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Systematic Reviews /Meta-analyses

Tranexamic acid dosing strategies and blood loss reduction in multilevel spine surgery: A systematic review and network meta-analysis ☆,☆☆
Tranexamic acid for multilevel spine surgery

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ABSTRACT

Background: For adults undergoing complex, multilevel spinal surgery, tranexamic acid (TXA) is an antifibrinolytic agent used to reduce blood loss. The optimal dosing of intravenous TXA remains unclear. This systematic review and meta-analysis compare various dosing regimens of intravenous TXA used in patients undergoing multilevel spine surgery (≥2 levels).

Methods: PubMed, Cochrane, and EMBASE databases were searched for English language studies published January 2001 through May 2021 reporting use of TXA versus placebo for multilevel spine surgery. Primary outcomes of interest were intraoperative blood loss volume (BLV) and total BLV. A separate random effects model was fit for each outcome measure. Effect sizes were calculated as pooled mean differences (Diff) with corresponding 95% confidence intervals (CIs). Random effects network meta-analyses assessed whether the specific TXA dosing regimen influenced BLV.

Results: Seven studies with 441 patients were included for meta-analysis. Four different TXA dosing regimens were found: 1) 10 mg/kg + 1 mg/kg/h, 2) 10 mg/kg + 2 mg/kg/h, 3) 15 mg/kg, 4) 15 mg/kg + 1 mg/kg/h. Compared to placebo, patients treated with TXA had reduced intraoperative BLV (Diff = -185.0 ml; 95% CI: -302.1, -67.9) and reduced total BLV (Diff = -439.0 ml; 95% CI: -838.5, -39.6). No significant differences in intraoperative BLV among any of the TXA treatment groups was found. Patients given a TXA dose of 15 mg/kg + 1 mg/kg/h had significantly reduced total BLV in comparison to both placebo (Diff = -823.1 ml; 95% CI: -1249.8, -396.4) and a dose of 15 mg/kg (Diff = -581.2; 95% CI: -1106.8, -55.7).

Conclusions: This study found that intravenous TXA is associated with reduced intraoperative and total BLV, but it remains unclear whether there is an optimal TXA dose. Additional trials directly comparing different TXA regimens and administration routes are needed.

Background

Instrumented multilevel spinal surgery (≥2 levels) is a common yet high-risk inpatient procedure performed to treat adult spinal deformity and other spinal pathologies. These surgeries may lead to substantial intraoperative and postoperative blood loss both visible and hidden in dead space, [1, 2] with research showing a significant association between the number of vertebral levels fused and volume of blood lost. [3] Perioperative blood loss in long-segment spinal surgery has been shown to increase hospital stays, procedure costs, and mortality rates [4]; this is partly due to the need for postoperative blood transfusions, with a reported need in as high as 50-80% of patients. [5] A blood transfusion is not a benign treatment and can have an 8- to 10-fold excess risk of adverse outcomes when administered. [6] Adverse effects can be quite severe and include fever, infection, hemolytic reactions, and transfusion-related acute lung injury. [4, 7]

Optimal strategies to decrease blood loss throughout these spinal surgeries are still under investigation and include intraoperative blood salvage, hypotensive anesthesia, and intravenous (IV) hemostatic agents. [2] Tranexamic acid (TXA), an anti-fibrinolytic, has successfully

☆ **Ethical Approval:** No Institutional Review Board or Ethics Committee approval was required for this study.

☆☆ **A short summary sentence:** Tranexamic acid (TXA) is used to reduce blood loss during spine surgery. In this network meta-analysis (including 7 studies, 4 dosing regimens, and 441 total patients), no TXA dosing regimen was clearly superior, highlighting the need for continued trials in this area.

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Table 1
Search Strategy for PubMed, Cochrane, and EMBASE.

Database	Search String
PubMed*	("tranexamic acid" or "txa") and (spine surgery [MESH])
PubMed*	("tranexamic acid" or "txa") and (scoliosis [MESH])
PubMed	("tranexamic acid" or "txa") and ("major spine surgery" or "posterior spine surgery" or "posterior spinal fusion")
Cochrane	("tranexamic acid" or "txa") and (spine surgery)
Cochrane	("tranexamic acid" or "txa") and (scoliosis)
Cochrane	("tranexamic acid" or "txa") and ("major spine surgery" or "posterior spine surgery" or "posterior spinal fusion")
EMBASE**	('tranexamic acid'/exp OR 'tranexamic acid' OR 'txa') AND 'spine surgery'/exp
EMBASE**	('tranexamic acid'/exp OR 'tranexamic acid' OR 'txa') AND 'scoliosis'/exp
EMBASE	("tranexamic acid" or "txa") and (major spine surgery or posterior spine surgery or posterior spinal fusion)

* The addition of [MESH] after a term in a PubMed search returns related MeSH terms.
** The addition of /exp to a term in an EMBASE search returns synonyms of the term.

been in use as a pharmacological intervention to decrease blood loss volume (BLV) throughout surgery when administered either through IV or topically. [2, 8–12] In a large scale review of TXA use in multilevel spine surgery including 23 studies and 1621 patients, Zhao et al. found that TXA significantly reduced both intraoperative BLV (Weighed Mean Difference [WMD]: -215.7 ml; 95% Confidence Interval [CI]: -307.5, -123.8) and total BLV (WMD: -284.4 ml; 95% CI: -437.7, -131.1) [13] when compared to placebo; however, they did not investigate different dosing strategies. The optimal dosing regimen of IV TXA in adult spinal surgeries is still under investigation, with loading doses (LD) ranging from 1.5-15 mg/kg [14, 15] and maintenance doses (MD) ranging 1-2 mg/kg/hour, [16, 17] if a maintenance dose is used at all. [18] Other high dose regimens may involve a single TXA bolus of >1 g. [11] All dosing regimens have been reported to effectively control blood loss and reduce postoperative need for transfusion. [19]

With approximately 1.62 million instrumented spinal procedures occurring annually in the United States, and a projected global market increase to $18 billion by 2023, [20] there is a need for further study into optimal methods of decreasing perioperative blood loss and associated healthcare costs. Here, this study investigates dosing regimens of IV TXA and their effect on intraoperative BLV, total BLV, and other clinical outcomes in adult multilevel spinal surgeries.

