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Is High-Dose Tranexamic Safe in Spine Surgery? A Systematic Review and Meta-Analysis

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Abstract

Study Design: Literature review and meta-analysis.

Objectives: Single-center series may be underpowered to detect whether high-dose (HD) tranexamic acid (TXA) confers a higher risk of complications. We sought to determine the safety and efficacy of HD TXA as compared to low-dose (LD) or placebo.

Methods: A systematic literature review was performed to find studies where spine surgery patients were given HD TXA (loading dose ≥30 mg/kg). Complication rates were pooled, and meta-analyses performed on outcomes of interest. Articles were evaluated for risk of bias and a strength of evidence assessment was given for each conclusion.

Results: Twenty three studies (n = 2331) were included. The pooled medical complication rate was 3.2% in pediatric patients, 8.2% in adults. Using lower dose TXA or placebo as the reference, meta-analysis showed no difference in medical complications (n = 1,723, OR 1.22 [95% CI, .78 to 1.22]; P = .388; I^2 = 0%) or thrombotic events (n = 1158 patients, OR 1.27 [95% CI, .71 to 2.63]; P = .528; I^2 = 0%). Compared to LD, HD TXA was associated with less intraoperative blood loss (823 patients, WMD = −285 [95% CI, −564 to −5.90]; P = .0454; I^2 = 86%), fewer perioperative transfusions (n = 505, OR .28 [95% CI, .082 to .96]; P = .043; I^2 = 76%) and lower perioperative transfusion volumes (n = 434, WMD −227.7 mL [95% CI, −377.3 to −78.02]; P = .0029; I^2 = 0%).

Conclusion: Compared to LD TXA or placebo, there is moderate evidence that HD is not associated with an increased risk of medical complications. Compared to LD, there is moderate evidence that HD reduces transfusion requirements. High-Dose TXA can be safely utilized in healthy patients undergoing major spine surgery.

Keywords

tranexamic acid, high dose, low dose, dosing, complications, spine

Introduction

Intraoperative administration of intravenous tranexamic acid (TXA) has gained increased popularity over the last decade as a method to decrease blood loss in spine surgery.[1-4] However, the optimal dose of TXA for spine surgery remains controversial. Compared to lower doses, it has been suggested that higher doses of TXA may confer additional benefits, such as lower transfusion rates and shorter operative times.[2,3,5] The

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clinical implication is that if TXA is safe, there could be a benefit in reducing intra- and peri-operative blood loss in spine surgery. The major barrier to the use of high-dose (HD) TXA is fear of associated medical complications, particularly seizures and complications secondary to clot formation (venous thromboembolism [VTE], myocardial infarction, etc.).[6]

While many series report that high dose TXA is safe, the use of HD TXA is not widely accepted.[5,7-10] Given that medical complications are rare, single-center series are underpowered to detect whether HD TXA increases the rate of medical complications. This is especially true with regards to VTE, which occurs in merely 1% of cases.[11] To date, no investigators have pooled the overall medical complication rate for the many series in which HD TXA has been used. Furthermore, while several reviews have stratified the effect of TXA based on dose (ie, compared the effect of HD to placebo and low-dose [LD] to placebo), no meta-analyses have directly compared the clinical efficacy of HD to LD TXA.[1-4]

The definition used to differentiate HD from LD TXA is of utmost importance when asking this question. For example, Xiong Z et al.[12] performed a meta-analysis comparing dosing regimens with a threshold of 1g TXA. However, this threshold is not in line with the pharmacokinetic and cardiac surgery literature of what constitutes true "HD" TXA. The secondary effects of HD TXA do not occur until a higher dosing threshold is reached.[13,14]

To these ends, the primary purpose of our systematic review and meta-analysis is to test whether HD TXA is as safe as placebo or LD TXA with regards to medical, surgical complications. The secondary goal is to compare clinical measures of efficacy (blood loss, transfusion rate and volume, and operative time) between high- and LD regimens.

Methods

Literature Search

A comprehensive literature search was conducted through the PUBMED, Embase, ERIC, and MEDLINE databases using a semi-automated software (AutoLit, Nested Knowledge).[15] Nested Knowledge is an online platform that facilitates querying, screening, and data extraction for secondary analyses. Full review of the details of our data collection can be accessed on their website. De-duplication was performed, and only original articles in English were included. Further details on the methodology of our search, screening, and data extraction process are publicly available on the Nested Knowledge website.

