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Review Article

Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis

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Abstract

BACKGROUND CONTEXT: Spine surgery is usually associated with large amount of blood loss, necessitating blood transfusions. Blood loss-associated morbidity can be because of direct risks, such as hypotension and organ damage, or as a result of blood transfusions. The antifibrinolytic, tranexamic acid (TXA), is a lysine analog that inhibits activation of plasminogen and has shown to be beneficial in reducing surgical blood loss.

PURPOSE: To consolidate the findings of randomized controlled trials (RCTs) investigating the use of TXA on surgical bleeding in spine surgery.

STUDY DESIGN: A metaanalysis.

STUDY SAMPLE: Randomized controlled trials investigating the effectiveness of intravenous TXA in reducing blood loss in spine surgery, compared with a placebo/no treatment group.

METHODS: MEDLINE, Embase, Cochrane controlled trials register, and Google Scholar were used to identify RCTs published before January 2014 that examined the effectiveness of intravenous TXA on reduction of blood loss and blood transfusions, compared with a placebo/no treatment group in spine surgery. Metaanalysis was performed using RevMan 5. Weighted mean difference with 95% confidence intervals was used to summarize the findings across the trials for continuous outcomes. Dichotomous data were expressed as risk ratios with 95% confidence intervals. A $p<.05$ was considered statistically significant.

RESULTS: Eleven RCTs were included for TXA (644 total patients). Tranexamic acid reduced intraoperative, postoperative, and total blood loss by an average of 219 mL ([−322, −116], $p<.05$), 119 mL ([−141, −98], $p<.05$), and 202 mL ([−299, −105], $p<.05$), respectively. Tranexamic acid led to a reduction in proportion of patients who received a blood transfusion (risk ratio

FDA device/drug status: Not approved for this indication (Tranexamic acid).

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0.67 [0.54, 0.83], p<.05) relative to placebo. There was one myocardial infarction (MI) in the TXA group and one deep vein thrombosis (DVT) in placebo.
CONCLUSIONS: Tranexamic acid reduces surgical bleeding and transfusion requirements in patients undergoing spine surgery. Tranexamic acid does not appear to be associated with an increased incidence of pulmonary embolism, DVT, or MI.

Keywords: Antifibrinolytics; Tranexamic acid; Epsilon-aminocaproic acid; Spine surgery; Blood loss; Transfusion rate; Adult spine deformity

Introduction

Spine surgery is usually associated with large amount of perioperative blood loss that may be attributed, at least in part, to the large wound surfaces, long operating times, and involvement of richly supplied cancellous bone. Although the amount of perioperative blood loss may vary widely across procedures, dependent on both surgical and nonsurgical factors, blood loss remains a major concern in the setting of spine surgery. Significant blood loss is associated with complications such as hypotension, end organ damage, or coagulopathy. Allogenic blood transfusions present additional risks, including hemolytic transfusion reactions, transfusion-related acute lung injuries, infection transmission, and immune modulation effects. Because of the significant risks and complications associated with blood loss and allogenic transfusions, efforts to identify safe and effective ways of minimizing blood loss during spine surgery are crucial.

Blood conservation strategies have been effectively used to reduce surgical bleeding and the need for allogenic transfusions in various surgical procedures. Such techniques include regional anesthesia, hypotensive anesthesia, intraoperative blood salvage, acute normovolemic hemodilution, and administration of intravenous, intramuscular, and oral medications [1,2]. Furthermore, the administration of antifibrinolytics, such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), has been shown to reduce bleeding in various surgeries including cardiac, trauma, hip, and knee arthroplasty, gynecological, and urologic procedures [3–11]. Tranexamic acid acts by competitively blocking the lysine-binding sites of plasminogen, thereby inhibiting fibrinolysis and blood clot degradation [8,10,12–16].

Recent research in spine surgery has demonstrated the efficacy of TXA to reduce perioperative blood loss and allogeneic blood transfusion in patients undergoing spine surgery, however, optimal dosing and duration is still unclear [2]. In spine surgery, the use of antifibrinolytics is not considered as routine. There are concerns regarding the safety profile of these drugs, including increased incidence of thromboembolic events, such as deep vein thromboses (DVTs), pulmonary embolisms (PEs), and myocardial infarctions (MIs), and increased incidence of seizures with moderate to high doses of TXA [17]. This metaanalysis investigated the efficacy of TXA on blood loss during spine surgery.

Methods

The metaanalysis was performed in accordance to published guidelines of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [18].

Literature search

Literature searches were conducted using MEDLINE, Cochrane central register of controlled trials, Embase, and Google Scholar by three independent reviewers. Medical Subject Heading terms included ‘‘tranexamic acid,’’ ‘‘epsilon-aminocaproic acid,’’ ‘‘amicar,’’ and ‘‘antifibrinolytics,’’ and the literature search was refined to randomized controlled trials (RCTs) in spine surgery. Reference lists of trials and reviews were also examined. No restrictions on language or publication year were applied. The last date of the search was December 31, 2013.

