

Efficiency and safety of tranexamic acid in reducing blood loss in total shoulder arthroplasty

A systematic review and meta-analysis

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Abstract

Objective: This meta-analysis aimed to evaluate the efficiency and safety of tranexamic acid for reducing blood loss and transfusion requirements in patients undergoing total shoulder arthroplasty.

Methods: A systematic search was performed in Embase (1980–2017.04, embase.com), Medline (1966–2017.04, medline.com), PubMed (1966–2017.04, pubmed.com), ScienceDirect (1985–2017.04, sciencedirect.com), and Web of Science (1950–2017.04, webofknowledge.com). Study which assessed the efficiency and safety of tranexamic acid in total shoulder arthroplasty was selected. Meta-analysis was performed using Stata 11.0 software.

Results: In all, 484 patients from 2 randomized controlled trials (RCTs) and 2 non-RCTs were subjected to meta-analysis. The present meta-analysis demonstrated that there was less total blood loss (mean difference [MD] -172.16 , 95% confidence interval [CI] -35.46 to -308.87 , $P = .01$, $d = 0.33$) and transfusion rate (odds ratio 0.34, 95% CI 0.13 to 0.91, $P = .03$, $d = 0.29$) in tranexamic acid groups compared with the control groups. There were no significant differences in duration of surgery (MD 0.02, 95% CI -0.12 to 0.22, $P = .89$, $d = 0.19$), length of stay (MD -0.06 , 95% CI -0.26 to 0.14, $P = .56$, $d = 0.20$), or incidence of adverse effects such as deep venous thrombosis (odds ratio 1.15, 95% CI 0.33 to 4.00, $P = .83$, $d = 0.53$).

Conclusion: Clinical application of tranexamic acid seemed to result in significant reductions in total blood loss, hemoglobin decline and transfusion requirements following total shoulder arthroplasty. Moreover, no increased risk of the thrombotic events was identified. Due to the limited quality of the evidence currently available, higher quality RCTs are required.

Abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, RCT = randomized controlled trial.

Keywords: blood loss, meta-analysis, total shoulder arthroplasty, tranexamic acid

1. Introduction

Total shoulder arthroplasty has been considered as a successful treatment with pain relief and functional improvement for glenohumeral arthritis.^[1] There was an estimated more than 60 thousands of total shoulder arthroplasties performed in 2011,

which predicted an increasing trend and requirement for the next few years.^[2] However, total shoulder arthroplasty was usually associated with substantial perioperative blood loss. Many methods have been used to manage blood loss including controlled permissive hypotension, administration of hemostatic agents, and autologous donation.^[3–5] Blood transfusions were still required to treat anemia in many cases. It was reported that overall rate of transfusions after total shoulder arthroplasty ranged from 7.4% to 43%.^[6–9] Allogenic blood transfusion would increase the risk of adverse events, such as virus infections, immunologically mediated diseases, and cardiovascular dysfunction, resulting in a financial burden and potentially life-threatening effects on patients.

Tranexamic acid is a synthetic analog of an amino acid whose biological activity inhibits plasminogen from dissolving clots, thereby decreasing the degradation of fibrin.^[10,11] This property results in less blood loss and fewer wound hematoma. Recently, the use of tranexamic acid has become popularized in multiple surgical procedures for reducing perioperative blood loss and transfusion requirements. A number of randomized controlled trials (RCTs) and high-quality meta-analyses have assessed the efficiency and safety of tranexamic acid in multiple routines and reported that tranexamic acid was a cost-effective antifibrinolytic agent for blood management in total joint arthroplasty without increasing the risk of thrombotic events or other side effects.^[12–14]

Currently, the both intravenous and topical application of tranexamic acid in total shoulder arthroplasty was seldom reported. Thus, there is a lack of scientific evidence regarding the hemostatic

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Table 1
EMBASE search strategy.

#1. 'blood loss':ti,ab
#2. 'bleeding'/exp
#3. 'hemorrhage'/exp
#4. hemoglobin*:ti,ab
#5. transfusion*:ti,ab
#6. infusion*:ti,ab
#7. #4 and #5
#8. #4 and #6
#9. #5 and #6
#10. #1 or #2 or #3 or #7 or #8 or #9
#11. tranexamic acid*:ti,ab
#12. 'transamin'/exp
#13. 'antifibrinolytic agent'/exp
#14. #11 or #12 or #13
#15. shoulder*:ti,ab
#16. arthroplasty/exp
#17. replacement/exp
#18. #15 or #16 or #17

effect of tranexamic acid in total shoulder arthroplasty. Therefore, we perform a meta-analysis to evaluate the efficiency and safety of tranexamic acid for reducing blood loss and transfusion requirements in patients undergoing total shoulder arthroplasty.

2. Methods

2.1. Search strategy

We systemically search electronic databases including Embase (1980–2017.04, embase.com), Medline (1966–2017.04, medline.com), PubMed (1966–2017.04, pubmed.com), ScienceDirect (1985–2017.04, sciencedirect.com), and Web of Science (1950–2017.04, webofknowledge.com) for potential relevant articles. Complete search strategy for Embase was provided Table 1. Gray academic studies are also identified from the reference of included studies. No language was restricted. The following terms was considered as key words: “Total shoulder replacement or arthroplasty”, “tranexamic acid” and “blood loss.” The retrieval process is presented in Fig. 1. The study was approved by the ethics committee of The Second Affiliated Hospital of Dalian Medical University.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: published clinical RCTs and non-RCTs; patients undergoing total shoulder arthroplasty, experiment group received intravenous or topical tranexamic acid for blood management, and control group received normal saline or none; the primary outcomes included total blood loss, postoperative hemoglobin level, transfusion rate, drainage volume. Secondary outcomes included duration of surgery, length of hospital stay, and postoperative adverse effects such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Studies were excluded if they were current meta-analyses for incomplete data, case reports, conference abstracts, or review articles.

2.3. Selection criteria

Two authors independently reviewed all the abstracts of the potential studies identified by the above searches. After an initial

decision, full text of the studies that potentially met the inclusion criteria were reviewed and final decision was made. A senior reviewer was consulted in case of disagreement regarding which studies to include.