Study Selection

Inclusion criteria for studies were as follows: (1) Patients underwent any form of spine surgery (2) TXA was administered intravenously before surgery (3) HD TXA was administered to all patients (for case series) or at least 1 treatment arm (for comparative studies) (4) Studies tracked the occurrence of one or more of the following complications: Renal, Cardiopulmonary, Gastrointestinal, Infection, Neurological, VTE, or Other. The combined cohort mean age threshold for classifying studies as "pediatric" instead of "adult" was 22 ≥. "High-dose TXA" was defined as a loading dose of ≥ 30 mg/kg or 2000 mg (29 mg/kg in a 70 kg adult), since a loading dose of 30 mg/kg with 16 mg/kg/hr maintenance is believed to maintain tissue concentrations necessary to achieve the "secondary" effects of TXA.[13,14] Any other TXA dosing regimen was defined as "LD".

Data Extraction

Predefined data, including study characteristics, group baselines, and outcomes, were extracted independently by 2 authors (Table 1). The primary outcomes of interest were the rates of medical, surgical complications, and VTE. Secondary outcomes included intra- and perioperative blood loss (mL), intra- and perioperative transfusion events (%) and volumes (mL), and operative time.

Quality Assessment and Strength of Evidence

Validated scoring systems were used to perform risk of bias assessments for each study. Namely, the Newcastle-Ottawa Scale was used to evaluate retrospective cohort studies,[16,17] and the Cochrane ROB-2 tool was used for randomized controlled trials[18] (Appendix 1a/1b). Two reviewers independently judged the quality of the eligible studies. The quality of evidence regarding the effect of HD TXA on each outcome of interest was evaluated qualitatively using the GRADE approach.

Statistical Analysis

Statistical analyses were performed using RStudio 4.1.2. For primary outcomes of interest, pooled complication rates were calculated for all patients receiving HD TXA. Comparative meta-analyses were performed for outcomes reported by at least 2 comparative studies. Notably, case series and studies comparing HD TXA to other anti-fibrinolytics without a control arm were excluded from comparative analysis. Primary outcomes testing the safety of TXA (medical, surgical complications, and VTE) were compared between HD and Not High Dose (NHD, defined as LD and placebo) studies. LD and placebo were combined into the NHD group to further evidence our hypothesis that HD TXA is safe. Namely, if our analyses showed that HD TXA is safe compared to placebo and LD TXA, this would provide further support for our hypothesis, than comparing HD TXA to LD TXA alone. Our purpose was to test whether HD TXA is more clinically efficacious than LD TXA, thus secondary outcomes were only

Table 1. Summary Characteristics for the 23 Included Studies.

First Author	Country	Year	Age Group	Study Design	Sample Size (E/C)	High Dose TXA Regimen	Surgical Procedure	Levels Fused (E/C)	Follow-Up Period	Risk of Bias
Ahlers	USA	2021	Pediatric	Retrospective cohort	106	50 mg/kg + 10 mg/kg/h	Deformity correction	[11]	30 days	Low
Chou	Taiwan	2021	Pediatric	Retrospective cohort	15/15	100 mg/kg + 10 mg/kg/h	Deformity correction	16/16	Inpatient	High
DaRocha	Brazil	2015	Pediatric	Retrospective cohort	21/19	100 mg/kg + 30 mg/kg/h	Deformity correction	9/9	35 days	Low
Dhawale	USA	2012	Pediatric	Retrospective cohort	30/40	100 mg/kg + 10 mg/kg/h	Deformity correction	16/16	-	Low
Elwatidy	Saudi Arabia	2008	Adult	Double-blind RCT	32/32	2000 mg (adults) or 30 mg/kg/h (peds) + 100 mg/h (adults) or 1 mg/kg/h (peds)	Multilevel or single-level fusion, multilevel decompression	-	30 days	Low
Goobie	USA	2018	Pediatric	Double-blind RCT	56/55	2000 mg (adults) or 30 mg/kg/h (peds) + 100 mg/h (adults) or 1 mg/kg/h (peds)	Deformity correction	[10]/[9]	30 days	Low
Haddad	USA	2020	Adult	Retrospective cohort	58/184	30 mg/kg + 3 mg/kg/h	Three-column osteotomy	13/13	-	High
Halanski	USA	2014	Pediatric	Double-blind RCT	22	100 mg/kg + 10 mg/kg/h	Deformity correction	11	Inpatient	Some concerns
Hasan	Malaysia	2021	Pediatric	Double-blind RCT	83/83	30 mg/kg + 10 mg/kg/h	Deformity correction	[11]/[11]	30 days	Low
Johnson	USA	2017	Pediatric	Retrospective cohort	44/72	50 mg/kg + 5 mg/kg/h	Deformity correction	11/11	Inpatient	High
Kushioka	Japan	2017	Adult	Retrospective cohort	30/30	2000 mg + 2000 mg 16h post-op	PLIF	-	-	Low
Lin	USA	2018	Adult	Case series	100	50 mg/kg + 5 mg/kg/h	Deformity correction	14	-	NA
Lykissas	USA	2013	Pediatric	Retrospective cohort	25/24	100 mg/kg + 10 mg/kg/h	Deformity correction	11/13	-	Low
Ng	Hong Kong	2015	Pediatric	Retrospective cohort	55/35	100 mg/kg + 10 mg/kg/h	Deformity correction	14/12	Inpatient	High
Raman	USA	2019	Adult	Retrospective cohort	60/258	40 mg/kg + 1 mg/kg/h 30 mg/kg10 mg/kg/h 50 mg/kg + 5 mg/kg/h	Deformity correction	12/11	3 months	Low
Ramkiran	India	2020	Pediatric	Double-blind RCT	12/12	50 mg/kg + 10 mg/kg/h	Deformity correction	Not provided	-	Some concerns
Sethna	USA	2005	Pediatric	Double-blind RTC	23/21	100 mg/kg + 10 mg/kg/h	Deformity correction	[14]/[13]	-	Some concerns
Shapiro	USA	2007	Pediatric	Retrospective cohort	20/36	100 mg/kg + 10 mg/kg/h	Deformity correction	14/14	2 weeks	Low
Shi	China	2017	Adult	Double-blind RCT	50/46	30 mg/kg + 2 mg/kg/h	PLIF	-	Inpatient	Some concerns

