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Comparative efficacy and safety of different hemostatic medications during spinal surgery

A network meta-analysis

Haitao Tan, MD[a], Songli Pan, MD[a], Chuanchun Wei, MD[b], Zhilin Chen, MD[c], Tao Chen, MD[a,*]

Abstract

Background: Significant blood loss is still one of the most frequent issues in spinal surgery. There were different hemostatic methods to prevent blood loss during spinal surgery. However, the optimal hemostatic therapy for spinal surgery is controversial. The purpose of this study was to assess the efficacy and safety of different hemostatic therapies in spinal surgery.

Methods: Two independent reviewers conducted electronic literature searches in 3 electronic databases (PubMed, Embase, and Cochrane library database) as well as a manual search to identify eligible clinical studies from inception to Nov 2022. Studies that including different hemostatic therapy (tranexamic acid [TXA], epsilon-acetyl aminocaproic acid [EACA], and aprotinin [AP]) for spinal surgery were included. The Bayesian network meta-analysis was performed with a random effects model. The surface under the cumulative ranking curve (SUCRA) analysis was performed to determine the ranking order. All analyses were performed by R software and Stata software. *P* value less than .05 was identified as statistically significant.

Results: Finally, a total of 34 randomized controlled trials met the inclusion criteria and finally included in this network meta-analysis. The SUCRA shows that TXA ranked first (SUCRA, 88.4%), AP ranked second (SUCRA, 71.6%), EACA ranked third (SUCRA, 39.9%), and placebo ranked the last (SUCRA, 0.3%) as for total blood loss. The SUCRA shows that TXA ranked first (SUCRA, 97.7%), AP ranked second (SUCRA, 55.8%), EACA ranked third (SUCRA, 46.2%), and placebo ranked the last (SUCRA, 0.2%) for need for transfusion.

Conclusions: TXA appears optimal in the reduction of perioperative bleeding and blood transfusion during spinal surgery. However, considering the limitations in this study, more large-scale, well-designed randomized controlled trials are needed to confirm these findings.

Abbreviations: AP = aprotinin, CI = confidence interval, DIC = deviance information criterion, DVT = deep venous thrombosis, EACA = epsilon-acetyl aminocaproic acid, MD = mean difference, OR = odds ratio, RCTs = randomized controlled trials, SUCRA = surface under the cumulative ranking curve, TXA = tranexamic acid.

Key words: epsilon-acetyl aminocaproic acid, network meta-analysis, spinal surgery, systematic review, tranexamic acid

1. Introduction

Significant blood loss is still one of the most frequent issues in spinal surgery, particularly for complex spinal surgeries with long operating times.[1,2] Massive intraoperative and postoperative blood loss may lead to anemia, organ (particularly cardiac, renal, and pulmonary) damage, infection, and other morbidities.[3] Excessive blood loss inevitably requires aggressive blood transfusions.[4] Many patients have to receive blood transfusion because of excessive blood loss, which may result in transfusion-related disease transmission and even immunological transfusion reactions.[5,6] The use of blood products, intraoperative blood salvage technology, and the management of complications have an economic disadvantage.[7] In recent years, spinal surgery has become increasingly complex, making the control of perioperative bleeding an increasingly important clinical concern.[8–10] There is evidence to support the effectiveness of multidisciplinary approaches to blood conservation in spinal surgery.[11] There is also evidence that enhanced fibrinolysis contributes to blood loss during spine surgery.[12] Among the antifibrinolytics available on the market, tranexamic acid (TXA), epsilon-acetyl aminocaproic acid (EACA), and aprotinin (AP)

HT, SP, and CW contributed equally to this work.

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[a] Department of Spinal Surgery, The First Affiliated Hospital of Hainan Medical University (Hainan Province Clinical Medical Center), Haikou, China, [b] Department of Anesthesia and Operation, The First Affiliated Hospital of Hainan Medical University, Haikou, China, [c] Department of Breast surgery, The First Affiliated Hospital of Hainan Medical University, Haikou, China.

**Correspondence: Tao Chen, Department of Spinal Surgery, The First Affiliated Hospital of Hainan Medical University (Hainan Province Clinical Medical Center), No. 31, Longhua Road, Longhua District, Haikou, Hainan 570102, China (e-mail: qio2582@163.com).*

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were used to decrease perioperative blood loss and transfusion requirements through inhibiting fibrinolysis.[13,14] AP differs significantly from TXA and EACA in terms of the mechanism of action.[15] The action mechanism of TXA and EACA is similar as competes to saturate the lysine binding site of plasminogen.[16] The fibrinolysis inhibitor AP inactivates free plasmin to inhibit fibrinolysis. Several studies and meta-analyses have identified antifibrinolytics as an effective method of hemostasis during spinal surgery.[17,18] However, the results revealed in those studies are inconsistent with each other. Although these antifibrinolytic therapy have been identified as effective methods for controlling blood loss in spinal surgery. However, the optimal regimen remains unclear. Through Bayesian network meta-analysis, we also compared therapies indirectly when there was no direct comparison, thus, more accurate evaluation for efficacy was obtained by jointly assessing direct and indirect comparisons.

The purpose of this study was to evaluate the efficacy and safety of different hemostatic methods during spinal surgery through network meta-analysis.

2. Methods

2.1. Search strategy

Two independent reviewers conducted electronic literature searches in 3 electronic databases (PubMed, Embase, and Cochrane library database) as well as a manual search to identify eligible clinical studies from inception to Nov 2022. Search terms used were: "Agents, Antifibrinolytic," "Antifibrinolysin," "Antifibrinolysins," "Antifibrinolytics" "Antifibrinolytic," "Antifibrinolytic Agent," "Agent, Antifibrinolytic," "Plasmin Inhibitors," "Inhibitors, Plasmin," "Antiplasmins" "Antiplasmin," "Plasmin Inhibitor," "Inhibitor, Plasmin, "spine surgery," "spinal surgery," "spine," "lumbar surgery," "thoracic surgery," and "cervical surgery." Reference lists in studies, reviews, and previous meta-analyses were checked to identify any initially omitted studies. In accordance with the abstract review, 2 investigators independently reviewed all titles, abstracts, and full texts of articles that were potentially eligible.

