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Tranexamic acid achieves less blood loss volume of primary shoulder arthroplasty: A Systematic Review and Meta-Analysis of Level I Randomized Controlled Trials

Running Title: Tranexamic acid in primary shoulder arthroplasty

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Title : Tranexamic acid achieves less blood loss volume of primary shoulder arthroplasty : A Systematic Review and Meta-Analysis of Level I Randomized Controlled Trials

Abstract

Background: Tranexamic acid (TXA) reduces blood loss in knee and hip arthroplasty, but the effectiveness of shoulder arthroplasty is unknown. This study aimed to evaluate current Level I randomized controlled trials (RCTs) examining the efficacy of TXA in primary shoulder arthroplasty.

Methods: A protocol for the study was designed and registered with PROSPERO (CRD42021230398). The PubMed, Embase, and Cochrane Library databases were searched using the following search strategy “shoulder replacement” OR “shoulder arthroplasty” OR “reverse shoulder arthroplasty” AND “tranexamic acid.” All RCTs were included in this study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was followed. Outcomes include blood loss, drain output, hemoglobin (Hb), thromboembolic complications and blood transfusion.

Results: Five randomized controlled trials of 435 patients (219 patients in the TXA group and 216 patients in the non-TXA group) were included in the systematic review. The results indicated that the group using TXA had less total blood loss（MD, -249.56 ml; 95% CI -347.60 to -151.52 ）, less drainage output (MD,-113.72 ml ; -155.92 to – 71.52 95% CI), and less of a change less in hemoglobin (MD,− 0.68 g/dl -0.94 to − 0.42 g/dl 95% CI). No significant differences in blood transfusion (RR,0.40 -0.11 to 1.45 95% CI), or thromboembolic events (RR 0.13, 0.02 to 1.12 95% CI) were

observed. Subgroup analyses showed that there was no significant difference in total blood loss, drainage output, or change in hemoglobin between single dose and multiple doses.

Conclusions: Tranexamic acid in primary shoulder arthroplasty can reduce blood loss, drain output and hemoglobin changes. Subgroup analysis showed that multiple TXA doses have similar results compared with single dose in primary shoulder arthroplasty. More RCTs comparing different administration routes of TXA in primary and revision shoulder arthroplasty are required.

Level of Evidence: Level Ⅰ. Systematic Review and Meta-Analysis

Keywords: tranexamic acid, shoulder, arthroplasty, shoulder arthroplasty, meta-analysis;

In recent years, total shoulder arthroplasty and reverse total shoulder arthroplasty have grown. [14,24,25,29,47,56] Currently, the indications for shoulder arthroplasty are very widespread, including cuff tear pathology, tumors, end-stage shoulder arthropathy, traumatic shoulder injuries and a history failure of the first operation.[33,53] Blood loss and transfusions are common complications for shoulder arthroplasty.[12] Several studies have reported that the blood transfusion rates after TSA range from 4% to 43%.[2,5,21,22,26,39,40,45,48,51] In addition, blood transfusion may cause allergic reactions, transmission of viruses, allergic reactions, infection, and cardiovascular dysfunction.[7,14,32,33] These may result in additional costs and longer hospital stays.

Tranexamic acid (TXA) is an antifibrinolytic agent that leads to blood clots

stabilization from the prevention of fibrin degradation by the lysine binding site on plasminogen.[1,2,17,38,50,52] Previous studies have shown that using TXA can achieve less perioperative blood transfusion and blood loss in joint surgery.[2,10,52,60,64] Several studies have reported using TXA in shoulder arthroplasty.[1,6,8,11,12,13,17,18,23,30,31,33,44,53,59,65,66] However, the existing studies have limitations, such as small samples, low quality studies, and different TXA administration.

As a new RCT study reported a single dose of tranexamic acid in shoulder arthroplasty, a meta-analysis needs to performed.[12] This systematic review and meta-analysis aimed to evaluate extant Level I randomized controlled trials (RCTs) examining the efficacy of TXA in primary shoulder arthroplasty.

2. Material and methods

2.1 Search strategy

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Fig 1). The PubMed, Cochrane Library and Embase were systematically searched from inception to January, 10th,2021. The search strategy include: “shoulder replacement” OR “shoulder arthroplasty” OR “reverse shoulder arthroplasty” AND “tranexamic acid by two reviewers (DYF, JM). There was no language restriction in the search process and manually searched the references of the included studies reference to identify additional eligible studies.

