
Design			
RCT	0.127 (–0.276, 0.530)	.538	0.0
Cohort	0.234 (0.037, 0.430)	.020	0.0
Postoperative hemoglobin			
Overall	0.433 (0.244, 0.622)	<.001	17.4
Design			
RCT	0.555 (0.137, 0.973)	.009	0.0
Cohort	0.401 (0.189, 0.613)	<.001	40.3
Preoperative platelet			
Overall			
Cohort	–12.170 (–39.830, 15.490)	.388	NA
RCT	14.069 (0.122, 28.015)	.048	0.0
Postoperative platelet			
Overall			
Cohort	–22.540 (–46.465, 1.385)	.065	NA
RCT	13.669 (–5.744, 33.082)	.168	53.0
Dosage			
Low-dose	15.138 (0.263, 30.013)	.046	0.0
High-dose	11.598 (–48.181, 71.376)	.704	84.0

*Note: RCT = randomized controlled trial, WMD: weighed mean difference, RR = risk ratio, CI = confidence interval, NA = not applicable.

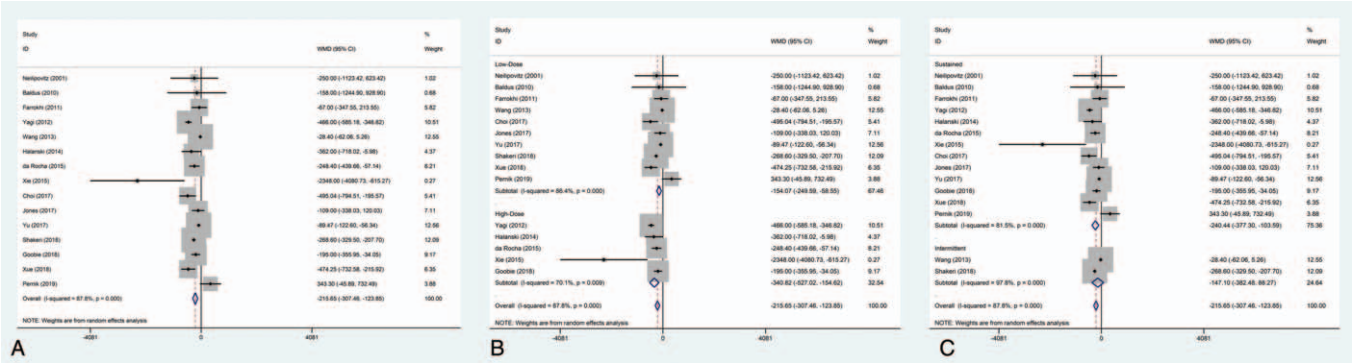

Figure 2. A–C: Forest plots for intraoperative volume of blood loss: (A) overall analysis; (B) subgroup analysis based on dosage; (C) subgroup analysis based on medication method.

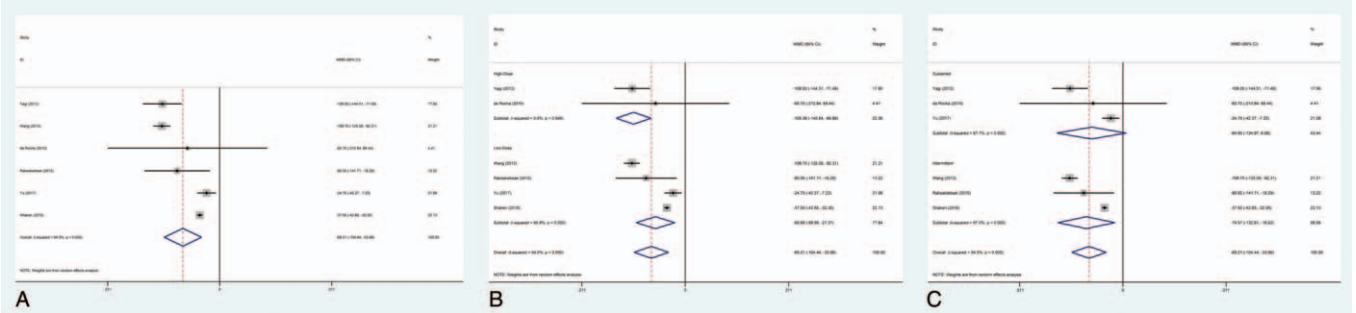

Figure 3. A–C: Forest plots for postoperative volume of blood loss: (A) overall analysis; (B) subgroup analysis based on dosage; (C) subgroup analysis based on medication method.