2.4. Data extraction

A standard form for data extraction was printed. Two authors independently extracted the relevant data from the included articles. Details of incomplete data of included studies were obtained by consulting the corresponding author. Following data were extracted: first author names, published year, sample size, study design, comparable baseline, anesthesia methods, intervention procedures, and transfusion trigger. Other relevant data were also extracted from individual studies.

2.5. Quality assessment

Quality assessment of the included RCTs was done by 2 authors independently using the Cochrane Collaboration's tool. We conducted “risk of bias” table including the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias. Each item was recorded by “Yes,” “No,” or “Unclear.” The Methodological Index for Non-Randomized Studies (MINORS) scale was used to assess non-RCTs with scores ranging from 0 to 24. A consensus was reached through a discussion.

The qualities of evidence of main outcomes in the present meta-analysis were evaluated using the Recommendations Assessment, Development, and Evaluation (GRADE) system including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two authors independently scored all the items of the GRADE systems that may influence quality of evidence. Items that may raise the quality of evidence was recorded by 0, +1, and +2. Items that may lower the quality of evidence was recorded by 0, −1, and −2. A senior reviewer was consulted in case of disagreement. Finally, GRADE systems evaluated the overall results. The recommendation level of evidence is classified into the following categories: high, which means that further research is unlikely to change confidence in the effect estimate; moderate, which means that further research is likely to significantly change confidence in the effect estimate and may change the estimate; low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and very low, which means that any effect estimate is uncertain.

2.6. Data analysis and statistical methods

All calculations were carried out by Stata 11.0 (The Cochrane Collaboration, Oxford, UK). We planned to pool the results using the random-effects model, which would better incorporate the clinical heterogeneity typical among small studies investigating the long-term efficiency and safety of tranexamic acid in total shoulder arthroplasty. We hypothesized that the different articles were estimating randomly different yet related intervention effects. By choosing the more conservative random-effects model, confidence intervals (CIs) for the average intervention effect would be wider. Publication bias was examined by Begg test and Egger test that showed statistical evidence. Size of the effect (Cohen *d*) for each outcome was calculated. Subgroup analysis was conducted to explore the origins of heterogeneity. The results of dichotomous outcomes were expressed as odds ratio (OR)

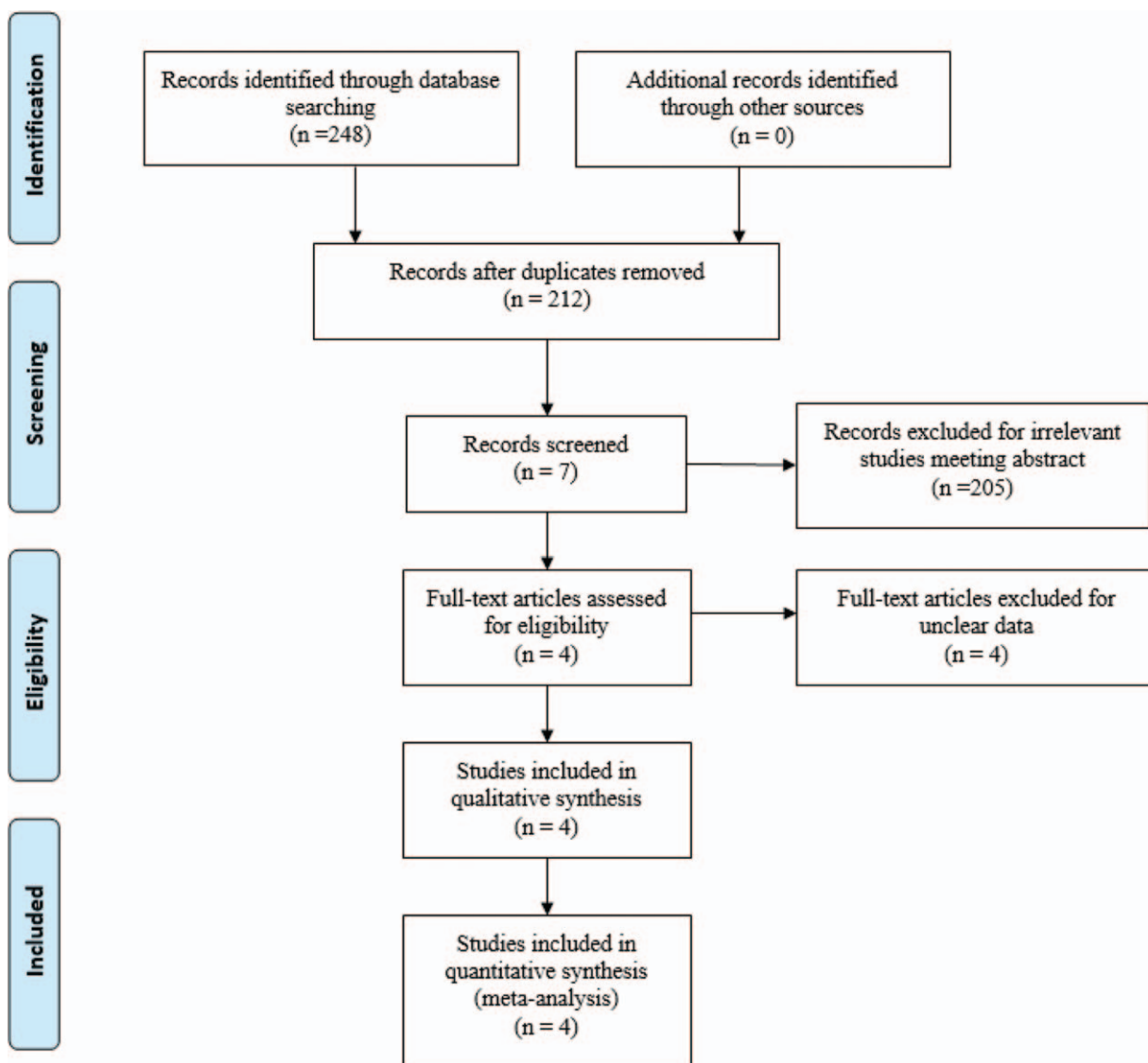


Figure 1. Search results and the selection procedure.

with a 95% CI. For continuous various outcomes, mean difference (MD) with a 95% CI was applied for assessment.