68 **2.2 Eligibility Criteria**

69 Eligible studies were considered for inclusion if they met the following criteria:(1)
70 the study was Level I randomized controlled trials. (2) patients of any age
71 undergoing primary shoulder arthroplasty were included (3) the intervention was TXA
72 and the study only compared patients who received TXA and those who did not
73 receive TXA (any form of placebo or no treatment). (4) at least one perioperative
74 outcome was compared between groups: hemoglobin, drain output, blood loss, and
75 thromboembolic or blood transfusion. (5) published in English. Two authors (DYF,
76 JM) independently reviewed the studies and a full-text review of all potentially
77 relevant trials was performed for final inclusion. A third author was consulted to
78 resolve disagreements

79 **2.3 Data extraction**

80 Two researchers (DYF, JM) independently extracted the relevant data. Then the third
81 reviewer (LZ) checked data for inaccuracies. The data included (1) year, country, the
82 number of patients in each group, age, gender, BMI, patients diagnosis, surgery,
83 approach, prosthesis properties and TXA administration (2) changes in Hb, drain
84 output, blood loss, thromboembolic complication and blood transfusion. Data were
85 extracted using Microsoft Excel and RevMan Version 5.3 (Cochrane Collaboration)
86 for data management.

87 **2.4 Evaluation of quality of the studies**

88 Two reviewers (DYF, JM) followed the Cochrane Collaboration, Oxford, UK
89 (Cochrane Handbook for Systematic Reviews of Interventions) using Cochrane

risk-of-bias tool for all included RCTs. This tool categorized bias into 6 domains and each domain was assigned a level of risk of bias (high risk, low risk, or unclear risk).

2.5 Statistical analysis

A random-effects model was used for all outcomes in this study. All forest plots were constructed with RevMan 5.3.0 (Cochrane Collaboration). Dichotomous data（blood transfusion and thromboembolic complication were calculated as risk ratios with 95% confidence interval (CI). Continuous data（blood loss, changes in hemoglobin, drain output, blood drainage）were shown as mean difference of 95% CI. Heterogeneity was quantified by using the chi-square test. I^2 values of 0–40% indicate low heterogeneity, values of 40–60% indicate moderate heterogeneity, and values of 60–100% indicate high heterogeneity. These values can be examined via forest plots.

Subgroup analysis

Subgroup analysis was planned to perform subgroups analysis if data were available

TXA: single dose or multiple doses

3.Results

The literature primary search yielded 72 articles, and no additional studies were obtained. After removing duplicates, screening title and abstracts, five RCTs [12,13,18,44,59] met the inclusion criteria, and a total of 435 patients (Table Ⅰ) were included in this study (216 in the Non-TXA group and 219 in the TXA group).

Study characteristics

Three randomized controlled trials were conducted in the United States, and two other studies were conducted in Austria and Switzerland, respectively. One study was a

multicenter trials[18], and 4 studies were single-center trial.[12,13,44,59]

Mean BMI

Four studies reported mean body mass index (BMI). Vara et al reported a mean BMI of 29.2±6.7 kg/m^2 for the TXA group and 30.7±8.3 kg/m^2 for the non-TXA group.[59] Pauzenberger et al reported a mean BMI of 31.1kg/m^2（22.0-53.0）for the TXA group, 30.8（20.0-40.6）kg/m2 for the non-TXA group.[44] Cvetanovich et al reported a mean BMI of 29.0±5.0 kg/m2 for the TXA, 29.7±5.2 kg/m^2 for the non- TXA group.[13] Cunningham et al reported a mean BMI of 30±7.0 kg/m2 for TXA group, and 31±7.8 kg/m^2 for the non-TXA group.[12] There were no significant differences between the two groups in any of the four studies.

Diagnosis and surgery type

As shown in Table Ⅱ, only two studies reported patient diagnosis, which included degenerative joint disease of the shoulder and massive rotator cuff deficiency with or without glenohumeral arthrosis. Only one study reported patients with primary reverse shoulder arthroplasty (RTSA)[59], and 4 studies reported that their patients received either primary anatomic shoulder arthroplasty (TSA) and reverse shoulder arthroplasty (RTSA).[12,13,18,44]

Prostheses properties and approach

Only three studies reported prosthesis properties.[13,44,59] Cvetanovich et al reported non-cemented prostheses for their patients.[13] Pauzenberger et al used an anatomical prosthesis (Eclipse; Arthrex Inc., Naples, Florida) with a cemented polyethylene glenoid component for TSA and a cemented humeral stem component（Delta Xtend,

DePuy Synthes , Warsaw , IN, USA ）for RTSA.[44] Vara et al reported 102 non-cemented prostheses（79 Zimmer, 11 DePuy, 4 Biomet, 2 Encore）for patiens.[59] All included studies used a deltopectoral approach for surgery.

