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Tranexamic acid achieves less blood loss volume of in primary shoulder arthroplasty: a systematic review and meta-analysis of level I randomized controlled trials

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Background: Tranexamic acid (TXA) reduces blood loss in knee and hip arthroplasty, but the effectiveness in shoulder arthroplasty is unknown. This study aimed to evaluate current level I randomized controlled trials 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 randomized controlled trials were included in this study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was followed. Outcomes include blood loss, drain output, hemoglobin, 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% confidence interval [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 in hemoglobin (MD, −0.68 g/dl; −0.94 to −0.42 g/dl 95% CI). No significant differences in blood transfusion (risk ratio 0.40; −0.11 to 1.45 95% CI) or thromboembolic events (risk ratio 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: TXA 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 randomized controlled trials comparing different administration routes of TXA in primary and revision shoulder arthroplasty are required.

In recent years, total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty have grown.[14,15,24,25,30,47,56] Currently, the indications for shoulder arthroplasty are very widespread, and include cuff tear pathology, tumors, end-stage shoulder arthropathy, traumatic shoulder injuries, and a history failure of the first operation.[33,53,55] 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.[8,14,32,33] These may result in additional costs and longer hospital stays.

Tranexamic acid (TXA) is an antifibrinolytic agent that leads to bloodclot stabilization from the prevention of fibrin degradation by the lysine-binding site on plasminogen.[1,3,17,38,50,52] Previous studies have shown that using TXA can achieve less perioperative blood transfusion and blood loss in joint surgery.[3,4,10,43,52,60,61,64] Several studies have reported using TXA in shoulder arthroplasty.[1,6,7,11,12,13,17,18,23,29,31,33,44,53,59,65,66] However, the existing studies have limitations, such as small sample size, low-quality studies, and different TXA administration.

As a recent randomized controlled trial (RCT) without meta analysis reported a single dose of TXA in shoulder arthroplasty.[12]

Institutional review board approval was not required because this study does not involve research on humans.

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This systematic review and meta-analysis aimed to evaluate extant level I RCTs examining the efficacy of TXA in primary shoulder arthroplasty.

Material and methods

Search strategy

This study was designed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Fig. 1). The PubMed, Cochrane Library, and Embase were systematically searched from inception to January, 10, 2021. The search strategy includes "shoulder replacement" OR "shoulder arthroplasty" OR "reverse shoulder arthroplasty" AND "tranexamic acid.

Eligibility criteria

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

Data extraction

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

Evaluation of quality of the studies

Two reviewers (DYF, JM) followed the Cochrane Collaboration, Oxford, UK (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).

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 (RRs) 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.

Results

The literature primary search yielded 72 articles, and no additional studies were obtained. After removing duplicates and 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 body mass index

Four studies reported mean body mass index (BMI). Vara et al[59] 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 nonTXA group. Pauzenberger et al[44] reported a mean BMI of 31.1 kg/m^2 (22.0-53.0)for the TXA group and 30.8 (20.0-40.6) kg/m^2 for the non-TXA group. Cvetanovich et al[13] reported a mean BMI of 29.0 ± 5.0 kg/m^2 for the TXA group and 29.7 ± 5.2 kg/m^2 for the non-TXA group. Cunningham et al[12] reported a mean BMI of 30 ± 7.0 kg/m^2 for the TXA group and 31 ± 7.8 kg/m^2 for the non-TXA group. 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 TSA and RTSA.[12,13,18,44]

Prostheses properties and approach

Only three studies reported prosthesis properties.[13,44,59] Cvetanovich et al[13] reported noncemented prostheses for their patients. Pauzenberger et al[44] used an anatomic 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. Vara et al[59] reported 102 noncemented prostheses (79 Zimmer, 11 DePuy, 4 Biomet, 2 Encore) for patients. All included studies used a deltopectoral approach for surgery.

