Tranexamic Acid in Shoulder Arthroplasty

A Systematic Review and Meta-Analysis

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Abstract

Background: The role of tranexamic acid (TXA) in reducing blood loss following primary shoulder arthroplasty has been demonstrated in small retrospective and controlled clinical trials. This study comprehensively evaluates current literature on the efficacy of TXA to reduce perioperative blood loss and transfusion requirements following shoulder arthroplasty.

Methods: PubMed, MEDLINE, CENTRAL, and Embase were searched from the database inception date through October 27, 2016, for all articles evaluating TXA in shoulder arthroplasty. Two reviewers independently screened articles for eligibility and extracted data for analysis. A methodological quality assessment was completed for all included studies, including assessment of the risk of bias and strength of evidence. The primary outcome was change in hemoglobin and the secondary outcomes were drain output, transfusion requirements, and complications. Pooled outcomes assessing changes in hemoglobin, drain output, and transfusion requirements were determined.

Results: Five articles (n = 629 patients), including 3 Level-I and 2 Level-III studies, were included. Pooled analysis demonstrated a significant reduction in hemoglobin change (mean difference [MD], −0.64 g/dL; 95% confidence interval [CI], −0.84 to −0.44 g/dL; $p < 0.00001$) and drain output (MD, −116.80 mL; 95% CI, −139.20 to −94.40 mL; $p < 0.00001$) with TXA compared with controls. TXA was associated with a point estimate of the treatment effect suggesting lower transfusion requirements (55% lower risk); however, the wide CI rendered this effect statistically nonsignificant (risk ratio, 0.45; 95% CI, 0.18 to 1.09; $p = 0.08$). Findings were robust with sensitivity analysis of pooled outcomes from only Level-I studies.

Conclusions: Moderate-strength evidence supports use of TXA for decreasing blood loss in primary shoulder arthroplasty. Further research is necessary to evaluate the efficacy of TXA in revision shoulder arthroplasty and to identify the optimal dosing and route of administration of TXA in shoulder arthroplasty.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Perioperative blood management is an important consideration for individuals undergoing shoulder arthroplasty. As the volume of shoulder arthroplasty procedures has steadily increased over the past decade[1-4], the need to improve strategies for reducing perioperative blood loss and

Disclosure: There was no source of funding for this review. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article,* one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (http://links.lww.com/JBJSREV/A257).

allogenic blood transfusion is critical, particularly with more complex or revision reconstructive procedures. Allogeneic blood transfusions can be associated with rare but substantial morbidity, including hemolytic reactions, immunomodulation, acute lung injury, and disease transmission[5-7]. Furthermore, allogeneic blood transfusion has been associated with increased risk of postoperative infection[8-10], prolonged hospital stay[8,11], and increased mortality[12] in patients undergoing total hip and knee arthroplasty. In addition to the potential adverse health risks, acute blood loss necessitating transfusion can be costly for patients and health-care systems[13,14].

Rates of allogeneic blood transfusion following shoulder arthroplasty have varied considerably in the literature (4% to 43%)[15-24], with recent transfusion rates ranging from 4.5% to 11.3%[15,16,18,21,24]. Similar blood transfusion rates have been reported following total hip and knee arthroplasty[12,25-27]. Various predictors of blood transfusion following shoulder arthroplasty have been identified[15-20,22-24]; however, these are often nonmodifiable risk factors such as patient age[18-22], posttraumatic or inflammatory arthritis[15,23], sex[18,20,23], and concomitant comorbidity[19,24]. In a recent large study utilizing the National Surgical Quality Improvement Program (NSQIP) database, Ricchetti et al.[22] reported that acute blood loss requiring transfusion accounted for approximately 50% of all reported complications of shoulder arthroplasty, with a frequency more than 3 times greater than the next most common complication.

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that inhibits the conversion of plasminogen to plasmin through competitive inhibition of the lysine binding site on plasminogen[28]. In essence, TXA stabilizes formed clots by preventing fibrin degradation. Recent meta-analyses of randomized control trials (RCTs) have demonstrated substantial reductions in the transfusion requirements and mean blood loss with TXA use in patients undergoing lower extremity arthroplasty and orthopaedic spine surgery[29-36]. Moreover, there has been no increased risk of thromboembolic events such as pulmonary embolism, myocardial infarction, stroke, or transient ischemic attack associated with TXA use[30,31,35,37-41]. Given the well-established benefits in lower extremity arthroplasty, recent publications have reported results of using TXA in shoulder arthroplasty[42-44].

