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REVIEW ARTICLE

Antifibrinolytic agents for paediatric scoliosis surgery: a systematic review and meta-analysis

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Abstract

Study design Systematic review and meta-analysis of randomised controlled trials.

Objective The purpose of this study is to perform a systematic review and meta-analysis of antifibrinolytic agents for paediatric spine surgery.

Background Bleeding is an important consideration in paediatric scoliosis surgery; blood loss leads directly to higher morbidity and mortality. Antifibrinolytics are an attractive non-invasive method of reducing bleeding as evidenced in arthroplasty, cardiac surgery and adult scoliosis surgery.

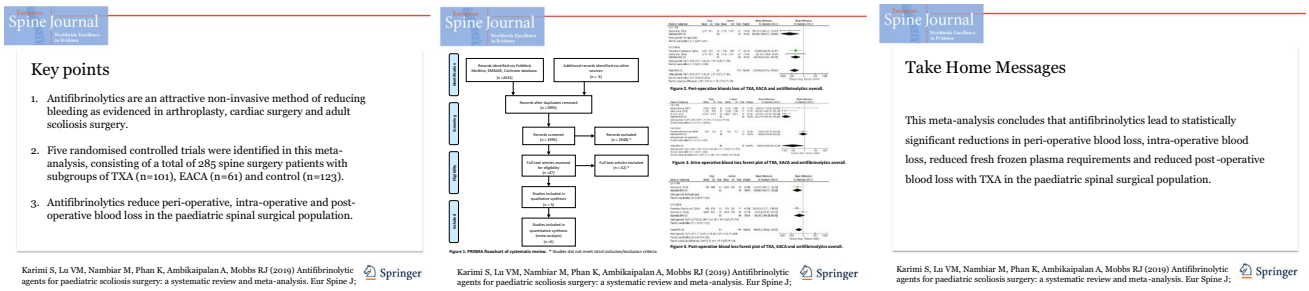
Methods A thorough database search of Medline, PubMed, EMBASE and Cochrane was performed according to PRISMA guidelines, and a systematic review was performed.

Results Five randomised controlled trials were identified in this meta-analysis, consisting of a total of 285 spine surgery patients with subgroups of tranexamic acid ($n=101$), epsilon aminocaproic acid ($n=61$) and control ($n=123$). This meta-analysis found that antifibrinolytics lead to statistically significant reductions in peri-operative blood loss (MD −379.16, 95% CI [−579.76, −178.57], $p<0.001$), intra-operative blood loss (MD −516.42, 95% CI [−1055.58, 22.74], $p<0.001$), reduced fresh frozen plasma requirements (MD −307.77, 95% CI [−369.66, −245.88], $p<0.001$) and reduced post-operative blood loss (MD − 185.95, 95% CI [−336.04, −35.87], $p=0.02$).

Conclusion This meta-analysis concludes that antifibrinolytics lead to statistically significant reductions in peri-operative blood loss, intra-operative blood loss, reduced fresh frozen plasma requirements and reduced post-operative blood loss with TXA.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.



Keywords Antifibrinolytic agents · Paediatric spine surgery · Tranexamic acid · Epsilon aminocaproic acid

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-019-05911-8) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Introduction

Blood loss is an important consideration in paediatric scoliosis surgery and can lead to end-organ damage and increased complications such as hypotension, metabolic acidosis, infection and acute respiratory distress [1, 2].

Paediatric patients should be individually distinct, divided from adults during surgery; firstly the absolute blood volume is much smaller in paediatric patients, meaning significant blood loss can occur with what is considered minor blood loss in adults [3]. Secondly paediatrics have effective compensatory mechanisms so will remain normotensive till a large volume of blood is lost [3].

There have been a number of studies focusing on the outcomes of antifibrinolytic agents including tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) to reduce the blood loss during cardiac surgery, arthroplasty and adult spinal fusion surgery [2, 4–10]. This is a non-invasive administration of antifibrinolytics, and it best avoids blood transfusions, this can pose adverse effects which include: blood borne infections, allergic transfusion reactions, volume overload, hyperkalemia, decreased alloimmunisation foreign antigens (particularly in females) and iron overload with multiple transfusions [11, 12].

Current available literature does not exclusively investigate antifibrinolytic (TXA and EACA) use in paediatric scoliosis populations and utilise randomized controlled trials (in order to establish class 1 evidence) [13–15]. TXA is a synthetic antifibrinolytic amino acid derivative forming a reversible complex with plasminogen and plasmin by binding at the lysine binding sites [6]. This leads to the blocking of the proteolytic action of plasmin on fibrin, thereby inhibiting fibrinolysis at the surgical wound preventing clot breakdown and decreasing blood loss [6]. EACA is also known as Amicar and is a synthetic antifibrinolytic agent with a similar mechanism to TXA and is also used to reduce post-operative blood loss [10]. However, it is contraindicated in the use of active intravascular clotting disorders, disseminated intravascular coagulation, bradycardia, elevated creatinine phosphokinase, muscle weakness, pulmonary embolism and thrombosis [16]. The concerns regarding thromboembolism with TXA have insignificant evidence [17, 18]. To address the relative benefits and risks of antifibrinolytic agents in the context of paediatric spinal surgery, a systematic review and meta-analysis of the most up-to-date published literature was performed.

Methods

Literature search strategy

PRISMA guidelines and recommendations were followed for this meta-analysis, and electronic databases were searched till 9/10/2017. The databases were Medline, PubMed, EMBASE and Cochrane database of systematic reviews [19–21]. Literature was searched with the MeSH terms "paediatric", "adolescent", "antifibrinolytic", "tranexamic acid", "epsilon aminocaproic acid" and "amicar". All identified articles and references were analysed against the inclusion and exclusion criteria.

Selection criteria

Inclusion criteria used to screen all identified articles were paediatric cases < 18 years of age, randomized controlled trials (RCT) in spine surgery (including all invasive surgery except full endoscopic surgery) in which TXA or EACA acid was compared with a placebo or control group. Outcome measures included: peri-operative blood loss, blood transfusion requirements, blood transfusion rate, or incidence of deep vein thrombosis. Studies with non-randomized groups, patient populations with ages > 18 years, endoscopic spine surgery and non-English papers were excluded from analysis to eliminate errors in translation. Of note a total of 40 patients excluded as the Xu study had 20 patients batroxobin and 20 with combined TXA and batroxobin; patients in the Xu study given batroxobin were excluded [22].

Data extraction and critical appraisal

The primary outcomes were operative duration, peri-operative blood loss (total blood loss during surgery and post-operatively), intra-operative (blood loss during surgery), post-operative blood loss, fresh frozen plasma (FFP) requirements and blood transfusion requirements. Secondary outcome measures were blood loss per vertebrae, number of vertebrae levels fused, length of hospital stay and post-operative haematological outcomes (Prothrombin time, partial thromboplastin time, platelet count, haemoglobin, INR and fibrinogen). Two reviewers (SK and KP) independently appraised each article included in our analysis according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria [23].