TXA administration

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

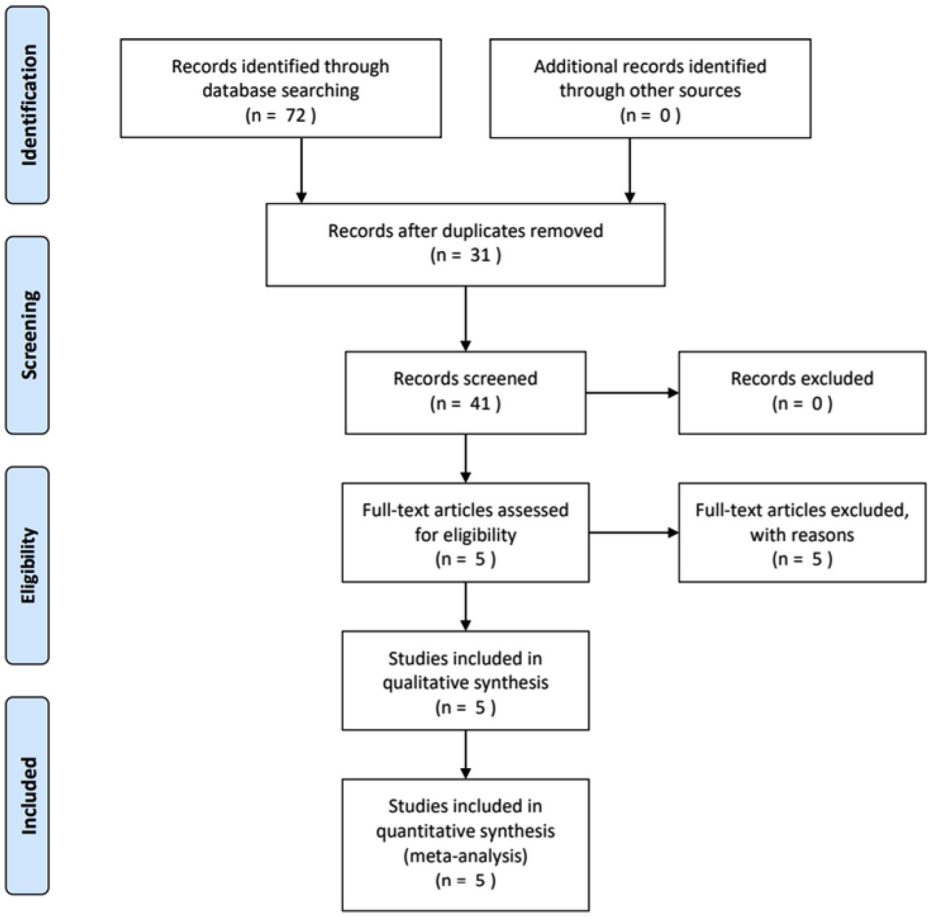

Figure 1 PRISMA flow diagram of search results. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Table I
General characteristics.

Study	Yr	Center	Country	Total patients	Mean age(yr)	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

F, female; *M*, male; *TSA*, total shoulder arthroplasty; *RTSA*, reverse total shoulder arthroplasty; *TXA*, tranexamic acid.

Risk of bias of the included studies

The risk of bias of the five studies is shown in Figures 2 and 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]

Blood loss

Four studies[12,13,44,59] reported that compared with the non-TXA group, the intervention of the TXA administration group resulted in less blood loss (MD, −249.56 mL; 95% CI −347.60 to −151.52), with low heterogeneity ($P = .31$, $I^2 = 16\%$) Figure 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 III.

