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Review Article

Efficacy of high-dose versus low-dose tranexamic acid for reduction of blood loss in adolescent idiopathic scoliosis surgery: A systematic review and meta-analysis

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ABSTRACT

Background: Recent studies have suggested that high-dose tranexamic acid (TXA) may be an effective method for reducing blood loss during adolescent idiopathic scoliosis (AIS) surgery. This study aims to perform a systematic review and meta-analysis to compare the outcomes of high-dose versus low-dose TXA for AIS surgery.

Methods: Searches were conducted in major databases such as PubMed, Scopus, Google Scholar, and Cochrane Library for relevant studies comparing high-dose and low-dose TXA outcomes in terms of blood loss, red blood cell transfusions, and hemoglobin changes. This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered with PROSPERO (CRD42024547735).

Results: Four studies were included, published between 2009 and 2022, encompassing a total of 531 patients. High-dose TXA showed less blood loss compared to low-dose TXA, with a pooled mean difference of −0.40 (95% CI, −0.79–−0.01). Neither the volume of blood products used nor the decrease in hemoglobin levels showed significant differences between the groups.

Conclusion: High-dose TXA appears to be more effective in reducing blood loss during AIS surgery compared to low-dose TXA. Further robust clinical trials with larger sample sizes are necessary to confirm these results and establish optimal dosing regimens for maximizing efficacy while ensuring safety.

Keywords: Abnormal curvature of the spine, Adolescent idiopathic scoliosis, Blood loss during surgery, Tranexamic acid

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is characterized by abnormal spinal curvature, affecting 1–3% of adolescents. Children aged 11–18 years commonly experience this condition, with a 3:1 prevalence in females compared to males.[14] The incidence of AIS in the US population stratified by age group reveals a higher prevalence in children aged 13–15 years, with females having a higher incidence than males.[21] Management strategies for AIS range from conservative

approaches, such as bracing, to surgical interventions for severe cases.[12]

Surgical treatment, particularly posterior spinal fusion (PSF), is a well-established method for correcting severe AIS deformities. While PSF generally yields positive outcomes, it is associated with significant risks, including dural tears, peripheral neuropathy, thromboembolic events, and postoperative infections.[2] Researchers commonly assess patient outcomes using the Scoliosis Research Society-22 (SRS-22) questionnaire, although some studies have also utilized the SRS-30 questionnaire.[16] A major concern during such surgeries is blood loss, which typically ranges from 275 to 907 mL.[4] To mitigate this issue, physicians frequently use tranexamic acid (TXA), an antifibrinolytic agent that reduces bleeding by inhibiting plasminogen activation.[4]

Recent investigations focused on determining the optimal dose of TXA to minimize intraoperative blood loss. Some studies suggest that high-dose TXA may be more effective than low-dose TXA in reducing both intraoperative blood loss and the need for red blood cell transfusions.[7,8,11] Despite these findings, the optimal dose regimen remains unclear. Therefore, this study aims to conduct a systematic review and meta-analysis to evaluate and compare the efficacy of high-dose versus low-dose TXA in AIS surgery, thereby providing a clear understanding of its relative effectiveness.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[14] The protocol is registered with PROSPERO under the identifier (CRD42024547735).

Literature search

We carried out a literature search on MEDLINE (through PubMed), Scopus, Google Scholar, and Cochrane Library using keywords composed of medical subject heading terms about TXA, idiopathic adolescent scoliosis surgery, pediatric scoliosis surgery, and blood loss. We employed a detailed search strategy for individual databases, as detailed in Table 1.

Inclusion and exclusion criteria

Inclusion criteria

- Study Design: Randomized controlled trials (RCTs), comparative retrospective cohort studies
- Patient Population: Age <18 years old, diagnosed with scoliosis, underwent surgical correction of scoliosis, treated with TXA to prevent blood loss
- Intervention: Studies comparing high-dose versus low-dose TXA groups.

Exclusion criteria

- Study Design: Quasi-experimental studies, observational studies, case reports, case series, reviews, nonhuman studies, editorials, conference abstracts, and editorials
- Patient Population: Patients who received anticoagulants other than TXA.