The purpose of this systematic review and meta-analysis was to comprehensively review the literature evaluating the efficacy of TXA with respect to perioperative blood loss and allogeneic blood transfusions following shoulder arthroplasty. Our hypotheses were that TXA would result in a significant decrease in perioperative blood loss as measured by the changes in hemoglobin (g/dL), drain output (mL), and transfusion requirements following shoulder arthroplasty, and would

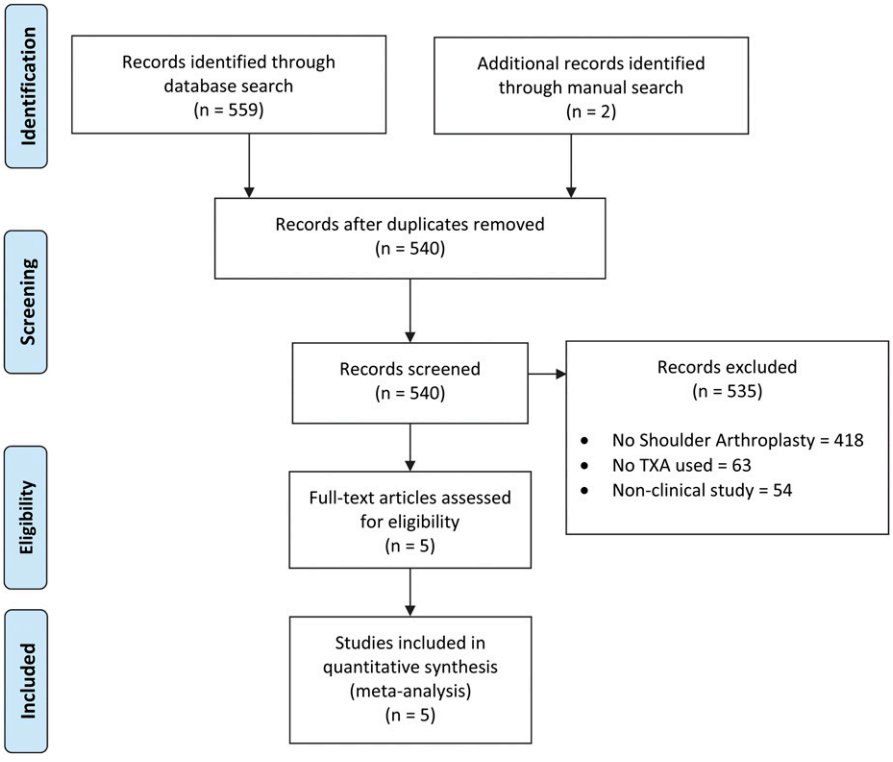


Fig. 1
Selection of studies for inclusion in the meta-analysis.

TABLE I Studies Included in the Meta-Analysis*

Study	Publication Year	Location	Study Design	Level of Evidence	Total No. of Patients	Procedures Performed	Mean MINORS Score
Abildgaard et al.[42]	2016	Single center: Mayo Clinic, Scottsdale, Arizona, U.S.	Retrospective cohort	III	168	Primary TSA and RTSA	18.5/24
Friedman et al.[43]	2016	Single center: Charleston, South Carolina, U.S.	Retrospective cohort	III	194	Primary TSA and RTSA	17.5/24
Gillespie et al.[44]	2015	Multicenter: Cleveland, Ohio, U.S.A.; Beachwood, Ohio, U.S.	Double-blinded RCT	I	111	Primary TSA and RTSA	
Vara et al.[55]	2017†	Single center: Royal Oak, Michigan, U.S.	Double-blinded RCT	I	102	Primary RTSA	
Pauzenberger et al.[54]	‡	Single center: Vienna, Austria	Double-blinded RCT	I	54	Primary TSA and RTSA	

*MINORS = Methodological Index for Non-Randomized Studies, TSA = total shoulder arthroplasty, and RTSA = reverse TSA. †Manuscript has been accepted for publication. ‡Manuscript has been submitted.

be associated with low rates of complications.

Materials and Methods

This study was conducted according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions*[45] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[46].