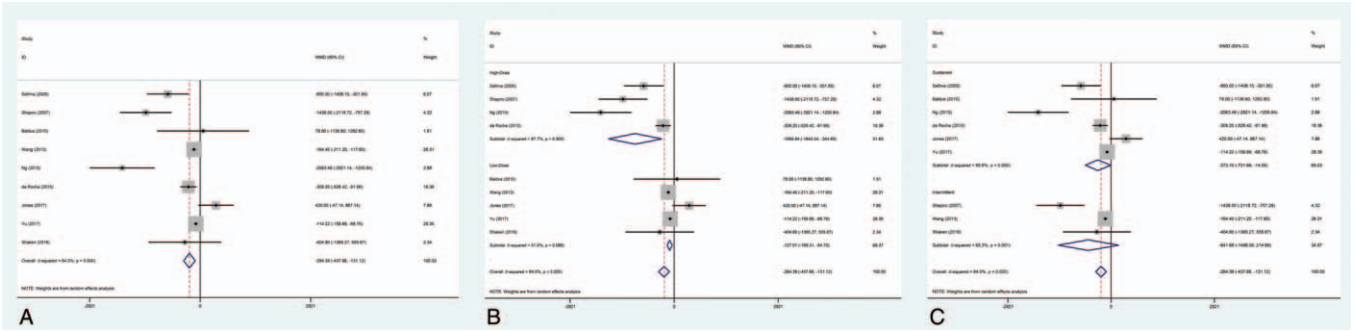

Figure 4. A–C: Forest plots for total volume of blood loss: (A) overall analysis; (B) subgroup analysis based on dosage; (C) subgroup analysis based on medication method.

postoperative volume of blood loss in the TXA group (n = 231) was significantly lower than that in the control group (n = 222) [WMD: –69.213, 95%CI: (–104.443, –33.983), $P = .001$] (Table 2, Fig. 3A).

Due to significant heterogeneity after merging studies ($I^2 = 94.0\%$), subgroup analysis according to dosage and medication method was carried out. The results indicated that the postoperative volumes of blood loss both in the low-dose and high-dose TXA groups were significantly lower than those in the control groups [low-dose group: WMD: –60.677, 95%CI: (–99.985, –21.368), $P = .002$; high-dose group: WMD: –105.359, 95%CI: (–140.835, –69.883), $P < .001$] (Table 2, Fig. 3B). Moreover, the postoperative volume of blood loss in the TXA group was significantly lower than that in the control group in terms of intermittent medication [WMD: –74.568, 95%CI: (–132.614, –16.522), $P = .012$], while no significant difference was found in postoperative volume of blood loss between the 2 groups when medicated continuously [WMD: –63.995, 95%CI: (–134.972, 6.981), $P = .077$] (Table 2, Fig. 3C).

3.2.3. Total volume of blood loss. There were 9 studies (n = 525) involving 3 RCTs (n = 154) [WMD: –423.441, 95%CI: (–921.121, 74.240)] and 6 cohort studies (n = 371) [WMD: –463.585, 95%CI: (–864.829, –62.341)] in total volume of blood loss. The results suggested that the total volume of blood loss in the TXA group (n = 285) was significantly lower than that in the control group (n = 240) [WMD: –284.388, 95%CI: (–437.66, –131.116), $P < .001$] (Table 2, Fig. 4A).