Study screening and selection

We used Mendeley version 1.19.8 (Mendeley Ltd., Amsterdam, the Netherlands) to carry out study selection and screening. Two authors independently performed deduplication, after which they performed an initial screening based on titles and abstracts. The remaining articles underwent screening based on full texts. A third author resolved any discrepancies related to study selection among the two authors.

Data extraction

We created a spreadsheet to extract relevant data items such as study name, details about the first author, sample size, year of publication, mean age of participants, mean weight of participants, number of female participants, mean major Cobb angle in degrees, and mean surgical duration in hours. The data relating to outcomes measures such as mean estimated blood loss (EBL) in Liters postoperatively, number of patients receiving intraoperative blood products in the form of packed red blood cells (PRBCs), fresh frozen plasma (FFP), or platelets, and mean fall in hemoglobin at least 24 h after surgery was also extracted on a separated spreadsheet. Two authors independently performed data extraction, and a third author reviewed the entries made on the spreadsheet and resolved any discrepancies.

Quality and risk of bias (RoB) assessment using RoB-2 tools

A third author resolved discrepancies after two separate writers evaluated the RoB. We employed the Cochrane RoB instrument (RoB 2.0) for RCTs, which has five areas, each accompanied by a series of questions. The responses to these inquiries are "yes," "no," "possibly yes," "possibly no," and "no information available." We then integrate the results into a graphic to determine one of three bias levels: low risk, moderate worry, or high risk. We consider a study to have a low overall RoB if all five domains demonstrate a low RoB. The study is considered to exhibit potential bias if at least one domain raises issues. We classify a study as having a high RoB if at least one domain exhibits a high RoB or numerous domains present problems.[19]

Outcomes measured

Our primary outcomes were the estimation of blood loss postoperatively and intraoperative blood products used, such as PRBCs, FFP, or platelets. Secondary outcomes were perioperative changes in hemoglobin, adverse events, and factors that influence total blood loss.

Statistical analysis and heterogeneity

We used Review Manager version 5.4 (RevMan, version 5.4; The Cochrane Collaboration, Copenhagen, Denmark)[15] for pooling mean differences (MD) and odds ratios (OR) along with their 95% confidence intervals (95% CIs). Due to the estimated heterogeneity of the true effect sizes, we employed the random effects model during our statistical analysis. We quantified heterogeneity using the I2 index, considering a value of 50% as significant heterogeneity. For outcomes with 3–10 studies, we used the Luis Furuya Kanamori (LFK) index to estimate publication bias. We constructed DOI plots using MetaXL version 5.3 (EpiGear International Pty., Sunrise Beach, Queensland, Australia). We performed sensitivity analysis by removing studies having a different study design or some concerns related to the RoB.

RESULTS

Literature search and study characteristics

Figure 1 shows the PRISMA flowchart of the study selection process. After database searching, we retrieved a total of 1889 records, of which we removed 313 after deduplication. We screened the remaining 1576 articles based on titles and abstracts, removing 1125 of them. A total of 451 articles underwent full-text screening, out of which four studies were included in this systematic review and meta-analysis.

Characteristics of the included studies

Among the four included studies, three were retrospective cohort studies, and one was RCT. All studies were published between 2009 and 2022 and included a total of 531 patients. The mean age of the patients ranged from 14 to 15.4 years. The mean weight of the participants ranged from 45.3 to 58 kg. The mean major Cobb angle ranged from 58.7 to 64.2° among the participants. The mean surgical duration for the groups which were administered high-dose TXA ranged from 2.17 to 7.2 h while it ranged from 2 to 6.4 h for the groups which were administered low-dose TXA.

Quality assessment of included studies

Figure 2 presents the overall summary plot of the quality assessment, which reveals a significant prevalence of certain concerns within the overall bias domain. Most of the concerts arose in the context of randomizing the included studies. Figure 3 shows the individual RoB assessment of the included studies, showing that Grant *et al.*,[7] Johnson *et al.*,[11] and Tumber *et al.*[21] had some concerns due to the randomization process. This contributes to lowering the quality of the evidence in this meta-analysis.