2.2. Study eligibility criteria and exclusion criteria

Studies were included in this review if they met all the following Population/Intervention/Comparison/Outcome(s) (PICOS) criteria: (P) The study included spinal surgeries of all types (lumbar, thoracic, thoracolumbar, and cervical) used either anteriorly or posteriorly. (I) antifibrinolytics (AP, TXA, or EACA); (C) Placebo; (O) Total blood loss, transfusion rate and the occurrence of deep venous thrombosis (DVT) and pulmonary embolism (PE); (S) randomized controlled trials (RCTs). Exclusion criteria were as follows: case control study, cohort study and retrospective study; duplicate publications; relevant specific data cannot be obtained; comments, letters, and guidelines; study did not report outcomes of interest.

2.3. Assessment of risk of bias

The meta-analysis was conducted following the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions and reported according to the PRISMA statement (www.prisma-statement.org).

In addition, the quality of included RCTs was also evaluated by the Cochrane handbook 5.1.0 recommended standard. A total of 6 domains were assessed as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blind outcome assessment, incomplete outcome data, selective reporting, and other sources of biases in the study. According to the report and the appropriateness of methods, the included studies were rated as follows: low risk (methods were appropriate and indicated); high risk (methods were indicated but not appropriate); unclear risk (methods were not indicated). Discrepancies between 2 review team members regarding risk of bias assessments were resolved through discussion with a third member.

2.4. Data extraction

The information from eligible studies was collected independently by 2 authors using standardized forms. General information about first author, publication year, number of participants, mean age, gender, mean body mass index, disease diagnosis, the surgery type and interesting outcomes (total blood losses, need for transfusion and the incidence of DVT and PE). As much as possible, we would prefer to select data from the intention-to-treat analysis to reduce withdrawal bias. For unclear outcome data, attempts were made to contact the corresponding author.

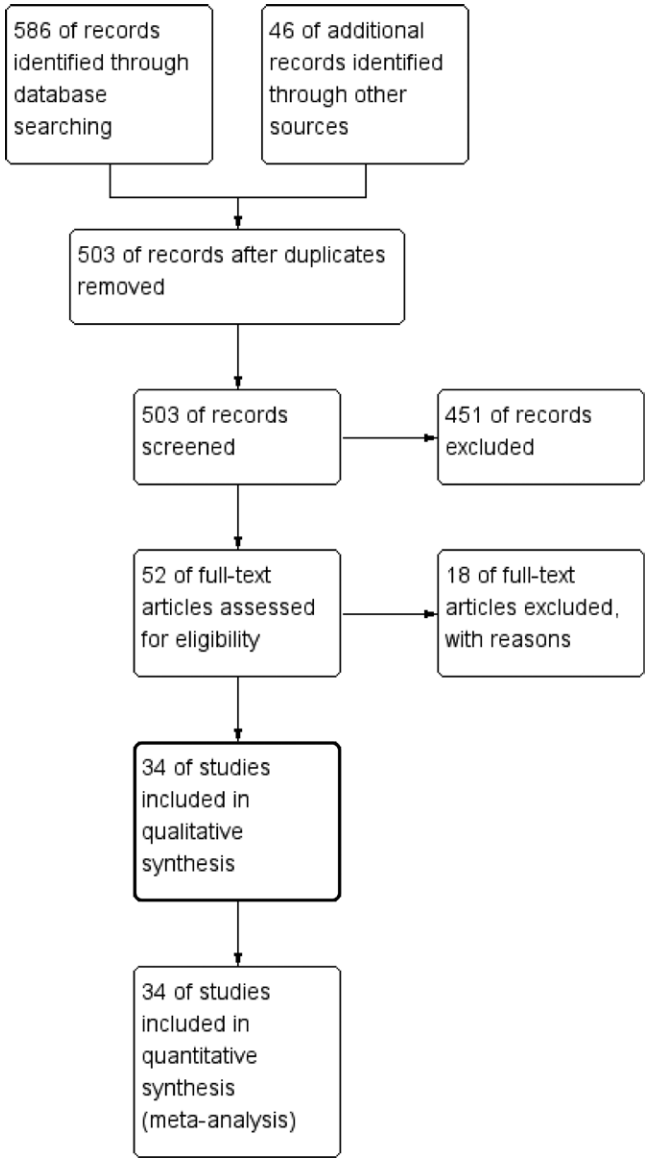

Figure 1. The flow chart of selection of included studies.

Table 1

General characteristic of the included studies.