Eligibility Criteria

We included studies that (1) involved patients of any age or sex who underwent primary or revision total shoulder arthroplasty (anatomic or reverse), (2) administered TXA as part of a perioperative medication regimen, and (3) compared perioperative blood loss in patients who received TXA with those who did not receive TXA. There were no restrictions regarding the dose or route of administration of TXA, the patient's primary indication for shoulder arthroplasty, previous treatment for shoulder pathology, length of follow-up, publication date, or language of publication. Exclusion criteria consisted of case reports, editorials, reviews, expert opinion, and basic science articles.

Identification of Studies

A systematic literature search of potentially eligible trials was conducted in CENTRAL, PubMed, MEDLINE, and Embase, from the database inception date through October 27, 2016. Investigators with methodological and content expertise developed and performed the search. Medical Subject Headings (MeSH) and Emtree headings and subheadings were used in various combinations in Ovid and supplemented with free text to increase sensitivity (see Appendix). The PubMed search included articles published online ahead of print. A manual search of related references and cited articles was also performed. We searched conference proceedings (American Academy of Orthopaedic Surgeons, American Orthopaedic Society for Sports Medicine, Canadian Orthopaedic Association, and International Society for Technology in Arthroplasty) from the previous 3 years and ClinicalTrials.gov to identify relevant unpublished trials.

Screening and Assessment of Eligibility

Two reviewers (J.M.K. and N.H.) independently screened the titles and abstracts of all studies for eligibility using piloted screening forms. Duplicate articles were manually excluded. Both reviewers evaluated the full text of all potentially eligible studies identified by title and abstract screening to determine final eligibility. All discrepancies were resolved by a consensus decision, requiring a rationale, with the first author.

Data Extraction and Assessment of Risk of Bias

Data were extracted independently and in duplicate by both reviewers (J.M.K. and N.H.) using a piloted electronic data extraction form (Excel; Microsoft). If essential data were unclear or not reported, authors were contacted for clarification. Critical outcomes were determined to be blood loss, transfusion rates, and postoperative complications. The primary outcome was change in hemoglobin (g/dL) and the secondary outcomes were drain output (mL), transfusion requirements, and complications. Extracted data included year

TABLE II Study Demographics*

Study	Mean Age (Range) *(yr)*		Males *(%)*	
	TXA	Control	TXA	Control
Abildgaard et al.[42]	TSA, 70 (53-87); RTSA, 74 (54-90)	TSA, 71 (58-87); RTSA, 76 (54-89)	TSA, 65.7; RTSA, 61.9	TSA, 59.5; RTSA, 50.0
Friedman et al.[43]	NA	NA	43.4	37.5
Gillespie et al.[44]	TSA, 62; RTSA, 71.21	TSA, 59.73; RTSA, 70.94	TSA, 59.09; RTSA, 29.41	TSA, 72.73; RTSA, 30.3
Vara et al.[55]	RTSA, 66.8 (42-84)	RTSA, 65.6 (40-82)	RTSA, 37.7	RTSA, 44.9
Pauzenberger et al.[54]	70.3 (53.7-84.3)	71.3 (46.3-87.8)	50.0	35.0

*BMI = body mass index, TSA = total shoulder arthroplasty, RTSA = reverse TSA, and NA = not available.

and journal of publication, study location and demographics, number of patients, sex, age at the time of surgery, demographic information regarding the use of TXA (dose and route of administration), indications for surgery, intraoperative details and operative approach, perioperative blood management strategies (including transfusion threshold), perioperative blood loss, blood transfusions, and postoperative complications.

Two reviewers (J.M.K. and N.H.) performed an independent assessment of the methodological quality using the Methodological Index for Non-Randomized Studies (MINORS)[47] tool for all nonrandomized studies and the Cochrane risk-of-bias tool[45] for all RCTs. Level of evidence was graded according to the criteria of Wright et al.[48]. The quality of the evidence and confidence in the estimate of the effect across outcomes were assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[49,50]. Data from RCTs were considered high-quality evidence, but the quality could be rated down because of risk of bias, imprecision, inconsistency, indirectness, or publication bias.

Statistical Analysis

Interobserver agreement for assessments of eligibility was calculated with the Cohen κ statistic. A κ of 0 to 0.2 represents slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and >0.80, almost perfect agreement[51]. Interobserver agreement for methodological quality assessment was calculated using the intraclass correlation coefficient (ICC). Both κ and ICC values were calculated using SPSS software (IBM).