Statistical analysis and heterogeneity

EBL

All four studies reported EBL postoperatively. The results revealed a nonsignificant benefit in terms of EBL postoperatively for the high-dose TXA group as compared to the low-dose TXA group with a pooled MD of −0.40 (95% CI, −0.79–−0.01; $P = 0.05$; $I^2 = 89\%$) [Figure 4]. Major asymmetry was observed in the DOI plot (LFK Index = −4.82), indicating the presence of publication bias [Figure 5].

A sensitivity analysis

It was performed by removing Hasan *et al.*[8] and revealed a significant reduction in EBL for the high-dose TXA group as compared to the low-dose TXA group with a pooled MD of −0.58 (95% CI, −1.03–−0.13; $P = 0.01$; $I^2 = 78\%$) [Figure 6].

Intraoperation blood products use

Compared to the low-dose TXA, the high-dose TXA group received fewer PRBCs with a pooled OR of 0.22 (95% CI, 0.09–0.57; $P = 0.002$; $I^2 = 61\%$) [Figure 7]. No significant results were observed for several patients receiving FFP and Platelets in the high-dose and low-dose TXA groups with pooled relative risk (RR) of 0.95 (95% CI, 0.22–4.17; $P = 0.94$; $I^2 = 22\%$) [Figure 7] and 0.18 (95% CI, 0.02–1.50; $P = 0.11$; $I^2 = 0\%$) [Figure 7].

A sensitivity analysis

It was performed to lower heterogeneity for PRBC use intraoperatively by removing Tumber *et al.*,[21] which yielded a pooled RR of 0.39 (95% CI, 0.17–0.90; $P = 0.03$; $I^2 = 0\%$). Analysis showed a lower number of patients receiving PRBC units intraoperatively in the high-dose TXA group as compared to the low-dose TXA group [Figure 8].

Fall in hemoglobin

The results yielded a statistically nonsignificant benefit for the patients in the low-dose group as compared to the patients in the high-dose group in terms of fall in hemoglobin with a pooled MD of 0.23 (95% CI, −0.08–0.54; $P = 0.14$; $I^2 = 0\%$) [Figure 9].

DISCUSSION

This study investigated the use of high-dose versus low-dose TXA for blood loss and transfusion requirements following