Author	Interventions	Participants	Age	Dose	Surgery	Study	Transfusion trigger
Wang 2017	TXA/Placebo	41/39	42.5/42	TXA: 10 mg/kg + 1 mg/kg/h	Transforaminal thoracic interbody fusion	RCT	Hb < 7.0 g/dL, 7.0–10.0 g/dL and symptomatic
Shi 2017	TXA/Placebo	46/50	55.9/53.8	TXA: 30 mg/kg + 2 mg/kg/h	Posterior lumbar terbody fusion	RCT	Hb < 7 g/dL, 7–9 g/dL and hypotension
Seddighi 2017	TXA/Placebo	20/20	43.7/49.9	TXA: 10 mg/kg + 0.5 mg/kg/h	Major spinal surgeries	RCT	Hb/packed cell volume <8 g/d, drain collection > 500 mL
Nagabhushan 2017	TXA/Placebo	25/25	51.7/49.6	TXA: 10 mg/kg + 1 mg/kg/h	Lumbar single level fusion surgery	RCT	NS
Kim 2017	TXA1/TXA2/Placebo	24/24/24	65.2/63.3	TXA: 5 mg/kg + 1 mg/kg/h	Posterior lumbar interbody fusion	RCT	Blood loss > 30% blood volume
				TXA: 10 mg/kg + 2 mg/kg/h		RCT	Hb < 8 g/dL
Geng 2017	TXA/Placebo	50/50	48.2/49.1	TXA: 15 mg/kg + 2 mg/kg/h	Spine tuberculosis surgery	RCT	Anesthesiologist decision
Colomina 2017	TXA/Placebo	51/44	50.8/59.2	TXA: 10 mg/kg + 2 mg/kg/h	Posterior thoracic/lumbar surgery	RCT	Hb < 10 g/dL or Hct < 30%
Carabini 2017	TXA/Placebo	30/31	68.0/65.0	TXA: 10 mg/kg + 1 mg/kg/h	Multilevel spine fusion surgery	RCT	Intraoperative, Hct < 25%; postoperative, Hct < 22%
Basavaraj 2017	TXA/Placebo	30/30	54.7/54.3	TXA: 15 mg/kg + 1 mg/kg/h	Thoracic spine fixation surgery	RCT	Intraoperative, Hct < 25%; postoperative, Hct < 22%
Raksakietisak 2015	TXA/Placebo	39/39	53.1/52.6	TXA: 2 dose of 15 mg/kg	Spine surgery	RCT	Hb < 7 g/dL or patient symptomology
Peters 2015	EACA/TXA/Placebo	13/19/19	47/43/60	TXA: 10 mg/kg + 1 mg/kg/h	Posterior spinal fusion of at least 5 levels	RCT	Hb < 80 g/L
				EACA: 100 mg/kg + 10 mg/kg/h		RCT	Hb < 10 g/dL
Verma 2014	EACA/TXA/Placebo	47/36/42	14.6/15.3/15.1	TXA: 10 mg/kg + 1 mg/kg/h	Posterior spinal arthrodesis	RCT	Intraoperative, Hct < 25%; postoperative, Hct < 22%
				EACA: 100 mg/kg + 10 mg/kg/h		RCT	
Halanski 2014	EACA/TXA	25/22	13.2/13.9	EACA: 100 mg/kg + 10 mg/kg/h	Posterior spinal fusion	RCT	Hb < 7 g/dL or patient symptomology
				TXA: 100 mg/kg + 10 mg/kg/h		RCT	NS
Wang 2013	TXA/Placebo	30/30	63.1/62.0	TXA: 15 mg/kg	Posterior lumbar interbody fusion	RCT	NS
Xu 2012	TXA/Placebo	20/20	19.1/20.4	TXA: 20 mg/kg + 10 mg/kg/h	AIS surgery	RCT	Hb < 80 g/L
Tsutsumimoto 2011	TXA/Placebo	38/38	68.0/65.8	TXA: 15 mg/kg	Cervical laminoplasty	RCT	
Farrokhi 2011	TXA/Placebo	20/20	45.5/51.4	TXA: 10 mg/kg + 1 mg/kg/h	Spinal fixation surgery	RCT	Hb < 10 g/dL
Taghaddomi 2009	TXA/Placebo	91/91	42.0/42.6	TXA: 15 mg/kg + 6 mg/kg/h	Lumbar hernial dics resection	RCT	Hb < 80 g/L
Berenholtz 2009	EACA/Placebo	74/73	55.5/55.4	EACA: 100 mg/kg + 10 mg/kg/h	Reconstructive spinal surgeries	RCT	Hb < 8 g/dL or < 10 g/dL (>60 years old or with heart or lung diseases)
Wong 2008	TXA/Placebo	32/32	56.8/50.0	TXA: 10 mg/kg + 1 mg/kg/h	Posterior thoracic/lumbar fusion surgery	RCT	Hb < 7 g/dL, continuing blood loss or signs or symptoms of anemia
Elwatidy 2008	TXA/Placebo	21/23	51.6/50.0	TXA: 2 g + 100 mg/h (for adults); 30 mg/kg + 1 mg/kg/h (for children)	Spine surgery‡	RCT	Hb < 9 g/L, or Hct <27%
Sethna 2005	TXA/Placebo	17/19	13.6/14.0	TXA: 100 mg/kg + 10 mg/kg/h	Elective spinal fusion	RCT	Hb < 7 g/dL
Florentino 2004	EACA/Placebo	28/15	13.5/14.5	EACA: 100 mg/kg + 10 mg/kg/h	Posterior spinal fusion instrumentation	RCT	Hb < 7 g/dL
Khoshhal 2003	AP/Placebo	23/21	14.5/14/.1	AP: 4 mg/kg + 1 mg/kg/h	Spinal fusion and instrumentation	RCT	Hb < 70 g/L, Hct < 20%
Cole 2003	AP/Placebo	25/24	13.0/12.2	AP: 240 mg/m^2	Long segment spinal fusion	RCT	Hb < 8.5 g/dL (Hct <27%)
Karapurkar 2002	AP/Placebo	18/17/20	NS	AP: 20,000 IU/kg + 5000 IU kg/4h	Posterior fusion instrumentation and bone grafting	RCT	Blood loss > 10% of blood volume, Hct < 30% and Hb < 10 g/dL
Urban 2001	AP/EACA/Placebo	18/22	47.2/46.6/47.3	EACA: 5 g + 15 mg/kg/h	Sequential anterior and posterior spinal fusions	RCT	Hb 8 g/dL (Hct 25–28%)
				AP: 1 million KIU + 0.25 million KIU/h		RCT	
Neilipovitz 2001	EACA/Placebo	29/31	14.1/13.7	TXA: 10 mg/kg + 1 mg/kg/h	Posterior spinal fusion	RCT	Hb < 7.0 g/dL
Lentschener 1999	AP/Placebo	37/35	46.0/51.0	AP: 2 × 106 KIU + 5 × 105 KIU/h	Posterior lumbar spine fusion	RCT	Hct < 26%
Haghighi 2006	TXA/Placebo	29/31	39.5/37.5	TXA: 10 mg/kg	Lumbar laminectomy	RCT	Hb 9 g/dL
Yan 2021	TXA/Placebo	50/50	46.5/53.0	TXA: 100 mg/kg + 10 mg/kg/h	elective posterior lumbar interbody fusion	RCT	Hb < 80 g/L
Yu 2022	TXA/Placebo	137/124	NS	TXA: 100 mg/kg + 10 mg/kg/h	Thoracolumbar spinal fusions	RCT	Hb < 80 g/L
Hasan 2021	TXA/Placebo	86/86	15.4/16.2	30 mg/kg TXA loading dose followed by 10 mg/kg/h infusion)	Posterior spinal fusion surgery	RCT	Hb 8 g/dL (Hct 25–28%)
Dong 2021	TXA/Placebo	40/40	NS	TXA: 100 mg/kg + 10 mg/kg/h	Spinal fusion surgery	RCT	Hb < 80 g/L

AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, RCT = randomized controlled trial, TXA = tranexamic acid.