Methods

Literature search

A systematic review of the literature compliant with Preferred Reporting Items for Systematic Review and Meta-Analyses checklist (PRISMA) [21] was performed using the PubMed, Cochrane, and EMBASE databases to identify relevant English language articles published between January 1, 2001, and May 24, 2021. Searches were performed using an online platform with literature search functionality and an online article library (AutoLit, Nested-Knowledge, MN). Search strings used in each database are provided in **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria for the qualitative analysis portion of this review stipulated that articles had to report use of IV TXA for multilevel (≥2 levels) spinal surgery in adult patients (≥18 years) and include at least one primary outcome of interest (intraoperative BLV or total BLV). Articles were excluded for the following reasons: not published in English; published before 2001; non-human study (cadaver, animal, *in vitro*); case report, meta-analysis, editorial, or protocol; adolescent or pediatric patients (<18 years) or insufficient age details; single level surgery or insufficient surgical details; non-IV TXA (e.g., topical) or insufficient dose details; at least one primary outcome not reported; not relevant to the study topic; and full text unavailable. For inclusion in the network meta-analysis portion of this review, articles had to describe randomized, placebo-controlled clinical trials evaluating TXA versus placebo, with complete LD and MD information for TXA.

Data collection

Data collected on patient and operation characteristics included: age, sex, and number of vertebral levels fused during spinal surgery, and TXA dose (including LD and MD). Each TXA dosing component was collected as a separate categorical variable nested within the TXA arm. The primary outcomes of interest included for quantitative synthesis were intraoperative BLV and total BLV (defined as intraoperative BLV plus postoperative BLV). Other outcomes collected included blood transfusion rate, length of hospital stay, and operation time.

Risk of bias assessment

The risk of bias and levels of evidence of each study were scored using the Scottish Intercollegiate Guidelines Network (SIGN) checklists for controlled clinical trials and cohort

Studies. [22] For every applicable category of potential risk, each study was rated as having "well addressed," "adequately addressed," "poorly addressed," "not addressed," or "not reported" that specific form of bias. The overall risk of bias for each study was rated as high quality (++), acceptable quality (+), low quality (-), or unacceptable (0); the scoring system also accounts for differences between randomized controlled trials and cohort studies. The risk of bias assessment was completed by two independent reviewers; any disagreements were discussed and resolved by a third reviewer.

Statistical methods

Data was extracted and tracked using the Nested Knowledge platform (Nested Knowledge, St Paul, MN). Where necessary, data was extracted from image data using the 'digitize' package from R. [23] (This occurred for one outcome in one study case, and the authors were contacted to verify the extracted data. [16]) Most studies reported continuous data as means and standard deviations (SDs); however, in cases where medians and interquartile ranges (IQRs) were reported, the statistical methods described by Luo et al. [24] and Wan et al. [25] were employed to estimate means and SDs, respectively. (This procedure was used in two cases. [5, 17]) For each study where data transformation procedures were used, the assumption of normal approximation was validated using methods described by Shi et al. prior to transformation. [26] Data were imported to RStudio (Version 1.3.959, RStudio, PBC, Boston, MA) running on R-4.0.2 for analysis. The 'meta' (Version 4.18-0) and 'metafor' (Version 2.4-0) packages were used to perform meta-analyses. [27, 28]

Effect sizes from each study were computed as pooled mean differences (Diff) with random-effects, inverse-variance weighting. The between-study variance component of random-effects models were estimated using the DerSimonian-Laird [29] procedure with 95% CIs com-