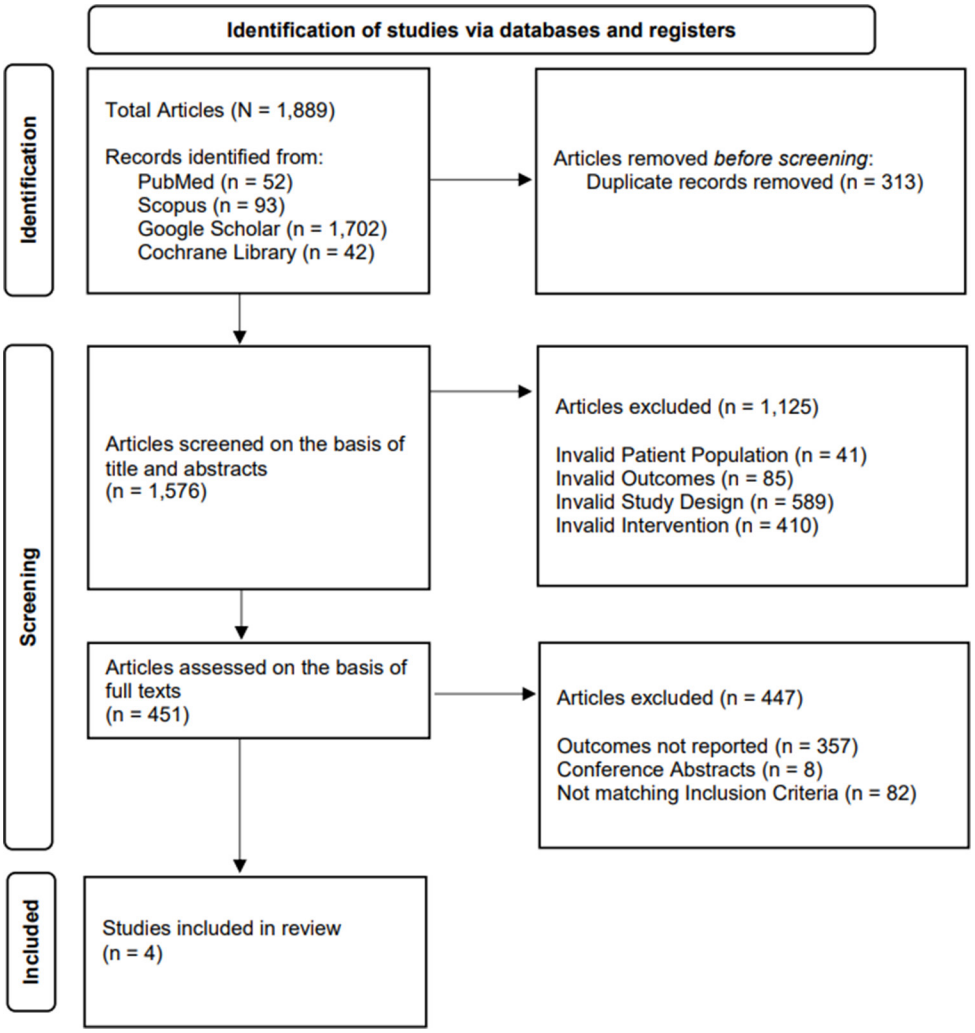

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart of the literature search and studies selection process. n/N refers to the number of cases or samples in a group (n) relative to the total number of cases or samples in the study (N).

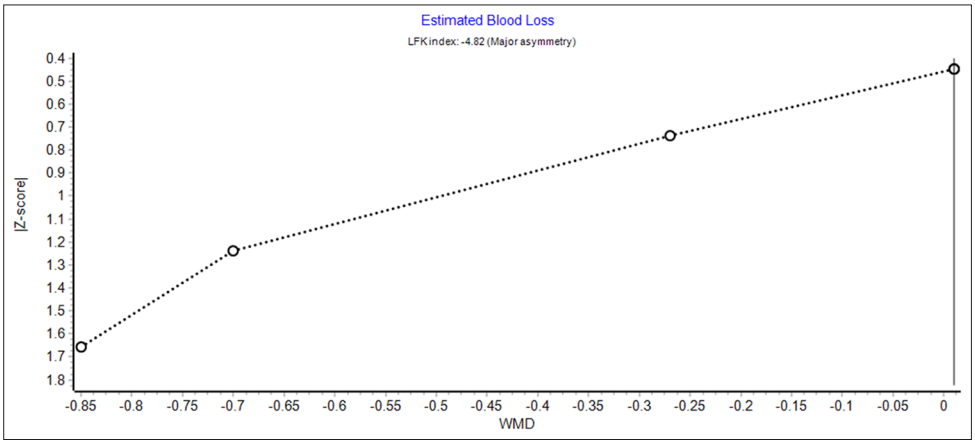

Figure 2: Summary plot of quality assessment. This figure provides a summary of the risk of bias assessment for each included study, categorized as low risk, high risk, or some concerns across various domains. WMD: Weighted mean difference, LFK: Luis furuya-kanamori

Table 1: Baseline characteristics of the included studies

Studies (Year)	Type	Sample size (n)		Age (years)		Females (n)		Weight (kg)		Major Cobb angle (degrees)		Surgical duration (Hours)	
		High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose
Grant *et al.* (2009)[7]	RCS	11	15	15.4 (2.3)	14.7 (2.0)	15	9	58.0 (10.8)	50.3 (8.6)	61.6 (8.6)	58.7 (8.0)	7.2 (1.1)	6.4 (1.6)
Hasan *et al.* (2021)[8]	RCT	83	83	14.1 (2.1)	14.6 (3.0)	76	68	45.3 (9.0)	46.6 (9.3)	63.0 [55.0, 82.0]*	64.0 [57.0, 74.0]*	2.17 [1.75, 2.58]*	2 [1.67, 2.5]*
Johnson *et al.* (2017)[11]	RCS	44	72	14.5 (1.9)	14.3 (1.9)	29	49	54 (16)	52 (16)	NR	NR	3.6 (0.7)	3.6 (0.9)
Tumber *et al.* (2022)[21]	RCS	126	97	14 [13, 16]*	14 [13, 15]*	NR	NR	55.6 [49, 64.6]*	57.2 [48.8, 67.4]*	60 [52.7, 69.5]*	59.1 [51.4, 65.9]*	4.98 [4.02, 5.96]*	5.95 [4.93, 6.65]*