TXA administration

TXA administration were different during arthroplasty procedures. Gillespie et al reported a single dose of 2 g TXA in 100 ml normal saline.[18] Vara et al reported 10 mg/kg TXA within 60 minutes before surgery and a second dose at wound closure.[59] Pauzenberger et al used 1 g TXA with 100 ml saline before skin incision and a second at wound closure.[44] Cvetanovich et al used 1 g TXA diluted in 10 ml normal saline before surgery.[13] Cunningham et al used 2 g TXA before skin incision.[12]

Risk of bias of the included studies

The risk of bias of the five studies is shown in Fig 2 and Fig 3. All included studies had a risk of bias in random sequence generation, blinding of participants and personnel and selective reporting. One study had unclear risk of selection bias.[18] Two studies had unclear risk of outcome assessment data.[13,18] Three studies reported incomplete outcome data.[12,44,59]

4. Blood loss

Four studies[12,13,44,59] reported that compared with the non-TXA group, the intervention of TXA administration group resulted in less blood loss（MD,-249.56 ml; 95% CI -347.60 to -151.52）, with low heterogeneity (p =0.31, I^2 =16%) Fig. 4.

Subgroup analysis was performed based on the different methods of TXA（single

dose or multiple doses. The outcome revealed there was no significant difference between the single dose（MD,-181.64 ml; 95% CI -293.37 to -69.91）and multiple doses（MD,- 357.92 ml; 95% CI -504.27 to -211.58）as shown in Table 3.

5.Blood transfusion

A total of 5 studies[12,13,18,44,59] with 435 patients reported blood transfusion in the two groups. The results indicated no significant difference between the TXA group and the non-TXA group. (RR,0.40, -0.11 to 1.45 95% CI; P = 0.16, I^2 = 0%) Fig.5.

6.Blood loss in drainage output

Four studies reported[12,18,44,59] data on blood loss via drainage. The pooled data showed that intervention with TXA could reduce blood loss in drainage (a mean of 113.72 ml, -155.82 to -71.52, 95% CI, P=0.04, I^2=64%)(Fig. 6).

Subgroup analysis was performed based on the different methods of TXA（single dose or multiple doses）The outcome revealed no significant difference between the single dose（MD,-96.41 ml; 95% CI -166.97 to -25.86）and multiple doses（MD, -137.92 ml; 95% CI -181.73 to -94.11）as shown in Table 3.

7.Changes in Hemoglobin

Four studies [12,18,44,59] indicated the data on changes in hemoglobin. The pooled data revealed that hemoglobin changed after shoulder arthroplasty (MD of − 0.68 g/dl -0.94 to − 0.42 g/dl 95% CI; P=0.85; I^2 = 0%;) in Fig. 7.

Subgroup analysis was performed based on the different methods of TXA（single dose or multiple doses）The outcome revealed no significant difference between the single dose (MD −0.73g/dl , -1.11 to – 0.35 g/dl 95% CI) ; and multiple doses（MD −0.63g/dl , -1.00 to – 0.27 g/dl 95% CI) in Table 3.

8.Thromboembolic complications

All five studies[12,13,18,44,59] provided the data on patients who had thromboembolic complications after surgery. No significant differences in thromboembolic complications between the TXA group and the non-TXA group (RR 0.13, 0.02 to 1.12 95% CI; P = 0.40.; I^2 = 0%) as shown in Fig. 8.

9.Discission

To our knowledge, this meta-analysis is the first include all five RCT studies to examined the efficiency of tranexamic acid in primary shoulder arthroplasty. The main findings of the study indicated that TXA can reduce blood loss, drainage output, and changes in hemoglobin in shoulder arthroplasty. In addition, TXA multiple doses had comparable effect when compared with single dose in primary shoulder arthroplasty. However, in blood transfusion and thromboembolic complication, the difference did not reach significance.

In orthopedic surgery, perioperative bleeding and postsurgical hemorrhage are common problems for surgeons. As anatomic shoulder arthroplasty and reverse shoulder arthroplasty originated in the 19th century, we faced the same question about blood transfusion management after surgery.

The results reported herein regarding total blood loss（MD,-249.56 ml; 95% CI -347.60 to -151.52, p =0.31, I^2 =16%） and blood drainage output (MD,-113.72 ml ; -155.92 to – 71.52 95% CI)) in primary shoulder arthroplasty is similar to previous findings, indicating that TXA is indeed helpful for reducing blood loss..[17,31,33,66] However, the subgroup in this study found multiple doses provide no more benefits than single dose for shoulder arthroplasty to reduce total blood loss. This results is not consistent with clinical trial studies in hip and knee arthroplasty and no related literature reported in shoulder arthroplasty.[27,34,35,36,62] There is a consensus among surgeons that less bleeding is better for patients, but it is unclear whether differences in bleeding for shoulder arthroplasty are clinically significant.

After surgery, blood transfusion is often linked to allergic reactions, transmission of viruses, allergic reactions, and bacterial infection.[7,14,32,33] Risk factors include; age, sex, BMI, preoperative diagnosis, comorbid conditions.**Error! Reference source not found.**,14,21,39,40,51 Kuo et al [33]showed that TXA group had a lower transfusion rate. Other studies reported that TXA led to a significantly reduction in blood transfusion after hip and knee surgery. [2,52,60] However, we found no significant difference in blood transfusion between the TXA group and non-TXA group (RR,0.40 -0.11 to 1.45 95% CI), this may be due to our small sample size.