Meta-analysis

The mean difference (MD) and odds ratio (OR) were utilised as summary statistics for each of the outcome measures. Each outcome is presented as a forest plot; the weighted summary statistic, the 95% confidence interval (CI) and the relative weightings are represented by the middle of the square, the horizontal line, and the relative size of the square, respectively. In the present study, a random-effect (RE) model was tested to take into account the possible clinical diversity and methodological variation between studies. χ^2 tests were used to study heterogeneity between trials. I^2

statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. I^2 can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom.

Publication bias was assessed through the generation of forest plots for all outcomes and assessed for asymmetry. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively and quantitatively, any outlying study was removed, and effect on overall trend direction and significance was reassessed for any significant change. All p values were two-sided. All statistical analysis was conducted with Review Manager Version 5.3.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

Results

Literature search

Figure 1 depicts the PRISMA flowchart summarising the meta-analysis search. A total of 2041 studies were obtained during the search strategy [21]. Duplicates were removed ($n = 46$), inclusion and exclusion criteria were applied to titles and abstracts. Forty-seven studies were procured and underwent full-text analysis. Five randomised control studies are included in this meta-analysis and systematic review for quantitative analysis.

Demographics

Cohort demographic characteristics are summarized in Table 1. The included studies describe a total of 285 spine surgery patients, with 162/285 (57%) receiving an intraoperative antifibrinolytic agent compared to 123/285 (43%) who received no antifibrinolytic agents. Of the antifibrinolytic agents, 101/285 (35%) were treated with TXA, 61/285 (21%) were treated with EACA, and the remaining patients

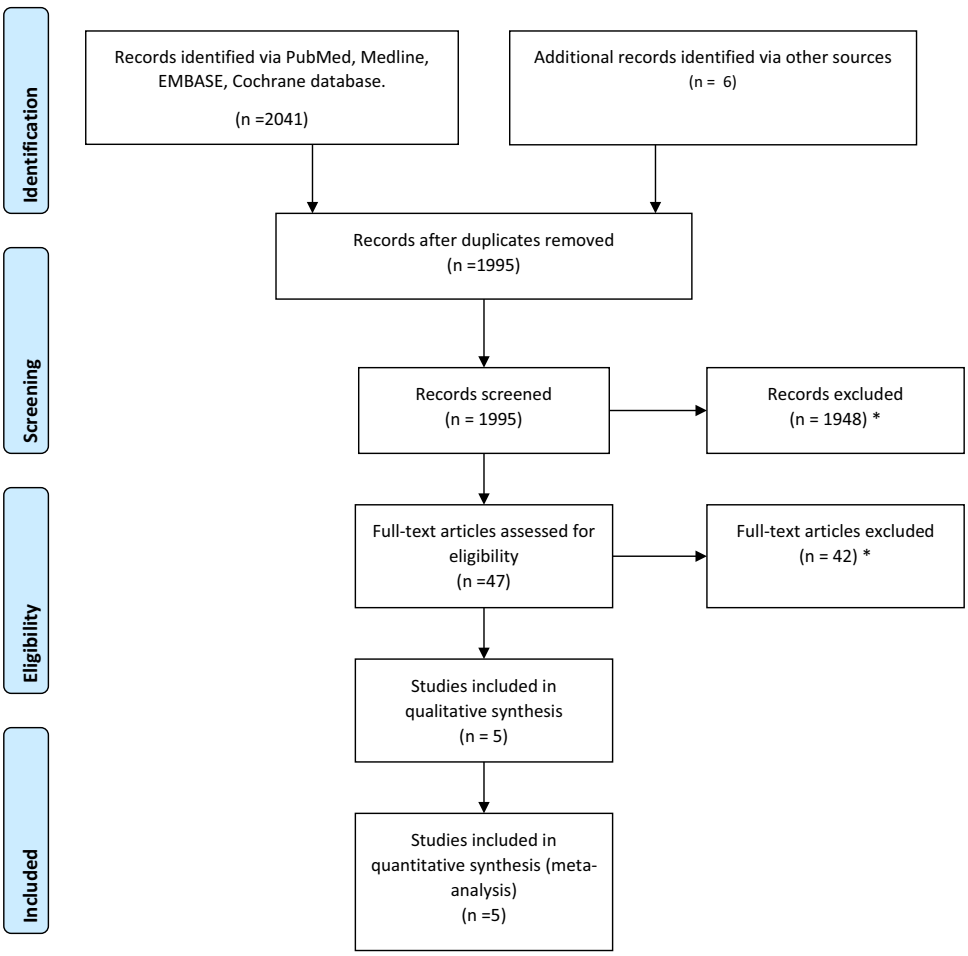


Fig. 1 PRISMA flowchart of systematic review. Asterisk represents the studies did not meet strict inclusion/exclusion criteria

Table 1 Patient demographics and details

Author	Florentino [7]	Neilipovitz [17]	Sethna [6]	Verma [18]	Xu [22]
Total patients	36	40	44	125	40[a]
TXA	n/a	22	23	36	20
EACA	19	n/a	n/a	42	n/a
Control	17	18	21	47	20
Mean age (year)					
TXA (mean ± SD)	n/a	14.1 ± 2.1	13.6 ± 1.8	15.3 ± 2.37	19.1 ± 3.2
EACA (mean ± SD)	13.5 ± 1.6	n/a	n/a	14.61 ± 1.89	n/a
Control (mean ± SD)	14.5 ± 1.3	13.7 ± 2.5	14.0 ± 2.0	15.01 ± 2.37	20.4 ± 3.1
Sex M/F					
TXA	n/a	12/10	17/6	4/32	12/8
EACA	5/14	n/a	n/a	8/34	n/a
Control	4/13	5/13	13/8	16/31	7/13
Vertebrae levels fused (*n*)					
TXA (mean ± SD)	n/a	14 (8–17)[b]	14 (9–16)[b]	8.8 ± 2.3	19.1 ± 3.2
EACA (mean ± SD)	n/a	n/a	n/a	9.5 ± 2.8	n/a
Control (mean ± SD)	n/a	15 (7–18)[b]	13 (7–18)[b]	9 ± 2	13.1 ± 1.8
Weight (kg)					
TXA (mean ± SD)	n/a	41.8 ± 16.7	59.4 ± 18.3	21.19 ± 5.62	48.2 ± 7.4
EACA (mean ± SD)	n/a	n/a	n/a	21.92 ± 4.5	n/a
Control (mean ± SD)	n/a	50.6 ± 20.2	52.4 ± 15.7	22.69 ± 5.22	49.6 ± 5.9

[a]Total 40 patients excluded as study has 20 patients batroxobin and 20 with combined TXA and batroxobin

[b]Median (range)

were treated with other 0.9% saline 123/285 (43%). The cohort involved 103/285 (36%) male and 182/285 (66%) female patients in both experimental and control arms. No significant difference exists in patient demographics between the antifibrinolytic agent and control groups. All surgeries involved correction of paediatric scoliosis with fusion.