RCS: Retrospective cohort study; RCT: Randomized controlled trial; NR: Not reported
* Data reported as Median [Interquartile range]

surgery; our findings demonstrated two key results. First, patients receiving the high dose experienced significantly lower EBL compared to those receiving the low dose. Second, the high-dose group required fewer units of PRBCs during surgery despite no statistically significant difference in the use of FFP or platelets between the groups. Interestingly, neither group showed a significant change in hemoglobin levels at least 24 hours after surgery.

Our study identified a statistically significant difference between the high-dose and low-dose TXA groups, with the high-dose group averaging 0.4 units less blood loss. However, the wide CI and high variation across studies limit the certainty of this effect. This variability raises questions about the generalizability of our findings and contradicts the findings of a previous study [8], which investigated TXA use to reduce blood loss during spinal surgery. The study divided the patients into two groups: a high-dose group, which received a larger initial dose of 30 mg/kg, followed by a higher maintenance infusion of 10 mg/kg/h, and a low-dose group, which received an initial dose of 10 mg/kg and a maintenance dose of 1 mg/kg/h. Interestingly, the total amount of blood lost during surgery was not statistically different between the two groups. While TXA dosing did not significantly impact blood loss in that study,[8] other factors such as sex, number of fused vertebrae, and surgery duration were associated with higher blood loss.

Another study by Johnson *et al.* (2017)[11] investigated the use of TXA to reduce blood loss during spinal fusion surgery for scoliosis in adolescents. The study compared a high dose (50 mg/kg loading + 5 mg/kg/h maintenance) with a low dose (10 mg/kg loading + 1 mg/kg/h maintenance) of TXA. Their findings indicate that the high dose of TXA is more effective in reducing blood loss and the need for blood transfusions, which is consistent with our analysis revealing that the high-dose TXA group required fewer PRBCs. However, it is important to note that the definition of high- and low-dose TXA varies across studies. For instance, studies by Hasan *et al.* (2021)[8] and Johnson *et al.* (2017)[11] used different dose regimens, highlighting the lack of standardization. This inconsistency complicates the comparison of results across studies, contributes to the ongoing controversy regarding optimal dosing, and results in heterogeneous findings. Hence, making a standard definition for high- and low-dose TXA in scoliosis surgery would make it easier to compare studies and figure out the best way to give TXA so that patients lose the least amount of blood and do not need as many transfusions.

Hasan *et al.* (2021)[8] found the mean duration of surgery in the general population to be 2 h, but our analysis showed a longer duration for surgeries involving high-dose TXA (ranging from 3.6 to 7.2 h) compared to low-dose TXA (3.6–6.4 h). We could attribute this discrepancy to the inclusion of a study by Tumber *et al.* (2022)[21] in our analysis, which demonstrated a high mean duration in both treatment groups (>6 h in low dose and >5 h in high dose).

Studies have demonstrated that hidden blood loss, which is not directly measurable during surgery, contributes to total blood loss after surgery for idiopathic scoliosis in children.[22] Anaesthetic techniques, including the use of multimodal strategies, play a vital role in optimizing outcomes and minimizing intraoperative risks, as highlighted by Young *et al.*[23] Hematocrit levels and blood transfusions might be risk factors for this hidden blood loss. Nevertheless, TXA, a commonly used medication to reduce bleeding in surgery, appears effective in reducing hidden blood loss in this population.[22] A study involving over 2000 children undergoing scoliosis surgery found no significant difference in the rate of complications between those who received TXA and those who did not, including complications such as seizures, blood clots, and stroke,[10] suggesting the safety of this drug.