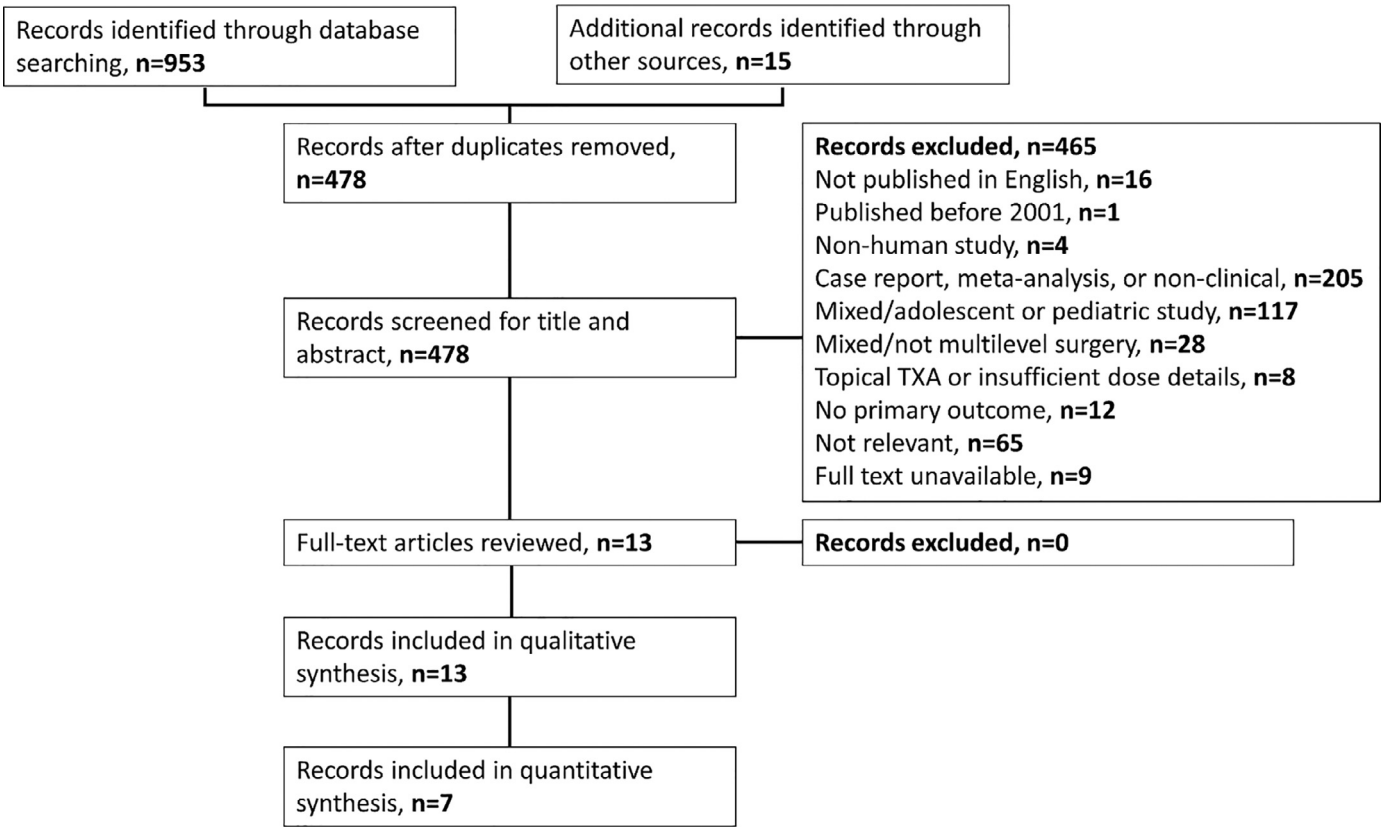


Fig. 1. PRISMA diagram of search records and included studies.

puted using methods described by Jackson. [30] Additionally, 95% prediction intervals (PIs) were also calculated around the pooled mean effect for each outcome measure using methods described by Higgins et al. [31] Effect size data were first collected from each study using 'metacont' in the meta package of R. [27] A random-effects model was incorporated into this general approach using a multivariate adaptation of the **DerSimonian-Laird** procedure [29] proposed by Jackson et al. [32] P-scores were calculated to measure the certainty that one treatment group is better than another treatment group, averaged over all competing treatments.

To evaluate comparisons of BLV between different TXA dosing regimens, separate random-effects network meta-analyses were performed using the R package 'netmeta'. [33] For each aggregated result, Higgin's I^2 statistics were used to measure the percentage of the total variability in effect estimates that can be attributed to heterogeneity rather than sampling error. [34] I^2 values of <25%, 25-75%, and >75% were considered low, moderate, and high between-study variability in effect estimates. The absolute value of the true variance in effect sizes is indicated by τ^2 values in forest plots, which were estimated using the DerSimonian-Laird procedure. [29] An analogue of the Higgin's I^2 statistic [34] described by Harrer et al. was used to measure the amount of inconsistency unrelated to sampling error in each network. [35] I^2 values of <50%, 50-75, and >75% were considered low, moderate, and high levels of heterogeneity, respectively.

Results

Literature search results

The initial database search identified 953 studies, with 15 additional records identified through expert recommendation, for a total of 968. After removing duplicates, 478 articles were screened for inclusion. A total of 465 articles were excluded based on title and abstract review; 13 articles underwent full text review, all of which were included in the review for qualitative synthesis. For quantitative review, 7 studies were included. A diagram of literature search results is shown in **Fig. 1**.

Risk of bias and quality of evidence

Our risk of bias assessment identified 1 RCT of high quality, 6 RCTs of moderate quality, and 6 retrospective cohort studies of moderate quality. The results of our quality appraisal are summarized in **Supplementary Tables I & II**. Of the 13 studies included in this systematic review, 12 studies recommended the use of TXA to reduce BLV; however, of these studies, 3 retrospective cohort studies did not provide adjusted effect size estimates that account for imbalances in important covariates between groups that may impact outcome comparisons. [15, 36, 37] Of note, a high-quality RCT showed that TXA did not reduce intraoperative BLV in comparison to placebo. [38] Another RCT did not find a significant difference between TXA and placebo, but their study was notably underpowered and did not provide justification for the small placebo arm size; they reported a large effect in BLV, so it appears likely that a larger sample would have shown an important difference in outcomes. [16] There were no direct comparisons of the effect of different TXA doses on patient outcomes, only direct comparisons of TXA and placebo.

Summaries of included literature

A full list of studies and patient characteristics are presented in **Table 2**. A total of 870 patients were identified in the 13 included studies, with 456 patients (456/870, 52.4%) receiving TXA and 414 patients (414/870, 47.6%) receiving placebo.

Study-level outcomes are shown in detail in **Table 3**. Mean total BLV was reported most often, with 752 patients (752/870, 86.4%) across 11 studies (11/13, 84.6%) having values reported; for intraoperative BLV, there were 580 total patients (580/870, 66.8%) in 9 stud-

Table 2
Summary of Included Studies and Patient Baseline Characteristics.