Study selection

A systematic review of medical literature was conducted for all RCTs that compared the efficacy of intravenous TXA with no or placebo treatment in spine surgery. All age groups were included. Studies were excluded if they were nonrandomized trials, retrospectively designed trials, or trials of low quality. Three reviewers independently selected eligible publications and any disagreement was settled by discussion with a fourth reviewer.

Validity assessment

Assessment of quality was done as outlined by Jadad et al. [19]. Assessments were conducted for each study by two independent reviewers and the criteria have been outlined in Table 1. Included studies were graded according to a three-category risk of bias scale. Studies that had a score of 0 to 1, 2 to 3, and 4 to 5 of a maximum score of 5 were classified to be of high, medium, and low bias, respectively. Studies graded as having a medium or high risk of bias were discussed among all reviewers to determine inclusion/exclusion.

Data collection and extraction

Each complete study report was thoroughly reviewed independently by two researchers to ensure that all data were collected entirely and accurately. The senior author made final decisions determining which studies would be

Table 1
Scoring of study validity described by Jadad et al. [19]

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	
2. Was the study described as double blind?	
3. Was there a description of withdrawals and dropouts?	
Scoring	
1 point for each "yes" or 0 points for each "no."	
1 additional point if:	For Question 1, the method to generate the sequence of randomization was described *and* it was appropriate (table of random numbers, computer generated, etc)
	If for Question 2, the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc)
Deduct 1 point if:	For Question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc)
	For Question 2, the study was described as double blind but the method of blinding was inappropriate (eg, comparison of tablet vs. injection with no double dummy)

Scoring is based on randomization, blinding technique, and description of withdrawals and dropouts in the study. The maximum possible score is 5 and represents minimum bias.

included. Data abstraction was done on a modified Cochrane abstraction form. General study characteristics extracted included aim and design of the study, sample size, mean age, and sex in each treatment group, geographical location and affiliated institution, inclusion/exclusion criteria, and publication date. Treatment groups, interventions, and dosages were recorded for all included studies. The following outcomes were extracted: intraoperative and total blood loss, number of patients receiving blood transfusions, and thromboembolic complications including PE, DVT, and MI. In cases of insufficient data, the corresponding author was contacted for clarification and information.

Statistical methods and analysis

The Mantel-Haenszel method for metaanalysis was performed using Review Manager software (RevMan 5.0; Cochrane Collaboration). For continuous (intraoperative, postoperative, and total blood loss) and dichotomous data (number of transfusions and thromboembolic events), weighted mean differences and relative risks were applied, respectively, both with 95% confidence interval (CI). Heterogeneity was assessed by a funnel plot, I^2, and chi-square value. A $p<.1$ and $I^2>50\%$ was considered suggestive of statistical heterogeneity, in which case, random effects analysis was performed.

Subgroup analysis

Subgroup analysis was performed on dose, mean age of patients, and the amount of blood loss. Dose subgroup analysis

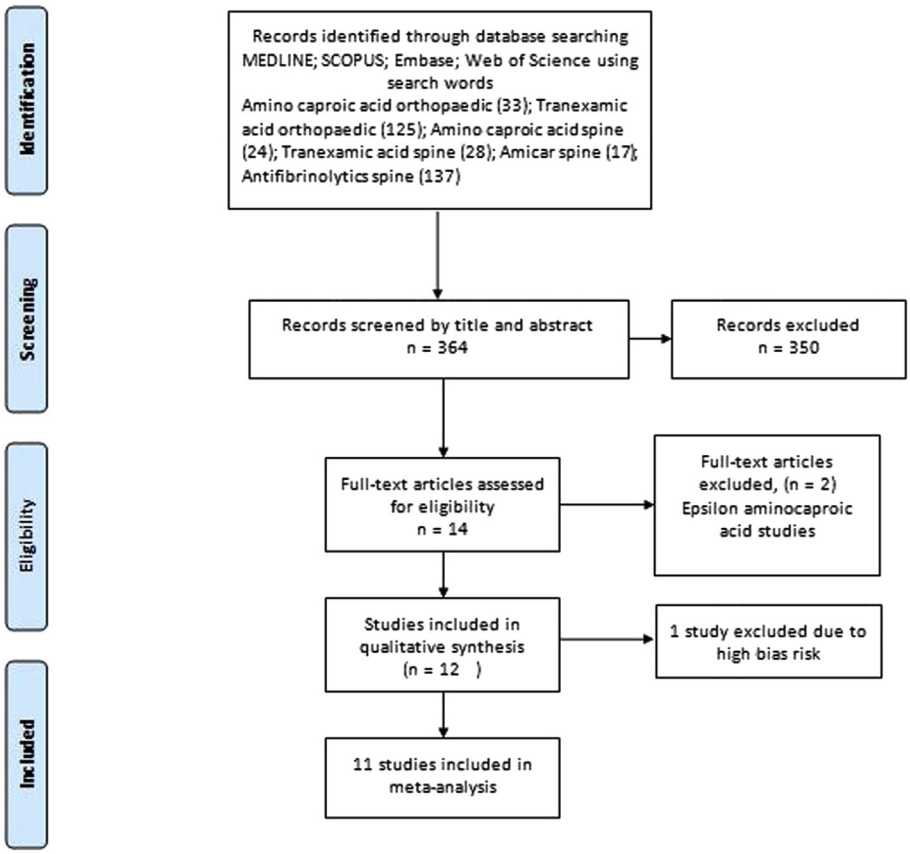

Fig. 1. Flowchart showing research strategy.