Because the significant heterogeneity existed after merging studies ($I^2 = 84.0\%$), subgroup analysis based on dosage and medication method was conducted. The results indicated that the total volumes of blood loss both in the low-dose and high-dose TXA group were significantly lower than those in the control groups [low-dose group: WMD: –127.008, 95%CI: (–199.314, –54.702), $P = .001$; high-dose group: WMD: –1094.84, 95%CI: (–1845.04, –344.650), $P = .004$] (Table 2, Fig. 4B). Additionally, the total volume of blood loss in the TXA group was significantly lower as compared with the control group in terms of sustained medication [WMD: –373.105, 95%CI: (–731.656, –14.553), $P = .041$] (Table 2, Fig. 4C), while there was no statistically significant difference in total volume of blood loss between the 2 groups when medicated intermittently [WMD: –641.682, 95% CI: (–1500, 214.693), $P = .142$] (Table 2).

3.2.4. Intraoperative rate of transfusion. The intraoperative rate of transfusion was identified in 5 studies (n = 408) containing 3 RCTs (n = 157) [RR: 0.789, 95%CI: (0.289, 2.149)] and 2 cohort studies (n = 251) [RR: 0.902, 95%CI: (0.798, 1.019)]. After merging studies, no significant heterogeneity was detected ($I^2 = 49.4\%$). Through the fixed-effect model, there was no significant difference in intraoperative transfusion rate between the TXA group (n = 240) and the control group (n = 168) [RR: 0.879, 95%CI: (0.767, 1.007), $P = .063$] (Table 2).

3.2.5. Postoperative rate of transfusion. A total of 6 studies (n = 519) including 3 RCTs (n = 171) [RR: 0.878, 95%CI: (0.488, 1.579)] and 3 cohort studies (n = 348) [RR: 0.905, 95%CI: (0.746, 1.098)] were enrolled to investigate the postoperative rate of transfusion, and no significant heterogeneity after merging studies was presented ($I^2 = 0.0\%$). The fixed-effect model

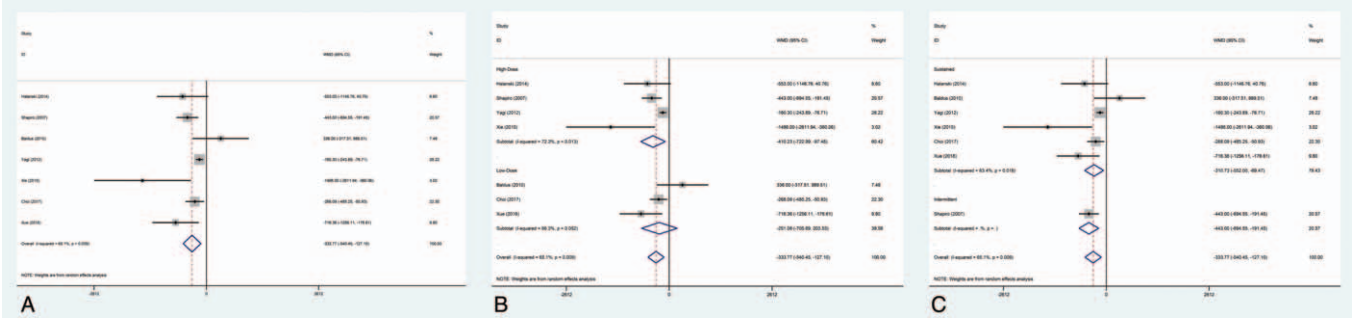

Figure 5. A–C: Forest plots for intraoperative volume of transfusion: (A) overall analysis; (B) subgroup analysis based on dosage; (C) subgroup analysis based on medication method.

exhibited that no significant difference was found in postoperative transfusion rate between the TXA group (n = 295) and the control group (n = 224) [RR: 0.901, 95%CI: (0.746, 1.087), $P = .276$] (Table 2).

3.2.6. Perioperative volume of transfusion. There were 3 RCTs (n = 160) on perioperative volume of transfusion. The results revealed that there was no significant difference in perioperative volume of transfusion between the TXA group (n = 83) and the control group (n = 77) [WMD: –217.042, 95%CI: (–579.274, 145.191), $P = .240$].