TXA, while effective in reducing blood loss during pediatric surgeries, is more costly.[19] Epsilon aminocaproic acid (EACA) offers a more cost-effective alternative, being 3 times cheaper than TXA. Studies have shown EACA to be as safe as TXA with a lower risk of seizures, but it might be slightly less effective in reducing blood loss compared to TXA.[3]

Several studies have explored the effectiveness of TXA in reducing blood loss during PSF surgery for AIS. One study found that TXA was associated with lower total blood loss compared to the control group.[9] A retrospective cohort study also provided evidence that topical TXA use was associated with lower blood loss in this surgery.[6] Furthermore, a RCT showed that combining intravenous TXA with topical injection through a drain improved blood loss prevention.[5] In addition, a meta-analysis suggested that high-dose TXA was associated with fewer thromboembolic events compared to the control group and was an effective option for reducing blood loss in pediatric scoliosis surgery repair.[17]

Finally, high-dose TXA has the potential to significantly reduce the need for blood transfusions during surgery, which could lower transfusion-related complications and optimize resource use in clinical practice. However, the variability in blood loss reduction across studies emphasizes the importance of developing standardized TXA dosing protocols to ensure consistent results. TXA's safety and its role in reducing hidden blood loss could enhance recovery outcomes, especially in pediatric scoliosis patients. However, the higher cost of TXA compared to alternatives like EACA may limit its widespread use, highlighting the need for further research to optimize its clinical applications. The safety of high-dose TXA was controversial, as some studies showed that it was not associated with an increased risk of complications such as venous thromboembolism or seizures when used in spine

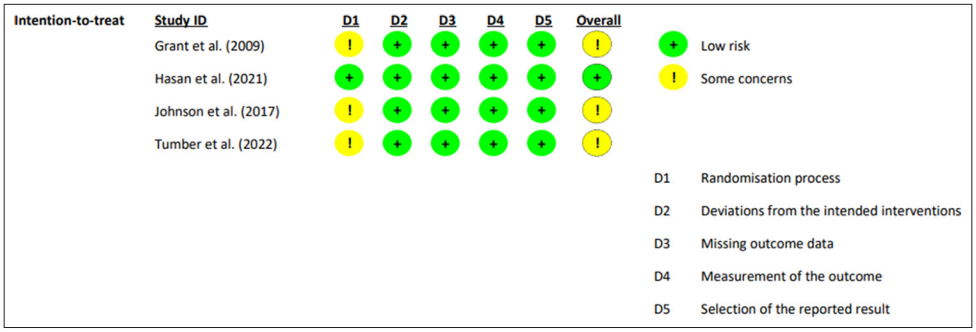

Figure 3: Traffic light plot of quality assessment. This figure presents a traffic light plot of the risk of bias assessment for each included study, categorized as low risk, high risk, or some concerns across various domains.

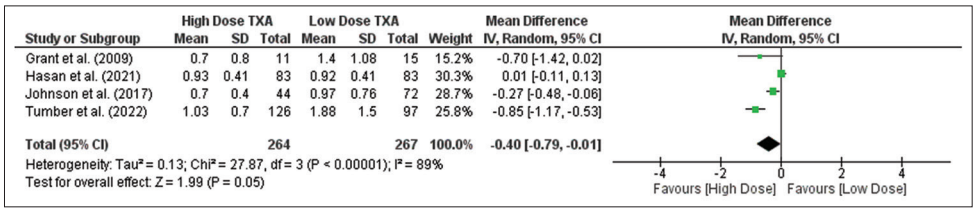

Figure 4: Forest plot of comparison between high-dose and low-dose tranexamic acid in estimated blood loss. TXA: Tranexamic acid, SD: Standard deviation, CI: Confidence interval