Table 2
Characteristics of the included studies

Study	Year	Country	Number (TXA/control)	Dose	Procedure	Transfusion criteria	Jadad score
Elwatidy et al. [24]	2008	Saudi Arabia	32/32	Loading dose 2 g (adults) or 30 mg/kg (children)+maintenance dose 1 g in 100 mL infusion at a rate of 100 mg/h (adults) or 1 mg/kg/h (children) during surgery and continued for 5 h after operation.	All spinal surgery	Hb<90 g/L and HCT<27%	2
Farrokhi et al. [2]	2011	Iran	38/38	10 mg/kg loading dose+maintenance dose 1 mg/kg/h	Spinal fixation surgery	—	4
Huang Cheng [20]	2011	China	34/34	Loading dose of 10 mg/kg+infusion 2 mg/kg/h	Spine fixation surgery	Hb<90 g/L	Not assessed (Manuscript in Chinese)
Kim and Bae [21]	2000	South Korea	11/11	15 mg/kg bolus administered once intraoperatively and once postoperatively	Spinal surgery	—	Not assessed (Manuscript in Korean)
Neilipovitz et al. [22]	2001	Canada	22/18	Loading dose 10 mg/kg+infusion 1 mg/kg/h	Adolescent scoliosis	Hb<7 g/L	3
Sethna et al. [12]	2005	USA	23/21	Loading dose of 100 mg/kg TXA and infusion of 10 mg/kg/h	Adolescent scoliosis	HCT<25%	4
Suksamosorn et al. [23]	2011	Thailand	22/21	Loading dose 10 mg/kg+infusion 1 mg/kg/h	Decompressive laminectomy with fusion	Hb<70 g/L or HCT<27%	4
Tsutsumimoto et al. [25]	2011	Japan	20/20	15 mg/kg over 15 min before skin incision	Cervical laminoplasty	—	0
Wang et al. [26]	2013	China	30/30	20 mg/kg bolus+10 mg/kg maintenance	Degenerative lumbar instability with stenosis	—	0
Wong et al. [13]	2008	Canada	73/74	10 mg/kg loading dose+infusion of 1 mg/kg/h	Spinal fusion	Hb<70 g/L	5
Xu et al. [27]	2012	China	20/20	Loading dose 20 mg/kg+infusion 10 mg/kg/h	Adolescent idiopathic scoliosis	Hb<80 g/L	0

TXA, tranexamic acid; Hb, hemoglobin; HCT, hematocrit.

was done based on low and high doses of TXA. Studies that had dose regimen of bolus infusion followed by a maintenance infusion were included for dose subgroup analysis. Low dose was defined as bolus dose of less than 10 mg/kg, followed by maintenance dose of less than 10 mg/kg/h [2,13,20–23]. High dose was defined as bolus dose of 10 to 100 mg/kg and/or followed by a maintenance dose of greater than 10 mg/kg/h [12,24–27]. Age-dependent analysis was conducted by categorizing the study by mean age in TXA group into: younger than 21 years [12,22,27], 21 to 50 years [2], and older than 50 years [13,20,21,23–26]. For subanalysis of the amount of blood lost, studies were categorized by intraoperative blood loss in the placebo group into the following groups: less than 500 mL [25], 500 to 1,500 mL [2,20,21,23,24,26], and greater than 1,500 mL blood loss [12,13,22,27].

Results

Study selection

Our search resulted in a total of 364 citations. After screening by title, abstract, and entire article, 13 randomized controlled studies were identified that met all inclusion criteria and had useable data. Fig. 1 shows the method of study selection and inclusion. Eleven studies compared the efficacy of TXA [2,12,13,20–29]. The 13 studies included a total of 862 patients. Study characteristics of the included studies are described in Table 2.

Quality assessment

Included studies had a Jadad et al. [19] score varying from 0 to 5 (Table 2). Sample size varied between 40 and 182 patients with a mean of 66 patients in each study. Dose ranged from 1 to 15 mg/kg for TXA. Blood transfusion protocol was defined in nine studies. A study by Jalaeian Taghaddomi et al. [30] was excluded from the metaanalysis because outcomes reported were not clearly defined, discrepancies in reported outcomes were noted, and the contact author was not reachable.

Effect on blood loss

Eleven TXA studies reported data on intraoperative blood loss (n=644; TXA/placebo=25/319). Tranexamic acid administration reduced intraoperative blood loss by an average of 219 mL, ranging from 116 to 322 mL compared with placebo (95% CI; p<.000001; I^2=92%) (Fig. 2). Data for postoperative blood loss were available in four TXA studies (n=322; TXA/placebo=161/161).