Author, Year	TXA LD (mg/kg)	TXA MD (mg/kg/h)	TXA Arm				Placebo Arm			
			Size (N)	Male (n, %)	Age (years)	Levels fused	Size (N)	Male (n, %)	Age (years)	Levels fused
Peters et al., 2015*	10	1	19	-	60, -	11, -	13	-	43, -	13, -
Perez-Roman et al., 2019	10	1	19	12 (63.2)	60 ± 12	6.8 ± 1.2	20	7 (25.0)	65 ± 12	7.2 ± 1.3
Xue et al., 2018	15	1	20	10 (50.0)	53.4 ± 7.9	4.1 ± 1.0	22	11 (50.0)	55.1 ± 8.4	4.3 ± 1.1
Mu et al., 2019*	15	1	45	27 (60.0)	54.2 ± 7.4	2 ± 0	42	23 (54.8)	52.6 ± 6.7	2 ± 0
Shakeri et al., 2018*	15	0	25	12 (48.0)	50.5 ± 6.5	-	25	8 (32.0)	49.1 ± 9.1	-
Carabini et al., 2018*	10	1	31	10 (32.3)	65 (62, 69)	10 (9, 16)	30	9 (30.0)	68 (62, 72)	15.5 (10, 16)
Colomina et al., 2017*	10	2	44	15 (34.1)	59.2 (20, 75)	5.5 (4, 9)	51	13 (25.5)	50.8 (18, 75)	6 (3, 11)
Yu et al., 2017	15	100†	73	62 (84.9)	64.4 ± 9.1	-	46	37 (80.4)	63.7 ± 8.9	-
Pong et al., 2018	10	1	17	10 (58.8)	60.7 ± 15.7	10.8 ± 3.2	17	3 (17.6)	60.9 ± 14.1	10.5 ± 3.0
Farrokhi et al., 2011*	10	1	38	11 (28.9)	45.5 ± 11.6	-	38	7 (18.4)	51.4 ± 11.6	-
Tsutsumimoto et al., 2011*	15	0	20	16 (80.0)	68 ± 11	-	20	15 (75.0)	65.8 ± 11.8	-
Todeschini et al., 2020	1.5	2.1	34	20 (58.8)	58 ± 12	12 ± 10.8	42	17 (40.5)	59.3 ± 12	12.5 ± 3.5
Pernik et al., 2020	10	1	71	22 (31.0)	66.5 ± 9.7	9.2 ± 3.4	48	19 (39.6)	69.2 ± 9.1	8.1 ± 2.8

* Randomized controlled trial included in the network meta-analysis.
† Units are mg/h instead of mg/kg/h.Data are reported as count (percentage), mean ± standard deviation, or median (interquartile range).-, data not available; TXA, tranexamic acid; LD, loading dose; MD, maintenance dose.

ies (9/13, 69.2%) with available data. Operation time was also reported frequently, for 691 patients (691/870, 79.4%) across 10 studies (10/13, 76.9%). Blood transfusion rate (5/13, 38.4%; n=372), length of hospital stay (8/13, 61.5%; n=535), and other outcomes were reported less consistently.

Network meta-analysis

For the network meta-analysis portion of the review, 7 of the 13 studies met inclusion criteria. [5, 16-18, 38-40] The total patient population for the meta-analysis was 441; TXA was administered to 222 patients (222/441, 50.3%), and placebo was administered to 219 patients (219/441, 49.7%). There were four different dosing strategies identified among the network meta-analysis studies:

Dose Strategy 1: 10 mg/kg LD + 1 mg/kg/h MD; (n=88)
Dose Strategy 2: 10 mg/kg LD + 2 mg/kg/h MD; (n=44)
Dose Strategy 3: 15 mg/kg LD; (n=45)
Dose Strategy 4: 15 mg/kg LD + 1 mg/kg/h MD; (n=45)

The different arms of the network meta-analysis and their conceptual relation to the placebo (and thus one other) is shown in **Fig. 2**.

Intraoperative blood loss volume

Six studies with 380 patients had sufficient data to evaluate differences in intraoperative BLV between TXA and placebo [16-18, 38-40] (one study only reported total BLV [5]). The pooled mean intraoperative BLV for the TXA group was 433.7 ml (95% CI: 220.3, 853.5), and for the placebo group was 621.9 ml (95% CI: 367.2, 1053.3). Intraoperative BLV was significantly lower in the TXA group compared to the placebo group (Diff = -185.0 ml; 95% CI: -302.1, -67.9). Between-study variability was very high (I^2=95.9%; 95% CI: 93.3%, 97.5%). Forest plot and exact values are shown in **Fig. 3A.**

Based on results from a random-effects network meta-analysis evaluating direct and indirect comparisons of intraoperative BLV between placebo and 5 different TXA dosing strategies, there were no significant differences in intraoperative BLV among any of the pairwise comparisons of treatment groups (**Table 4**). Pairwise comparisons of intraoperative BLV among each of the different TXA doses relative to the placebo group as well as P scores showing the relative ranking of each treatment strategy is shown in **Fig. 3B**. The estimated amount of variability in effect estimates in the network model was very high (I^2=96.5%; 95% CI: 92.7%, 98.3%).

Total blood loss volume

Six studies with 365 patients had sufficient data to evaluate differences in total BLV between TXA and placebo [5, 16-18, 39, 40] (one study only reported intraoperative BLV [38]). The pooled mean total BLV for the TXA group was 1038.7 ml (95% CI: 625.8, 1723.8), and for the placebo group was 1460.7 ml (95% CI: 885.1, 2410.6). Total BLV was significantly lower in the TXA group compared to the placebo group (Diff = -439.0 ml; 95% CI: -838.5, -39.6). Between-study variability was very high (I^2=99.1%; 95% CI: 98.7%, 99.3%). Forest plot and exact values are shown in **Fig. 4A.**

From a random-effects network meta-analysis, patients receiving 15 mg/kg + 1 mg/kg/h TXA were shown to have significantly reduced total BLV in comparison to both placebo (Diff = -823.1 ml; 95% CI: -1249.8, -396.4) and patients receiving 15 mg/kg TXA (Diff = -581.2; 95% CI: -1106.8, -55.7). There were no other significant differences in total BLV among pairwise comparisons of treatment groups (**Table 5**). Pairwise comparisons of total BLV and P scores showing the relative ranking of each treatment are shown in **Fig. 4B**. The estimated amount of variability in effect estimates in the network model was very high (I^2=91.6%; 95% CI: 78.6%, 96.7%).