(continued)

Table 1. (continued)

First Author	Country	Year	Age Group	Study Design	Sample Size (E/C)	High Dose TXA Regimen	Surgical Procedure	Levels Fused (E/C)	Follow-Up Period	Risk of Bias
Sui	China	2016	Pediatric	Retrospective cohort	71/66	100 mg/kg + 10 mg/kg/h	Deformity correction	13/13	90 days	Low
Tumber	USA	2021	Pediatric	Retrospective cohort	126/97	>30 mg/kg + 10 mg/kg/h	Deformity correction	11/11	-	Low
Xie	China	2015	Pediatric	Retrospective cohort	26/33	100 mg/kg + 10 mg/kg/h	Vertebral column resection	13/12	-	High
Zhang	China	2021	Pediatric	Double-blind RCT	108	50 mg/kg + 10 mg/kg/h + oral TXA	Deformity correction	10	-	Some concerns

E/C = experimental (high dose)/control (low dose or placebo). Mean surgical levels fused is rounded to a whole number, median values are shown as [n]. TXA regimen are given as pre-op loading dose + continuous infusion. Values that were not provided are shown as `-`. Fields that are not applicable are shown as 'NA'. Risk of bias was assessed either using the Cochrane ROB2 tool for randomized trials or the Newcastle Ottawa Scale for retrospective cohort studies, with a score of 7-9 classified as low risk of bias, and a score of 4-6 as a high risk of bias (Appendix 1a/1b).