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

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: 2 g TXA in 100 ml NS Non-TXA group: 100 ml NS
Vara	TXA group: 29.2 ± 6.7, Non-TXA group: 30.7 ± 8.3	Massive rotator cuff deficiency ± glenohumeral arthrosis	Primary RTSA	102 noncemented RTSA 79 Zimmer, 11 DePuy, 4 Biomet, 2 Encore)	DA	Multiple doses, intravenous TXA group: 10 mg/kg TXA within 60 min 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, Warsaw, Indiana)	DA	Multiple doses, intravenous TXA group: 1 g TXA with 100 ml saline before skin incision and a second at wound closure Non-TXA group: 100 ml saline before skin incision
Cvetanovich	TXA group: 29.0 ± 5.0, Non-TXA group : 29.7 ± 5.2	N/S	Primary TSA and RTSA	110 noncemented TSA or RTSA	DA	Single doses, Intravenous TXA group: 1 g TXA diluted in 10 ml NS with 10 mins before incision Non-TXA group: 10 ml NS with 10 min 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: 2 g TXA before skin incision Non-TXA group: saline placebo solution before skin incision

DA, deltopectoral approach; *N/S*, not shown; *RTSA*, reverse total shoulder arthroplasty; *TSA*, total shoulder arthroplasty; *TXA*, tranexamic acid.

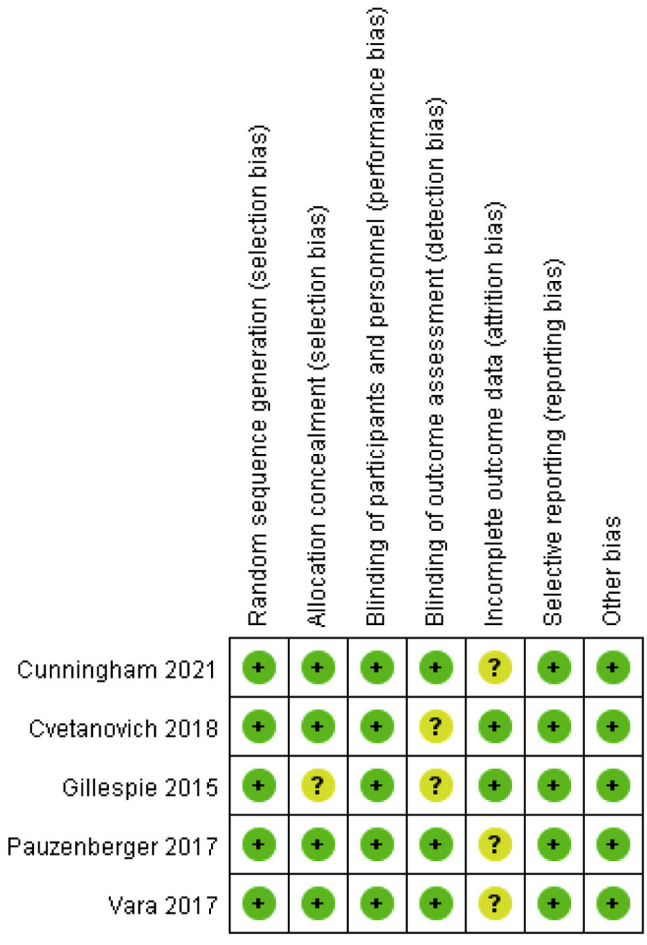

Figure 2 Risk-of-bias assessment of this meta-analysis.

difference between the TXA group and the non-TXA group (RR, 0.40, −0.11 to 1.45 95% CI; $P = .16$, $I^2 = 0\%$) Figure 5.

Blood loss via 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 drainage (a mean of 113.72 mL; −155.82 to −71.52, 95% CI; $P = .04$; $I^2 = 64\%$) (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 III.

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; $P = .85$; $I^2 = 0\%$) in Figure 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 −0.73 g/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 III.

Thromboembolic complications

All five studies[12,13,18,44,59] provided the data on patients who had thromboembolic complications after surgery. There were 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; $P = .40$; $I^2 = 0\%$) as shown in Figure 8.