Discussion

In this meta-analysis of adult patients undergoing multilevel spine surgery, patients treated with IV TXA demonstrated significantly reduced intraoperative and total BLV in comparison to those who received placebo. The network meta-analysis comparing different TXA dosing regimens revealed that 15 mg/kg LD + 1 mg/kg/h MD was shown to be the most effective in reducing total BLV, with significantly reduced BLV when compared to both placebo and 15 mg/kg LD with no MD. However, there was no significant change in total BLV seen when compared to the 10 mg/kg LD + 1 mg/kg/h MD and 10 mg/kg LD + 2 mg/kg/h MD dosing regimens. There were also no significant differences in intraoperative BLV among any of the pairwise comparisons of TXA dosing regimens (**Table 5**). These results closely reflect those of the literature and strengthen the evidence in favor of using IV TXA to reduce blood loss in spine surgery, though it remains unclear what the optimal TXA dose is. Although there are many systematic reviews and meta-analyses on the topic of TXA in spine surgery, this review fulfills a unique niche by specifically investigating dosing regimens in adults undergoing multilevel spine surgery.

Most of the literature investigating TXA dosing regimens does so along a “low dose” versus “high dose” binary; however, there are var-

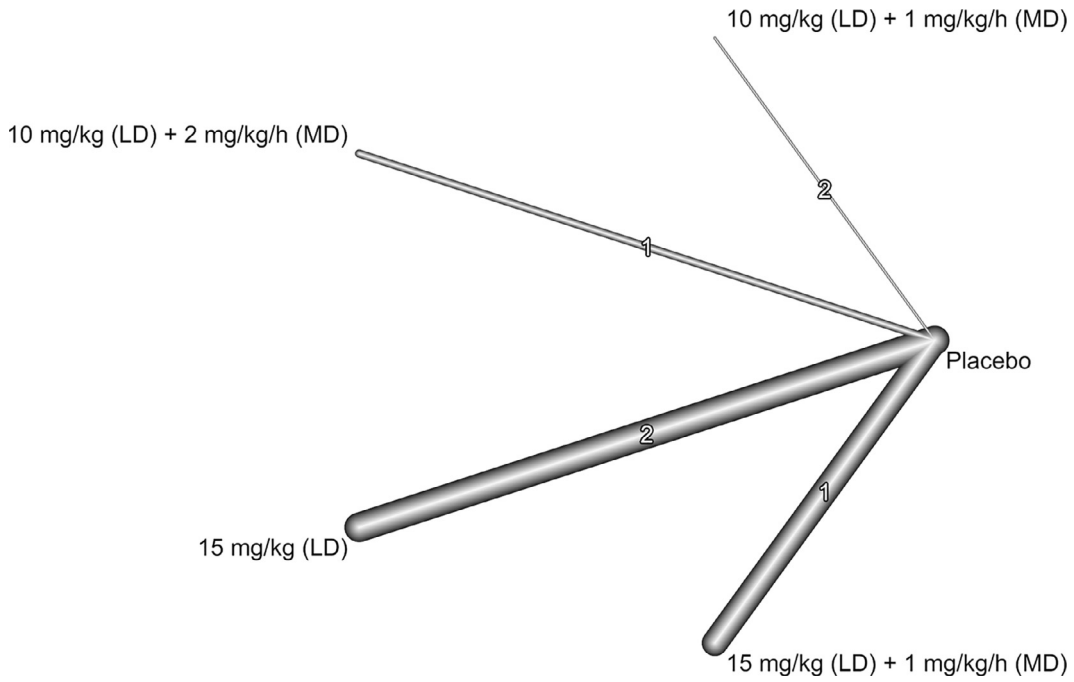
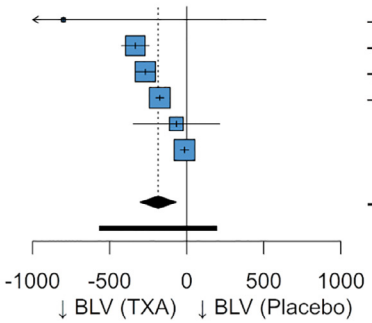


Fig. 2. Network plot showing the number of direct comparisons to placebo by each TXA dose category. The number of direct comparisons is shown along each line, and the width of each line corresponds to the relative weight of a specific treatment comparison within the network model. Comparisons of intraoperative BLV between TXA and placebo. LD=Loading dose; MD=Maintenance dose.

A

Study	TXA Total	TXA Mean	TXA SD	Placebo Total	Placebo Mean	Placebo SD	Diff.	95%-CI	Weight
Peters et al. (2015)	19	1400.0	900.0	13	2200.0	2300.0	-800.0	[-2114.1; 514.1]	0.8%
Colomina et al. (2017)	44	951.0	195.4	51	1284.4	251.0	-333.4	[-423.3; -243.5]	20.6%
Shakeri et al. (2018)	25	261.6	106.9	25	530.2	112.7	-268.6	[-329.5; -207.7]	22.1%
Mu et al. (2019)	45	301.8	34.7	42	476.3	77.2	-174.5	[-200.0; -149.1]	23.3%
Farrokhi et al. (2011)	38	1269.0	690.0	38	1336.0	550.0	-67.0	[-347.6; 213.6]	10.0%
Tsutsumimoto et al. (2011)	20	49.1	30.6	20	63.4	53.0	-14.3	[-41.1; 12.5]	23.2%
Random effects model	**191**			**189**			**-185.0**	**[-302.1; -67.9]**	**100.0%**
95% PI								**[-565.2; 195.3]**	

Heterogeneity: I^2 = 95.9% [93.3%; 97.5%], τ^2 = 15187.72 [0.00; 155570.92]