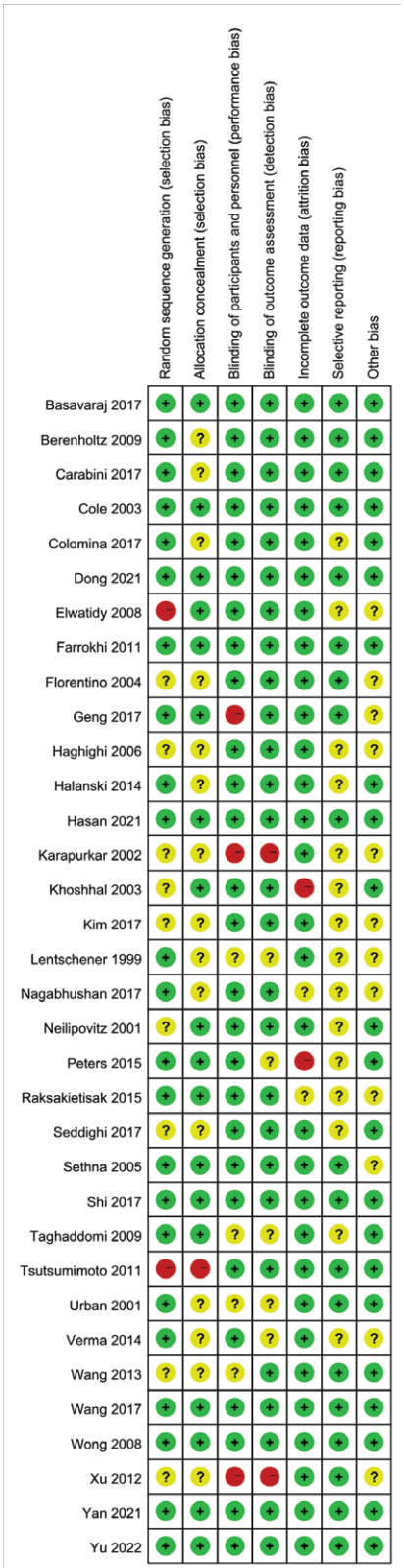

Figure 2. The risk of bias summary: review authors' judgement of each risk of bias items for each included studies.

2.5. Statistical analysis

A random-effects network meta-analysis within a Bayesian framework was conducted using the R software (version 3.5.1, https://www.r-project.org/) with the gemtc and rjags packages, which interface with Just Another Gibbs Sampler software (version 3.4.0). Four iteration chains, with 20,000 iterations were fitted to the Markov chain Monte Carlo Bayesian network meta-analysis to check convergence. A total of 150,000 sample iterations were generated for each chain, which included 10 thinning intervals and 100,000 burn-ins. Based on the posterior distribution medians, all estimate outcomes (mean differences [MDs] or odds ratio [ORs]) with 95% confidence intervals (CIs) were calculated. A statistically significant difference was presumed if 95% CIs of ORs did not contain 1 and 95% CIs of MDs did not contain 0. A value of $P < .05$ was considered statistically significant. In order to find the top-ranking interventions, the surface under the cumulative ranking curve (SUCRA) values were used in a network meta-analysis. A higher SUCRA index indicates better efficacy than lower SUCRA values, which range between 0 and 1. A cluster-ranking plot was constructed to determine the best outcome indicator from multiple outcomes. Heterogeneity was evaluated using the I^2 test, and thresholds of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively. Inconsistency models using deviance information criterion (DIC) differences of DIC between consistency and inconsistency models was performed to assess global inconsistency.

A value of dDIC > 10 indicated appreciable global inconsistency. The node-splitting analysis was used to assess the local inconsistency, a P value > .05 indicated no significant inconsistency between the direct pairwise results and the indirect results. Funnel plots evaluated the presence of publication bias within each network.

3. Results

3.1. Search results

As 3 databases (PubMed, Embase, and Cochrane library database) were scrutinized, the initial database search yielded 586 citations and 46 citations from additional sources. After duplicate removal (n = 129), a total of 503 records were screened on title and abstract, and 451 were excluded. Out of 52 studies, 34 RCTs[3,10,19–50] were selected, and 34 of them met the inclusion criteria to be included in this network meta-analysis. The research selection and flow chart of literature retrieval are reflected in Figure 1. The characteristics of included studies are presented in Table 1.

3.2. Risk of bias

According to the Cochrane Handbook for Systematic Reviews of Interventions, the risk of bias of the included RCTs were evaluated as follows: randomization; allocation concealment; blind method; selective reporting; incomplete outcome data; other bias. The bias of assessment of RCTs are presented in Figures 2 and 3.

3.3. Results of network meta-analysis

The iteration history graph was drawn to evaluate the convergence degree of the 4 chains of Markov chain Monte Carlo, showing that the convergence of the 4 chains was satisfactory, and the number of iterations was sufficient (Fig. 4).

3.3.1. Total blood loss. A total of 30 studies, including 4 treatments (TXA, EACA, AP, and placebo) contributed to the clinical outcome of the total blood loss. As displayed in Figure 5A, the network structure diagrams detailed the direct comparisons between different drugs in the total blood loss. Network meta-analysis showed considerable heterogeneity with global I^2 = 0% (Fig. 5B). In head-to-head comparison, TXA (MD −250.96, 95% CrI −307.17, −194.57, Fig. 5C),

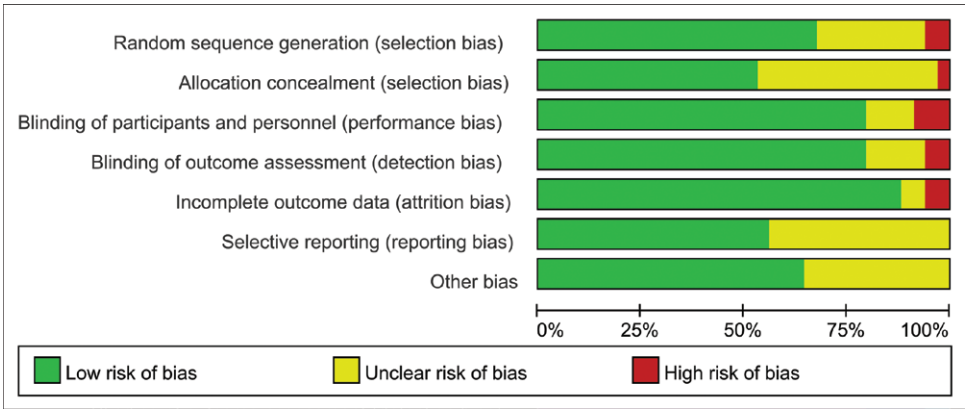

Figure 3. The risk of bias graph of the included studies.