Hemoglobin is a predictor of blood transfusion. In our studies, the pooled data showed a change in hemoglobin levels (MD, − 0.68 g/dl -0.94 to − 0.42 g/dl 95% CI), and this result was supported by other studies.[23,31,33,66] However, comparing two studies[53,66] , we found no significant difference in blood transfusion. This finding may

be due to different blood transfusion trigger criteria, small sample size and the small number of literature reports.

Compared with non-TXA group, previous literature has demonstrated that TXA has no increased risk of thromboembolic events.[53,66]A recent study that retrospective national claims data with patients who underwent a total or reverse shoulder arthroplasty between 2010 and 2016, found that TXA use was not associated with increased complication odds, independent of a history of thrombotic events[8]. In our study, we found similar results (RR 0.13, 95% CI 0.02 to 1.12), but we still need to be aware of the potential risks and whether the two non-administration methods had an impact on the occurrence of thromboembolic complications.

The optimal effect of TXA administration in arthroplasty remains unclear. Intravenous (IV), topical, combined intravenous and topical are three administrations of TXA for arthroplasty. Previous studies found no significant differences in the transfusion requirement, postoperative complications, blood loss, and change in hemoglobin levels between IV and topical administration of total hip and knee arthroplasty.[49,68] In addition, three other studies found that the combination of using TXA was associated with significantly reduced total blood loss, transfusion requirements, and maximum hemoglobin drop when compared IV and topical administration.[37,54,63] However, a prospective study with 285 total hip arthroplasty showed that TXA topically, intravenously and combination in primary total hip arthroplasty provided equivalent reductions in hemoglobin and blood loss.[19]

TXA dose is another variable factor affecting blood loss. In this study, subgroup

analysis showed that the multiple doses resulted in similar blood loss compared with single doses. However, Li et al reported a prospective pilot study that conducted less blood loss than a single dose by using additional dose of intravenous TXA.[36] Kang et al found that three doses of TXA decreased blood loss and diminished inflammatory and fibrinolytic responses more than a single dose or two doses in elderly patients.[27] Similar results were reported by using a five-dose in hip and knee surgery.[34,35] Goyal et al showed that there was no significant beneficial effect of three doses of TXA in bilateral total knee arthroplasty compared to a single dose.[20] Chalmers et al reported that a double IV TXA dose and a combined single IV and topical TXA dose were equally effective in minimizing blood transfusions at primary total hip and knee arthroplasties.[9] A recent randomized controlled trial by Palija et al divided 200 patients into five groups of 40 patients each(non-TXA , intravenous, topical, combined intravenous + topical and ,combined with double dose).[42] The results showed that none of the TXA routes are superior to the others, but multiple doses could statistically significantly reduce blood loss and transfusion requirements. Therefore, the optimal use of tranexamic acid still needs further research.

The cost of using TXA during shoulder arthroplasty is an important problem for patients and the health-care system. A study projected that the demand for primary shoulder arthroplasties in young patients will increase by 333.3%, and in older patients, it will increase by 755.4% in 2030.[41] The median costs for primary shoulder arthroplasty including the 60-day preoperative workup and 90-day postoperative

recovery, were $14,675 for TSA and $17,407 for RSA.[28] The mean cost of TXA is $ 58 to $ 68.[17,57] In total knee arthroplasty, TXA resulted in savings of 337.78 € per patient.[58] In simultaneous bilateral total knee arthroplasty, TXA use was associated with a hospital length of stay reduction of 0.9 days, an increased likelihood of hospital discharge over skilled nursing facilities and reduced total hospital cost of care , room and board costs, and transfusion costs by 6.45%, 11.76% and 81.65% respectively.[16] Compared with non- TXA, TXA was associated with a 36% decrease in transfusion risk, a 35% decreased risk for combined complications and a 6.2% shorter hospital stay in shoulder arthroplasty.[6] Carbone A, et al found that TXA use was associated with a reduction in hospitalization cost (-8.9% CI: -13.1%; -4.6%; P < .0001; group median $18,830) in retrospective national claims data (Premier Healthcare) on 71,174 patients.[8] Therefore, TXA is an effective measure for cost savings in shoulder arthroplasty.

This study has several potential limitations. First, only five RCTs with a small sample were included, two of which displayed patient diagnosis; therefore, more RCTs need to be reported. In addition, some outcomes including range of motion (ROM) and function score were not fully described when we tried to extract the data. According to current RCTs, only the effectiveness of TXA in decreasing blood loss is answered, but postoperative infection and hematoma formation is still unclear when compared with placebo. Last, it is hard to compare TXA for TSA versus RTSA due to the limitation of the content included in the article.