Study bias assessment

The assessment of bias risk by the MOOSE criteria of each included study is presented in Table 2, with no obvious heterogeneous bias risk implicated. Generated forest plots did not indicate evidence of publication bias in the outcomes reported (Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Study characteristics are summarised in Table 3 including dosages of antifibrinolytics and standardised techniques utilised for measurement of blood loss.

Operative duration

Figure 2 shows antifibrinolytics (TXA and EACA) had similar operative durations (MD 0.21, 95% CI [−0.03, 0.46], $p = 0.89$) based on a total four articles and therefore can be compared [6, 7, 17, 22]. Operative duration in relation to TXA use was noted by three articles [6, 17, 22]. Figure 2 shows that TXA and the control groups had similar operative durations among three articles within this meta-analysis; they reported a non-significant difference of operative duration between TXA and control groups (MD 0.24, 95% CI [−0.19, 0.67], $p = 0.28$). Florentino et al. [7] is the only

Table 2 MOOSE guidelines

Author	Florentino [7]	Neilipovitz [17]	Sethna [6]	Verma [18]	Xu [22]
Clear definition of study population	Yes	Yes	Yes	Yes	Yes
Clear definition of outcomes and outcome assessment	Yes	Yes	Yes	Yes	Yes
Independent assessment of outcome parameters	Yes	Yes	No	Yes	No
Sufficient data of follow-up[a]	Yes	Yes	Yes	Yes	Yes
No selective loss during follow-up	No	No	No	No	No
Important confounders and prognostic factors identified	Yes	Yes	Yes	Yes	Yes

[a]All studies performed follow-up for patient population (Review in the post-operative and peri-operative period)

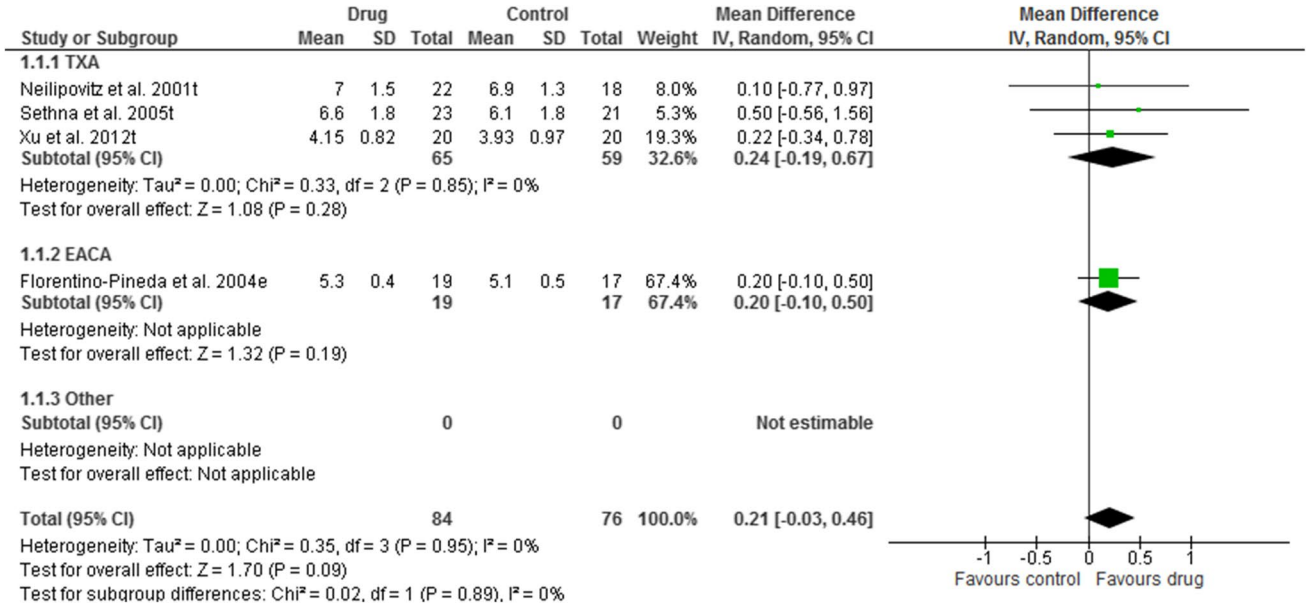


Fig. 2 Operative duration forest plot of TXA, EACA and antifibrinolytics overall

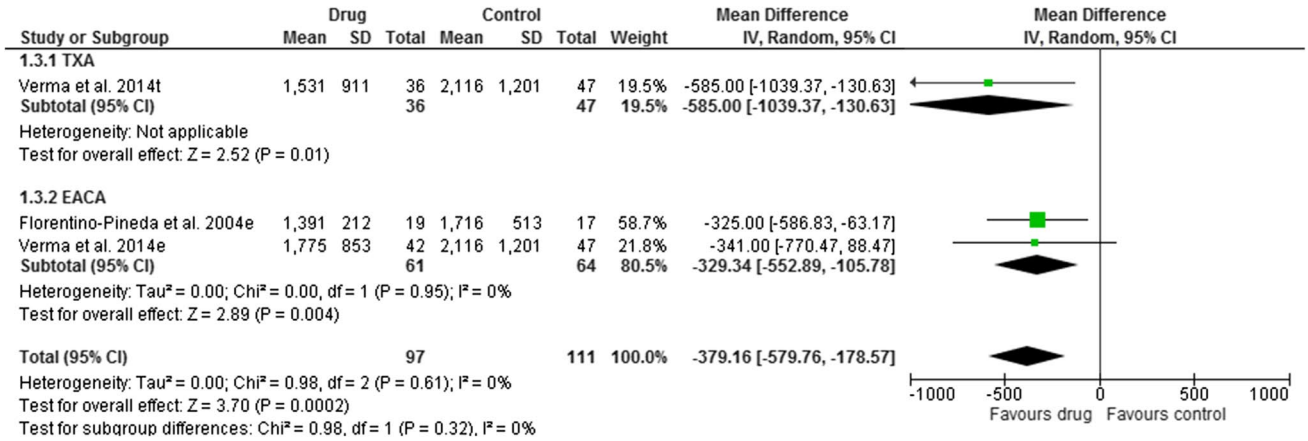


Fig. 3 Peri-operative blood loss forest plot of TXA, EACA and antifibrinolytics overall

study reporting on operative duration of patients receiving EACA to controls, the study reported a non-significant length of duration between EACA and the control groups (MD 0.20, 95% CI [−0.10, 0.50], $p=0.19$).

Peri-operative blood loss

The use of an antifibrinolytic (TXA and EACA) had significant effects on peri-operative blood loss (MD −379.16, 95% CI [−579.76, −178.57], $p<0.001$) determined by two journal articles as demonstrated in Fig. 3 [7, 18]. TXA was shown to significantly reduce peri-operative blood loss by one paper (MD −585.00, 95% CI [−1039.37, −130.63], $p=0.01$) [18]. Two papers reported peri-operative blood loss were shown to be significantly reduced with the use of EACA (MD −329.34, 95% CI [−552.89, −105.78], $p=0.004$) [7, 18].