3. Results

3.1. Search result

In the primary search, 248 articles were reviewed. Finally, 4 studies meet eligibility criteria of the present meta-analysis—2 of them were RCTs^[15,16] and 2 were non-RCTs.^[17,18] Overall, the 4 studies included 250 patients in the tranexamic acid group and 234 patients in the control group.

3.2. Study characteristics

The sample size of the included studies ranged from 77 to 194. All of them compared efficiency and safety of tranexamic acid for reducing perioperative blood loss in total shoulder arthroplasty. Experimental groups received intravenous or topical tranexamic

acid, whereas control groups received normal saline or none. There was variation in dosage of tranexamic acid among included studies. Two studies applied general anesthesia^[15,18] and others did not provide a detailed description. All studies^[15–18] reported that surgical procedure was operated by the same team. Prophylactic anticoagulation therapy was performed as a routine in all included articles. All of them suggested the outcomes for at least 95% of the patients. The follow-up period ranged from 1 to 2 months.

3.3. Risk of bias assessment

Demographic characteristics and the details about the included studies are summarized in Table 2. Quality assessment of the RCTs was based on the Cochrane Collaboration tool (Table 3). All RCTs^[15,16] provided clear inclusion and exclusion criteria and suggested a methodology of randomization, all of which described that randomization algorithm was generated from computer. One RCT^[15] stated allocate concealment was achieved

Table 2
Cohort characteristics.

Studies	Study design	Cases (T/C)	Mean age (T/C)	Female patients (T/C)	TXA intervention	Basal Hb (T/C)	Transfusion trigger	Follow-up
Friedman, 2016 ^[17]	Retrospective study	106/88	69/70	60/55	E: intravenous 20 ml/kg TXA C: none	13.6 /13.5	HB less than 7 g/dL	2 mos
Gillespie et al, 2015 ^[16]	RCT	56/55	66/67	28/30	E: topical use of 2g TXA C: 100 mL normal saline	NS	HB less than 7 g/dL	2 mos
Abildgaard, 2016 ^[18]	Retrospective study	35/42	70/71	12/17	E: intravenous 1 g of TXA C: none	13.7/14.1	HB less than 7 g/dL	1 mo
Vara, 2017 ^[15]	RCT	53/49	67/66	33/27	E: intravenous 10 mg/kg TXA C: equivalent volume of saline	13.7 /13.6	HB less than 7 g/dL	1.5 mos

C=control group, HB=hemoglobin, NS=not stated, T=TXA group, TXA=tranexamic acid.

by sealed envelope. Double blinding was provided in all RCTs. One of them had attempted to blind assessors.^[15] Each risk of bias item was presented as the percentage across all included studies, which indicated the proportion of different levels of risk of bias for each item (Table 4). All RCTs demonstrated complete outcome data. None of them performed intent-to-treatment analysis, thus a potential risk for type II statistical error would exist. The MINORS scale was used to assess non-RCTs by assigning scores ranging from 0 to 24 (Table 5).

Table 3
Methodological quality of the randomized controlled trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alexander 2017	+	+	+	+	+	?	?
Gillespie 2015	+	?	+	?	+	?	?

3.4. Outcomes for meta-analysis

3.4.1. Total blood loss. Four studies^[15-18] reported the total blood loss after total shoulder arthroplasty. A random-effects model was applied ($\chi^2 = 11.09$, $df = 3$, $I^2 = 72.9\%$, $P = .01$). We found that there was significant difference between the tranexamic acid groups and control groups regarding the total blood loss (MD -172.16, 95% CI -35.46 to -308.87, $P = .01$, $d = 0.33$; Fig. 2).

3.4.2. Postoperative hemoglobin level. Four studies^[15-18] reported the postoperative hemoglobin level after total shoulder arthroplasty. A random-effects model was used ($\chi^2 = 9.64$, $df = 3$, $I^2 = 68.9\%$, $P = .02$). The result of meta-analysis showed that there was significant difference between the tranexamic acid groups and control groups regarding the postoperative hemoglobin level (MD 0.88, 95% CI 0.44-1.33, $P = .00$, $d = 0.48$; Fig. 3).

3.4.3. Transfusion requirements. Transfusion requirements after total shoulder arthroplasty were presented in 4 studies.^[15-18] A random-effects model was used ($\chi^2 = 3.13$, $df = 3$, $I^2 = 4.0\%$, $P = .373$). The present meta-analysis showed that there was significant difference between the tranexamic acid and control groups in terms of transfusion requirements (OR 0.34, 95% CI 0.13-0.91, $P = .03$, $d = 0.29$; Fig. 4).

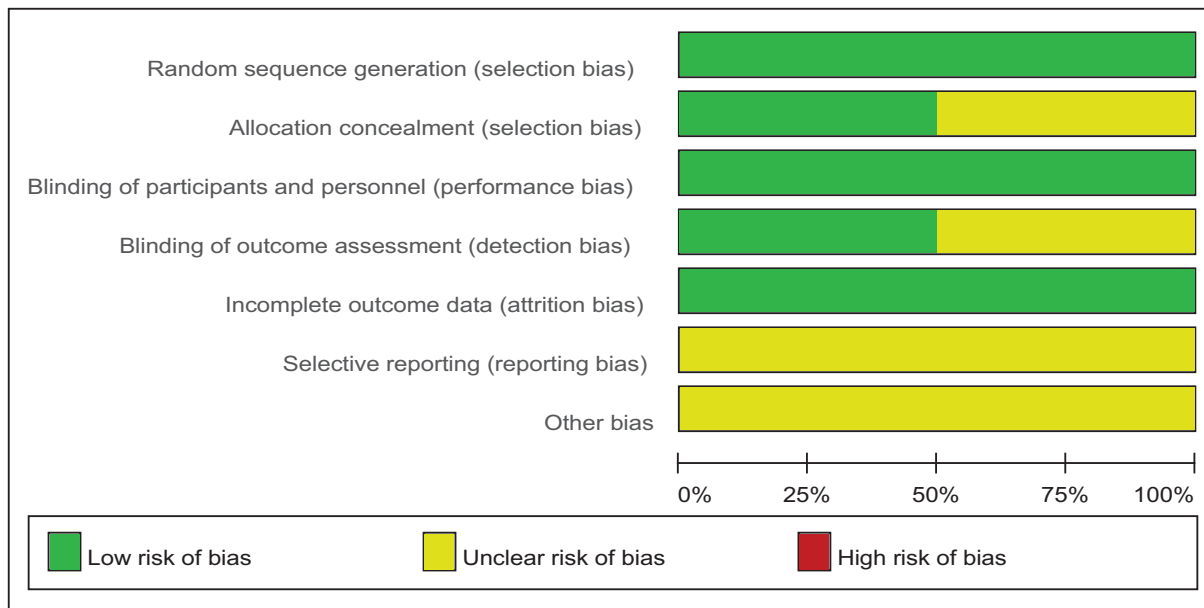
3.4.4. Duration of surgery. The duration of surgery was reported in 3 studies.^[15-17] A random-effects model was used ($\chi^2 = 0.88$, $df = 2$, $I^2 = 0.0\%$, $P = .643$). No significance difference was observed regarding duration of surgery between the 2 groups (MD=0.02, 95% CI -0.12 to 0.22, $P = .89$, $d = 0.19$; Fig. 5).