For significant heterogeneity after merging studies ($I^2 = 66.3\%$), subgroup analysis based on dosage was performed. The results showed that no statistically significant difference was found in perioperative volume of transfusion between the low-dose TXA group and the control group [WMD: –188.766, 95% CI: (–777.636, 400.103), $P = .530$], so did between the high-dose group and the control group [WMD: –325.000, 95%CI: (–685.062, 35.062), $P = .077$] (Table 2).

3.2.7. Intraoperative volume of transfusion. Totally 7 studies (n = 472) involving 1 RCT (n = 47) [WMD: –533.000, 95%CI: (–1100, 40.760)] and 6 cohort studies (n = 425) [WMD: –314.092, 95%CI: (–532.783, –95.401)] were included in the analysis of intraoperative volume of transfusion. The intraoperative volume of transfusion in the TXA group (n = 240) was found significantly lower as compared with the control group (n = 232) [WMD: –333.775, 95%CI: (–540.45, –127.099), $P = .002$] (Table 2, Fig. 5A).

The significant heterogeneity was presented after merging studies ($I^2 = 65.1\%$), so the subgroup analysis was carried out based on dosage and medication method. The results revealed that there was no statistically significant difference in the intraoperative volume of transfusion between the low-dose TXA group and the control group [WMD: –251.078, 95%CI: (–705.689, 203.532), $P = .279$], while the volume in the high-dose group was significantly lower than that in the control group [WMD: –410.235, 95%CI: (–722.993, –97.476), $P = .010$] (Table 2, Fig. 5B). Moreover, the intraoperative volumes of transfusion in the TXA group was significantly lower than that in the control group in terms of both sustained and intermittent medication group [sustained medication group: WMD: –310.733, 95%CI: (–551.999, –69.467), $P = .012$; intermittent medication group: WMD: –443.000, 95%CI: (–694.548, –191.452), $P = .001$] (Table 2, Fig. 5C).

3.2.8. Postoperative volume of transfusion. There were 2 cohort studies (n = 172) on postoperative volume of transfusion, and there was no significant heterogeneity after merging studies ($I^2 = 0.0\%$). According to the fixed-effect model, the postoperative transfusion volume in the TXA group (n = 110) was significantly lower than that in the control group (n = 62) [WMD: –114.661, 95%CI: (–219.58, –9.742), $P = .032$] (Table 2).

3.2.9. Preoperative hemoglobin. A total of 9 studies (n = 843) containing 3 RCTs (n = 211) [WMD: 0.127, 95%CI: (–0.276, 0.530)] and 6 cohort studies (n = 632) [WMD: 0.234, 95%CI: (0.037, 0.430)] were included in investigating the preoperative hemoglobin. After merging studies, there was no significant heterogeneity ($I^2 = 0.0\%$). The results showed that the preoperative hemoglobin in the TXA group (n = 452) was significantly higher than that in the control group (n = 391) [WMD: 0.213, 95%CI: (0.037, 0.389), $P = .018$] (Table 2, Fig. 6A).

3.2.10. Postoperative hemoglobin. There were 9 studies (n = 843) involving 3 RCTs (n = 211) [WMD: 0.555, 95%CI: (0.137, 0.973)] and 6 cohort studies (n = 632) [WMD: 0.401, 95%CI: (0.189, 0.613)] on hemoglobin 1 day after operation, and no significant heterogeneity was detected after merging studies ($I^2 = 17.4\%$). Through the fixed-effect model, the postoperative hemoglobin in the TXA group (n = 452) was significantly higher than that in the control group (n = 391) [WMD: 0.433, 95%CI: (0.244, 0.622), $P < .001$] (Table 2, Fig. 6B).