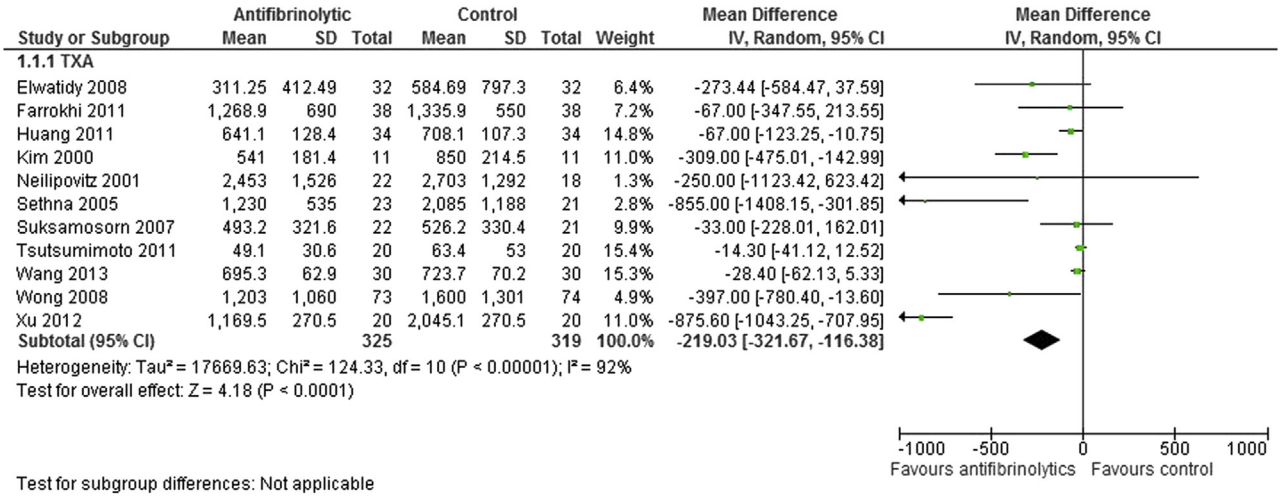

Fig. 2. Forest plot showing effect of TXA on intraoperative blood loss. SD, standard deviation; CI, confidence interval; TXA, tranexamic acid.

Tranexamic acid reduced postoperative blood loss by an average of 119 mL (−141, −98; p<.00001) (Fig. 3). A total of six studies reported data on total blood loss (n=354; TXA/placebo=166/188). Tranexamic acid administration reduced total blood loss by an average of 319 mL, ranging from 104 to 299 mL compared with placebo (95% CI; p<.000001; I^2=73) (Fig. 4).

Effect on transfusion rates

Eight studies contributed data to blood transfusion rates. Intravenous TXA administration reduced allogenic blood transfusion requirement by an average of 33% (0.54, 0.83; p<.000001) (Fig. 5).

DVT, PE, and MI

There were no incidences of DVT in the TXA group, with one report of DVT in the corresponding placebo group. There were no reports of PE in either the TXA or the placebo group. There was just one reported case of MI in the TXA group and no cases reported in any other group (Table 3).

Subgroup analysis

Subgroup analysis was done on dose, mean age, and the amount of blood loss. The results are shown in Table 4.

Discussion

This metaanalysis concludes that the use of TXA is effective in reducing intraoperative, postoperative, and total blood loss and transfusion rates in spine surgery. There does not appear to be any increased risk of complications with the use of TXA, when compared with placebo.

We concluded that the average reductions in intraoperative, postoperative, and total surgical bleeding in spine surgery were 219, 119, and 201 mL, respectively, with a 33%

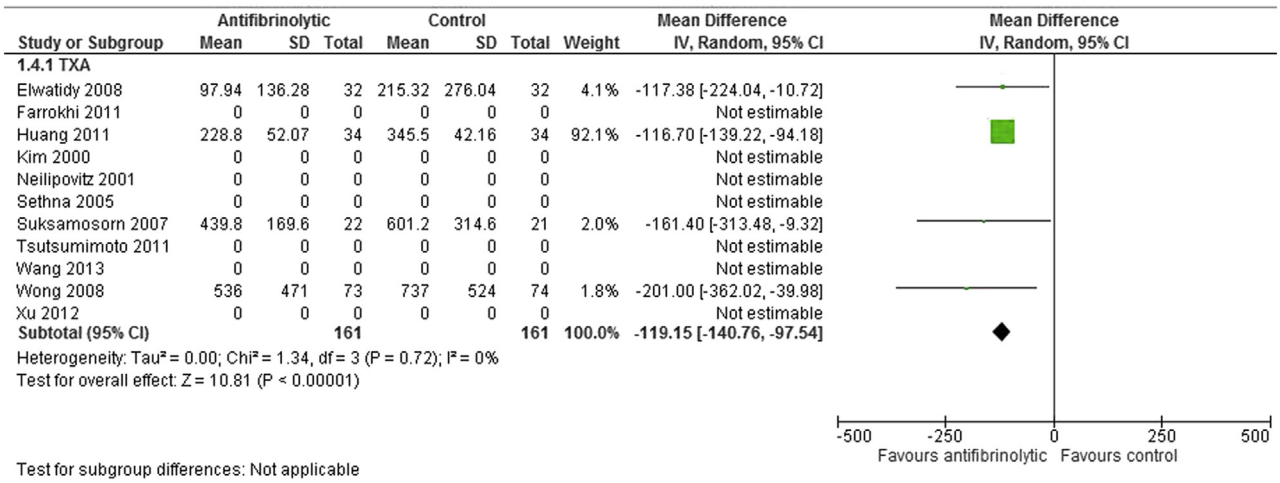

Fig. 3. Forest plot showing effect of tranexamic acid on postoperative blood loss. SD, standard deviation; CI, confidence interval; TXA, tranexamic acid.