Intra-operative blood loss

Figure 4 depicts the use of an antifibrinolytic (TXA and EACA) has significant impacts on intra-operative blood loss (MD −516.42, 95% CI [−1055.58, 22.74], $p<0.001$) formulated with four articles [6, 7, 17, 22]. Our meta-analysis reports only three papers explored intra-operative blood loss in relation to TXA [6, 17, 22]. Figure 4 depicts the meta-analysis of the TXA shows significant reduced intra-operative bleeding (MD −822.21, 95% CI

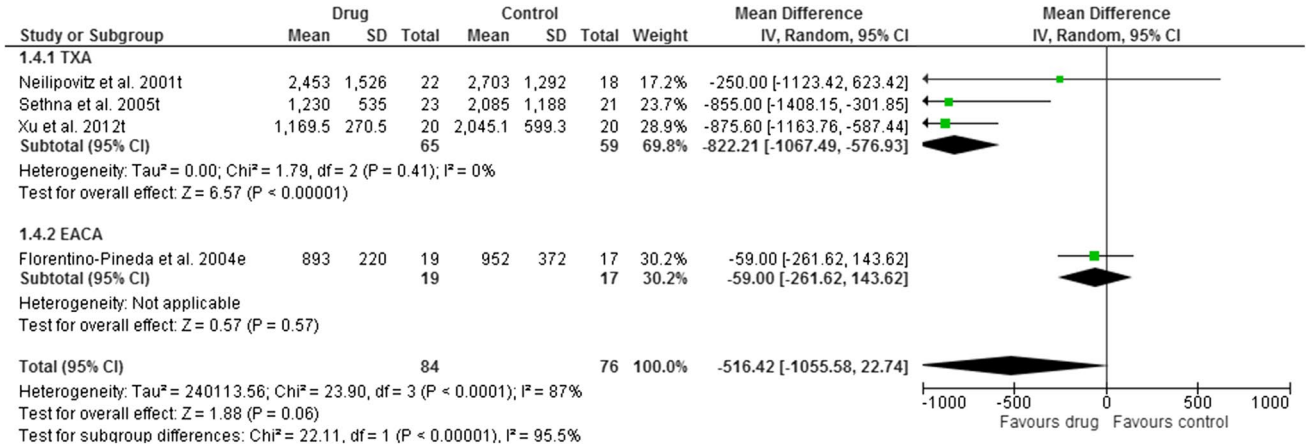


Fig. 4 Intra-operative blood loss forest plot of TXA, EACA and antifibrinolytics overall

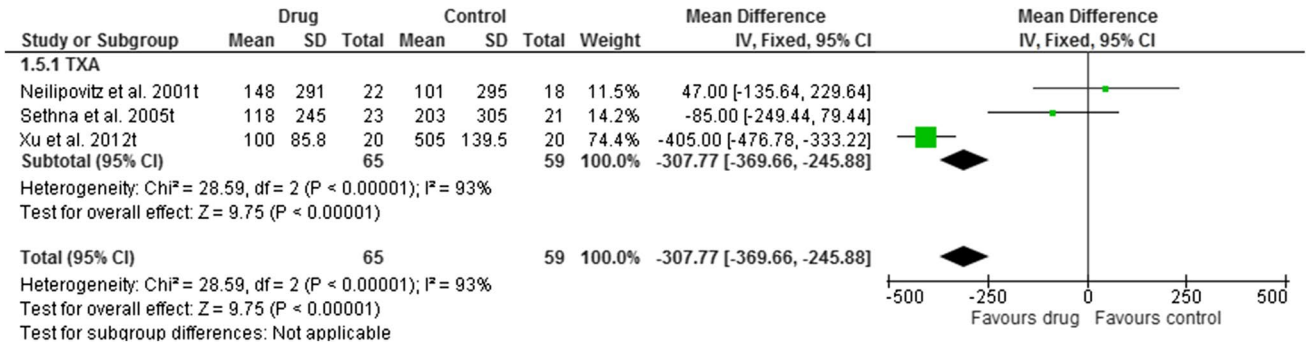


Fig. 5 Fresh frozen plasma requirements forest plot of TXA

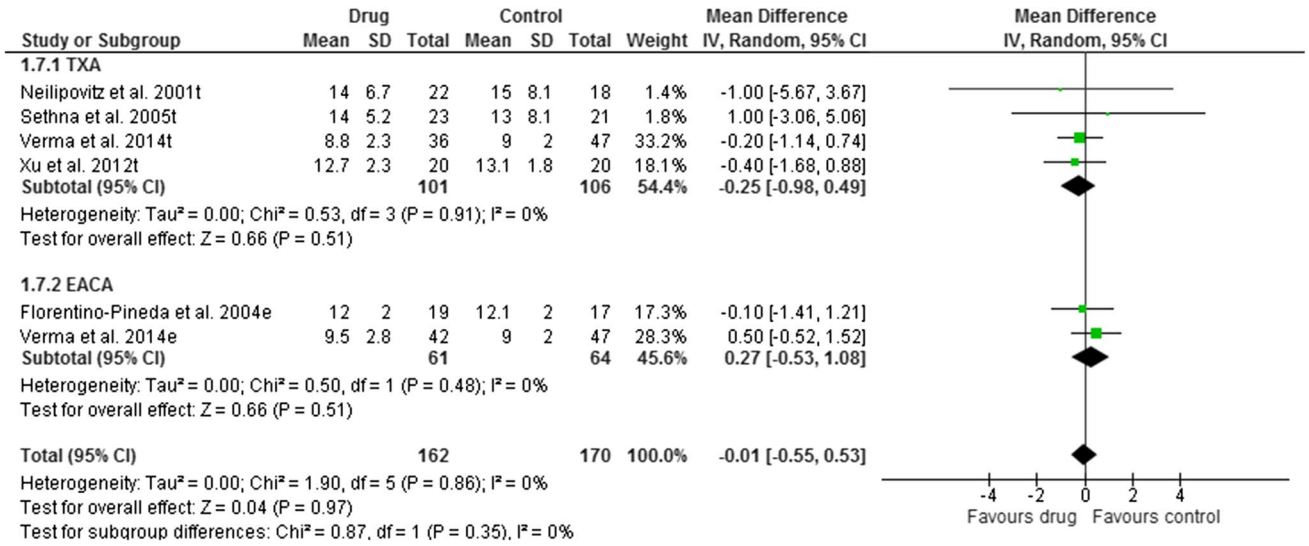


Fig. 6 Number of vertebrae levels fused forest plot of TXA, EACA and antifibrinolytics overall