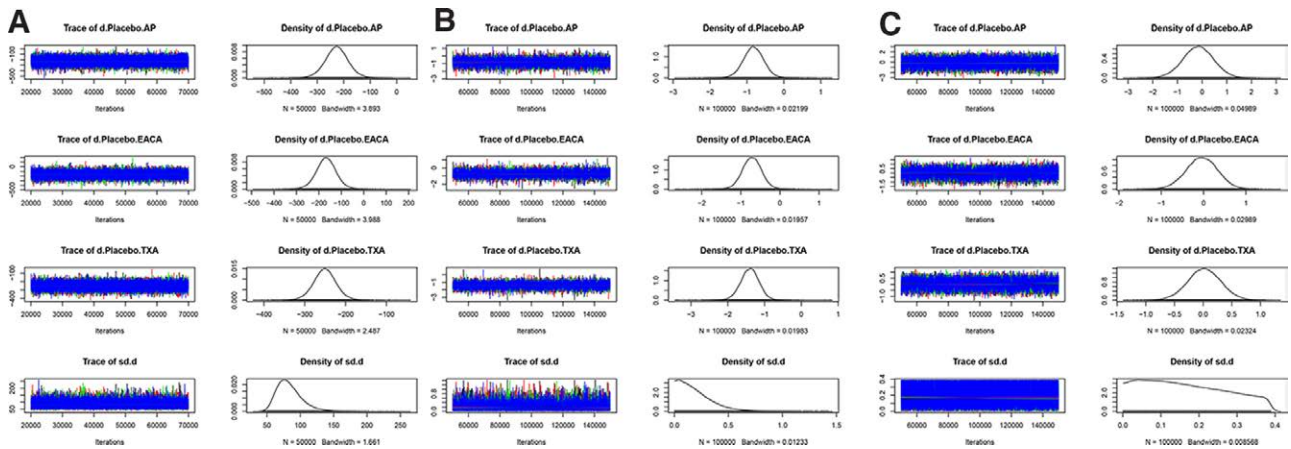

Figure 4. The history plots of iteration traces. AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, TXA = tranexamic acid.

EACA (MD −167.66, 95% CrI −258.73, −77.17, Fig. 5C) and AP (MD −226.69, 95% CrI −315.11, −138.05, Fig. 5C) was more effective than the placebo, and the difference was statistically significant. However, there was no statistically significant between TXA and EACA in terms of the total blood loss (MD −89.39, 95% CrI −7.78, 173.9, Table 2). There was no statistically significant between AP and TXA in terms of the total blood loss (MD 24.35, 95% CrI −80.74, 129.02, Table 2). The SUCRA shows that TXA ranked first (SUCRA, 88.4%), AP ranked second (SUCRA, 71.6%), EACA ranked third (SUCRA, 39.9%), and placebo ranked the last (SUCRA, 0.3%, Fig. 5D).

3.3.2. Need for transfusion. A total of 28 studies, including 4 treatments (TXA, EACA, AP, and placebo) contributed to the clinical outcome of need for transfusion.

As displayed in Figure 6A, the network structure diagrams detailed the direct comparisons between different drugs in the need for transfusion. Network meta-analysis showed considerable heterogeneity with global I^2 = 0% (Fig. 6B).

In head-to-head comparison, TXA (OR 0.25 95% CrI 0.15, 0.4, Fig. 6C), EACA (OR 0.49 95% CrI 0.3, 0.79, Fig. 6C) and AP (OR 0.44, 95% CrI 0.25, 0.76, Fig. 6C) was more effective than the placebo, and the difference was statistically significant. TXA was more effective than EACA in terms of the need for transfusion (OR 1.98, 95% CrI 1.19, 3.36, Table 3). There was no statistically significant between AP and EACA in terms of the need for transfusion (OR 0.9, 95% CrI 0.43, 1.88, Table 3).

The SUCRA shows that TXA ranked first (SUCRA, 97.7%), AP ranked second (SUCRA, 55.8%), EACA ranked third (SUCRA, 46.2%), and placebo ranked the last (SUCRA, 0.2%, Fig. 6D).

3.3.3. Occurrence of DVT and PE. A total of 30 studies, including 4 treatments (TXA, EACA, AP, and placebo) contributed to the clinical outcome of occurrence of DVT and PE. As displayed in Figure 7A, the network structure diagrams detailed the direct comparisons between different drugs in the occurrence of DVT and PE. Network meta-analysis showed considerable heterogeneity with global I^2 = 0% (Fig. 7B). There was no statistical significance in pairwise comparisons between any two of the 4 groups (P > .05, Fig. 7C, Table 4).

There was no statistically significant between AP and EACA in terms of the occurrence of DVT and PE (OR 0.89, 95% CrI 0.21, 3.79, Table 4). There was no statistically significant between AP and placebp in terms of the occurrence of DVT and PE (OR 0.86, 95% CrI 0.25, 2.88, Table 4). There was no statistically significant between EACA and placebo in terms of the occurrence of DVT and PE (OR 0.96, 95% CrI 0.46, 1.97, Table 4). There was no statistically significant between AP and TXA in terms of the occurrence of DVT and PE (OR 0.84, 95% CrI 0.22, 3.24, Table 4). There was no statistically significant between EACA and TXA in terms of the occurrence of DVT and PE (OR 0.94, 95% CrI 0.39, 2.21, Table 4). There was no statistically significant between placebo and TXA in terms of the occurrence of DVT and PE (OR 0.98, 95% CrI 0.56, 1.74, Table 4). The SUCRA shows that AP ranked first (SUCRA, 59.0%), EACA ranked second (SUCRA, 51.1%), TXA ranked third (SUCRA, 43.8%), and placebo ranked the last (SUCRA, 46.1%, Fig. 7D).