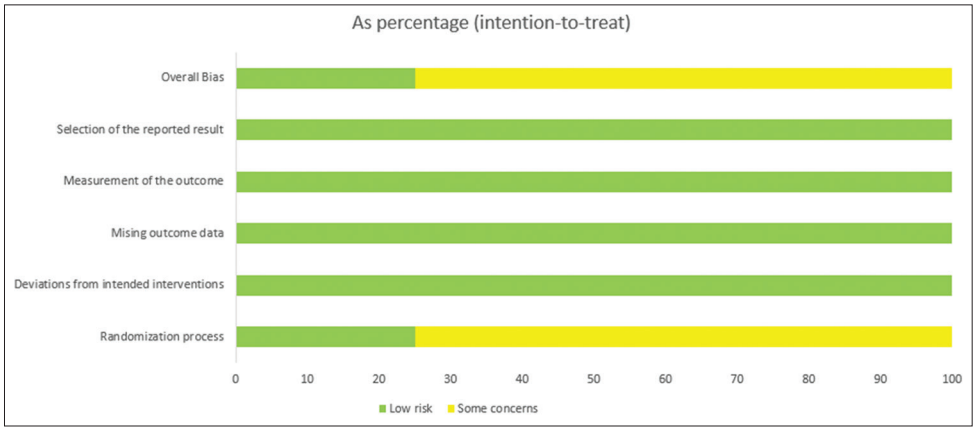

Figure 5: Doi plot assessing publication bias. This figure presents a Doi plot for assessing publication bias among the included studies, indicating potential asymmetry.

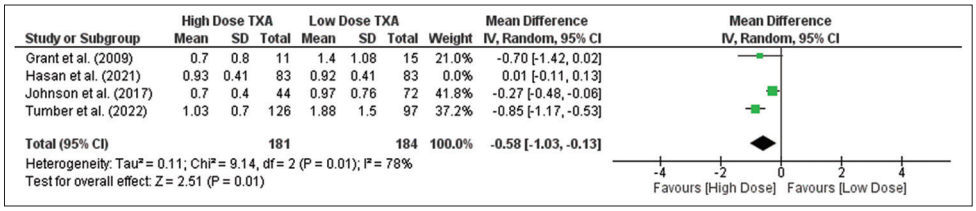

Figure 6: Sensitivity analysis of estimated blood loss. TXA: Tranexamic acid, SD: Standard deviation, CI: Confidence interval

surgeries.[1,17] Other research, on the other hand, found that 1.3–3.8% of people who had cardiopulmonary bypass or open heart-chamber cardiac surgery and were given a high dose of TXA also had clinically significant seizures.[13,18]

Strengths and limitations

To the best of our knowledge, this meta-analysis is the first study to explore pooled outcomes of high-dose versus low-

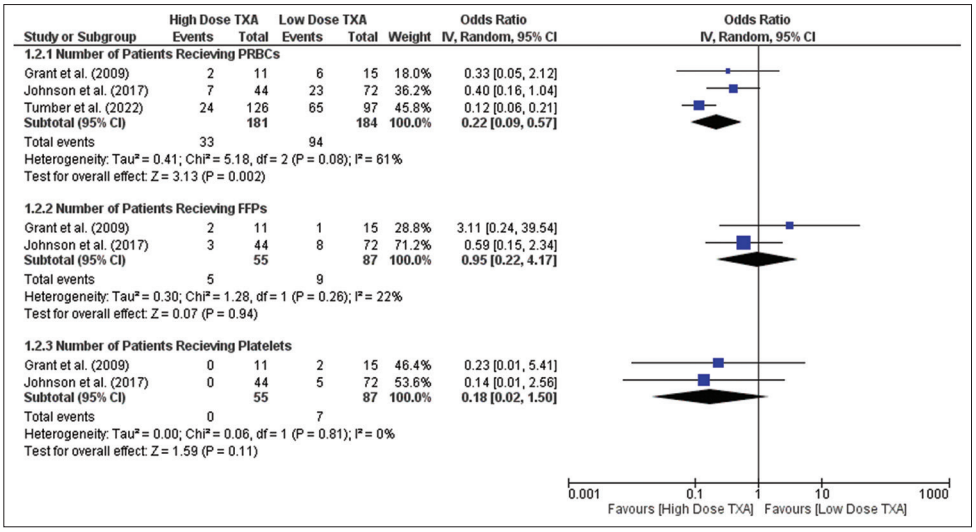

Figure 7: Forest plot of comparison between high-dose and low-dose tranexamic acid in blood product usage intraoperatively. TXA: Tranexamic acid, SD: Standard deviation, CI: Confidence interval