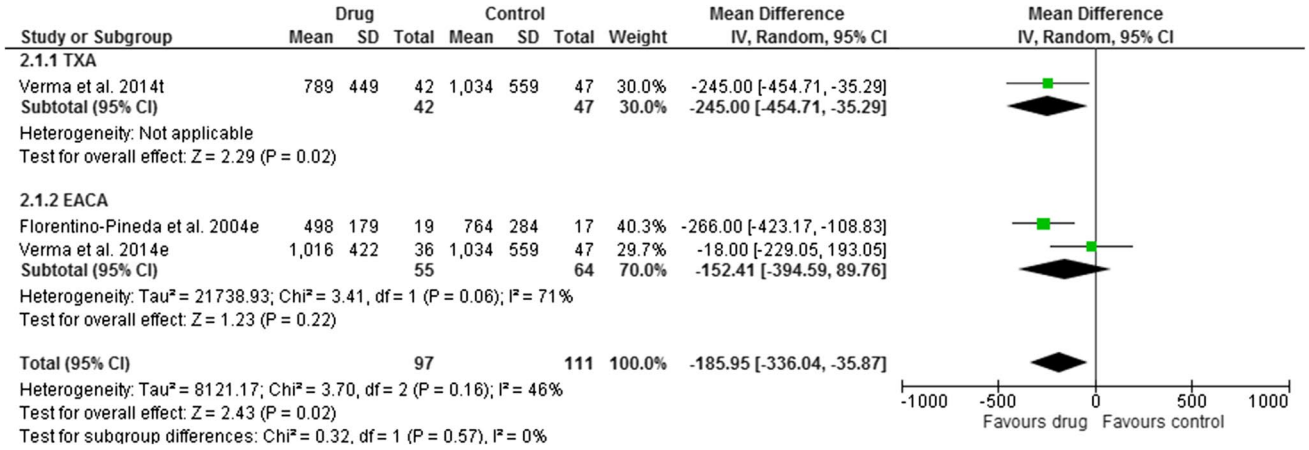


Fig. 7 Post-operative blood loss forest plot of TXA, EACA and antifibrinolytics overall