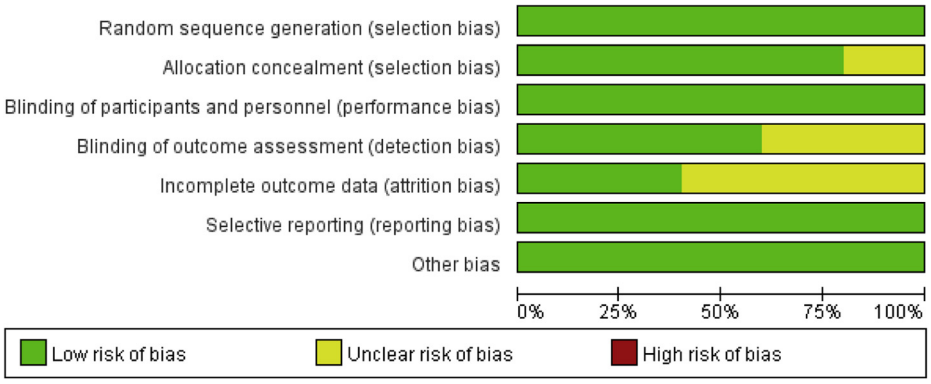

Figure 3 Graph of the risk of bias for the included studies.

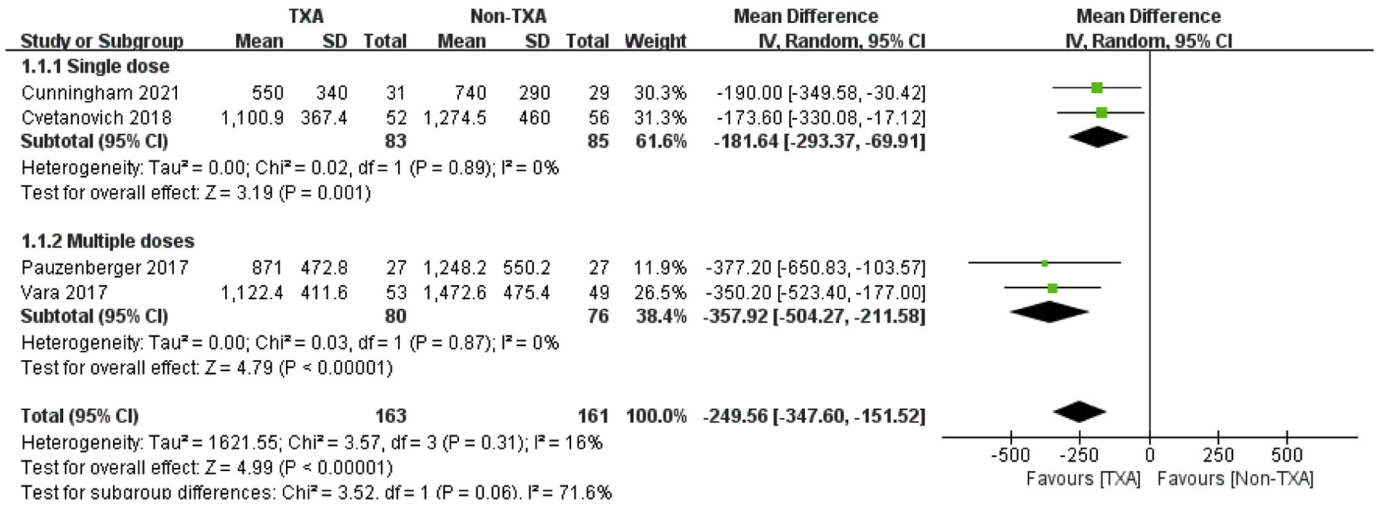

Figure 4 Meta-analysis forest plot of total blood loss.

Table III
Summary of meta-analysis and subgroup analysis of included studies.

Outcomes	No. of studies	Patients (TXA/non-TXA)	Effect size		Heterogeneity	
			MD/RR	95% CI	I^2	*P* value
Total blood loss	4	163/161	−249.56	−347.60 to −151.52	16%	.31
Single dose	2	83/85	−181.64	−293.37 to −69.91	0%	.89
Multiple doses	2	80/76	−357.92	−504.27 to −211.58	0%	.87
Drainage output	4	167/160	−113.72	−155.92 to −71.52	64%	.04
Single dose	2	87/84	−96.41	−166.97 to −25.86	82%	.02
Multiple doses	2	80/76	−137.92	−181.73 to −94.11	0%	.49
Changes in hemoglobin	4	167/160	−0.68	−0.94 to −0.42	0%	.85
Single dose	2	87/84	−0.73	−1.11 to −0.35	0%	.44
Multiple doses	2	80/76	−0.63	−1.00 to −0.27	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%	.40

CI, confidence interval; *MD*, mean difference; *RR*, risk ratio; *TXA*, tranexamic acid.
Data from Gillespie 2015 were estimated from median and range.