3.4.5. Length of hospital stay. Three studies reported the lengths of the hospital stays for the groups.^[15-17] A random-effects model was used ($\chi^2 = 12.78$, $df = 2$, $I^2 = 84.3\%$, $P = .002$). No significant difference in the length of hospital stay was observed between the 2 groups (MD -0.06, 95% CI -0.26 to 0.14, $P = .56$, $d = 0.20$; Fig. 6).

3.4.6. Deep vein thrombosis. Four articles^[15-18] reported the incidence of DVT after total shoulder arthroplasty. A random-effects model was used ($\chi^2 = 0.64$, $df = 2$, $I^2 = 0.0\%$, $P = .726$). No significant difference was found between the groups (OR 1.15, 95% CI 0.33-4.00, $P = .83$, $d = 0.53$; Fig. 7).

3.4.7. Publication bias and subgroup analysis. Publication bias was examined for transfusion rate by Begg test ($P = .174$) and Egger test ($P = .531$) that showed statistical evidence (Fig. 8). Low risk of publication bias was observed. However, we could not

Table 4
Risk of bias.



eliminate publication bias as a small number of articles were enrolled. Subgroup analysis is presented in Table 6. We have not found the source of heterogeneity regarding total blood loss. Age might be the source of heterogeneity for postoperative hemoglobin level.

4. Discussion

To the best of our knowledge, this study is the first systemic review and meta-analysis to evaluate the efficiency and safety of the tranexamic acid use in patients undergoing total shoulder arthroplasty. The most important finding of the present meta-analysis was that the application of tranexamic acid seemed to reduce total blood loss, hemoglobin decline, and transfusion requirements compared with controls. All outcomes in this meta-analysis were evaluated using the GRADE system. The evidence quality for each outcome was low to very low (Table 7), which

means that any effect estimate is uncertain. This finding may lower the confidence in any recommendations.

Tranexamic acid, which acts as antifibrinolytic agent, is famous for proven success in reducing perioperative and postoperative blood loss and is widely used in surgical procedure. Tranexamic acid can be applied by various routes including intravenous, intra-articular, oral, and intramuscular. Total shoulder arthroplasty is a major orthopedic surgery with a considerable perioperative blood loss and complications. Previous articles have reported improved outcomes in patients with total shoulder arthroplasty who have been administered this agent. Vara et al^[15] reported that intravenous application of tranexamic acid for patients undergoing primary total shoulder arthroplasty was effective and safe. Anthony et al^[19] demonstrated that allogenic blood transfusion was the most frequent complication after total shoulder arthroplasty. Optimal blood management could relieve pain and achieve preferable functional outcome. With more total shoulder arthroplasties being performed, there is a crucial need for blood management appropriately. Although administration of tranexamic acid in joint arthroplasty surgery has been studied widely and demonstrated significant clinical improvements in minimizing the blood loss, the application of tranexamic acid in the setting of total shoulder arthroplasties has been limited due to the seldom published studies. Currently, it is unknown for us whether tranexamic acid would be considered an excellent hemostatic efficiency in total shoulder arthroplasty. The present meta-analysis indicates that the application of tranexamic acid in total shoulder arthroplasty seems to significantly reduce total blood loss and hemoglobin decline.

With the ageing population, the occurrence of glenohumeral arthritis is increasing, and total shoulder arthroplasty is a popular treatment to improve motor function and relieve pain. It was reported that total shoulder arthroplasty without antifibrinolytics was associated with massive blood loss ranging from 650 to 1540 mL^[6,19-21] within the first few postoperative days and allogenic blood transfusion was frequently performed to relieve

Table 5
Methodological quality of the non-randomized controlled trials.

Quality assessment for non-randomized trials	Richard, 2015	Alexander, 2017
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective data collection	2	2
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	0	0
A follow-up period appropriate to the aims of study	2	2
Less than 5% loss to follow-up	2	2
Prospective calculation of the sample size	0	0
An adequate control group	2	2
Contemporary groups	2	0
Baseline equivalence of groups	1	2
Adequate statistical analyses	2	2
Total score	19	18