3.3.4. Publication bias. A publication bias funnel plot was used to investigate the potential publication bias of the chosen studies. This meta-analysis was characterized by

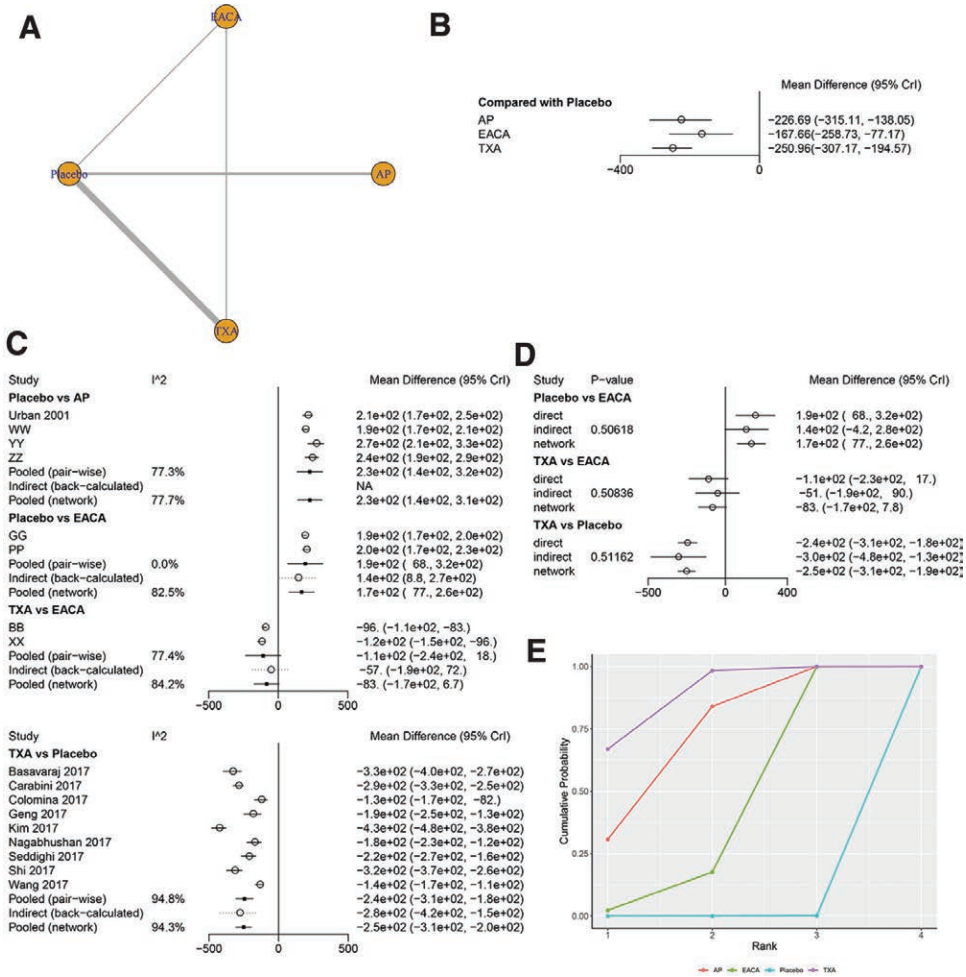

Figure 5. (A) Structure of network formed by interventions. The lines between treatment nodes indicate the direct comparisons made within randomized controlled trials. (B) Forest plot comparing different treatment with placebo for total blood loss. (C) Heterogeneity between the included study for direct and indirect comparisons. (D) SUCRA values of different treatment for total blood loss. AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, SUCRA = surface under the cumulative ranking curve, TXA = tranexamic acid.

Table 2

Indirect comparison of the total blood loss.

AP			
−59.23 (−185.71, 67.39)	EACA		
−226.69 (−315.11, −138.05)	*−167.66 (−258.73, −77.17)*	Placebo	
24.35 (−80.74, 129.02)	83.39 (−7.78, 173.9)	*250.96 (194.57, 307.17)*	TXA

A *P* value in oblique type denotes a significant difference ($P < .05$).

AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, TXA = tranexamic acid.

symmetrical funnel plots, which indicated no publication bias (Fig. 8).

4. Discussion

Since the early 1990s, spinal surgeries, particularly spinal fusions, have increased exponentially.[51] Generally spinal procedures, including reconstructive and multilevel surgeries are accompanied by loss of larger amounts of blood.[52,53] Blood loss following spinal surgery requires abundant blood transfusion. Blood transfusion is fraught with risks of serious complications including blood-borne infections, clotting abnormalities and hypothermia.[54,55] In addition to the increased length of hospital stay, blood transfusion has significantly increased morbidity and mortality rates.[56]

TXA, EACA, and AP were antifibrinolytic drug, were used to treat or prevent excessive blood loss in orthopedic surgery.[57,58] The antifibrinolytic drug for blood loss controlling is controversial and need of further investigation. Therefore, we performed this network meta-analysis to identify the optimal drug for blood loss during spinal surgery. This study performed a meta-analysis of 34 RCTs, which is based on the largest sample size to date. Moreover, we performed the heterogeneity and consistency for each outcome to increase the robustness of out meta-analysis.

Most studies focused on the TXA for blood loss in spinal surgery. We compared the total blood loss, need for transfusion and the occurrence of DVT and PE between different groups. AP, TXA, and EACA are 3 commonly used antifibrinolytics have been studied extensively in cardiac surgery.[59–62] The AP inhibits the activity of serine proteases such as trypsin, chymotrypsin, plasmin, and kallikrein.[63]