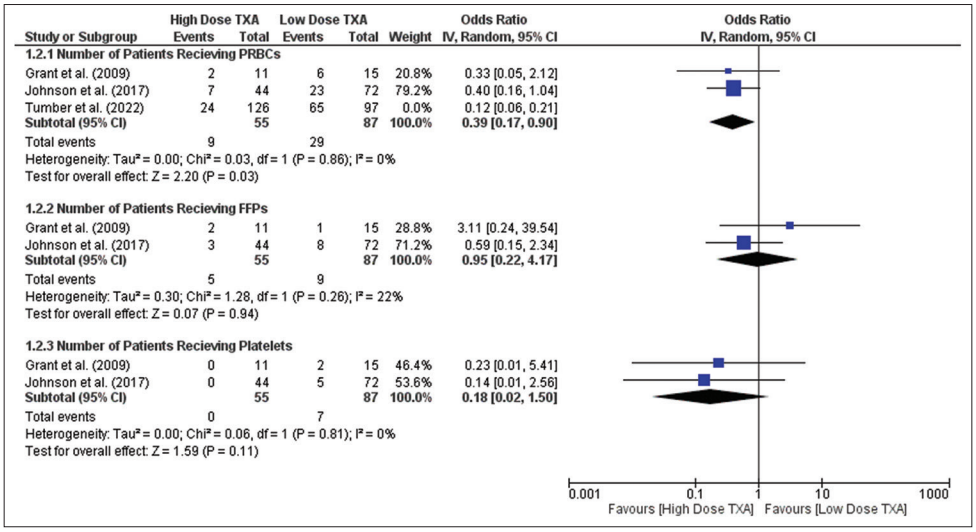

Figure 8: Sensitivity analysis of blood product usage intraoperatively. TXA: Tranexamic acid, SD: Standard deviation, CI: Confidence interval

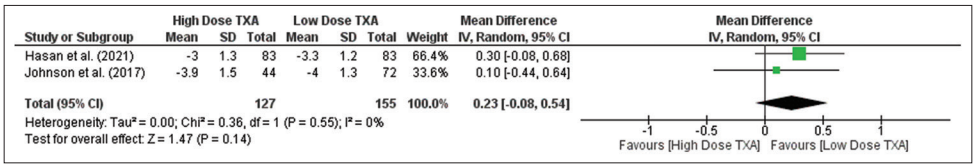

Figure 9: Forest plot of comparison between high-dose and low-dose tranexamic acid in fall in hemoglobin at least 24 h after surgery. TXA: Tranexamic acid, SD: Standard deviation, CI: Confidence interval

dose TXA for pediatric scoliosis surgery. Although our meta-analysis provides robust evidence that high-dose TXA is associated with less blood loss as compared to low-dose TXA, some important limitations should be considered while interpreting our results. First, the presence of high heterogeneity might limit the generalizability of our findings. We used the random effects model and performed a sensitivity analysis to limit excess heterogeneity. Second, we solely considered English-published literature, potentially leading to publication bias. Third, the small sample size and retrospective nature of our studies limited the level of evidence presented in the pooled results, and the statistical analysis failed to reach

significance. Finally, the baseline characteristics, including age, Cobb angle, and surgical duration, vary among the studies, which may affect the results. Future clinical trials should strive to develop robust protocols, preferably RCTs, to investigate the comprehensive effectiveness of TXA in AIS surgery.

CONCLUSION

This study demonstrates that high-dose TXA is more effective than low-dose TXA in reducing intraoperative blood loss and decreasing the need for PRBC transfusions in AIS surgery. While both groups maintained stable postoperative hemoglobin levels, the high-dose group exhibited a statistically significant reduction in EBL and showed a trend toward fewer transfusions of blood products overall. However, high heterogeneity across the included studies influenced the results, and the small sample sizes limited the generalizability of the findings. These results emphasize the need for further robust clinical trials with larger sample sizes to confirm the efficacy of high-dose TXA and establish a standardized dosing regimen. Such research is essential to ensure both optimal efficacy and safety in minimizing blood loss during surgery while addressing the limitations observed in this meta-analysis.

Author contributions

All authors contributed to Conceptualization, Writing – original draft preparation, and Writing – review and editing.

Data availability statement

All the data are publicly available on the internet.

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Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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