3.2.11. Preoperative platelet. A total of 5 studies (n = 359) including 4 RCTs (n = 262) [WMD: 14.069, 95%CI: (0.122, 28.015)] and 1 cohort study (n = 97) [WMD: –12.170, 95%CI: (–39.830, 15.490)] (Table 2) were enrolled, and no significant heterogeneity was found after merging studies ($I^2 = 0.0\%$). According to the fixed-effect model, the preoperative platelet in the TXA group (n = 173) was significantly higher than that in

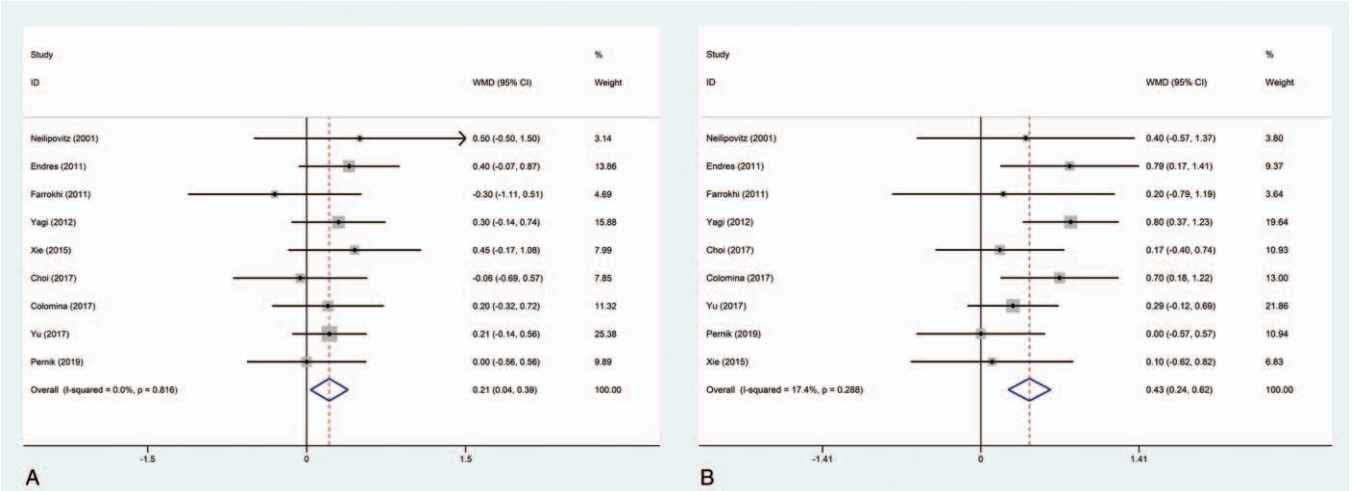

Figure 6. A-B: Forest plots for hemoglobin: (A) preoperative; (B) postoperative.

the control group (n=186) [WMD: 14.069, 95%CI: (0.122, 28.015), P=.048] (Table 2).

3.2.12. Postoperative platelet. There were 5 studies (n=359) involving 4 RCTs (n=262) [WMD: 13.669, 95%CI: (–5.744, 33.082)] and 1 cohort study (n=97) [WMD: –22.540, 95%CI: (–46.465, 1.385)] (Table 2) on platelet 1 day after operation. The results revealed that there was no significant difference in the postoperative platelet between the TXA group (n=173) and the control group (n=186) [WMD: 13.669, 95%CI: (–5.744, 33.082), P=.168].

The significant heterogeneity was detected after merging studies (I^2=53.0%), so the subgroup analysis based on dosage was carried out. The results showed that the postoperative platelet in the low-dose TXA group was significantly higher than that in the control group [WMD: 15.138, 95%CI: (0.263, 30.013), P=.046], while there was no significant difference in postoperative platelet between the high-dose TXA group and the control group [WMD: 11.598, 95%CI: (–48.181, 71.376), P=.704] (Table 2).

3.3. Publication bias assessment

Begg test was used for the assessment of publication bias, and the results showed that there was no publication bias in intraoperative volume of blood loss (Z=0.10, P=.921), total volume of blood loss (Z=0.73, P=.466), preoperative hemoglobin (Z=0.94, P=.348), and postoperative hemoglobin (Z=0.10, P=.914).

4. Discussion

In this meta-analysis, we performed a comprehensive search of literatures from a variety of databases to explore the role of TXA in multilevel spine surgery. A total of 23 studies involving 1621 participants were enrolled. The results indicated that the application of TXA in multilevel spine surgery can play a positive role in decreasing the volumes of blood loss and transfusion both intraoperatively and postoperatively, but not in transfusion rate and perioperative volume of transfusion. Moreover, TXA can effectively improve the preoperative and postoperative hemoglobin levels as well as postoperative platelet counts. These results were in accordance with most TXA-related studies and meta-analyses.