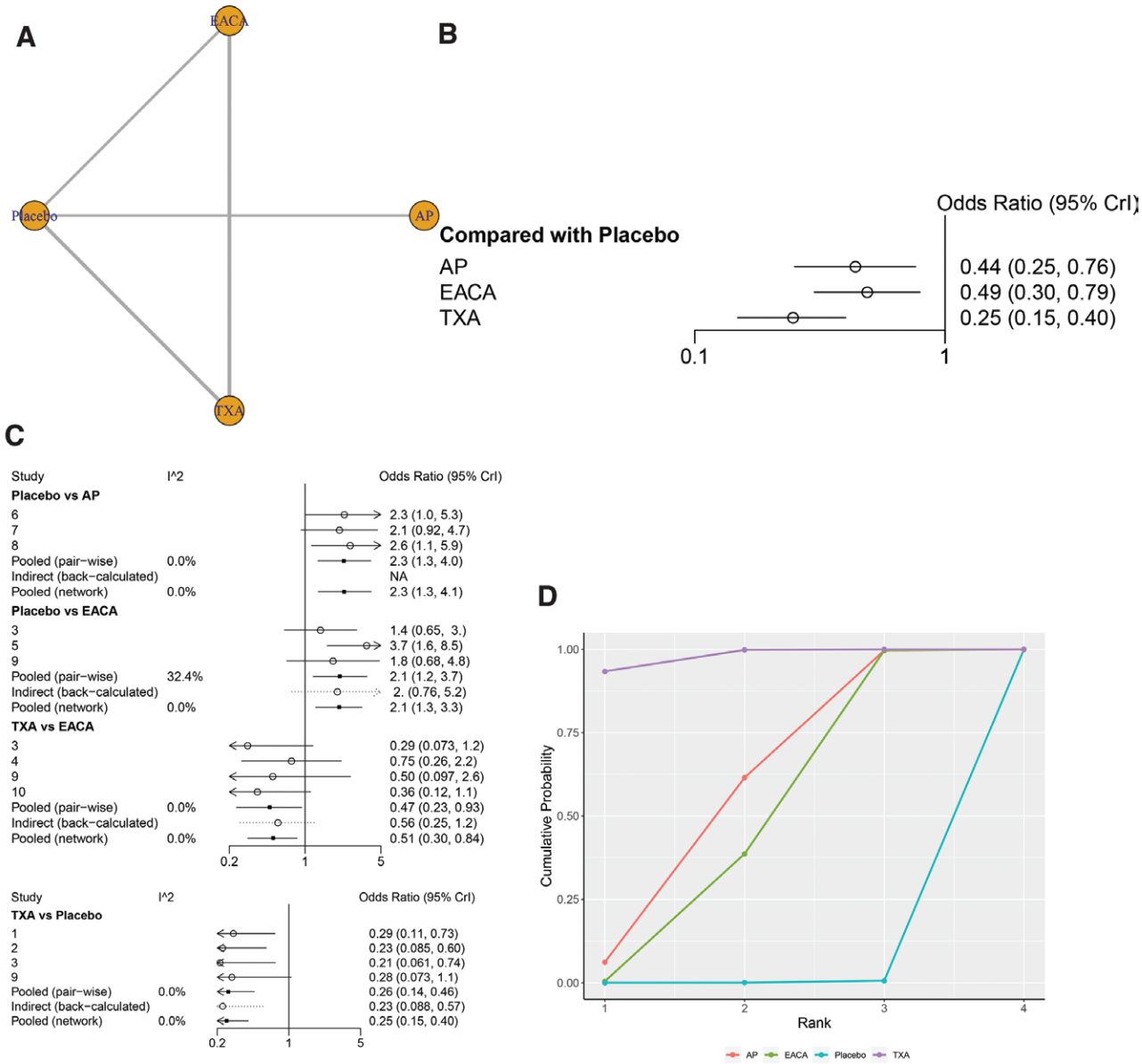

Figure 6. Structure of network formed by interventions. (A) The lines between treatment nodes indicate the direct comparisons made within randomized controlled trials. (B) Forest plot comparing different treatment with placebo for need for transfusion. (C) Heterogeneity between the included study for direct and indirect comparisons. (D) SUCRA values of different treatment for need for transfusion. AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, SUCRA = surface under the cumulative ranking curve, TXA = tranexamic acid.

Table 3

Indirect comparison of the need for transfusion.

AP			
0.9 (0.43, 1.88)	EACA		
0.44 (0.25, 0.76)	*0.49 (0.3, 0.79)*	Placebo	
1.78 (0.84, 3.79)	1.98 (1.19, 3.36)	*4.05 (2.5, 6.74)*	TXA

A *P* value in oblique type denotes a significant difference ($P < .05$).

AP = aprotinin, EACA = epsilon-acetyl aminocaproic acid, TXA = tranexamic acid.

In this network meta-analysis, we found that TXA ranked first (SUCRA, 88.4%) for reducing blood loss in spinal surgery patients. The effects of TXA in reducing blood loss were consistent with findings from the previous literatures.[64,65] Qin et al[66] conducted a systematic review about TXA for blood loss in spinal surgery. A total of 10 RCTs were finally included for systematic review and final results suggested that high dose of TXA was superior than low dose of TXA and placebo for blood loss in spinal surgery. However, there is still a concern about the safety of high dose of TXA in surgery patients.[67] Bao et al[68] compared the efficacy and safety of TXA in spinal surgery and results found that TXA significantly reduce perioperative blood loss without increasing the thrombosis events. Thus, TXA can be applied for reducing blood loss in spinal surgery. Gill