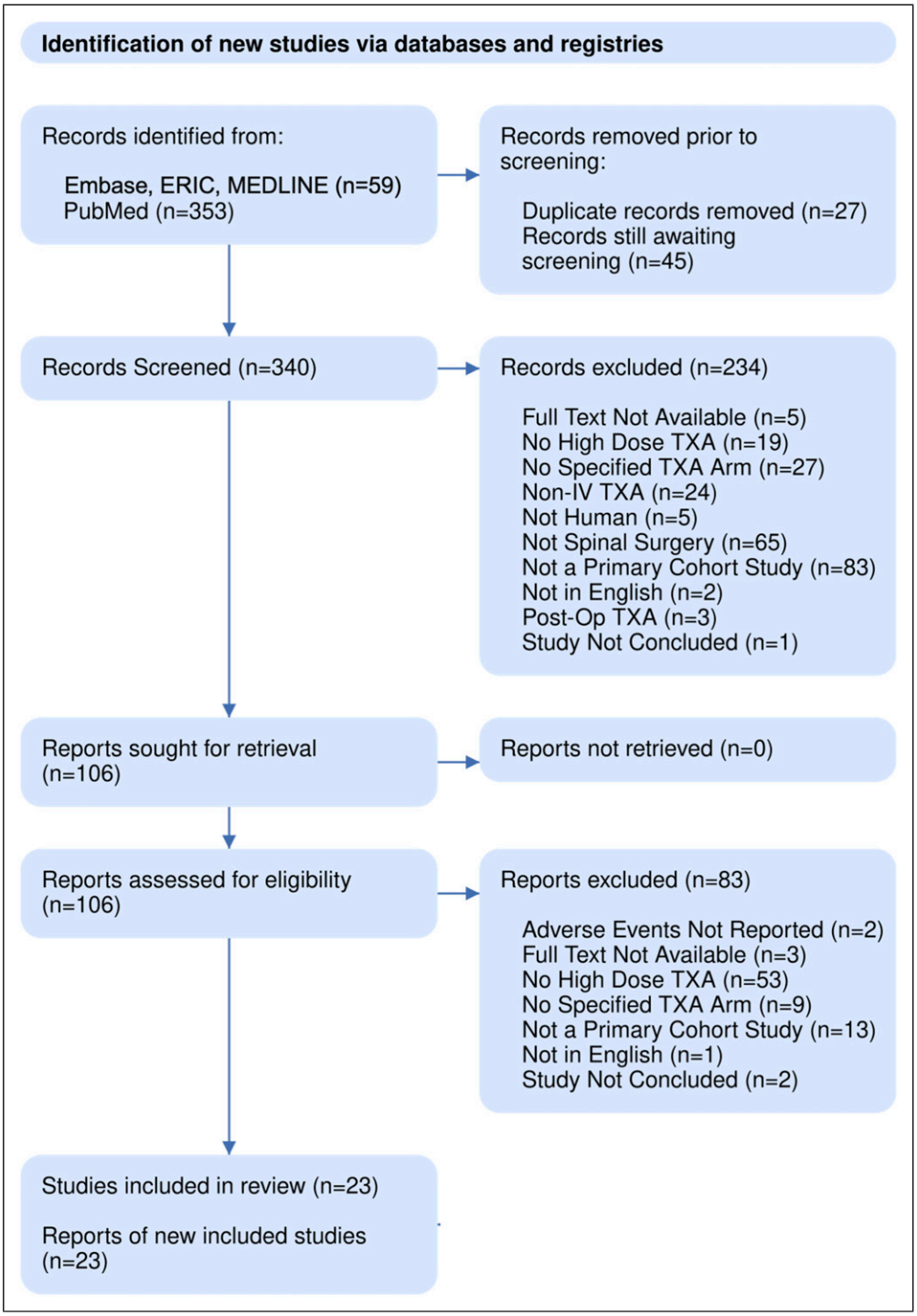

Figure 1. PRISMA diagram showing the literature search and screening process.

evaluated within studies comparing HD vs LD. For dichotomous outcomes, odds ratios (OR) and 95% confidence intervals (CI) were calculated as pooled metrics with the Mantel-Haenszel method. The pooled effect size for continuous outcomes was reported as a weighted mean difference (WMD) and 95% CI calculated using pooled means and standard deviations.[19] Heterogeneity was assessed using I^2 statistics. If there was no evidence of substantial heterogeneity ($I^2 \leq 50\%$), a fixed-effect model was used. For further details on statistical methods, see Appendix 2. Risk of publication bias was evaluated using a funnel plot analysis performed on the most frequently reported outcome (VTE).

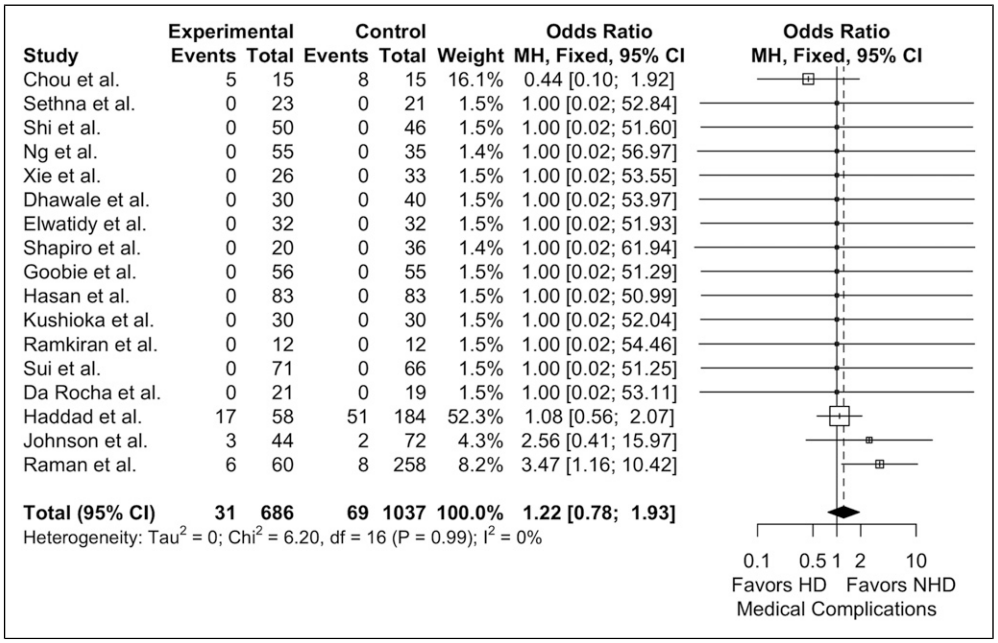

Figure 2. Meta-analysis with a fixed effects model of studies reporting medical complications for high-dose (HD) vs not high-dose (NHD = placebo or low-dose) cohorts across all age groups. OR = odds ratio, MH = Mantel-Haenszel, df = degrees of freedom.