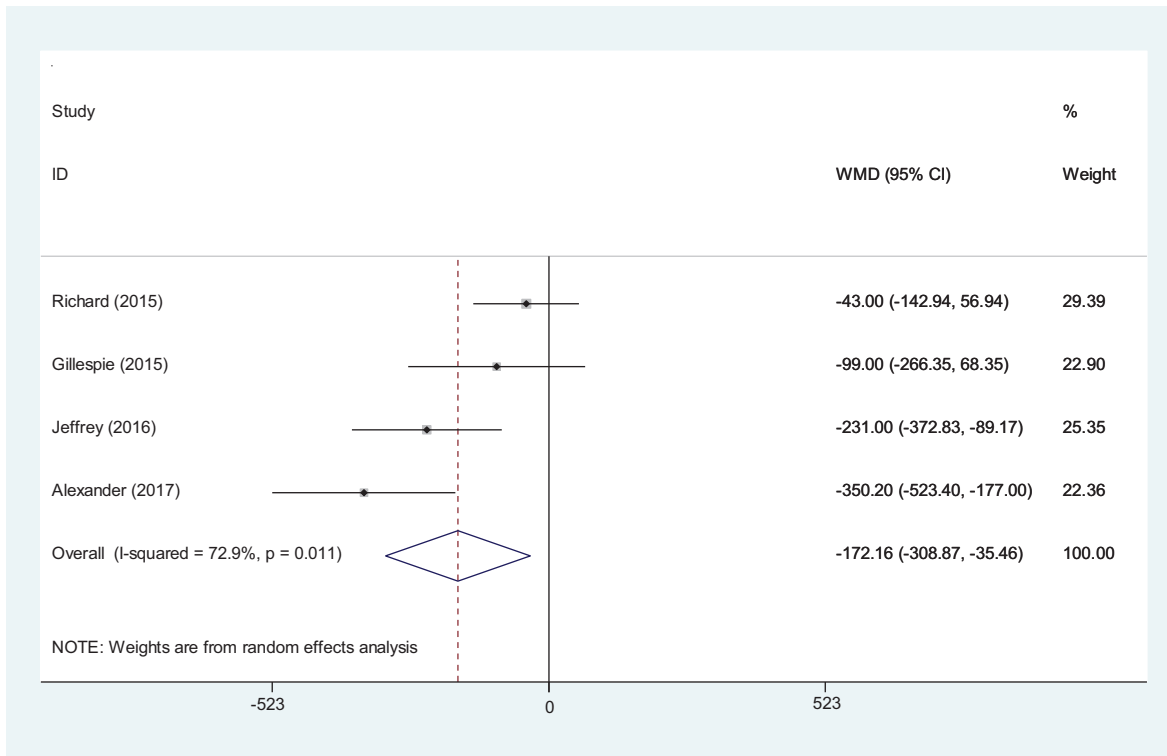


Figure 2. Forest plot diagram showing effect of tranexamic acid on total blood loss.

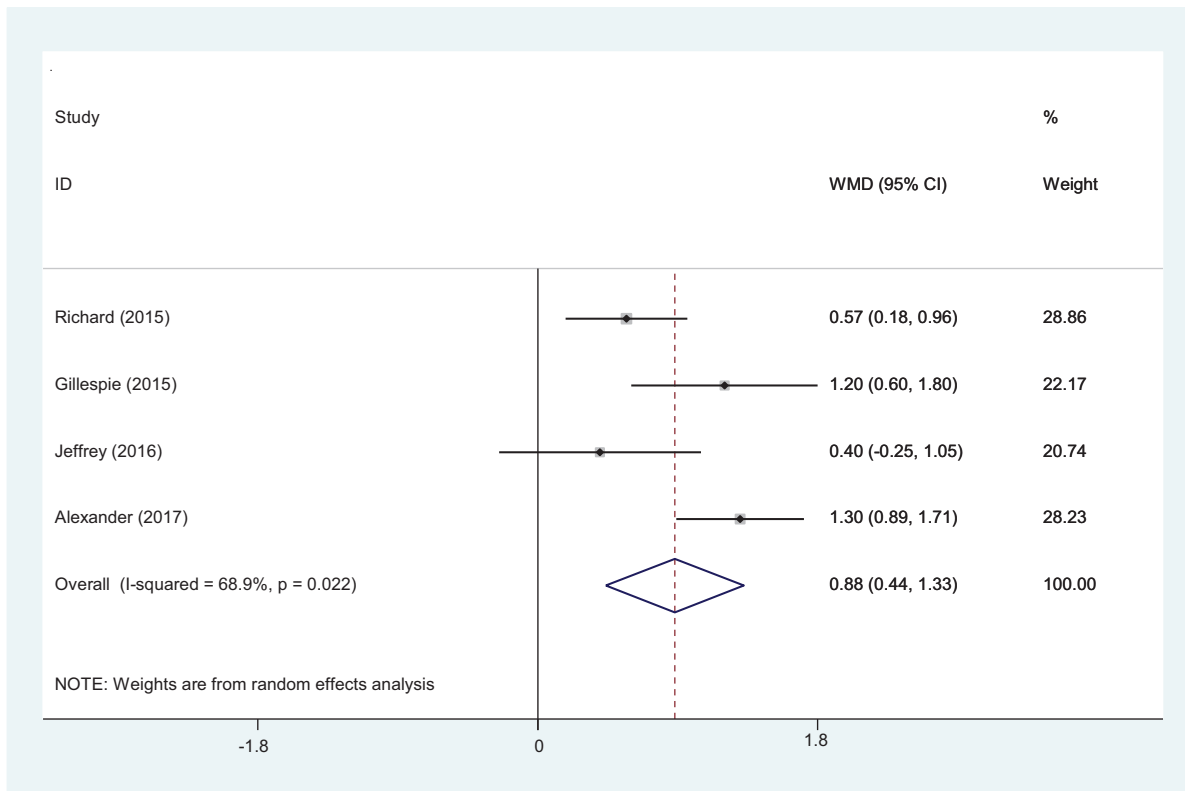


Figure 3. Forest plot diagram showing effect of tranexamic acid on hemoglobin level.