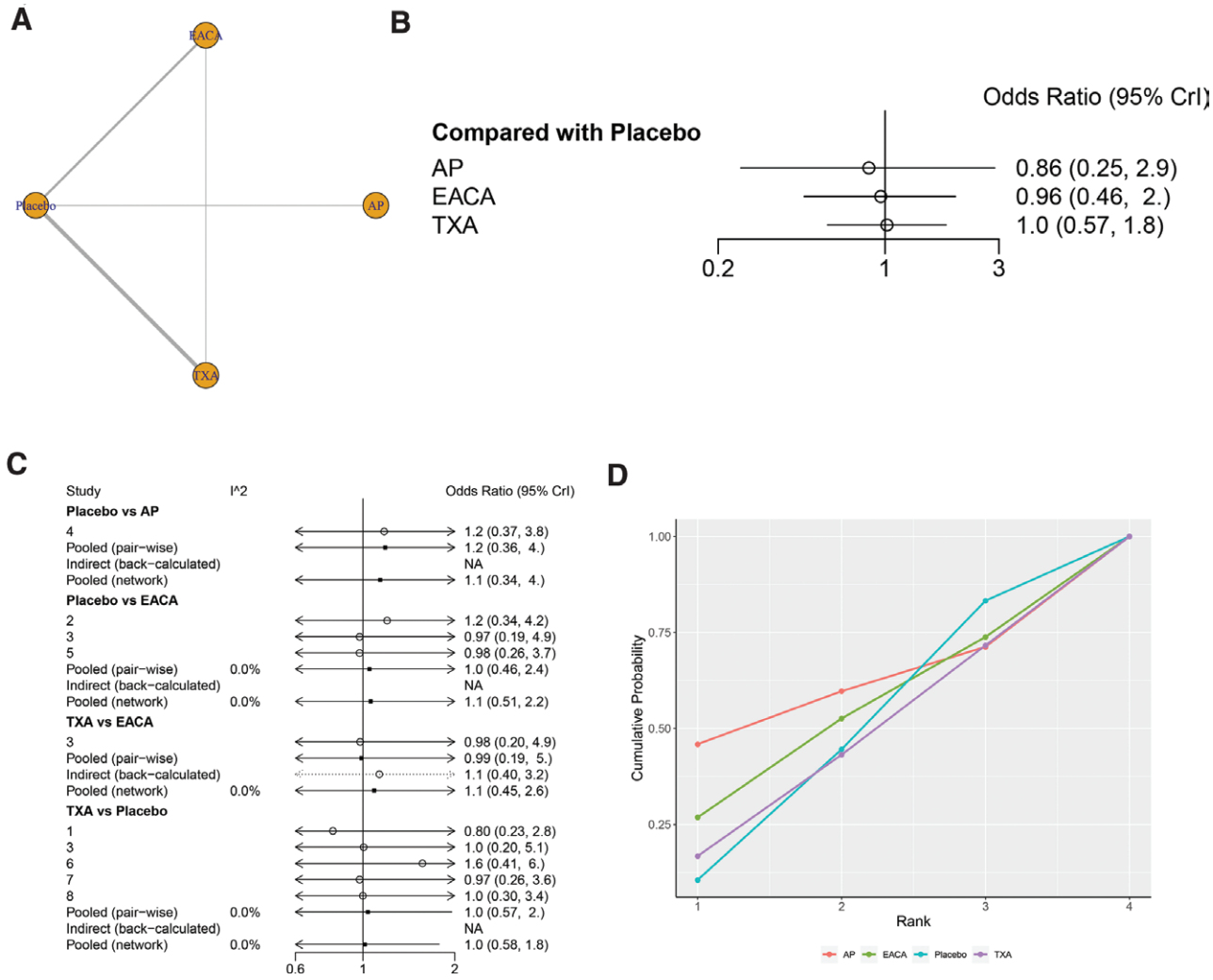

Figure 7. Structure of network formed by interventions. (A) The lines between treatment nodes indicate the direct comparisons made within randomized controlled trials. (B) Forest plot comparing different treatment with placebo for occurrence of DVT and PE. (C) Heterogeneity between the included study for direct and indirect comparisons. (D) SUCRA values of different treatment for occurrence of DVT and PE. AP = aprotinin, DVT = deep venous thrombosis, EACA = epsilon-acetyl aminocaproic acid, PE = pulmonary embolism, SUCRA = surface under the cumulative ranking curve, TXA = tranexamic acid.

Table 4

Indirect comparison of the occurrence of DVT and PE.

AP			
0.89 (0.21, 3.79)	EACA		
0.86 (0.25, 2.88)	0.96 (0.46, 1.97)	Placebo	
0.84 (0.22, 3.24)	0.94 (0.39, 2.21)	0.98 (0.56, 1.74)	TXA

AP = aprotinin, DVT = deep venous thrombosis, EACA = epsilon-acetyl aminocaproic acid, PE = pulmonary embolism, TXA = tranexamic acid.

et al[69] conducted a The use of antifibrinolytic agents in spine surgery. Gill et al[69] conducted a meta-analysis about AP, TXA and EACA versus placebo in spinal surgery. AP, TXA, and EACA were all effective for reducing blood loss and transfusion in spinal surgery patients.

As for the occurrence of DVT and PE between AP, TXA, and EACA. There was no statistically significant difference for the occurrence of DVT and PE between these drugs. Akosman et al[70] performed a meta-analysis about the safety of high-dose TXA in spinal surgery. Results suggested that high dose of TXA is not associated with an increased risk of complications, including DVT and PE. Cao et al[6] also verified that AP, TXA and EACA were all safe for reducing blood loss in spinal surgery without increasing DVT and PE in spinal surgery.

Despite the obvious advantages of this meta-analysis containing large sample sizes, there are some limitations to this study. To be first, the included researches differed in the approaches of evaluating transfusion trigger. Second, there was a marked discrepancy between estimated and actual blood loss in spinal surgery. Third, most of the included studies had limited sample sizes and majority of the studies were conducted in western countries, and so more subgroups or sensitivity analyses could not be conducted. Moreover, the mean age and the sex ratio of each included studies also varied largely, which may in turn also cause heterogeneity of the results. The follow-up time for assessing the outcome of the studies were differ from each other. Therefore, only few studies can be included for combining functional outcomes. Last, potential language bias might exist as our

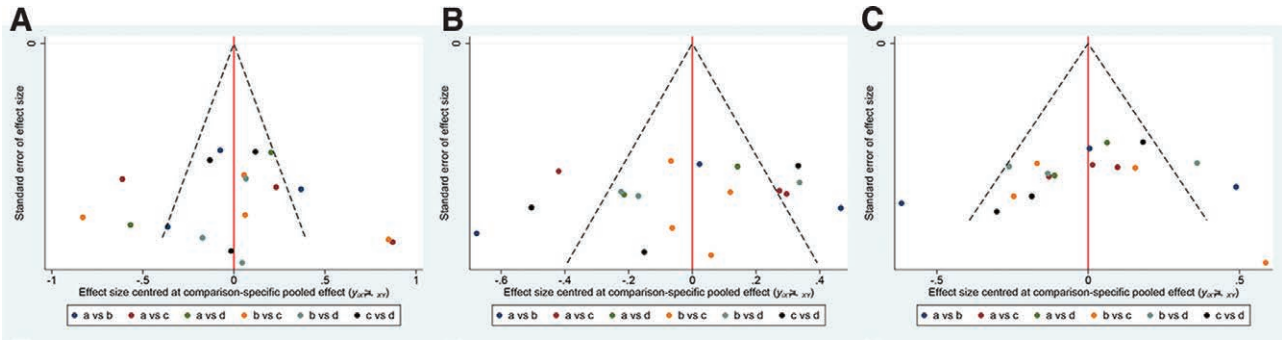

Figure 8. Funnel pot of the total blood loss, need for transfusion and the occurrence of DVT and PE by comparisons. DVT = deep venous thrombosis, PE = pulmonary embolism.

literature search considered those articles published in English only.

5. Conclusion

In conclusion, this network meta-analysis suggests that the TXA might be the optimal administration with high efficacy and safety when compared with EACA, AP, and placebo in spinal surgeries, which significantly reduces the total blood loss and the need for transfusion. There was no evidence that use of antifibrinolytic agents was a risk factor for thromboembolism, in spinal surgery. However, considering limitations of network meta-analysis, more high-quality studies will need to be conducted to eliminate heterogeneity.

Author contributions

Conceptualization: Songli Pan.
Data curation: Songli Pan, Zhilin Chen.
Formal analysis: Zhilin Chen.
Resources: Haitao Tan.
Software: Haitao Tan.
Validation: Tao Chen.
Visualization: Chuanchun Wei, Tao Chen.
Writing – original draft: Chuanchun Wei.

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