Results

Search Outcomes

Database queries retrieved a total of 367 results. No further studies were identified through other sources and 27 duplicates were removed. After abstract and full-text screening, a total of 23 studies and 2331 patients were included in the present review. Figure 1 details our PRISMA screening process.

Study Characteristics

Included studies were either retrospective cohort reviews (n = 14), double blinded RCTs (n = 8), or case series (n = 1), published between 2005 and 2021, with sample sizes ranging from 22 to 318 total participants (Table 1). Of the 23 studies, 1 was a case series of HD interventions,[20] 1 compared various HD regimens to each other,[7] 4 compared HD and LD cohorts,[9,21-23] 15 compared HD to placebo controls, and 2 compared HD to other anti-fibrolytics.[24,25] Funnel plot analysis was performed using VTE as the outcome of interest, the funnel plot showed some asymmetry with a moderate risk of publication bias (Appendix 3).

Primary Outcomes

The pooled medical complication rate for patients receiving HD TXA was 4.7% (21 studies, 1022 patients). This rate was lower in pediatric patients (3.18%, 15 studies, 692 patients) than in adults (8.19%, 6 studies, 330 patients) (Incidence rate difference = 5%, P = .0006, Incidence rate ratio = 2.57, P = .0011). Meta-analysis of 17 studies, using NHD as the reference group, showed no significant difference in medical complication rates between HD and NHD TXA (1723 patients; P = .388) (Figure 2). Similarly, meta-analyses within adult (n = 5) and pediatric (n = 12) study subgroups showed no significant differences in medical complication rates (780 patients, OR = 1.37 [95% CI, .802 to 2.37]; P = .246; I^2 = 0% and 943 patients, OR = .932 [95% CI, .401 to 2.13]; P = .867; I^2 = 0%, respectively).

The pooled rate of VTE in HD patients was .682% (23 studies, 1173 patients), again, lower in pediatric patients (0%, 17 studies, 843 patients) compared to adults (2.42%, 6 studies, 330 patients) (Incidence rate difference = 2.4%, P < .0001, Incidence rate ratio = n/a). Using NHD as the reference, there was no appreciable difference in our 17 study meta-analyses between HD and NHD groups (1158 patients, P = .528) (Figure 3). Subgroup analysis of adult (n = 5) and pediatric (n = 14) studies also showed no significant differences in VTE outcomes (780 patients, OR = 1.58 [95% CI, .583 to 4.26]; P = .369; I^2 = 0% and 1215 patients, OR = 1.00 [95% CI, .345 to 2.90]; P = 1.00; I^2 = 0%, respectively).

Analyzing the 3 comparative studies[21,26,27] that reported surgical outcomes also did not reveal any appreciable difference between HD and NHD groups (590 patients, OR = 1.23 [95% CI, .530 2.86]; P = .629; I^2 = 0%).

Secondary Outcomes

Four studies were included in the meta-analysis for intraoperative blood loss which showed that, with LD as the reference, HD TXA is significantly more effective in reducing

blood loss ($P = .0454$) (Figure 4). Meta-analysis with 2 studies on perioperative allogenic transfusion volumes also showed that HD is more effective than LD ($P = .0029$) (Figure 5). Results for intraoperative transfusion volumes similarly showed significant results favoring HD (2 studies, 434 patients, WMD = −228 [95% CI, −360 to −95.1]; $P = .0008$; $I^2 = 0\%$).

Analysis on perioperative transfusion events showed significant results favoring HD over NHD (2 studies, 505 patients, $P = .043$) (Figure 6) while there was a present but insignificant difference for intraoperative transfusion events (2 studies, 339 patients, OR = .244 [95% CI, .053 to 1.115]; $P = .069$; $I^2 = 88\%$). Lastly, 3 studies were included in the meta-analysis for surgical duration,[9,21,22] which demonstrated no correlation with TXA dose ($P = .904$) (Appendix 4).