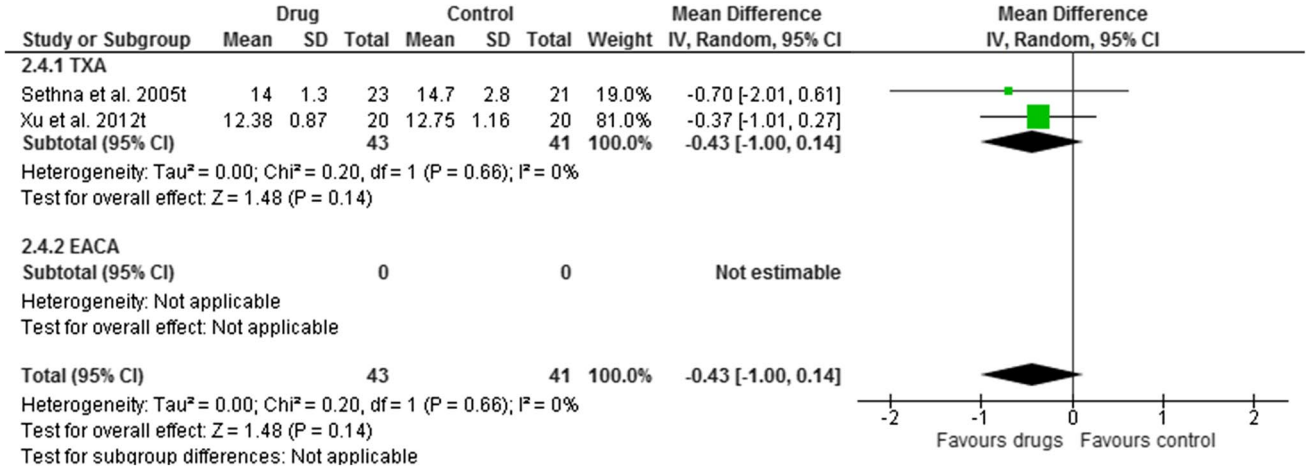


Fig. 8 Prothrombin time (PT) forest plot of TXA

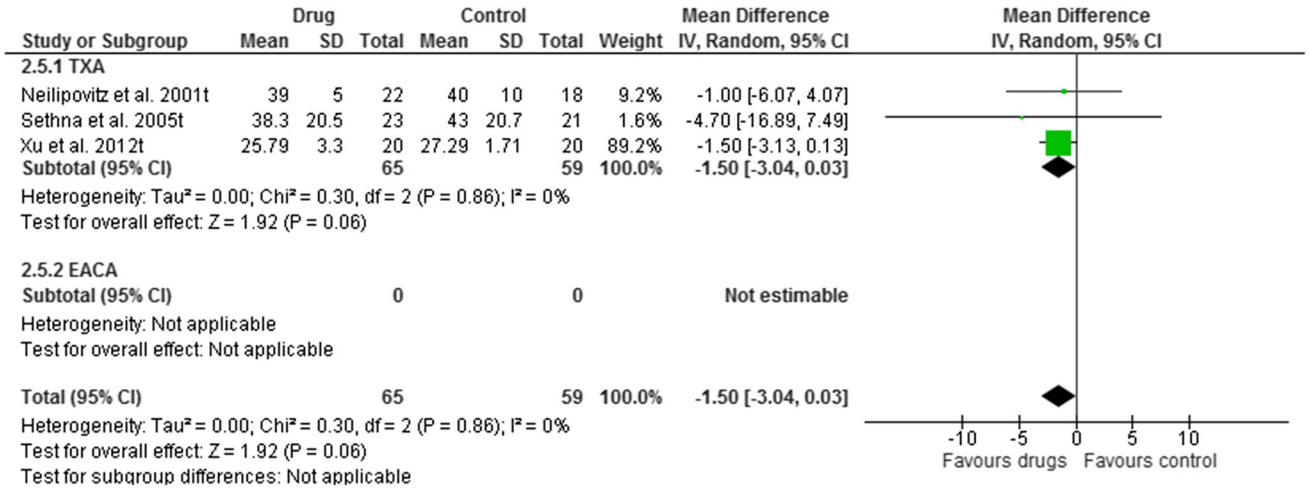


Fig. 9 Partial thromboplastin time (PTT) forest plot of TXA

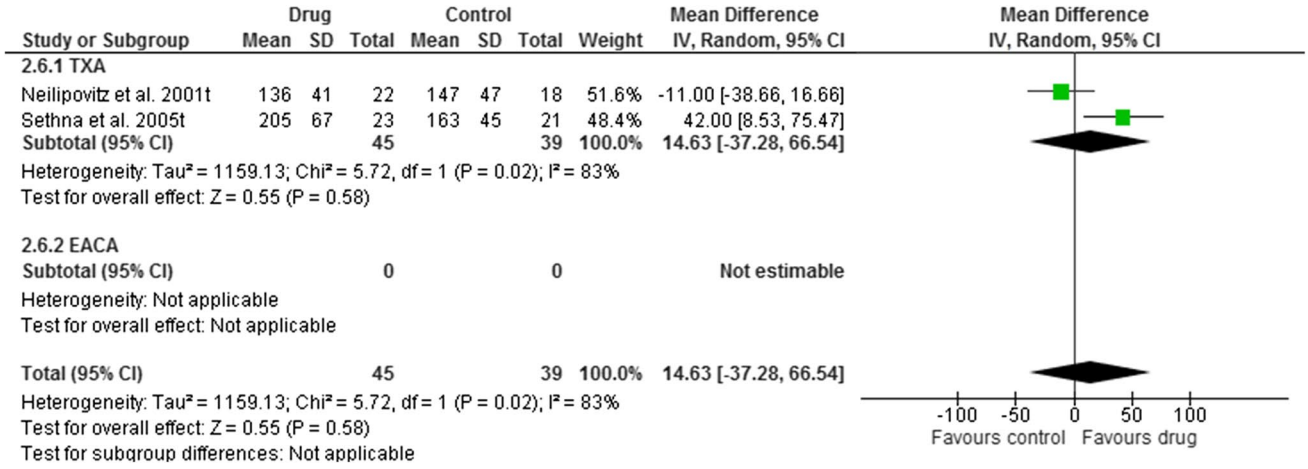


Fig. 10 Platelet count forest plot of TXA

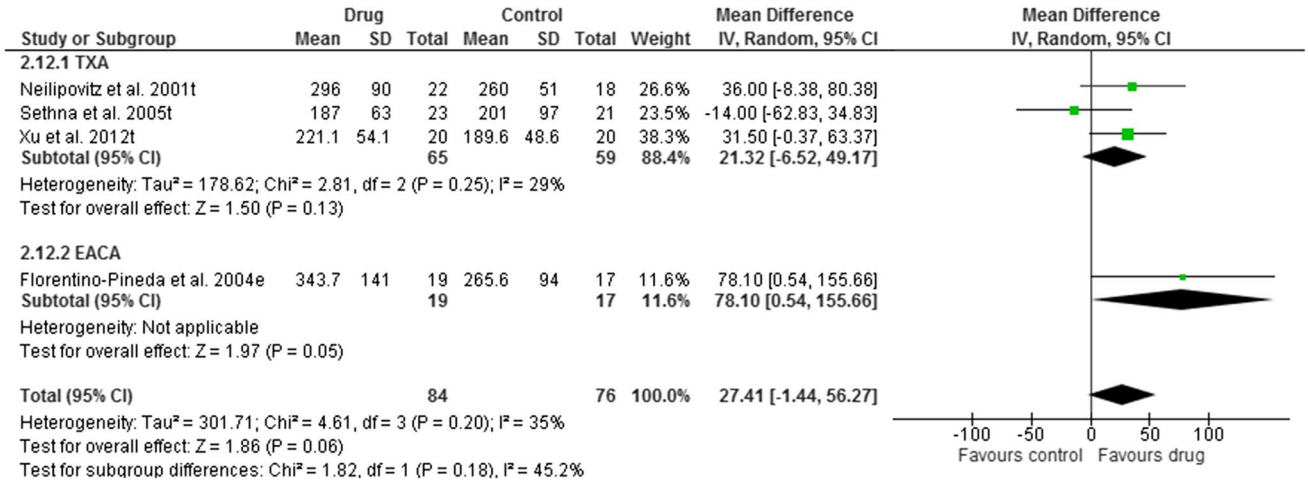


Fig. 11 Fibrinogen forest plot of TXA, EACA and antifibrinolytics overall

[− 1067.49, − 576.93], $p < 0.001$). However, Florentino et al.'s study reports non-significant changes to intraoperative blood loss with the use of EACA (MD − 59.00, 95% CI [− 261.62, 143.62], $p = 0.57$) [7].

Fresh frozen plasma requirements

Figure 5 shows the use of an antifibrinolytic (TXA) has significant impacts on reducing FFP requirements (MD − 307.77, 95% CI [− 369.66, − 245.88], $p < 0.001$) utilising three studies for our meta-analysis; our systematic review has not included any studies on EACA [6, 17, 22]. The findings were a significant reduction of FFP with the aid of TXA (MD − 307.66, 95% CI [369.66, − 245.88], $p < 0.001$).

Blood loss per vertebrae

Verma et al. [18] reported on the use of an antifibrinolytics (TXA and EACA) and was able to show they reduce blood loss per vertebrae significantly (MD − 50.57, 95% CI [− 80.35, − 20.79], $p < 0.001$) overall and was the only study to report on this outcome. The amount of blood loss per vertebrae shows significant results in reducing blood loss regarding TXA (MD − 57.60, 95% CI [− 102.18, − 13.02], $p = 0.01$) and EACA (MD − 44.9, 95% CI [− 84.92, − 4.88], $p = 0.03$) [18].

Number of levels vertebrae fused

Figure 6 shows no difference of the number of levels fused between the antifibrinolytic groups (TXA and EACA) and

Table 3 Study characteristics

Author	Florentino [7]	Neilipovitz [17]	Sethna [6]	Verma [18]	Xu [22]
Country	USA	Canada	USA	USA	China
Publication year	2004	2001	2005	2014	2012
Study design	Prospective randomised double-blinded study placebo-controlled study	Prospective, double-blinded, placebo-controlled study	Prospective randomised placebo-controlled study	Prospective randomised double-blinded placebo-controlled study	Prospective randomised placebo-controlled study
Inclusion/exclusion	Inclusion: diagnosis of idiopathic scoliosis, age 11–18, posterior spinal fusion and segmental spinal instrumentation only	Inclusion: posterior spinal fusion Ages 9–18 years	Inclusion: correction of scoliosis (idiopathic and secondary) either anterior or posterior Adolescents with American Society of Anaesthesiologists physical status of I–III	Inclusion: adolescent idiopathic scoliosis undergoing posterior spinal fusion Ages 8–18 years	Inclusion: adolescent idiopathic scoliosis surgery
Outcomes reported	Operative duration, peri-operative blood loss, intra-operative blood loss, number of levels fused, post-operative blood loss, length of hospital stay, blood transfusion requirements, fibrinogen	Operative duration, intra-operative blood loss, fresh frozen plasma requirements, number of levels fused, partial thromboplastin time, platelet count, international-ised normal ratio, fibrinogen	Operative duration, intra-operative blood loss, fresh frozen plasma requirements, number of levels fused, prothrombin time, partial thromboplastin time, platelet count, haemoglobin, fibrinogen	Peri-operative blood loss, blood loss per vertebrae, number of levels fused, post-operative blood loss	Operative duration, intra-operative blood loss, fresh frozen plasma requirements, prothrombin time, partial thromboplastin time, fibrinogen
Timing of haematological measurements	Fibrinogen post-operative day 1, 2, 3	Immediately post-operatively and day 1	Before antifibrinolytic and hourly till end of operation	–	Pre-operatively, post-operatively and day 1
Antifibrinolytic protocol					
TXA	–	Loaded 10 mg/kg for 15 min then 1 mg/kg	100 mg/kg/h for 15 min then 10 mg/kg/h	Loaded 10 mg/kg for 15 min then 1 mg/kg/h	20 mg/kg/h at incisions site followed by 10 mg/kg/h
EACA	Loaded 100 mg/kg over 15 min then 10 mg/kg/h	–	–	Loaded 100 mg/kg for 15 min then 10 mg/kg/h	–
Complications	Nil complications reported Blood transfusion requirements were measured	Nil complications reported Fresh frozen plasma requirements were measured	Nil complications reported Fresh frozen plasma requirements were measured	On-going bleeding ($n=1$), readmission for persistent wound drainage ($n=1$). No renal, thromboembolic, or other major complications were observed	No thrombotic complications or other adverse events reported. Fresh frozen plasma requirements were measured
Intra-operative, post-operative and peri-operative blood loss measurements	Intra-operative equals post-operative plus post-operative suction drainage Suction drainage minus irrigation fluid and weight of tape and sponges	Intra-operative blood loss measured by weighing sponges, suction drainage (cell saver and non-cell saver) and estimate loss of blood on drapes. Post-operative blood loss amount of blood recovered in surgical drains	Estimated blood volume loss was determined hourly from the surgical suction and autotransfusion system reservoirs and by weighing sponges from the operative field	Estimated blood loss was estimated to be three times the volume in the cell saver	Blood loss was the sum of blood volume from surgical field suction, autotransfusion system reservoirs and weighing sponges from the operative field