Conclusions

Tranexamic acid in primary shoulder arthroplasty can reduce blood loss, drain output and hemoglobin changes. Subgroup analysis showed that multiple TXA doses have similar results compared with single dose in primary shoulder arthroplasty. More RCTs comparing different administration routes of TXA in primary and revision shoulder arthroplasty are required.

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Figure and Table Legends

Table Ⅰ General Characteristics

Study	Year	Center	Country	Total Patients	Mean Age（year）	Gender
Gillespie	2015	multicenter	USA	111	67（41-86）, TXA group：TSA 62, RTSA 71.21 Non-TXA group：TSA59.73, RTSA 70.94	M49 F62 ,TXA group：TSA 59.09, RTSA 29.41 Non-TXA group：TSA72.73, RTSA 30.3
Vara	2017	single	USA	102	TXA group：67±9，Non-TXA group：66±9	TXA group：M20 F33，Non-TXA group：M22 F27
Pauzenberger	2017	single	Austria	54	TXA group：70.3（46.3-87.8）, Non-TXA group：71.3（53.7-84.3）	TXA group：M20 F7 Non-TXA group：M18 F9
Cvetanovich	2018	single	USA	108	66.4±10.1	M51 F59
Cunningham	2021	single	Switzerland	60	TXA group：72±8 Non-TXA group：73±9	TXA group：M11 F20 Non-TXA group：M6 F23

TXA: Tranexamic acid; TSA：Total shoulder arthroplasty：RTSA：Reverse total shoulder arthroplasty；M：male；F：female

Table Ⅱ BMI，Diagnosis，Surgery information，TXA Administration

Study	Mean BMI	Patients Diagnosis	Surgery type	Prostheses Properties	Approach	TXA Administration
Gillespie	N/S	Degenerative joint disease of shoulder（based on the integrity of the rotator cuff）	Primary TSA and RTSA	N/S	DA	Single dose，Topical TXA group：2g TXA in 100ml NS Non-TXA group：100ml NS
Vara	TXA group：29.2±6.7， Non-TXA group：30.7±8.3	Massive rotator cuff deficiency± glenohumeral arthrosis	Primary RTSA	102 Non-cemented RTSA（79 Zimmer, 11 DePuy, 4 Biomet, 2 Encore）	DA	Multiple doses，Intravenous TXA group: 10mg/kg TXA within 60minutes before surgery and a second at wound closure Non-TXA group: an equivalent volume of normal saline
Pauzenberger	TXA group：31.1（22.0-53.0）， Non-TXA group：30.8（20.0-40.6）	N/S	Primary TSA and RTSA	TSA（Eclipse；Arthrex Inc；Naples；Florida） RTSA（Delta Xtend，DePuy Synthes，	DA	Multiple doses, Intravenous TXA group: 1g TXA with 100ml saline before skin incision and a second at wound closure Non-TXA group: 100ml saline before skin incision

				Warsaw，Indiana）		
Cvetanovich	TXA group：29.0±5.0，Non-TXA group ：29.7±5.2	N/S	Primary TSA and RTSA	110 Non-cemented TSA or RTSA	DA	Single doses, Intravenous TXA group: 1g TXA diluted in 10ml NS with 10 mins before incision Non-TXA group：10ml NS with 10 mins before incision
Cunningham	TXA group：30±7.0，Non-TXA group ：31±7.8	N/S	Primary TSA and RTSA	N/S	DA	Single dose, Intravenous TXA group：2g TXA before skin incision Non-TXA group: saline placebo solution before skin incision

TXA: Tranexamic acid; TXSA：Total shoulder arthroplasty; RTSA：Reverse total shoulder arthroplasty；N/S：Not Shown；DA：Deltopectoral approach;

Table 3 Summary of meta-analysis and subgroup analysis of included studies

Outcomes	Number of studies	Patients (TXA/Non-TXA)	Effect Size		Heterogeneity	
			MD/RR	95% CI	I^2	p
Total blood loss	4	163/161	-249.56	-347.60 to -151.52	16%	0.31
Single dose	2	83/85	-181.64	-293.37 to -69.91	0%	0.89
Multiple doses	2	80/76	-357.92	-504.27 to -211.58	0%	0.87
Drainage output	4	167/160	-113.72	-155.92 to -71.52	64%	0.04
Single dose	2	87/84	-96.41	-166.97 to -25.86	82%	0.02
Multiple doses	2	80/76	-137.92	-181.73 to -94.11	0%	0.49
Changes in hemoglobin	4	167/160	-0.68	-0.94 to -0.42	0%	0.85
Single dose	2	87/84	-0.73	-1.11 to -0.35	0%	0.44
Multiple doses	2	80/76	-0.63	-1.00 to -0.27	0%	0.80
Blood transfusion	5	219/216	0.40	0.11 to 1.45	NR	NR
Thromboembolic complication	5	219/216	0.13	0.02 to 1.12	0%	0.40

TXA: Tranexamic acid; MD: Mean difference; RR: Risk ratio; CI: Confidence interval;
Data from Gillespie 2015 were estimated from median and range.