Discussion

In our systematic literature review we found a pooled medical complication rate after HD TXA consistent with medical complication rates in non-TXA outcomes studies.[28-31] Furthermore, our meta-analyses provided high-quality evidence that HD TXA is not associated with an increased risk of medical complication after adult or pediatric spine surgery. This lack of association has been previously reported in systematic reviews on the use of TXA in pediatric spine surgery, scoliosis correction, and lumbar interbody fusion.[2,32,33] Our review found only one retrospective cohort study with an increased rate of medical complications in the HD TXA cohort. Out of the 60 patients who received HD

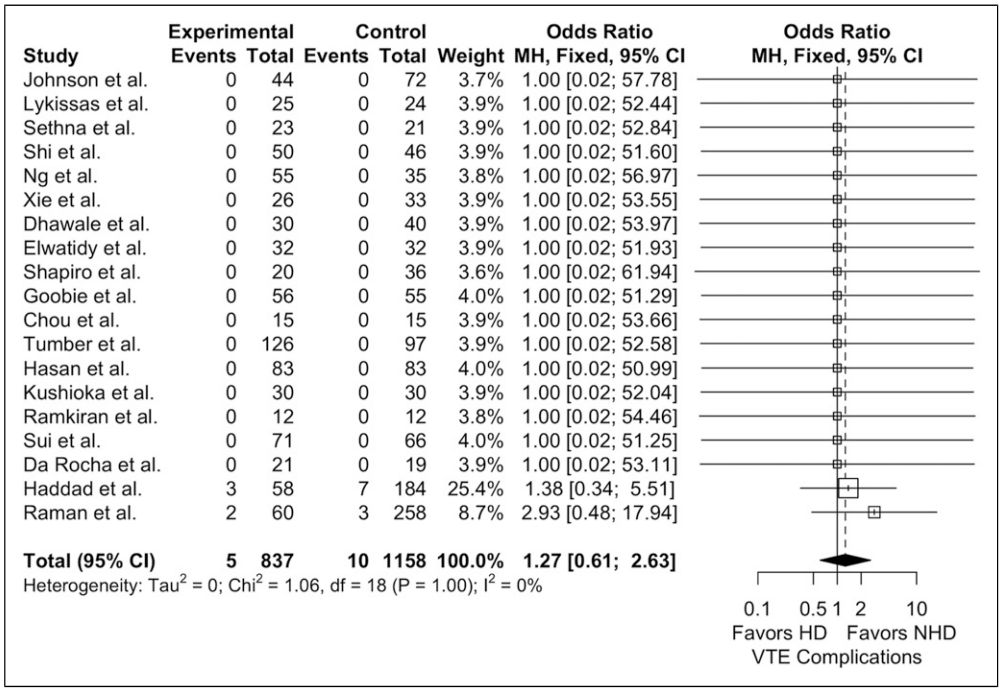

Figure 3. Meta-analysis with a fixed effects model of studies reporting VTE complications for high-dose (HD) vs not high-dose (NHD = placebo or low-dose) cohorts across all age groups. OR = odds ratio, MH = Mantel-Haenszel, df = degrees of freedom.

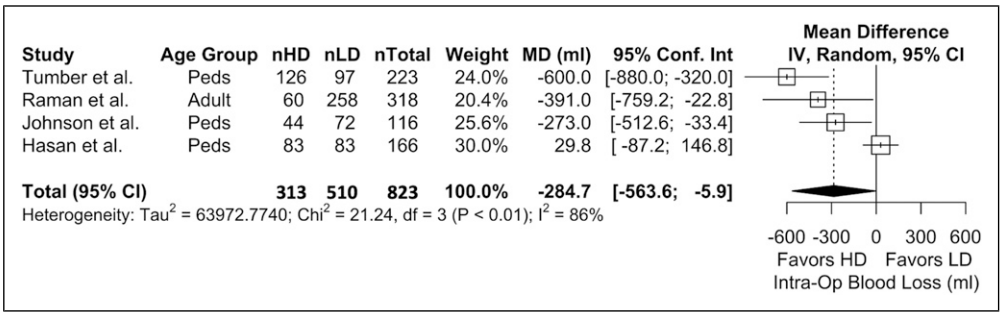

Figure 4. Meta-analysis with a random effects model comparing intraoperative blood loss (ml) between highdose (HD) and low-dose (LD) cohorts across all age groups. nHD = number of HD patients, nLD = number of LD patients, nTotal = total patients. MD = mean difference, IV = inverse variance, df = degrees of freedom.