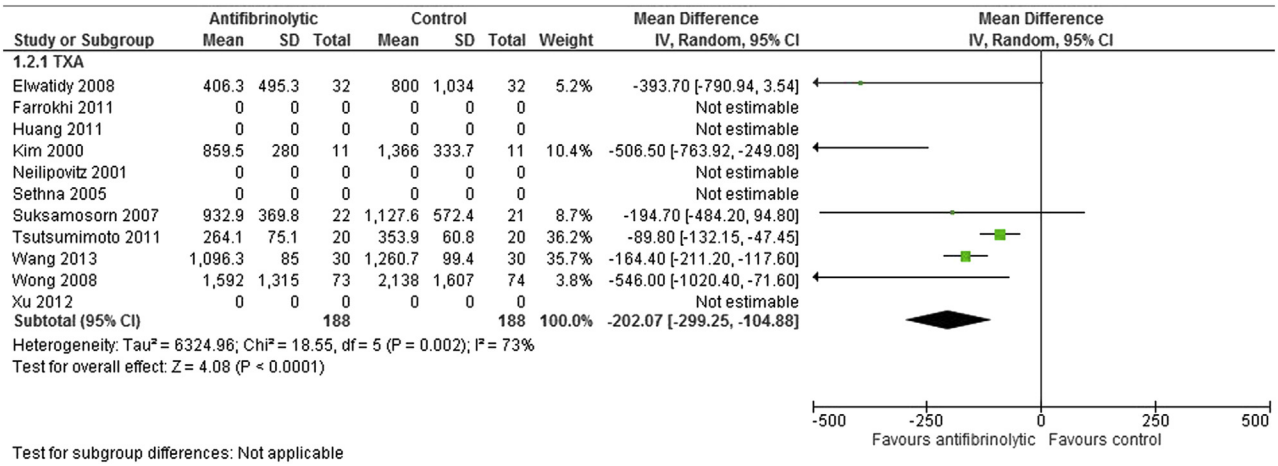

Fig. 4. Forest plot showing effect of tranexamic acid on total blood loss. SD, standard deviation; CI, confidence interval; TXA, tranexamic acid.

reduction in transfusion rates when TXA was administered. However, the number of studies that reported on each outcome was not consistent, resulting in the apparent greater reduction in intraoperative blood loss than total blood loss. Nonetheless, the evidence on efficacy of TXA in reducing surgical bleeding in spine surgery is overwhelming. This is underlined by the fact that the benefit of TXA is not dependent on any singular study result.

Subgroup analysis on TXA dosage (Table 4) showed an average intraoperative blood loss reduction of 301 mL and 143 mL in high-dose and low-dose administrations, respectively, when compared with control. Postoperative and total blood loss were reduced by an average of 118 mL and 396 mL, respectively, in the low-dose patients. Although a high dose of TXA was shown to be more effective than a low dose in reducing intra- and postoperative blood loss, low dose seemed to be more efficacious for total blood loss. This could be attributed to the significant difference in studies contributing to each outcome, as not all RCTs provided data on all blood loss outcomes. While the optimal dose for surgery has not yet been established, a dose of 1 g is considered adequate with no evidence that higher doses have any additional benefit [31]. The seemingly greater benefit of a higher dose of TXA on intraoperative blood loss might be because of the reduction in drug concentration associated with the blood loss, which might provide a rationale for the use of high dosage. However, regardless of dose and blood loss category, the use of TXA during spine surgery showed a reduction in blood loss.

Subgroup analysis of age (Table 5) showed greater intraoperative and total blood loss in patients younger than 20 years when compared with older age groups. Average intraoperative, postoperative, and total blood reduction in younger than 21 years age subgroup was 854, 161, and 358 mL,