B

Treatment	Diff.	95%-CI	P-score
10 mg/kg (LD) + 2 mg/kg/h (MD)	-333.4	[-694.1; 27.3]	0.814
15 mg/kg (LD) + 1 mg/kg/h (MD)	-174.5	[-524.8; 175.7]	0.554
15 mg/kg (LD)	-139.9	[-389.1; 109.3]	0.499
10 mg/kg (LD) + 1 mg/kg/h (MD)	-138.8	[-564.3; 286.7]	0.483
Placebo	0.0		0.149

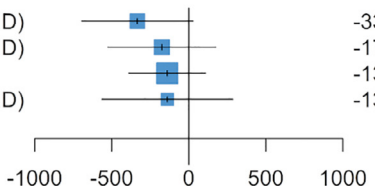


Fig. 3. A) Forest plot showing overall mean differences in intraoperative BLV between TXA and placebo from a random-effects meta-analysis (not accounting for TXA dose). **B)** Forest plot showing mean differences in intraoperative BLV among each TXA dose category relative to the placebo reference arm from a random-effects network meta-analysis. BLV=Blood loss volume; CI=Confidence interval; LD=loading dose; Diff=Mean differences; MD=Maintenance dose; NMA=Network meta-analysis; PI = Prediction interval; TXA = Tranexamic acid.

Table 3
Summary of Patient Outcomes by Study

Author, Year	Intraoperative BLV (ml)		Total BLV (ml)		Blood transfusion rate (n, %)		Operation time (min)		Length of stay (days)	
	TXA	P	TXA	P	TXA	P	TXA	P	TXA	P
Peters et al., 2015*	1400, -	2200, -	3100, -	4100, -	10 (52.6)	6 (46.2)	310, -	280, -	, -	8, -
Perez-Roman et al., 2019	307 ± 167	340 ± 201	761 ± 261	1042 ± 429	3 (15.8)	3 (15.0)	269 ± 58	328 ± 107	-	-
Xue et al., 2018	1520.5 ± 419.7	1994.8 ± 434.1	-	-	-	-	-	-	4.2 ± 1.0	5.6 ± 1.3
Mu et al., 2019*	301.8 ± 34.7	476.3 ± 77.2	814.8, -	1637.9, -	6 (13.3)	17 (40.5)	-	-	6.3 ± 1.8	8.0 ± 1.1
Shakeri et al., 2018*	261.6 ± 106.9	530.2 ± 112.7	632.2 ± 193.1	1037 ± 242.6	-	-	-	-	2.3 ± 6.1	3.4 ± 1.1
Carabini et al., 2018*	-	-	1600 (1200, 2500)	1550 (1200, 3200)	-	-	602 (522, 653)	576 (529, 690)	-	-
Colomina et al., 2017*	945 (826, 1081)	1277 (1123, 1452)	1695 (1499, 1916)	2112 (1878, 2375)	23 (52.3)	34 (66.7)	297 (247, 390)	300 (250, 395)	10 (8,14)	11 (8,16)
Yu et al., 2017	179.7 ± 81.5	269.1 ± 94.7	287.7 ± 115.4	402.0 ± 128.9	0 (0.0)	0 (0.0)	153.5 ± 11.9	155.7 ± 15.6	-	-
Pong et al., 2018	-	-	932 ± 539.4	1800 ± 1029.3	-	-	363.8 ± 67.3	376.7 ± 56.8	8.2 ± 5.1	8.2 ± 6.0
Farrokhi et al., 2011*	1269 ± 690	1336 ± 550	-	-	-	-	212.3 ± 58.9	211.3 ± 40.6	-	-
Tsutsumimoto et al., 2011*	49.1 ± 30.6	63.4 ± 53	264.1 ± 75.1	353.9 ± 60.8	-	-	89.4 ± 19.5	89 ± 10.7	-	-
Todeschini et al., 2020	-	-	2184.2 (1290.2, 3078.3)	3494.1 (2689.7, 4298.5)	-	-	432 ± 96	498 ± 138	8.7 ± 4.2	8.8 ± 3.1
Pernik et al., 2020	-	-	1838.4 ± 1293.8	1494.7 ± 863	-	-	305.9 ± 110.2	282.8 ± 84.4	5.7 ± 1.7	5.8 ± 1.8

* Randomized controlled trial included in the network meta-analysis.Data are reported as count (percentage), mean ± standard deviation, or median (interquartile range).-, data not available; BLV, blood loss volume; TXA, tranexamic acid; P, placebo.

ious problems with this approach. First, there is no consensus around what qualifies as a low dose or high dose of TXA. In their retrospective cohort study of patients undergoing surgery for adult spinal deformity, Raman et al. defined low dose IV TXA as 10-20 mg/kg LD + 1-2 mg/kg/h MD, while high dose TXA was 30-50 mg/kg LD + 1-10 mg/kg/h MD. [41] In contrast, Yuan et al. defined low dose IV TXA as any dose ≤10 mg/kg LD + ≤10 mg/kg/h MD, and high dose as 10-100mg/kg LD + >10 mg/kg/h MD. [42] Not all studies use LD and MD to define high vs. low dosing regimens. Some rely on LD alone or on the total administered dose; for example, Xiong et al. defined high dose TXA as ≥20 mg/kg LD, or any total dose >1 g. [11] The heterogeneity of dosing regimens and definitions thus compromises conversations around the effectiveness of "low dose" versus "high dose" IV TXA.