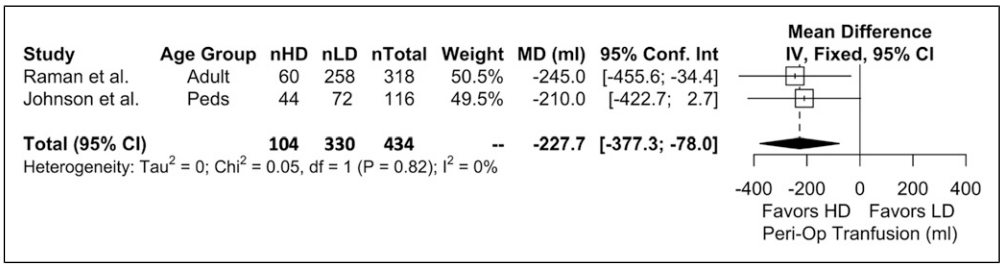

Figure 5. Meta-analysis with a fixed effects model comparing perioperative RBC transfusions (ml) between high-dose (HD) and low-dose (LD) cohorts across all age groups. nHD = number of HD patients, nLD = number of LD patients, nTotal = total patients. MD = mean difference, IV = inverse variance, df = degrees of freedom.

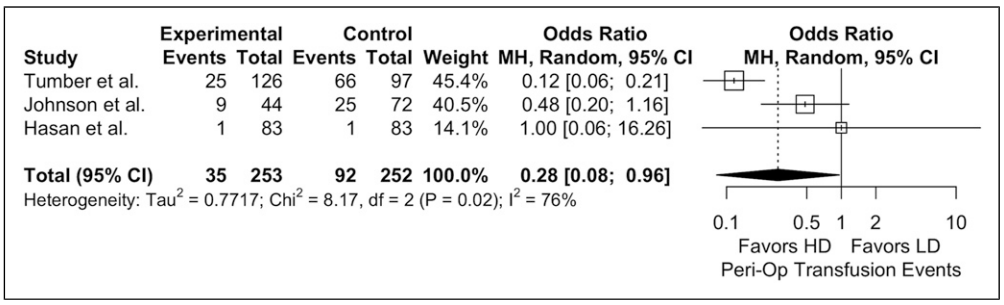

Figure 6. Meta analysis with a random effects model comparing perioperative RBC transfusion events between high-dose (HD) and low-dose (LD) cohorts across all age groups. OR = odds ratio, MH = Mantel- Haenszel, df = degrees of freedom.

TXA, 3 patients developed postoperative atrial fibrillation (of which 1 had an NSTEMI), compared to none in the LD cohort.[10] Notably, the authors specify that these 3 patients all had a history of cardiac disease and/or diabetes mellitus and that all patients returned to sinus rhythm while inpatient or at first follow-up.

Regarding specific medical complications, we found a pooled VTE rate of 2.4% in adults, similar to reported single- and multicenter rates of VTE in non-TXA focused studies.[11] Meta-analysis revealed high-quality evidence that HD TXA did not confer an increased risk of VTE compared to NHD. However, our findings regarding medical complications and VTE must be interpreted with caution. First, except for a few patients in the case series by Xie et al,[7] no adult patient received a TXA regimen higher than 50 mg/kg loading with 5 mg/kg/h maintenance, so we cannot comment on the safety of regimens higher than this for adults. Second, most studies were retrospective, introducing selection bias in terms of which patients received HD TXA. Third, all randomized trials excluded patients with thromboembolic disorders, and several others also excluded patients with hepatic, renal, or cardiac disease.[34-38] Thus, while HD TXA seems to be safe in patients without a significant medical history, the risk-benefit relationship in patients with cardiac, renal, hematologic, or neurologic conditions requires further investigation.

A special note must be made regarding seizures. Within the field of cardiac surgery, TXA has shown a dose-dependent relationship with risk of seizures.[6] However, this association has not borne out in other fields in which TXA is used and was not demonstrated in our meta-analysis.[6,39] Out of the 1173 patients receiving HD TXA in our meta-analysis, no seizure occurred, and in NHD patients, only 1 seizure was reported.[21] This finding may be secondary to 2 differences. First, the maintenance dose used in the cardiac surgery literature (16 mg/kg/h) is higher than that reported in spine surgery (Table 1).[6,13,40] Second, use of cardiopulmonary bypass is unique to cardiac surgery. Pharmacokinetics and tissue concentrations of TXA may vary based on these factors. Future studies on *in vivo* pharmacokinetics are needed to understand the TXA blood concentrations achieved by varying dosage regimens during spine surgery.

We found low-quality evidence that the rate of surgical complications is not decreased by the use of HD TXA. Our quality of evidence assessment for this conclusion is lower because this outcome was heterogeneously defined and reported by comparatively fewer studies.[10,20,27,41] Given that rates of surgical complications are highly variable among procedures, defining this outcome will require procedure-specific trials.