Mean differences (MDs) were utilized to summarize identical continuous outcome measures, and risk ratios (RRs) were utilized to assess the effect of dichotomous outcomes from individual studies[45]. The MDs were weighted by sample size using the

TABLE III Blood Loss and Blood Transfusion Characteristics*

Study	Change in Hgb† *(g/dL)*		Change in Hct† *(g/dL)*	
	TXA	Control	TXA	Control
Abildgaard et al.[42]	TSA, 1.8 (0.9-3.9); RTSA, 2.3 (0.5-4.1)	TSA, 2.6 (0.9-4.4); RTSA, 2.9 (0.9-4.6)	TSA, 5.2 (3-10.8); RTSA, 6.4 (1.9-11.9)	TSA, 7 (2.9-12.2); RTSA, 8.3 (4.8-12.8)
Friedman et al.[43]	2.13 ± 2.21	2.63 ± 1.96	6.4	8.14
Gillespie et al.[44]	1.7 (0.2-7.0)	2.6 (−0.5-5.1)	NA	NA
Vara et al.[55]	3.30 ± 1.19	3.88 ± 1.05	RTSA, 11.06 ± 7.27	RTSA, 12.21 ± 6.15
Pauzenberger et al.[54]	2.3 ± 1.2	3.0 ± 1.1	7.1 ± 3.8	9.2 ± 3.7

*Hgb = hemoglobin, Hct = hematocrit, TSA = total shoulder arthroplasty, RTSA = reverse TSA, and NA = not available. †Values are given as the mean and the SD or as the mean with the range in parentheses.

TABLE II (*continued*)

No. of Shoulders		Mean BMI (kg/m^2)		
TXA	Control	TXA	Control	TXA Administration
TSA, 35; RTSA, 42	TSA, 42; RTSA, 52	TSA, 29.8; RTSA, 28.4	TSA, 29.6; RTSA, 28.6	Single dose, intravenous: 1 g TXA following induction of anesthesia
TSA, 54; RTSA, 52	TSA, 43; RTSA, 45	29.3	30.3	Single dose, intravenous: 20 mg/kg TXA during skin preparation
TSA, 22; RTSA, 34	TSA, 22; RTSA, 33	NA	NA	Single dose, topical: 2 g TXA mixed with 100 mL of normal saline solution poured into wound at the end of the case and left for 5 minutes
RTSA, 53	RTSA, 49	29.20	30.72	Multiple doses, intravenous: 10 mg/kg TXA within 60 minutes prior to surgery and at the time of wound closure
27	27	31.1	30.8	Multiple doses, intravenous: 1 g TXA prior to skin incision and 1 g TXA during wound closure

random effects model based on the inverse variance (IV) method[45]. Standard deviations (SDs) not available in the original article were calculated from confidence intervals (CIs), standard errors, p values, or ranges when possible, or otherwise estimated from trials within the same comparison with similar scales, outcomes, and time periods[45,52]. Reported complications were presented descriptively. To assess for publication bias, funnel plots were constructed to examine sample size versus exposure effect across included trials for the change in hemoglobin from preoperative values. Both the forest and funnel plots were created with RevMan 5.2 (Cochrane Collaboration).

Evaluation of Heterogeneity and Sensitivity Analyses

Heterogeneity was quantified using the chi-square test for heterogeneity and the I^2 statistic[45], which estimates the proportion of total variability among studies due to heterogeneity rather than chance alone. I^2 values were interpreted according to the *Cochrane Handbook:* 0% to 40% might not be important, and 30% to 60% may represent moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity[45]. A priori hypotheses were developed to explore both potential artefactual and real differences of treatment effects across trials[53]. We planned for sensitivity analysis to assess the differences in studies at higher risk of bias (non-RCTs) compared with those at low risk (RCTs), and to assess drain output in trials using topical compared with intravenous administration of TXA.

Results

Search Results and Study Characteristics

The literature search generated 559 relevant citations. Following duplicate removal and application of eligibility criteria, 538 articles from the electronic search and 2 from the manual search underwent title and abstract screening. Following this, 5 articles underwent full-text review, which indicated that these 5 articles met the inclusion criteria for this report (Fig. 1)[42-44,54,55]. The κ value for overall agreement between reviewers for the final eligibility decision was 1.0 (perfect agreement).