To further complicate matters, TXA has multiple possible routes of administration, but language around TXA dosing strategies is sometimes unclear. For example, in their randomized controlled trial (RCT) of patients undergoing posterior lumbar interbody fusion, Zhang et al. administered TXA topically and intravenously. [8] Meanwhile, other studies have investigated the effect of topical TXA administration alone. [43] Investigating alternative routes of TXA administration are valuable additions to the literature and innovations that should continue to be explored; however, when reviews of TXA in spine surgery include both IV and topical TXA in their meta-analysis, [9] care should be taken in interpreting these results. Moreover, when meta-analyses make recommendations for low dose or high dose TXA, [42, 44] it is crucial to clarify that as the science develops, a certain dose regimen that is optimal for one route of administration may not necessarily be optimal when administered via another route.

For complex spinal surgery it has been seen that a perioperative Hb level <9g/dL can lead to a longer hospital stay and increased mortality. [45] To minimize the incidence of unfavorable adverse effects from a blood transfusion, there are strict hemoglobin (Hb) thresholds recommended for transfusions as well as numerous strategies to decrease blood loss. TXA is one of several antifibrinolytics that can be used during spine surgery to reduce blood loss. Other common antifibrinolytic agents include epsilon-aminocaproic acid (EACA) and aprotinin, all of which have shown efficacy in reducing BLV and improving outcomes following spine surgery. In a study including 11 RCTs with 937 patients undergoing spinal fusion surgery, Lu et al. found that patients who were administered antifibrinolytics (either TXA or EACA) had significantly lower intraoperative BLV (-127.1 ml; p=0.002) and total blood loss (-229.76 ml; p<0.001). [46] Compared to EACA and aprotinin, TXA may have a slight advantage in terms of BLV and blood transfusion. Li et al. asserted in their meta-analysis of 17 studies with 1191 that TXA appeared more effective than aprotinin and EACA in reducing intraoperative and total BLV; however, all three antifibrinolytics were better than placebo, without any observed risk for thromboembolic events. [47] Yuan et al. did not directly compare antifibrinolytics to one another in their meta-analysis, but they recommended high dose TXA over low dose TXA, EACA, and aprotinin due to its superiority in terms of blood transfusion volume. [42] Taken collectively, this evidence points to clear advantages of TXA in terms of blood loss for spine surgery, but additional RCTs are needed to more clearly determine the effects of different TXA dosing strategies.

Limitations

The major limitation of this study is that there were no direct comparisons of different TXA doses among the included studies. The produced network meta-analyses rely heavily on the assumption of transitivity (i.e., the assumption that direct comparisons between TXA dosing regimens and placebo within one study can be used to indirectly compare TXA dosing regimens across studies and induce a "ranking" of treatment strategies). Due to lack of reliable data, the transitivity assumption cannot be tested statistically, though the risk for violating this assumption is somewhat attenuated by only including placebo-controlled trials

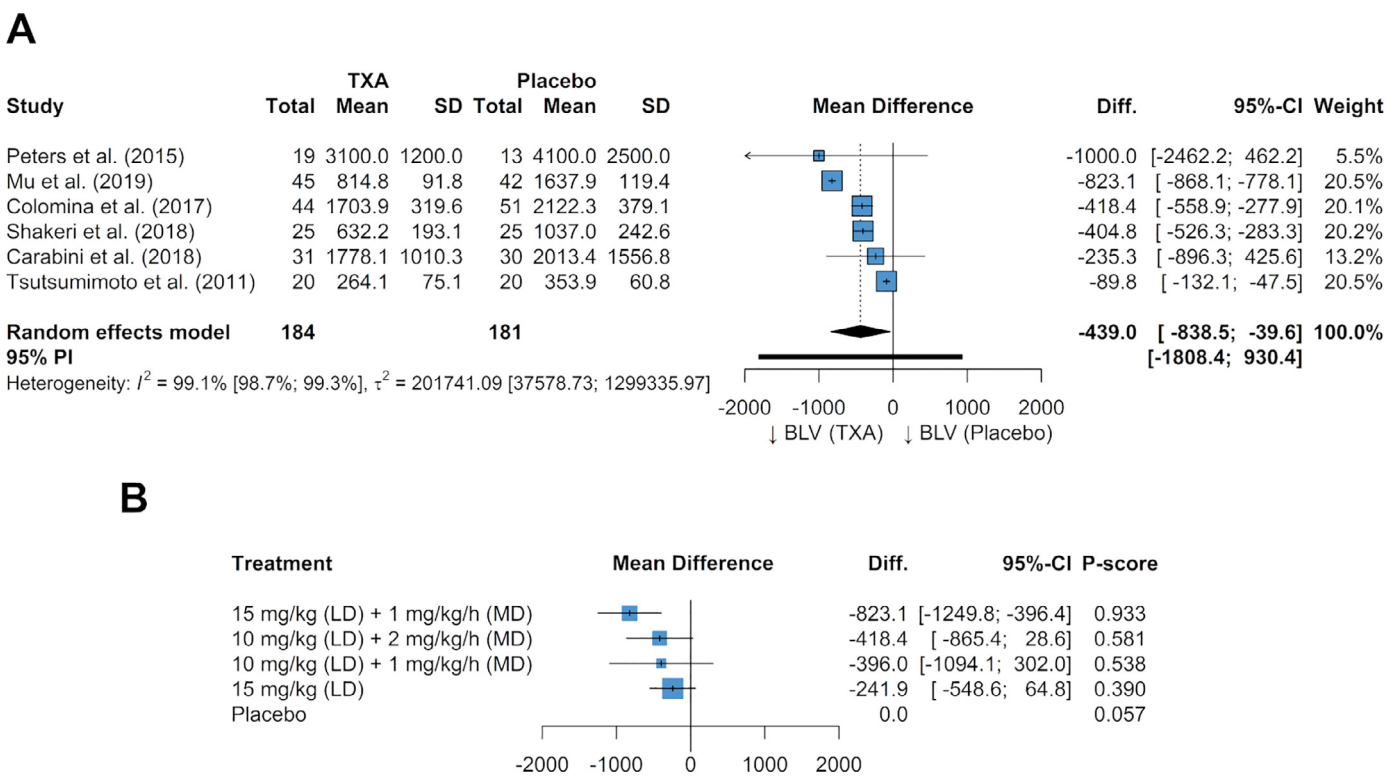


Fig. 4. Comparisons of total BLV between TXA and placebo. **A)** Forest plot showing overall mean differences in total BLV between TXA and placebo from a random-effects meta-analysis (not accounting for TXA dose). **B)** Forest plot showing mean differences in total BLV among each TXA dose category relative to the placebo reference arm from a random-effects network meta-analysis. BLV=Blood loss volume; CI=Confidence interval; LD=loading dose; Diff=Mean differences; MD=Maintenance dose; NMA=Network meta-analysis; PI = Prediction interval; TXA = Tranexamic acid.