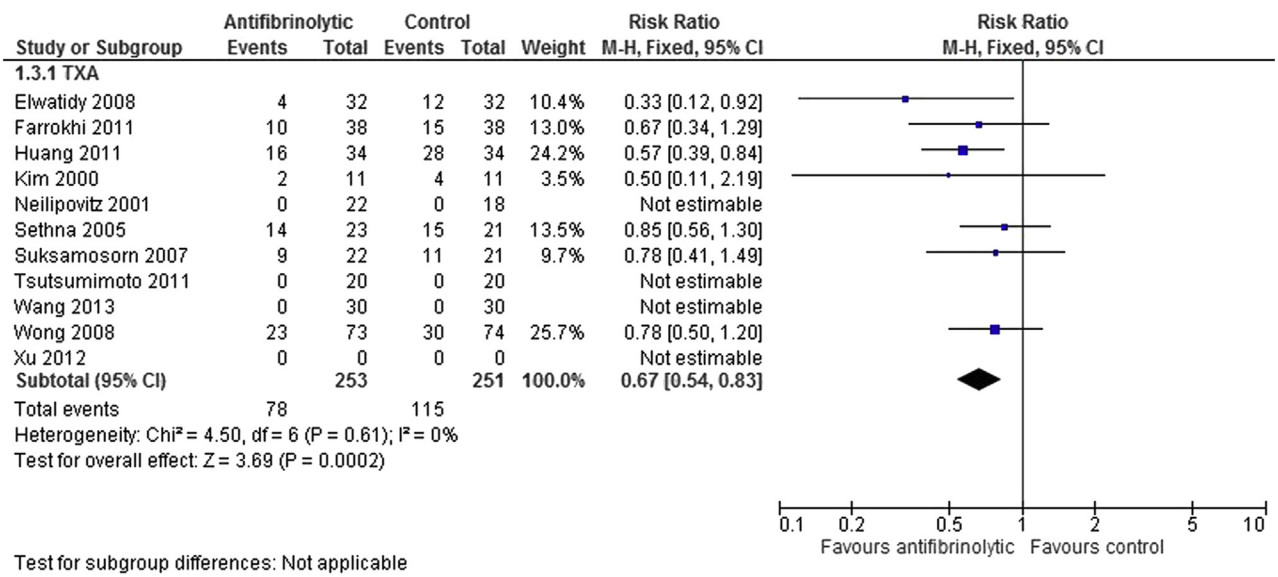

Fig. 5. Forest plot showing effect of tranexamic acid on transfusion rate. CI, confidence interval; TXA, tranexamic acid; M-H, Mantel-Haenszel.

Table 3
Incidence of thromboembolic complications

Adverse event	TXA/placebo
MI	1/0
DVT	0/1
PE	0/0

TXA, tranexamic acid; MI, myocardial infarction; DVT, deep vein thrombosis; PE, pulmonary embolism.

respectively. However, all contributions to younger than 21 years age group were studies on adolescent scoliosis surgeries, where large blood loss is expected and the interpretation of subgroup analysis results should be done carefully. Only one study contributed to the 21 to 50 years age group. For studies in older than 50 years age subgroup, intraoperative, postoperative, and total blood loss was reduced by an average of 68, 118, and 202 mL, respectively. However, reduction in transfusion was similar in all age groups.

Because of differences in the type of spine surgery performed and the lack of definition of surgeries performed in RCTs included in this metaanalysis, subgroup analysis was done based on the amount of blood loss (Table 6). As expected, there is greater benefit in reducing blood loss during large blood loss surgeries, which is consistent with the Bayesian linear regression model suggested by Ker et al. [31]. For surgeries where the mean blood loss in the placebo group was greater than 1,500 mL, the average reduction in intraoperative, postoperative, and total blood loss was 676, 161, and 546 mL, respectively.

There were four studies that had an average blood loss greater than 1,500 mL in the control group [12,13,22,27]. Three of them were in young adults (younger than 21 years) [12,22,27]. There was only one study in older patients (older than 50 years) that used low dose [13]. This study concluded that there was a 30% decrease in perioperative blood loss in the TXA cohort when compared with placebo, with a trend toward reduced packed red cell transfusions in the TXA group [13].

There were three studies [12,22,27] in young adults with intraoperative blood loss more than 1,500 mL in the control group. Two studies used a high-dose regimen [12,27], with metaanalysis showing a beneficial effect of TXA on intraoperative blood loss by 873.8 mL (1,034.31, 713.42; p<.00001). In these studies, while Sethna et al. [12] did not find a difference in the transfusion rates, Xu et al. [27] reported a 72.4% decrease in allogenic transfusions in the TXA group [12]. Neilipovitz et al. [22] used a low-dose regimen in pediatric patients with scoliosis and did not find a significant difference in intraoperative blood loss between the TXA and control groups. However, the authors concluded that total blood transfused was less the TXA cohort, although the number of patients who received transfusion in each group was not reported. In the setting of large blood loss pediatric scoliosis surgery, although both low- and high-dose regimens seem to be beneficial, a high-dose regimen may have greater efficacy in reducing surgical bleeding.

Six studies had an average blood loss between 500 and 1,500 mL in the control group [2,20,21,23,24,26]. A high-dose regimen was used in two [24,26] and low dose in four [2,20,21,23]. A subgroup metaanalysis of three studies with blood loss between 500 and 1,500 mL, with an mean age of greater than 50 years, and using low-dose regimen [20,21,23] did not show a difference in intraoperative blood loss (−131 mL [−284.87, 23.51], p=.02, I^2=74%), with only one study reporting on postoperative [20] and total blood loss [21]. However there was a beneficial effect of the use of TXA on transfusion rate (0.62 [0.44, 0.86], p=.005, I^2=0%). However, the lack of beneficial effect of TXA on intaoperative blood loss should take into account the low sample size and the proximity of results to statistical significance. The study by Wang et al. [26] was the only study with blood loss between 500 and 1,500 mL, with a mean age of greater than 50 years that used a high-dose regimen. Although the authors did not find a significant difference in intraoperative blood loss,