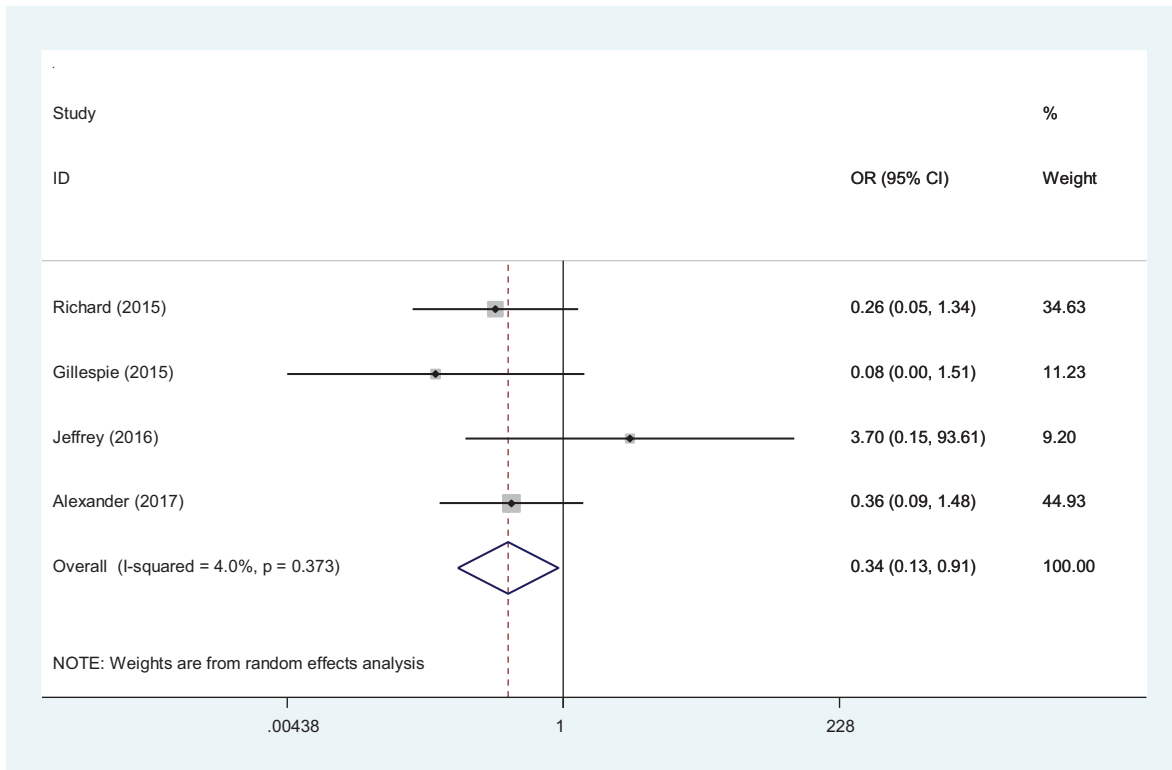


Figure 4. Forest plot diagram showing effect of tranexamic acid on transfusion rate.

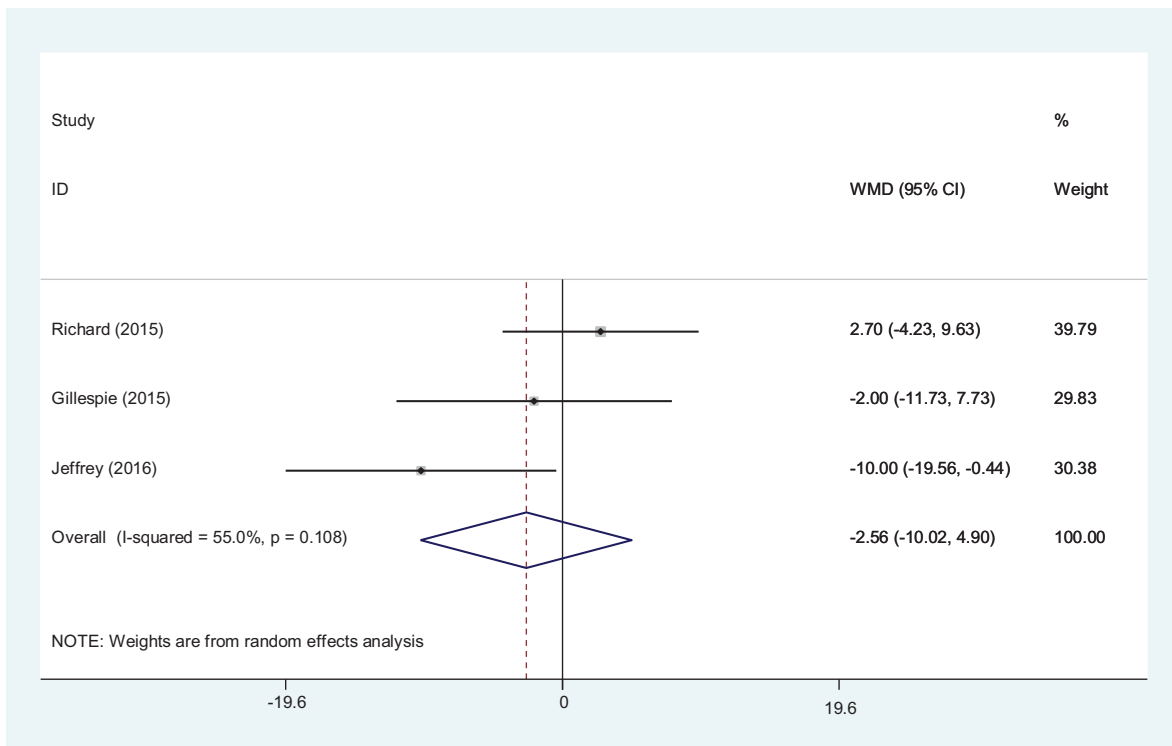


Figure 5. Forest plot diagram showing effect of tranexamic acid on duration of surgery.