Discission

To our knowledge, this meta-analysis is the first to include all five RCT studies to examine the efficiency of TXA 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.

The results reported herein regarding total blood loss (MD, −249.56 mL; 95% CI −347.60 to −151.52; $P = .31$; $I^2 = 16\%$) and blood drainage output (MD, −113.72 mL; −155.92 to −71.52

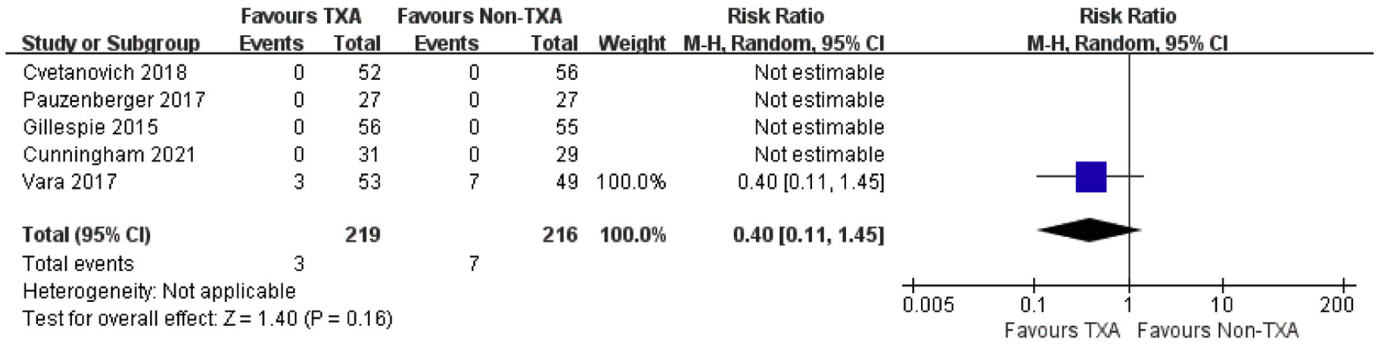

Figure 5 Meta-analysis forest plot of blood transfusion.