Table 4
Dose-dependent subgroup analysis

Outcome and subgroup	Studies	Participants	Statistical method	Effect estimate	p	X^2*	I^2* (%)
Intraoperative blood loss	11		Mean difference (IV, random, 95% CI)				
Low dose	6	396	Mean difference (IV, random, 95% CI)	−143.86 (−263.77, −23.94)	.02	10.26	51
High dose	5	248	Mean difference (IV, random, 95% CI)	−301.20 (−464.05, −138.36)	.0003	109.70	96
Postoperative blood loss	4		Mean difference (IV, random, 95% CI)				
Low dose	2	111	Mean difference (IV, random, 95% CI)	−117.66 (−139.94, −95.38)	<.00001	0.32	0
High dose	2	211	Mean difference (IV, random, 95% CI)	−142.88 (−231.80, −53.96)	.002	0.72	0
Total blood loss	6		Mean difference (IV, random, 95% CI)				
Low dose	3	212	Mean difference (IV, random, 95% CI)	−395.55 (−620.57, −170.53)	.0006	2.95	32
High dose	3	164	Mean difference (IV, random, 95% CI)	−135.73 (−211.92, −59.54)	.03	7.13	72
Transfusion rate	10		Risk ratio (M-H, fixed, 95% CI)				
Low dose	6	396	Risk ratio (M-H, fixed, 95% CI)	0.68 (0.53, 0.87)	.002	1.48	0
High dose	4	295	Risk ratio (M-H, fixed, 95% CI)	0.70 (0.52, 0.96)	.22	3.03	34

M-H, Mantel-Haenszel; CI, confidence interval.

Low dose was defined as a bolus dose of less than 10 mg/kg, followed by a maintenance dose of less than 10 mg/kg/h. High dose was defined as bolus dose of 10 to 100 mg/kg and/or followed by a maintenance dose of greater than 10 mg/kg/h.

* X^2, chi-squared heterogeneity statistic; I^2, index of heterogeneity.

Table 5
Age-dependent subgroup analysis

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate	p	X^2*	I^2 (%)*
Intraoperative blood loss (y)	11		Mean difference (IV, random, 95% CI)				
<21	3	124	Mean difference (IV, random, 95% CI)	−853.50 (−1,011.31, −695.69)	.39	1.9	0
21–50	1	76	Mean difference (IV, random, 95% CI)	−67.00 (−347.55, 213.55)	.64	N/A	N/A
>50	7	444	Mean difference (IV, random, 95% CI)	−67.94 (−120.40, −15.47)	.02	7.65	74
Postoperative blood loss (y)	4		Mean difference (IV, random, 95% CI)				
<20	1	43	Mean difference (IV, random, 95% CI)	−161.40 (−313.48, −9.32)	.04	N/A	N/A
20–50	0	0	Mean difference (IV, random, 95% CI)	Not estimable			
>50	3	279	Mean difference (IV, random, 95% CI)	−118.28 (−140.11, −96.45)	.31	1.03	0
Total blood loss (y)	7		Mean difference (IV, random, 95% CI)				
<20	2	65	Mean difference (IV, random, 95% CI)	−357.92 (−663.15, −52.70)	.11	2.49	60
20–50	0	0	Mean difference (IV, random, 95% CI)	Not estimable			
>50	6	376	Mean difference (IV, random, 95% CI)	−202.07 (−299.25, −104.88)	.002	18.55	73
Transfusion rate (y)	9		Risk ratio (M-H, fixed, 95% CI)				
<20	2	84	Risk ratio (M-H, fixed, 95% CI)	0.73 (0.54, 0.98)	.28	1.18	15
20–50	1	76	Risk ratio (M-H, fixed, 95% CI)	0.67 (0.34, 1.29)	.23	N/A	N/A
>50	6	491	Risk ratio (M-H, fixed, 95% CI)	0.67 (0.54, 0.84)	.59	3.7	0

M-H, Mantel-Haenszel; CI, confidence interval; N/A, not applicable.
Studies were grouped into three categories, younger than 20 years, 20 to 50 years, and older than 50 years based on the mean age in the control group.
* X^2, chi-squared heterogeneity statistic; I^2, index of heterogeneity.

postoperative blood loss in the TXA group was 13% lower than in the control.

In the only study that investigated the efficacy of TXA in surgeries were the blood loss was less than 500 mL in the control group, Tsutsumimoto et al. [25] did not find difference in intraoperative blood loss when compared with control. However, they found that TXA significantly reduced postoperative and total blood loss in cervical laminoplasty surgery.

The pooled data from included studies do not appear to show an increase in the rate of complications of TXA. Ker at al. [31] also did not find an increase in thromboembolic events associated with the use of TXA. There is strong Level-I evidence that TXA reduces surgical bleeding in various types of surgeries, with more than 130 RCTs completed to date. A comprehensive metaanalysis by Ker et al. [31] comprising 10,488 surgical patients from 129 RCTs concluded that there was strong evidence that TXA reduced blood transfusion during surgery. Our findings are consistent with the conclusions of three previous metaanalyses, which showed that antifibrinolytics are effective in reducing surgical bleeding in spine surgery [8,10,32]. Two of the metaanalyses included RCTs [8,10] and the other included prospective studies [32]. Strengths of our metaanalysis included analysis of RCTs on both antifibrinolytics drugs—TXA and EACA. We have also included additional RCTs and made corrections to erroneous data presented in previous metaanalyses.