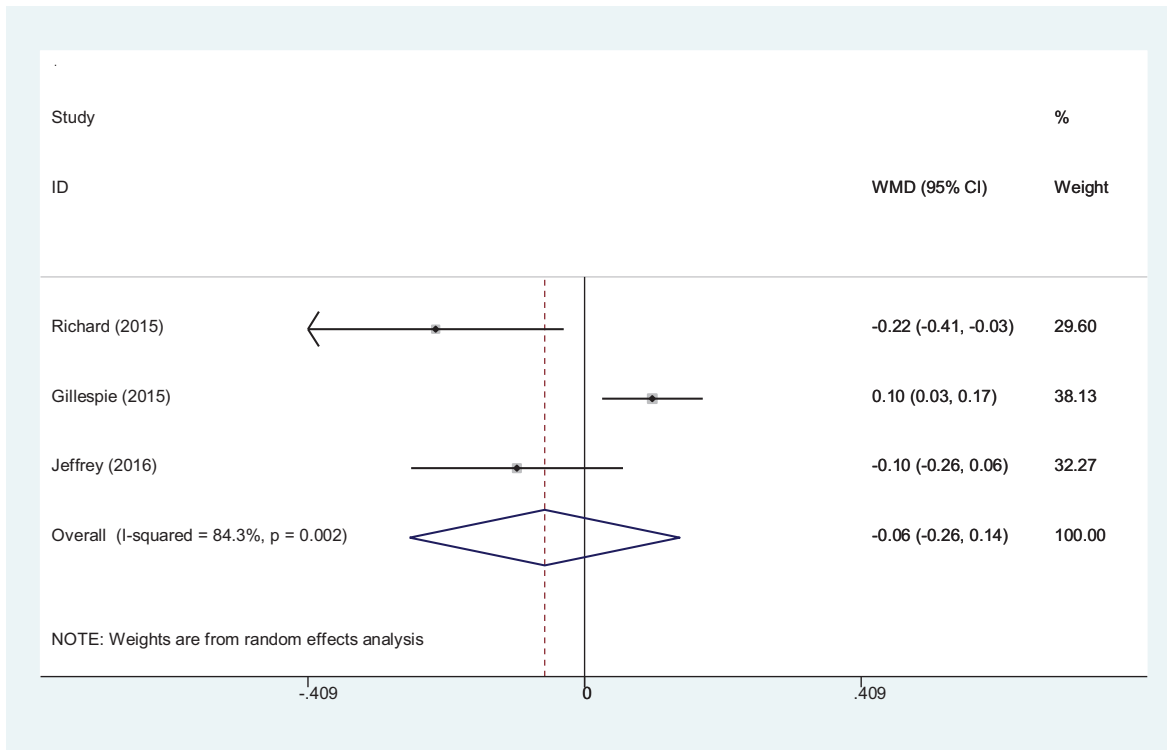


Figure 6. Forest plot diagram showing effect of tranexamic acid on the length of hospital stay.

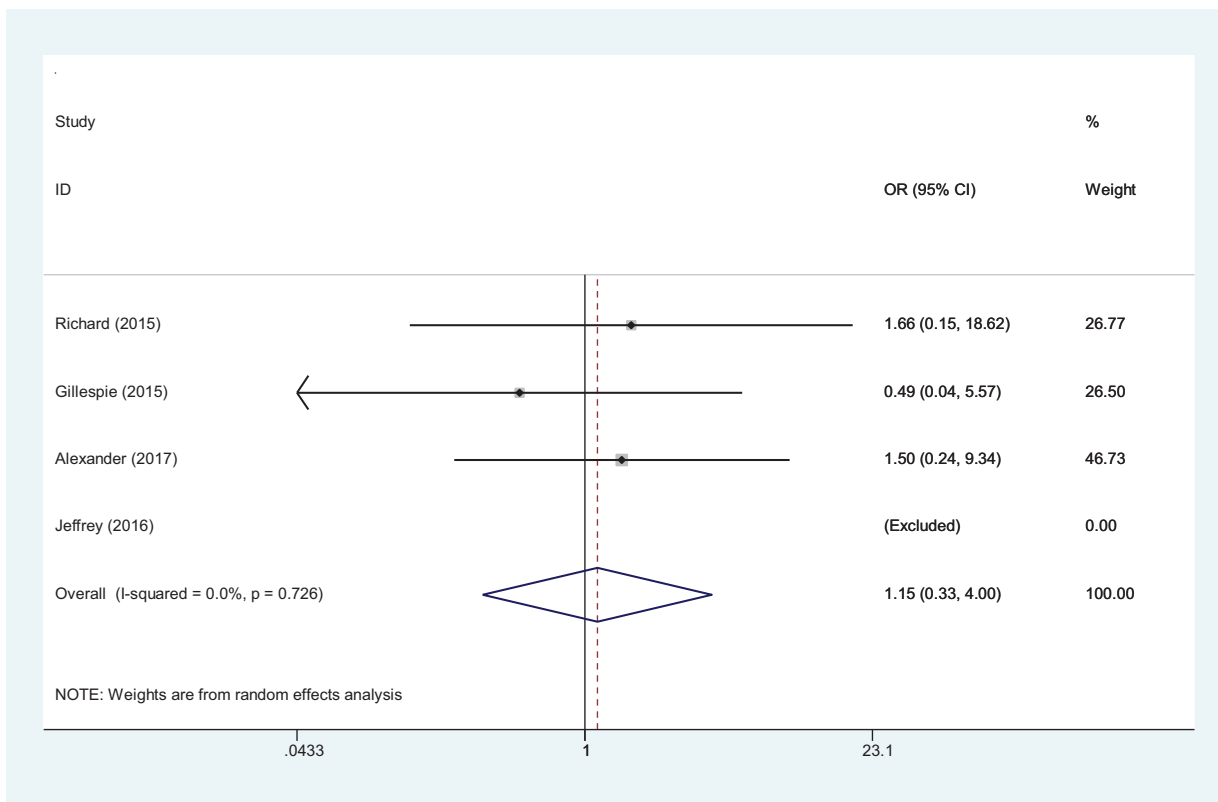


Figure 7. Forest plot diagram showing effect of tranexamic acid on the risk of DVT.

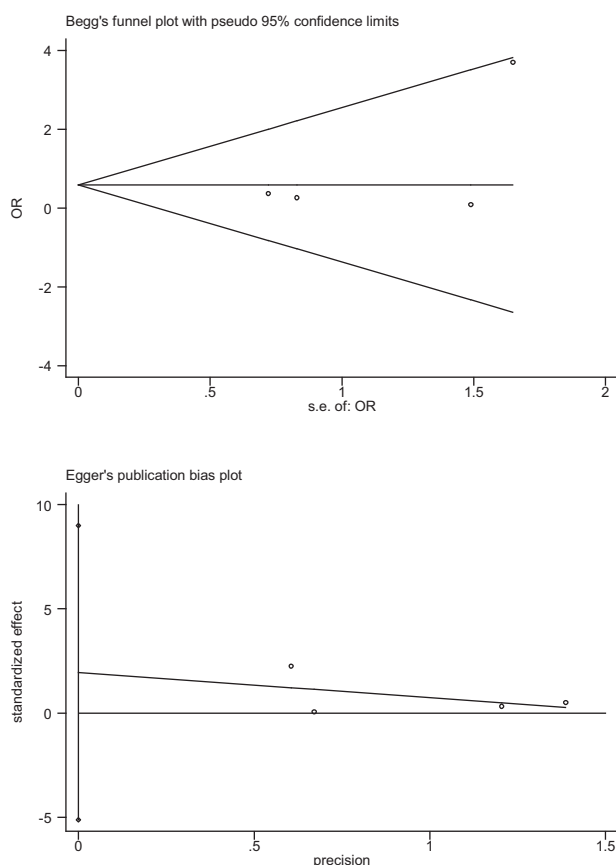


Figure 8. Plots of Begg test and Egger test for publication bias of transfusion rate.