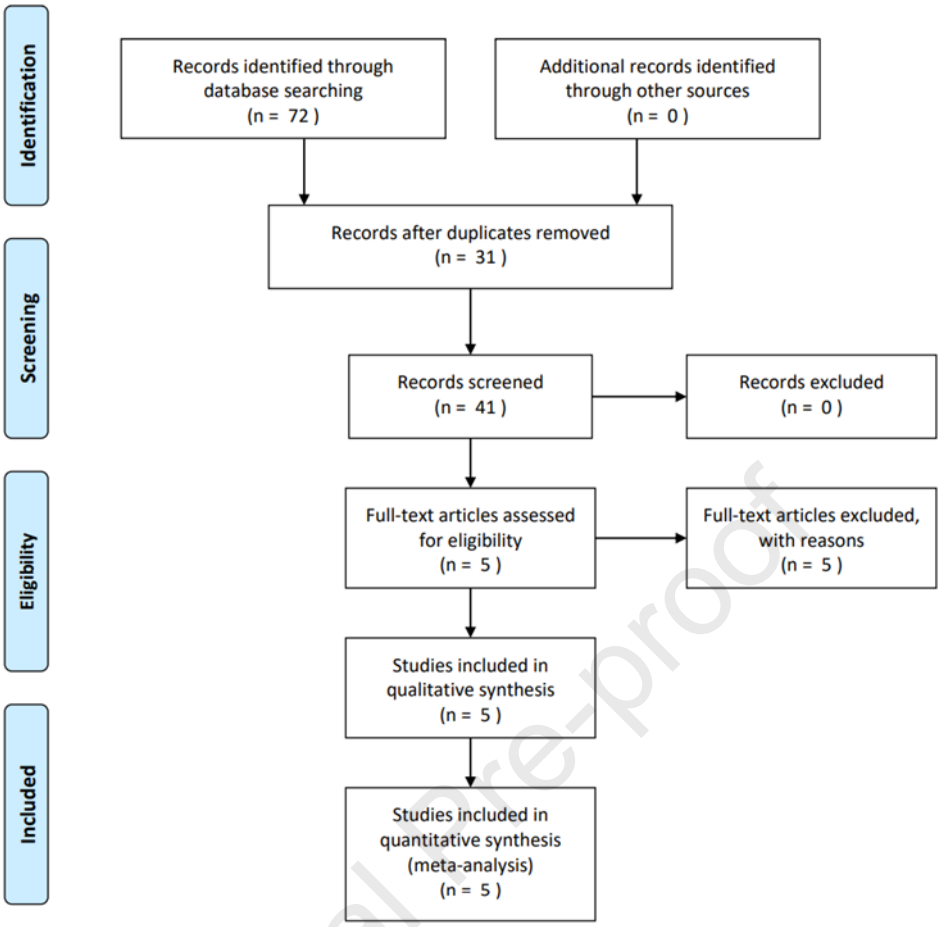

Figure 1. PRISMA Flow Diagram of Search Results

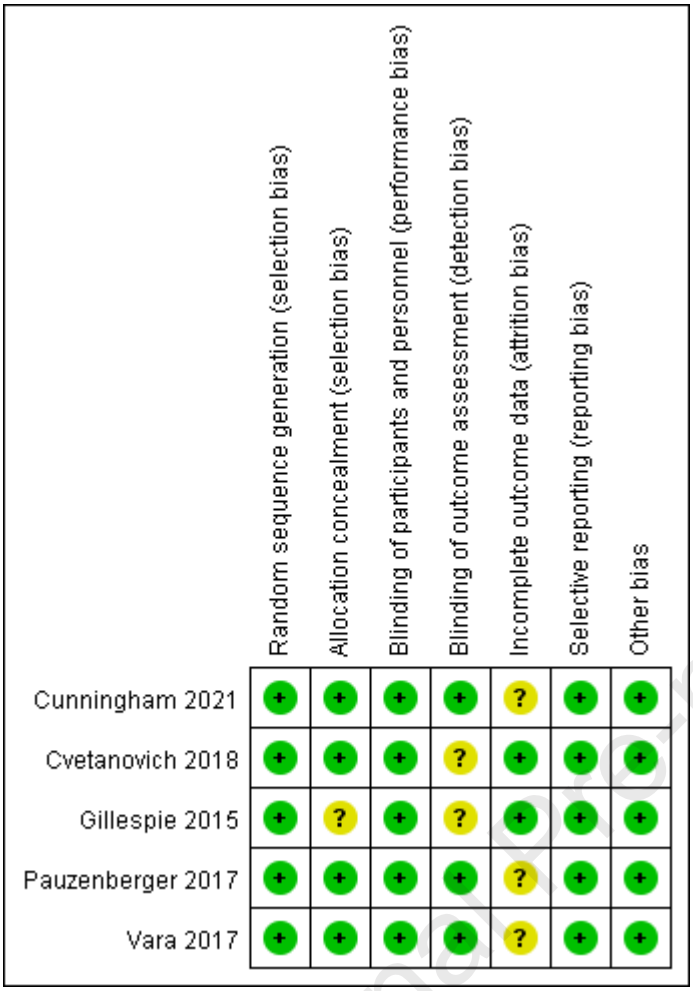

Fig 2 Risk-of-bias assessment of this meta-analysis

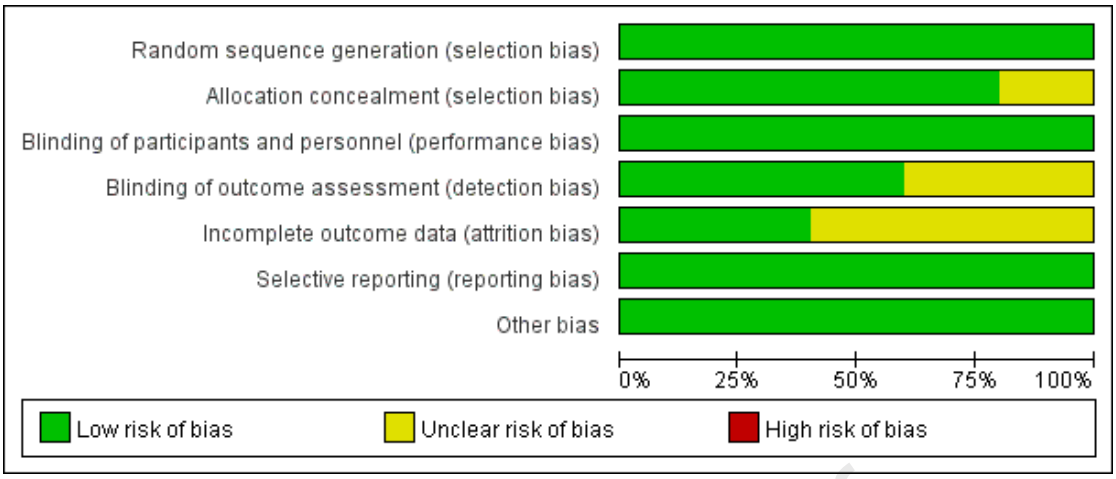