The clinical benefit of HD TXA is dependent on its ability to reduce blood loss by a greater extent than that of LD regimens. Physiologically, TXA at low tissue concentrations (10 µg/mL) inhibits fibrinolysis by approximately 80% in animal models.[42] Higher concentrations (126-152 µg/mL) have the potential to further inhibit fibrinolysis and enhance

hemostasis by increasing thrombin formation, improving platelet function.[9,13,14,43] There may be an anti-inflammatory effect as well through its action on cytokine production.[39]

Our analysis provides moderate evidence that there is a clinical benefit (in terms transfusion requirements and blood loss) to the use of HD over LD TXA in spine surgery. Past meta-analyses have indirectly supported this notion, finding that the effect of HD TXA vs placebo is larger than that of LD vs placebo with regards to transfusion rate.[1,2,4] We showed that intraoperative blood loss and both perioperative allogeneic transfusion rate and volume was lower with HD regimens.[44] Notably, the effect size was greatest in studies with the largest blood loss.[9,10] For example, Tumber et al reviewed 223 patients with AIS, with an average EBL per vertebral body fused (EBL/VB) of 160 and 104 mL in the LD and HD cohorts, respectively.[9] They found a statistically significant 48% reduction in pRBC transfusion rate (67% LD vs 19% HD, $P < .001$). On the other hand, Johnson et al also examined 116 AIS patients, reporting an average EBL/VB of 87 and 63, respectively.[45] However, while they reported a lower transfusion volume in the HD cohort (.4 unit pRBC LD vs 1 unit pRBC HD, $P = .04$), rates of transfusion were comparable (35% LD vs 21% HD, $P = .1$). Thus, it appears that the clinical benefit (ie, reduction of allogeneic transfusion rates) of high-vs LD TXA is likely only realized in spine surgeries with the greatest expected blood loss.

Theoretically, a reduction in blood loss could translate to a clearer surgical field with subsequent improvement in operative efficiency. However, we found low-quality evidence that HD TXA does not reduce operative time. Though Hui et al reported a reduction in operative time with any TXA vs placebo, the mean difference was likely clinically insignificant (−4.7 min, 95% CI −8.8 to −.7)[4]. To this end, any conclusions regarding the effect of TXA on operative time would be premature.

There were several limitations to this investigation. First, medical complication rates after spine surgery are widely variable and procedure dependent.[28-31] There was a wide variety of procedures both within and among the trials. Despite this variability, the finding was consistent in nearly every study, regardless of the dose or population. For this reason, we believe there is still high quality evidence supporting this finding. Second, follow-up times for our primary outcome varied among studies, with some reporting complication rates but not specifying follow up times.[7,9,20,26,40,46-49] However, regardless of follow-up time, our findings were largely consistent, leading us to maintain our conclusions. Third, there may have been reporting bias among the studies in how complications were defined. This was especially relevant for studies which reported "complications related to TXA" without giving further detail.[25,46,47] To this end, our overall pooled rate of complications likely underestimates the true rate. However, the comparative analyses are still valid given that each study definition was applied to both the HD and NHD group. Finally, there were not enough comparative studies that reported perioperative blood loss to allow meta-analyses on this outcome.

Conclusions

With regards to the primary purpose of our study, HD TXA does not appear to confer any increased risk of medical complication when given to the "right" patient (ie, those with a medical history consistent with the patients in our reviewed studies). Our analysis also provides moderate evidence that HD TXA may reduce intraoperative blood loss and allogeneic transfusions (rates and volume), a clinical advantage over LD regimens. Thus, future research should address 3 major deficiencies. First, the exact risk-benefit relationship between dosage and comorbidities must be addressed. The question still stands whether HD (or any) TXA is safe in patients with hematologic, cardiac, or epileptic conditions. Second, trials should be prioritized to target patients which stand to benefit the most, namely those undergoing surgeries with largest expected blood losses (adult deformity corrections, oncologic resections, etc.). Patients undergoing such surgeries are also often those with the largest comorbidity burden, giving further impetus to the need for an accurate understanding of risks associated with HD TXA in patients without pristine medical histories. Finally, the pharmacokinetics of TXA in humans remain unknown. HD TXA is associated with seizures in cardiopulmonary bypass but not spine surgery, suggesting that the pharmacokinetics may vary based on the patterns and timing of blood loss specific to varying surgical procedures. Pharmacokinetic data is an essential endpoint that must be included in any well-designed study of TXA, with real implications for amount and timing of dose.

Declaration of Conflicting Interests

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IRB approval statement

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Supplemental Material

Supplemental material for this article is available online

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