Table 4
Pairwise Comparisons of Intraoperative Blood Loss Volume by Treatment Group.

		Placebo	*Strategy 4* 15 mg/kg + 1 mg/kg/h	*Strategy 3* 15 mg/kg	*Strategy 2* 10 mg/kg + 2 mg/kg/h	*Strategy 1* 10 mg/kg + 1 mg/kg/h
Strategy 1	**10 mg/kg + 1 mg/kg/h**	-138.8 (-564.3; 286.7)	35.8 (-515.4; 586.9)	1.1 (-492.0; 494.3)	194.6 (-363.1; 752.4)	–
Strategy 2	**10 mg/kg + 2 mg/kg/h**	-333.4 (-694.1; 27.3)	-158.9 (-661.6; 343.9)	-193.5 (-631.9; 244.9)	–	
Strategy 3	**15 mg/kg**	-139.9 (-389.1; 109.3)	34.6 (-395.2; 464.5)	–		
Strategy 4	**15 mg/kg + 1 mg/kg/h**	-174.5 (-524.8; 175.7)	–			
Placebo		–				

Data are reported as mean difference with corresponding 95% confidence intervals shown in parentheses; units are in ml. Shaded cells in green indicate a statistically significant difference.

Table 5
Pairwise Comparisons of Total Blood Loss Volume by Treatment Group.

		Placebo	*Strategy 4* 15 mg/kg + 1 mg/kg/h	*Strategy 3* 15 mg/kg	*Strategy 2* 10 mg/kg + 2 mg/kg/h	*Strategy 1* 10 mg/kg + 1 mg/kg/h
Strategy 1	**10 mg/kg + 1 mg/kg/h**	-396.0 (-1094.1; 302.0)	427.1 (-391.1; 1245.2)	-154.2 (-916.6; 608.3)	22.4 (-806.6; 851.3)	–
Strategy 2	**10 mg/kg + 2 mg/kg/h**	-418.4 (-865.4; 28.6)	404.70 (-213.3; 1022.7)	-176.5 (-718.7; 365.6)	–	
Strategy 3	**15 mg/kg**	-241.87 (-548.6; 64.8)	581.2 (55.7; 1106.8)	–		
Strategy 4	**15 mg/kg + 1 mg/kg/h**	-823.1 (-1249.8; -396.4)	–			
Placebo	–					

Data are reported as mean difference with corresponding 95% confidence intervals shown in parentheses; units are in ml. Shaded cells in green indicate a statistically significant difference.

where patient populations and methodologies were similar, and there was a within-study balancing of covariates. Overall, the comparisons of TXA dosing regimen in this study should be considered exploratory; nevertheless, it is clear that TXA outperforms placebo for reducing intraoperative and total BLV. There is considerable heterogeneity in TXA dosing strategies in the literature, with few directly comparing dosing strategies in terms of efficacy and outcomes. High-quality RCTs are still needed to evaluate the optimal TXA dose for patients undergoing spine surgery, including those undergoing complex, multilevel surgeries.

Another major limitation of this analysis is that the data reporting quality varied widely across studies. For example, many studies did not report key metrics (e.g., blood transfusion rate), which limits the ability to perform robust meta-analysis. In addition, some studies reported data as means and SDs while others reported medians and quantiles; as such, estimation methods were required to aggregate effect size data.

Furthermore, programming methods were used to extract quantitative data from images, so there may be some imprecision in the extracted values.

Controlling for sources of variability and bias at the patient-level were outside the scope of this meta-analysis, but it must be acknowledged that factors such as surgical technique and preoperative diagnoses for multilevel spine surgery can substantially influence outcomes. A future meta-analysis involving patient-level data to critically evaluate the performance of TXA when controlling for interactions among patient, procedural, and study characteristics would be beneficial to the medical community. Finally, TXA dosing regimens are only considered as a single categorical variable, but there may be important interactions between the specific LD and MD used which could be investigated further in future planned RCTs.

Conclusions

This meta-analysis found that IV TXA is associated with reduced intraoperative and total BLV for adults undergoing multilevel spine surgery; however, the optimal TXA dosing regimen remains unclear. The many meta-analyses that have been performed regarding TXA use in spine surgery point to its efficacy in reducing intraoperative and total BLV, with generally low rates of complications such as thromboembolic events. Additionally, the trend in the literature that high dose TXA may be more effective than low dose TXA was reflected in the present study, with the highest dose in this network meta-analysis (15 mg/kg + 1 mg/kg/h) representing the only dose regimen that showed significant benefits over another TXA dose upon pairwise comparison. Nevertheless, there is substantial heterogeneity in studies reporting TXA dose regimens, which limits the ability for comparison. More randomized controlled trials directing comparing TXA dosing strategies are needed for not only adult patients undergoing multilevel spine surgery, but all patients undergoing spine surgery.

Declaration of Competing Interests

One or more authors declare potential competing financial interests or personal relationships as specified on required ICMJE-NASSJ Disclosure Forms. John M. Pederson is employed by and has ownership interest in both Superior Medical Experts and Nested Knowledge.

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Supplementary materials

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