Fig.3 Graph of the risk of bias for the included studies

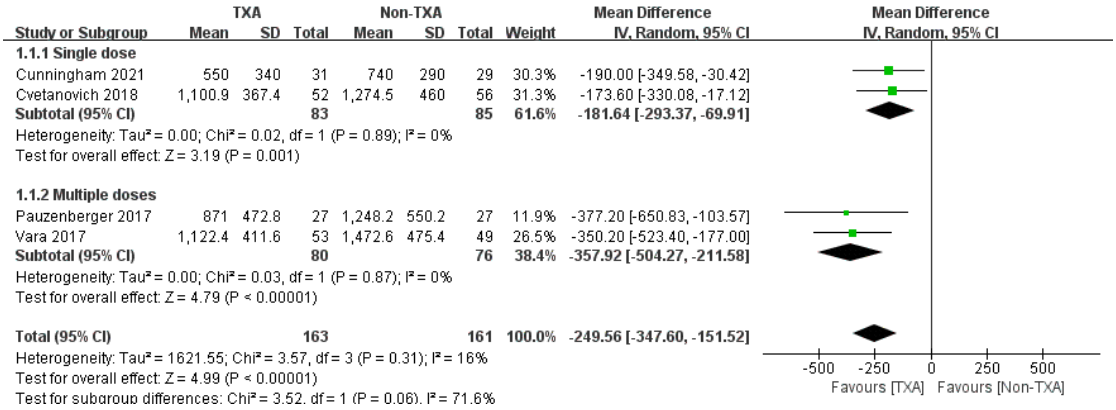

Fig. 4 Meta-analysis forest of total blood loss

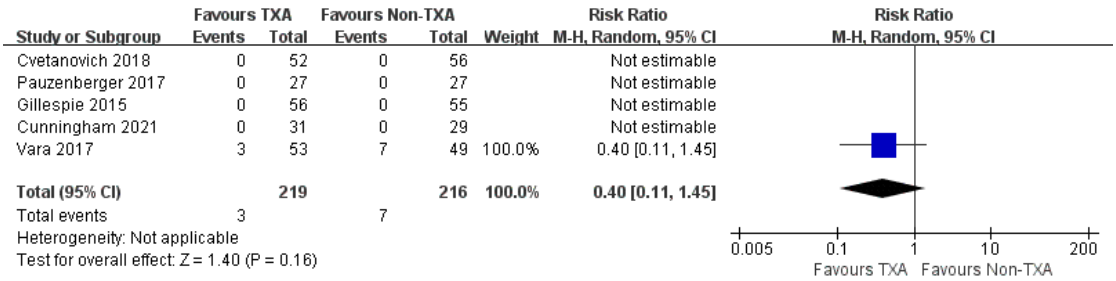

Fig. 5 Meta-analysis forest of blood transfusion

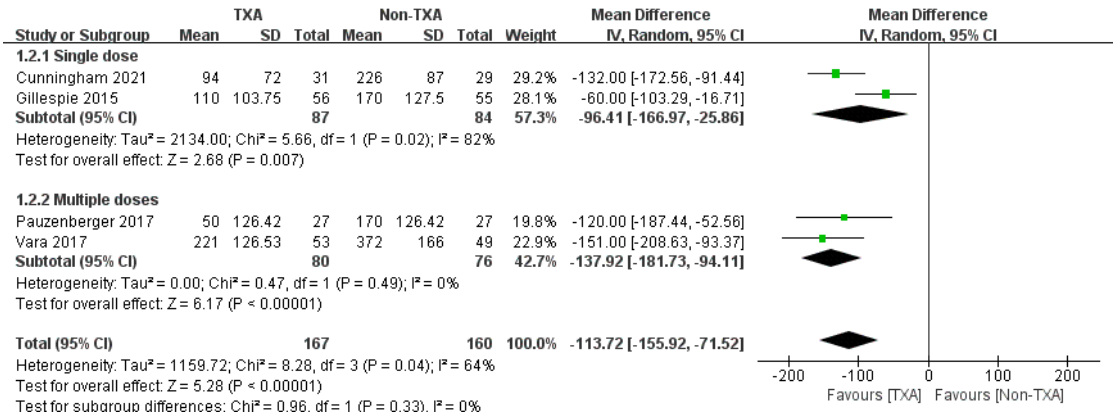