TABLE III (*continued*)

Total Blood Loss† (*mL*)		Drain Output† (*mL*)		Blood Transfusions	
TXA	Control	TXA	Control	TXA	Control
TSA, 679 (293-1,318); RTSA, 791 (185-1,318)	TSA, 910 (445-1,522); RTSA, 959 (372-1,511)	TSA, 99 (0-235); RTSA, 180 (60-455)	TSA, 235 (45-856); RTSA, 370 (105-680)	TSA, 1; RTSA, 1	TSA, 0; RTSA, 2
NA	NA	NA	NA	2	6
NA	NA	TSA, 120 (22-415); RTSA, 100 (0-350)	TSA, 220 (70-540); RTSA, 150 (30-350)	0	0
RTSA, 1,122.4 ± 411.6	RTSA, 1,472.6 ± 475.4	RTSA, 221.4 ± 126.2	RTSA, 371.9 ± 166.3	RTSA, 3	RTSA, 7
871.0 ± 472.8	1,248.2 ± 550.2	50 (0-350)	170 (0-730)	0	0

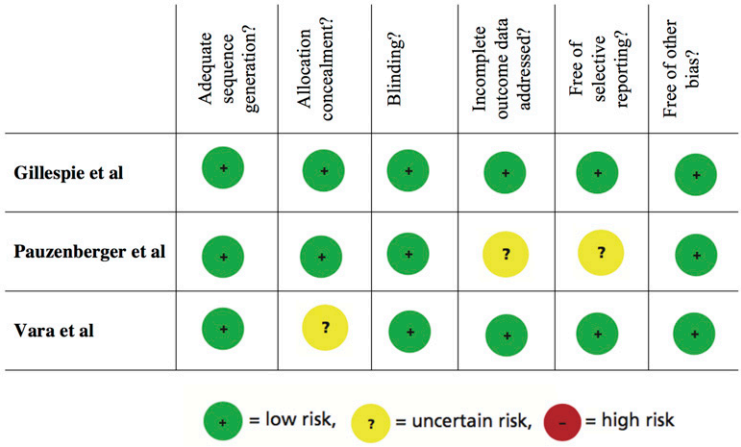


Fig. 2
Risk-of-bias assessment for RCTs included in the meta-analysis.

A total of 629 patients (632 shoulders) were included in this analysis. Of the 5 included studies, 4 were conducted in the U.S. and 1, in Austria[54]. Four studies were single-center trials[42,43,54,55], and 1 was a multicenter trial[44]. Four studies included patients undergoing either anatomic or primary reverse total shoulder arthroplasty[42-44,54], whereas 1 study included only patients undergoing primary reverse total shoulder arthroplasty[55] (Table I). Demographics were tabulated by treatment group (Table II). Blood loss and blood transfusion characteristics as defined by the study were also tabulated by treatment group and procedure (Table III).

Study Quality and Risk of Bias

Three studies were RCTs (Level-I evidence)[44,54,55], whereas the other studies were retrospective cohort trials with Level-III evidence[42,43]. The 2 nonrandomized studies had a mean MINORS score for comparative studies of 18 of 24 (Table I). All RCTs were found to have a low risk of bias[44,54,55] (Fig. 2). Interobserver agreement in the assessment of study quality was excellent (ICC, 0.97; 95% CI, 0.94 to 0.98).

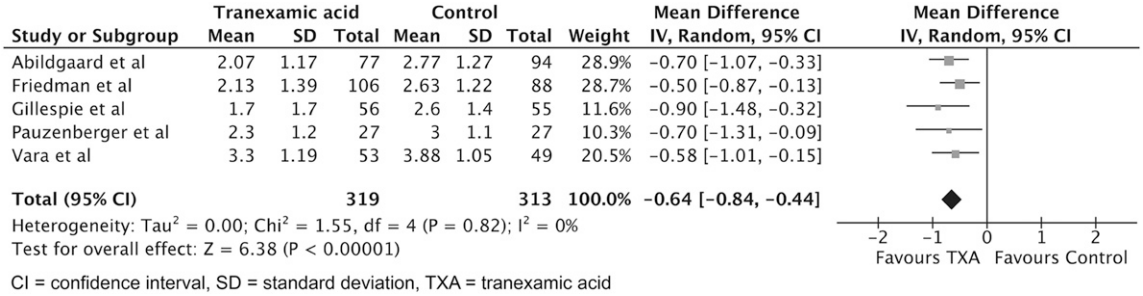
Reviewers rated the quality of evidence for all comparisons of blood loss (change in hemoglobin, drain output, and transfusion risk) down from a GRADE score of high to moderate because of potential risk of bias from inclusion of non-RCTs in the analysis. The Appendix presents an evaluation of the quality of evidence (based on the GRADE approach) as well as a figure showing the funnel plot for possible publication bias.