the control groups (MD −0.01, 95% CI [−0.53, 1.08], $p=0.97$) among four journal articles [6, 17, 18, 22]. The four studies demonstrated no difference between the TXA and control group (MD −0.25, 95% CI [−0.98, 0.49], $p=0.51$). Two studies showed no difference between the EACA and the control groups in the two studies (MD −0.27, 95% CI [−0.53, 1.08], $p=0.51$) [7, 18].

Post-operative blood loss

Figure 7 depicts the use of an antifibrinolytic (TXA and EACA) showing significant impacts on post-operative blood loss (MD −185.95, 95% CI [−336.04, −35.87], $p=0.02$) based on two articles that underwent a meta-analysis. [7, 18] Post-operative blood loss of patients on TXA was reported only in one paper, showing significant reduced blood loss with the use of TXA (MD −245, 95% CI [−454.71, −35.29], $p=0.02$) [18]. Two studies have reported non-significant results for the use of EACA to reduce blood loss (MD −152.41, 95% CI [−394.59, 89.76], $p=0.22$) [7, 18].

Length of hospital stay

No papers have reported on the length of hospital stay regarding TXA, whereas only one paper reported on length of hospital stay for EACA. Florentino et al.'s study illustrates insignificant results between the control and EACA regarding the length of hospital stay (MD −0.10, 95% CI [−0.43, 0.23], $p=0.55$) [7].

Blood transfusion requirements

Florentino et al. [7] was the only paper to report on the amount of blood transfusions with EACA; however, no studies have reported on TXA. There were significant results, showing reduced transfusion requirements when given EACA compared to the control group (MD −0.59, 95% CI [0.02, 1.16], $p=0.04$) [7].

Post-operative haematological outcomes

Prothrombin, partial thromboplastin time, platelet count, haemoglobin, INR and fibrinogen

Figures 8, 9, 10 and 11 depict the measurements of prothrombin ($p=0.14$), partial thromboplastin time ($p=0.06$), platelet count ($p=0.58$), haemoglobin ($p=0.94$), INR ($p=0.79$) and fibrinogen ($p=0.06$). Only patients who had administered TXA had these figures reported, except fibrinogen where both TXA and EACA were detailed [6, 7, 17, 18, 22]. All parameters were insignificant; only subgroup analysis of EACA regarding fibrinogen was shown to be significant ($p=0.05$) [7].

Discussion

Managing blood loss is important for optimal patient outcomes. The use of fluids, platelets, crystalloids and blood transfusions to manage bleeding is mainly reactive, and decreasing peri-operative bleeding can minimise the need for these measures [24–26]. There are multiple factors that are thought to influence peri-operative bleeding, including but not limited to surgical approach (anterior versus posterior), surgical haemostasis, duration of surgery, number of vertebral levels fused, site of autologous bone graft harvest, patient positioning and reducing abdominal compression to lower mean arterial pressure [7, 25, 27].

This meta-analysis is able to provide a comprehensive review of the most up-to-date quantitative evidence for the consideration of administrating non-invasive antifibrinolytics with minimal clinical adverse risks to lead to statistically significant reduced peri-operative blood loss in solely paediatric scoliosis, even with subgroup analysis of TXA and EACA. This meta-analysis uses randomised controlled trials and shows antifibrinolytics to significantly reduce intra-operative blood loss and upon subgroup analysis, significance was gained with TXA but not EACA. The reasons for EACA not reaching significance could be that current literature report TXA is more potent than EACA, or potentially studies did not have the statistical power as there were fewer patients in the EACA than the TXA group as shown in Table 1 [7, 17, 18, 28, 29].

Operative duration was not statistically significant for patients amongst the control and antifibrinolytics groups, which enables comparison of these two groups in this meta-analyses. Previous studies have reported operative duration was the main variable for increased operative bleeding and transfusion requirements [30]. In addition to operative bleeding, the number of vertebrae fused was shown to increase blood loss in both control and antifibrinolytics groups [18]. Five studies have looked at the number of levels of vertebrae that were fused amongst the antifibrinolytics and control group; these were similar amongst these groups. If there were an increased number of levels fused between the TXA, EACA or control groups, it would have made it difficult to make the comparisons. While differences were not found, the report did find significantly reduced post-operative blood loss with the administration of antifibrinolytics, with the subgroup of TXA showing significant reduction and EACA having insignificant findings.

Managing blood loss with FFP and blood transfusions are important for patient outcomes. Our meta-analysis reports on only TXA use with FFP requirements; it found paediatric

patients undergoing surgery required significantly reduced FFP with the use of TXA. However, FFP administration is at the discretion of treating physicians just like transfusion requirements where its administration is due to many variables [6, 17, 22]. Verma et al. [18] suggests that the measurement of transfusion is unreliable due to the fact that it depends on operative measures such as patient comorbidities, patient Jehovah Witness status and clinical judgement. Verma et al's [18] protocol for transfusion depends on haematocrit being less than or equal to 25, protocols differ and a unified approach would be of benefit to reporting and comparing the studies. In addition, the doses of TXA in each study are important as reported in Table 3; it depicts each antifibrinolytic regime and adverse complications. More adverse complications are not related to the dose of antifibrinolytics utilised in the studies included in this meta-analysis. Sethna et al. had ten times the TXA dose of the two other studies included in the data measuring FFP requirements; this could explain the reduced plasma requirements in that study. Sethna did report the least intra-operative bleeding with the use of TXA at such high doses, a higher dose might be considered to replicate similar results [6].