Fig. 6 Meta-analysis forest of blood loss in drainage output

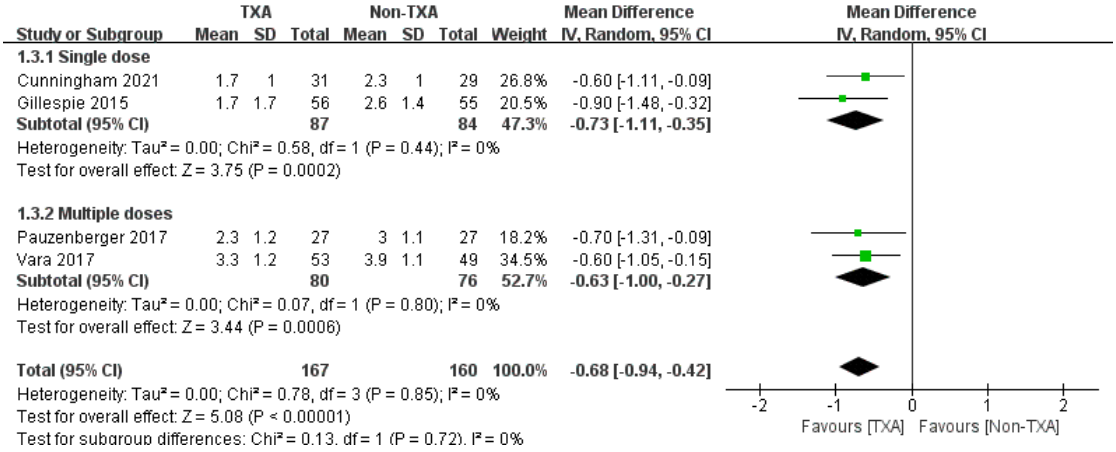

Fig. 7 Meta-analysis forest of changes in hemoglobin

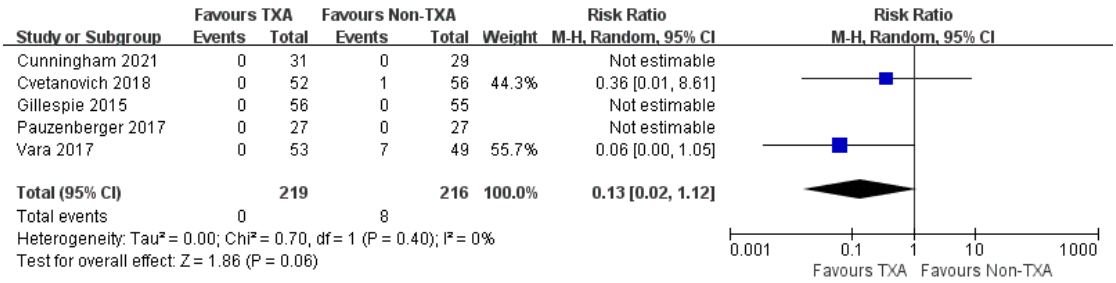

Fig. 8 Meta-analysis forest of thromboembolic complication