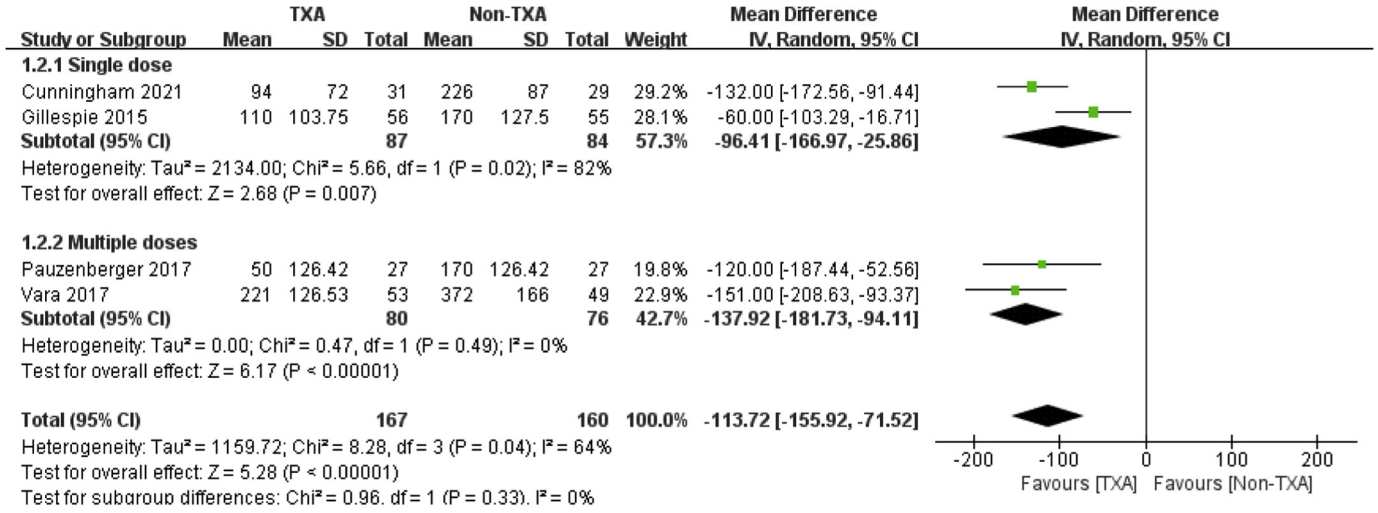

Figure 6 Meta-analysis forest plot of blood loss in drainage output.

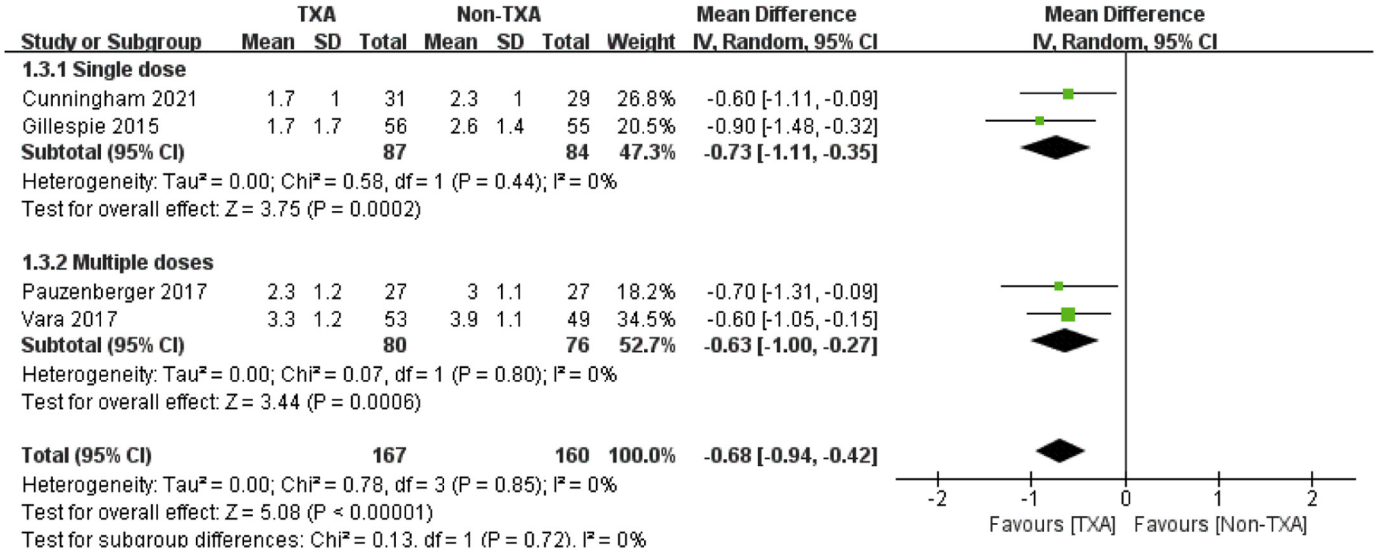

Figure 7 Meta-analysis forest plot of changes in hemoglobin.

95% CI) in primary shoulder arthroplasty are 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 result is not consistent with clinical trial studies in hip and knee 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.