Haematological outcomes were measured at varying times; potential timings of variables may have impacted this meta-analysis to find significance as listed in Table 3.

There are misconceptions over synthetic antifibrinolytics; concerns of adverse effects include thromboembolism, hypersensitivity, renal impairment and risks to pregnant patients [31]. Review of the literature has shown that the use of antifibrinolytics has not been associated with complications such as thromboembolic events; however, surveillance should be present for deep venous thrombosis [7, 17, 29, 32]. Overall the use of antifibrinolytics avoids complications from blood transfusions in a non-invasive manner with minimal clinical risk [7].

Limitations of study

This meta-analysis and systematic review was restricted to five journal articles and adhered to PRISMA guidelines. The highly strict inclusion of randomised controlled trials should improve the validity of the results obtained. Notable limitations of this study include the limited number of studies incorporated in this analysis; the heterogeneity of the studies with varying approaches, operators, therapeutic dosages and the outcome analysis not being homogenous as listed in Table 3. However, this varied between the studies limiting the reliability of meta-regression. The exclusion of non-English papers is a common practice, and it avoids translation errors. The length of follow-up in the five studies appears to be only in the peri-operative and post-operative settings, more than just one paper exploring the length of hospital stay and it would be of benefit to view long-term outcomes with longer follow-up.

Conclusion

Increased bleeding should be avoided in the vulnerable paediatric population as bleeding worsens outcomes, worsens mortality and morbidity. This meta-analysis utilised RCT's to conclude antifibrinolytics lead to significant reductions in peri-operative blood loss, intra-operative blood loss, and reduced FFP requirements with TXA and reduced post-operative blood loss non-invasively with minimal clinical risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest and no funding was provided to aid this research.

References

1. Szpalski M, Gunzburg R, Sztern B (2004) An overview of blood-sparing techniques used in spine surgery during the perioperative period. Eur Spine J 13(1):S18–S27
2. Hu SS (2004) Blood loss in adult spinal surgery. Eur Spine J 13(1):S3–S5
3. Soud T (1992) Airway, breathing, circulation, and disability: What is different about kids? J Emerg Nurs 18(2):107
4. Brown JR, Birkmeyer NJ, O'Connor GT (2007) Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 115(22):2801–2813
5. Hiippala ST, Strid LJ, Wennerstrand MI, Vesa J, Arvela V, NiemelÄa HM et al (1998) Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Surv Anesthesiol 42(2):116
6. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F (2005) Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. Anesthesiology 102(4):727–732
7. Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC (2004) The effect of amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized double-blind study. Spine 29(3):233–238
8. Lu VM, Ho Y-T, Nambiar M, Mobbs RJ, Phan K (2018) The perioperative efficacy and safety of antifibrinolytics in adult spinal fusion surgery: a systematic review and meta-analysis. Spine 43:E949–E958
9. Gill JB, Rosenstein A (2006) The use of antifibrinolytic agents in total hip arthroplasty: a meta-analysis. J Arthroplasty 21(6):869–873
10. Rao B, Saxena N, Chauhan S, Bisoi A, Venugopal P (2000) Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. Indian J Med Res 111:57
11. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG et al (2011) Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 365(26):2453–2462
12. Klein HG (1999) Immunomodulatory aspects of transfusion a once and future risk? Anesthesiology 91(3):861

13. Yuan Q-M, Zhao Z-H, Xu B-S (2017) Efficacy and safety of tranexamic acid in reducing blood loss in scoliosis surgery: a systematic review and meta-analysis. Eur Spine J 26(1):131–139
14. Willner D, Spennati V, Stohl S, Tosti G, Aloisio S, Bilotta F (2016) Spine surgery and blood loss: systematic review of clinical evidence. Anesth Analg 123(5):1307–1315
15. Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB (2008) Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database Syst Rev (3)
16. Slaughter TF, Greenberg CS (1997) Antifibrinolytic drugs and perioperative hemostasis. Am J Hematol 56(1):32–36
17. Neilipovitz DT, Murto K, Hall L, Barrowman NJ, Splinter WM (2001) A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. Anesth Analg 93(1):82–87
18. Verma K, Errico T, Diefenbach C, Hoelscher C, Peters A, Dryer J et al (2014) The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: a prospective randomized trial. J Bone Joint Surg 96(10):e80–e81
19. Phan K, Mobbs RJ (2015) Systematic reviews and meta-analyses in spine surgery, neurosurgery and orthopedics: guidelines for the surgeon scientist. J Spine Surg 1(1):19
20. Phan K, Tian DH, Cao C, Black D, Yan TD (2015) Systematic review and meta-analysis: techniques and a guide for the academic surgeon. Ann Cardiothorac Surg 4(2):112
21. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097
22. Xu C, Wu A, Yue Y (2012) Which is more effective in adolescent idiopathic scoliosis surgery: batroxobin, tranexamic acid or a combination? Arch Orthop Trauma Surg 132(1):25–31
23. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. J Am Med Assoc 283(15):2008–2012
24. Mcneill TW, Dewald RL, Kuo KN, Bennett EJ, Salem M (1974) Controlled hypotensive anesthesia in scoliosis surgery. J Bone Joint Surg 56(6):1167–1172
25. Phillips WA, Hensinger RN (1988) Control of blood loss during scoliosis surgery. Clin Orthop Relat Res 229:88–93
26. Cowell HR, Swickard JW (1974) Autotransfusion in children's orthopaedics. J Bone Joint Surg 56(5):908–912
27. Guay J, Haig M, Lortie L, Guertin M-C, Poitras B (1994) Predicting blood loss in surgery for idiopathic scoliosis. Can J Anaesth 41(9):775–781
28. Urban MK, Beckman J, Gordon M, Urquhart B, Boachie-Adjei O (2001) The efficacy of antifibrinolytics in the reduction of blood loss during complex adult reconstructive spine surgery. Spine 26(10):1152–1156
29. Halanski MA, Cassidy JA, Hetzel S, Reischmann D, Hassan N (2014) The efficacy of amicar versus tranexamic acid in pediatric spinal deformity surgery: a prospective, randomized, double-blinded pilot study. Spine Deform 2(3):191–197
30. Colomina MJ, Bagó J, Vidal X, Mora L, Pellisé F (2009) Antifibrinolytic therapy in complex spine surgery: a case–control study comparing aprotinin and tranexamic acid. Orthopedics 32(2):91–96
31. Tengborn L, Blombäck M, Berntorp E (2015) Tranexamic acid—an old drug still going strong and making a revival. Thromb Res 135(2):231–242
32. Gill JB, Chin Y, Levin A, Feng D (2008) The use of antifibrinolytic agents in spine surgery: a meta-analysis. J Bone Joint Surg 90(11):2399–2407

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