Table 6
Blood loss-dependent subgroup analysis

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate	p	X^2	I^2
Intraoperative blood loss (mL)	11		Mean difference (IV, random, 95% CI)				
<500	1	40	Mean difference (IV, random, 95% CI)	−14.30 (−41.12, 12.52)	.30	N/A	N/A
500–1,500	6	333	Mean difference (IV, random, 95% CI)	−90.76 (−163.57, −17.94)	.02	13.29	62
>1,500	4	271	Mean difference (IV, random, 95% CI)	−676.16 (−982.89, −369.42)	.09	6.56	54
Postoperative blood loss (mL)	4		Mean difference (IV, random, 95% CI)				
<500	0	0	Mean difference (IV, random, 95% CI)	Not estimable	N/A		
500–1,500	3	279	Mean difference (IV, random, 95% CI)	−118.28 (−140.11, −96.45)	.60	1.03	0
>1,500	1	43	Mean difference (IV, random, 95% CI)	−161.40 (−313.48, −9.32)	.04	N/A	N/A
Total blood loss (mL)	5		Mean difference (IV, random, 95% CI)				
<500	1	40	Mean difference (IV, random, 95% CI)	−89.80 (−132.15, −47.45)	<.0001	N/A	N/A
500–1,500	3	146	Mean difference (IV, random, 95% CI)	−323.43 (−578.32, −68.54)	.02	7.71	74
>1,500	1	147	Mean difference (IV, random, 95% CI)	−546.00 (−1,020.40, −71.60)	.02	N/A	N/A
Transfusion rate (mL)	9		Risk ratio (M-H, fixed, 95% CI)				
<500	0	0	Risk ratio (M-H, fixed, 95% CI)	Not estimable	N/A		
500–1,500	6	420	Risk ratio (M-H, fixed, 95% CI)	0.64 (0.50, 0.81)	.68	3.14	0
>1,500	3	231	Risk ratio (M-H, fixed, 95% CI)	0.75 (0.58, 0.97)	.76	1.27	0

X^2, chi-squared heterogeneity statistic; I^2, index of heterogeneity; M-H, Mantel-Haenszel; CI, confidence interval; N/A, not applicable.
Studies were grouped into three categories based on the amount of intraoperative blood loss in the control group: <500 mL, 500 to 1,500 mL, and >1,500 mL.

Table 7
Cumulative cost comparison between high and low dose TXA versus EACA*

Low dose	TXA: 10 mg/kg loading + 1 mg/kg maintenance	EACA: 100 mg/kg loading + 10 mg/kg maintenance
Time (h)	Cumulative cost: TXA*	Cumulative cost: EACA*
1	$3.17	$0.25
2	$5.97	$0.47
3	$8.77	$0.69
4	$11.57	$0.91
5	$14.37	$1.13
6	$17.17	$1.35
7	$19.97	$1.57
8	$22.77	$1.79
High dose	**TXA: 100 mg/kg loading+10 mg/kg maintenance**	**EACA: 1000mg/kg +100mg/kg maintenance**
1	$29.36	$2.51
2	$55.05	$4.71
3	$80.74	$6.91
4	$106.43	$9.11
5	$132.12	$11.31
6	$157.81	$13.51
7	$183.5	$15.71
8	$209.19	$17.91

* TXA, tranexamic acid; EACA, epsilon-aminocaproic acid.

Epsilon-aminocaproic acid is the other antifibrinolytic that has been shown to reduce surgical blood loss. Epsilon-aminocaproic acid has a similar mechanism of action. However, there are only two RCTs (n=218; EACA/placebo=110/108) that investigated the efficacy of EACA on surgical bleeding in spine surgery. A metaanalysis of the studies showed that EACA reduced intra- and postoperative loss by an average of 325 mL (−587, −128, p<.05) and 274 mL (−427, −121, p<.05), respectively. The one study that reported on the efficacy of EACA on transfusion rates did not show any benefit. (risk ratio 0.99 [0.86, 1.1], p=.85). In the EACA studies, one PE in the EACA group and two DVTs and three PEs in the placebo group were reported. Although there is a paucity of evidence on the efficacy of EACA in reducing surgical bleeding in spine surgery, EACA is advantageous over TXA in that it is less expensive. A cumulative cost comparison of the two drugs is shown in Table 7.

A limitation of this study was the significant heterogeneity of dose, age, type of surgery, and the reported outcome measures. Interpretation of subgroup analyses for reported outcomes should not be done without the consideration of study characteristics of contributing studies. Furthermore, the RCTs included in this trial were powered to analyze primary outcomes and not to assess safety. Future research on the effect of antifibrinolytics on complication rates should include a larger number of patients to adequately detect a difference between groups, if a difference does indeed exist. However, despite these limitations, the present metaanalysis supports the efficacy of TXA in reducing blood loss in the setting of spine surgery.

Given the overwhelming evidence on the efficacy of TXA in reducing surgical bleeding there is not doubt about it's indication for use. Future research should be directed towards identifying the appropriate dosing in both our pediatric and adult age groups.

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