A lot of studies have demonstrated that the application of TXA can effectively reduce intraoperative blood loss and transfusion requirements in spine surgery, especially in multilevel spine surgery.[10,24,33] Wong et al reported significantly less blood loss in the TXA group as compared with the control group.[33] Similarly, Shapiro et al found a significant reduction in intraoperative blood loss in patients treated with TXA.[24] The same result was found in another study, which indicated that the use of TXA can effectively reduce the surgical bleeding. Besides, Choi also discovered that postoperative blood loss tended to be lower in the TXA group, but this difference was not statistically significant.[10] However, some other researchers demonstrated a significant difference in postoperative blood loss. Neilipovitz et al showed that postoperative bleeding was significantly lower in the TXA group as compared with the control group.[16] After analysis, the main reason may be lie in the fact that the participants enrolled in his study were adolescents aged from 9 to 18 years old, while the age range of our participants was from 9 to 80 years old. Additionally, various characteristics were incorporated in our analysis. To the best of our knowledge, the results can be affected by many baseline characteristics, such as age, gender, medical history, etc.

In addition to the intraoperative and postoperative blood loss, the transfusion volume was also considered as an indicator for analyzing the effect of TXA. Xie et al reported that the TXA group showed significantly less blood transfusion requirement compared to the control group. And they also found that high-dose TXA was effective in reducing blood transfusion without adverse drug reactions.[12] It was suggested that high-dose TXA was more effective than low doses. The study by Shapiro et al demonstrated that the transfusion requirement was significantly lower when the patients were treated with high doses of TXA.[24] Consistent with these findings, our study showed that the volume of perioperative blood transfusion in high-dose TXA group was significantly lower than that in the control group, while not the low-dose.

Pre- and post-operative parameters such as hemoglobin levels and platelet counts were also compared between the TXA group and the control group. Plenty of studies showed no significant difference in hemoglobin levels between the TXA group and the control group.[10,27,31] However, these results were not in line with ours. According to our data, the preoperative and postoperative hemoglobin levels were all significantly higher compared to the controls. Similar result was found in the study by Endres et al, which discovered that the postoperative hemoglobin concentration demonstrated a statistically significant difference showing superiority for TXA use.[26] The platelet count is another indicator that we adopted for assessing the TXA effect. The studies have found that there was no significant difference in preoperative platelet count between the TXA group and the control group.[15,27] Farrokhi et al also demonstrated that the platelet count in the TXA group was higher than the control group, but this difference was not statistically significant.[14] However, the study by Sethna et al suggested that the platelet count was significantly higher preoperatively in the TXA group as compared with the control group,[17] which was in accordance with our study.

A strength of our study was that there were few studies focusing on the effect of TXA on patients undergoing multilevel spine surgery. What's more, our study had a wide age range, which made our results more general. In addition, although there existed significant heterogeneity in some outcomes, we performed subgroup analysis based on dosage and medication method to ensure the accuracy of our results. And no evident publication bias was detected in our study. However, some limitations needed to be concerned. Firstly, only 23 relevant literatures were included in this meta-analysis, of which 5 were determined as low or moderate quality. We should enroll more related high-quality literatures in the future to improve the credibility of our study. Secondly, the sample size under each indicator of the results was variable. The sample sizes of some indicators were limited, which may affect the uniformity of the results.

5. Conclusions

Our current results suggested that TXA can effectively decrease the intraoperative and postoperative volumes of blood loss and transfusion, and maintain better preoperative and postoperative hemoglobin levels as well as preoperative platelet count. However, there was no significant difference in blood transfusion rates, perioperative transfusion volume and postoperative platelet count between the TXA group and the control group.

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Resources: Wenxiao Xu.
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Validation: Wenxiao Xu.
Writing – original draft: Jinglong Yan.
Writing – review & editing: Jinglong Yan.

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