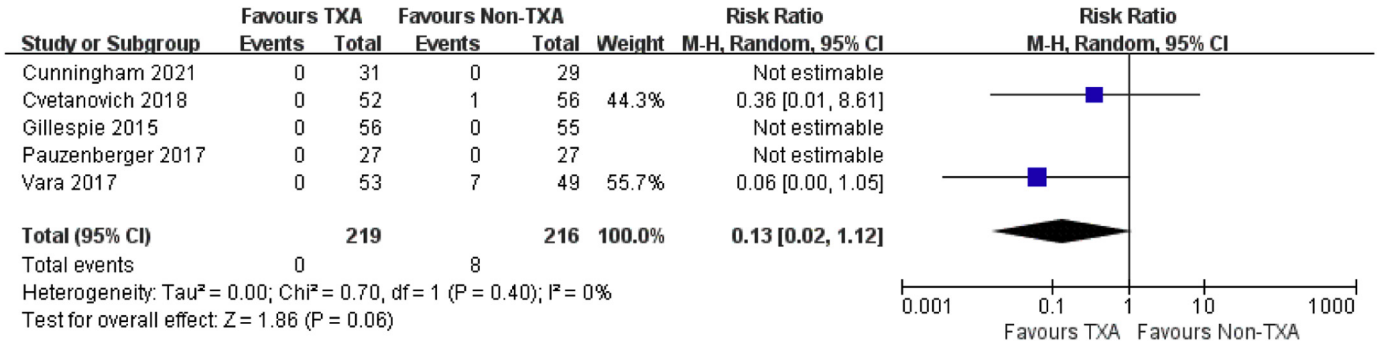

Figure 8 Meta-analysis forest plot of thromboembolic complication.

After surgery, blood transfusion is often linked to allergic reactions, transmission of viruses, and bacterial infection.[8,14,32,33] Risk factors include age, sex, BMI, preoperative diagnosis, and comorbid conditions.[2,14,21,39,40,46,51] Kuo et al[33] showed that the 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.[3,52,60] However, we found no significant difference in blood transfusion between the TXA group and non-TXA groups (RR, 0.40; −0.11 to 1.45 95% CI), this may be owing 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 owing to different blood transfusion trigger criteria, small sample size, and the small number of literature reports.

Compared with the non-TXA group, previous literature has demonstrated that TXA has no increased risk of thromboembolic events.[53,66] A recent study of retrospective national claims data with patients who underwent a total or RTSA between 2010 and 2016 found that TXA use was not associated with increased complication odds, independent of a history of thrombotic events.[7] 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 nonadministration methods had an impact on the occurrence of thromboembolic complications.

The optimal effect of TXA administration in arthroplasty remains unclear. Intravenous (IV), combined IV, 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 in total hip and knee arthroplasty.[49] In addition, three other studies found that using TXA in combination was associated with significantly reduced total blood loss, transfusion requirements, and maximum hemoglobin drop when compared with IV and topical administration.[37,54,63] However, a prospective study with 285 total hip arthroplasties showed that TXA topically, intravenously, and in 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[36] reported a prospective pilot study that additional doses conducted less blood loss than a single dose. Kang et al[27] found that three doses of TXA reduced blood loss and diminished inflammatory and fibrinolytic responses more than a single dose or two doses in elderly patients. Similar results were reported by using five doses in hip and knee surgery.[34,35] Goyal et al[20] showed that there was no significant beneficial effect of three doses of TXA in bilateral total knee arthroplasty compared with a single dose. Chalmers et al[9] reported that a double IV TXA dose and a combined single IV and topical TXA dose were equally effective in minimizing blood transfusions in primary total hip and knee arthroplasties. A recent randomized controlled trial by Palija et al[42] divided 200 patients into five groups of 40 patients each (non-TXA, IV, topical, combined IV+ topical, and combined with double dose). 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 TXA still needs further research.

The cost of using TXA during shoulder arthroplasty is an important problem for patients and the healthcare 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 et al[7] 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. 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 and function score were not fully described when we tried to extract the data. As per 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. Finally, it is hard to

compare TXA for TSA vs. RTSA owing to the limitation of the content included in the article.

Conclusions

TXA 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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