anemia. However, potential adverse effects might occur, for instance, transmission of infection, possible hemolytic transfusion reactions, and so on.^[22,23] Substantial high-quality RCTs and meta-analysis have been published to confirm that administration of tranexamic acid could diminish the need for

allogeneic blood transfusions in patients undergoing total joint arthroplasty. Currently, the efficiency of tranexamic acid in reducing transfusion rate in total shoulder arthroplasty remains controversial. Meta-analysis is performed as major statistical method in the present study. It could strengthen statistical power and enlarge sample size by pooling results of published articles that could point out stronger evidence. In addition, no guidelines have been proposed to normalize the administration of tranexamic acid in total shoulder arthroplasty. Thus, there is a requirement for an evidence base to help orthopedists make clinical decisions. The present meta-analysis indicates that the application of tranexamic acid seems to be associated with a further significant reduction in the transfusion requirements.

Deep vein thrombosis has been considered as a common postoperative complication that may develop into PE and even result in death after major orthopedic surgery.^[24] All patients received routine prophylactic antithrombotic therapy. Published articles have suggested a potential higher risk of DVT and PE when tranexamic acid was used. This result may be due to the tendency of tranexamic acid, which is an antifibrinolytic agent, to increase the risk of clotting. Although the intravenous application of tranexamic acid could be more likely to result in the formation of a thrombus because of the higher tranexamic acid level of blood concentration, there was no significant difference between both groups regarding the incidence of DVT in the present analysis. However, more high-quality RCTs are required to further assess the safety of tranexamic acid.

Several potential limitations of the study should be noted. Apart from the 2 RCTs, we also included non-RCTs, which lowered evidence grade, and the sample size was relatively small. Some important parameters, for instance, the functional outcome and drainage volume, were not fully introduced in the meta-analysis. We have tried to contact authors for incomplete data; however, there was no response and no other methods were used to obtain data, which can result in a source of bias in this review. Short-term follow-up may lead to the underestimation of complications. Publication bias is an inherent weakness that exists in all meta-analyses.

Despite the aforementioned limitations, this study was the first meta-analysis to evaluate the efficiency and safety of the application of tranexamic acid in patients undergoing total

Table 6
Subgroup analysis for main outcomes.

Variables	Studies (n)	Patients (n)	P	MD or OR (95% CI)	Heterogeneity P value (I ²)	Model
Total blood loss						
All studies	4	484	.01	-172.16 [-35.46 to -308.87]	.01 (72.9%)	Random
Follow up period <2 mos	2	179	.00	-283.20 [-399.11 to -167.29]	.00 (13.3%)	Random
Follow up period 2 mos	2	305	.19	-57.72 [-143.52 to 28.08]	.57 (0%)	Random
Mean age >70 y	2	271	.17	-129.99 [-313.72 to 53.74]	.03 (77.8%)	Random
Mean age <70 y	2	213	.08	-223.57 [-469.73 to 22.59]	.04 (76.1%)	Random
Female% >55%	2	296	.22	-188.12 [-488.71 to 112.47]	.00 (89.0%)	Random
Female% <55%	2	188	.01	-172.78 [-301.24 to -44.33]	.24 (28.1%)	Random
Postoperative hemoglobin level	4	484	.00	0.88 [0.44 to 1.33]	.02 (68.9%)	Random
Follow-up period <2 mos	2	179	.01	0.93 [0.22 to 1.65]	.01 (84.3%)	Random
Follow-up period 2 mos	2	305	.04	0.81 [0.03 to 1.59]	.08 (68.3%)	Random
Mean age >70 y	2	271	.00	0.53 [0.19 to 0.86]	.66 (0%)	Random
Mean age <70 y	2	213	.00	1.27 [0.93 to 1.61]	.79 (0%)	Random
Female% >55%	2	296	.01	0.93 [0.22 to 1.65]	.01 (84.3%)	Random
Female% <55%	2	188	.04	0.81 [0.03 to 1.59]	.08 (68.3%)	Random

CI=confidence interval, MD=mean difference, OR=odds ratio.

Table 7

The GRADE evidence quality for main outcome.

No. of studies	Design	Limitations	Inconsistency	Quality assessment			Imprecision	Other considerations	No. of patients		Effect		Quality	Importance
				Indirectness	Inconsistency	Indirectness			TXA groups	Control groups	Relative (95% CI)	Absolute		
4	Observational studies	No serious limitations (follow-up 1–2 mos; better indicated by lower values)	No serious inconsistency	No serious indirectness	No serious imprecision	None	None	250	234	—	MD -172.16 lower (-35.46 to -308.87 lower)	Low	Critical	
4	Observational studies	No serious limitations (follow-up 1–2 mos)	No serious inconsistency	No serious indirectness	Serious imprecision	None	None	250	234	—	MD 0.88 higher (0.44 to 1.33 higher)	Very low	Critical	
4	Observational studies	No serious limitations (follow-up 1–2 mos)	No serious inconsistency	No serious indirectness	No serious imprecision	None	None	6/250 (2.4%)	18/234 (7.7%)	RD: -0.054 (-0.095 to -0.014)	77 fewer per 1000 (from 77 fewer to 78 fewer)	Low	Critical	

CI = confidence interval, RD = risk difference, TXA = tranexamic acid.

shoulder arthroplasty. Long-term of high-quality RCTs is needed to explore the dose–response effect and other adverse effects.

5. Conclusions

Clinical application of tranexamic acid seemed to result in significant reductions in total blood loss, hemoglobin decline, and transfusion requirements after total shoulder arthroplasty. Moreover, no increased risk of the thrombotic events was identified. Due to the limited quality of the evidence currently available, higher-quality RCTs are required.

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