TXA Administration

The dosing and route of administration of TXA varied among studies. TXA was administered intravenously in 4 studies[42,43,54,55] and topically in 1 study[44]. Of the intravenous trials, those by Abildgaard et al.[42] and Friedman et al.[43] used a single dose of TXA prior to surgery. The former administered a 1-g bolus[42], whereas the latter administered 20 mg/kg[43]. In contrast, Vara et al.[55] and Pauzenberger et al.[54] administered TXA prior to surgery and at the time of wound closure. The former administered 10 mg/kg[55], whereas the latter administered a 1-g bolus[54] (Table II).

Blood Loss

Administration of TXA resulted in a significant decrease in blood loss compared with controls as measured by the mean difference in hemoglobin change across all 5 trials[42-44,54,55] (MD, −0.64 g/dL; 95% CI, −0.84 to −0.44 g/dL), with low heterogeneity ($p = 0.82$, $I^2 = 0\%$) (Fig. 3). This effect was unchanged when comparing only pooled outcomes from RCTs (MD, −0.70 g/dL; 95% CI, −1.00 to



CI = confidence interval, SD = standard deviation, TXA = tranexamic acid

Fig. 3
Pooled change in hemoglobin (g/dL) with TXA compared with controls after primary shoulder arthroplasty. df = degrees of freedom.

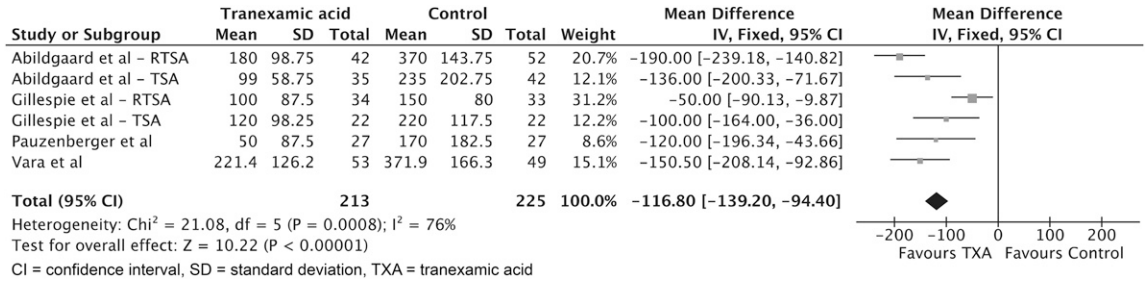


Fig. 4

Pooled change in drain output (mL) with TXA compared with controls after primary shoulder arthroplasty. df = degrees of freedom, and RTSA = reverse total shoulder arthroplasty.

20.39 g/dL), with low heterogeneity ($p = 0.69$, $I^2 = 0\%$).

TXA also significantly decreased blood loss compared with controls as measured by the mean difference in drain output across all 4 studies[42,44,54,55] that used a postoperative drain (435 patients, 438 shoulders) (MD, −116.80 mL; 95% CI, −139.20 to −94.40 mL), with high heterogeneity ($p = 0.0008$, $I^2 = 76\%$) (Fig. 4). This effect was unchanged when comparing only pooled outcomes from RCTs (MD, −90.71 mL; 95% CI, −118.05 to −63.37 mL), with significant heterogeneity ($p = 0.03$, $I^2 = 66\%$). A sensitivity analysis was performed to assess drain output in those studies using intravenous[42,54,55] in comparison with topical[44] TXA. Removal of a study in which topical TXA was used[44] decreased heterogeneity substantially (I^2, 76% to 3%; $p = 0.38$).

Administration of TXA was associated with a trend toward a meaningful difference in transfusion rates (55% decrease) compared with controls (RR, 0.45; 95% CI, 0.18 to 1.09; $p = 0.08$), with low heterogeneity ($p = 0.49$, $I^2 = 0\%$); however, the difference did not reach significance (Fig. 5). Overall, there were few total events (22 transfusions), representing an overall transfusion rate of 3.5%. There were 7 total transfusions in patients receiving TXA (2.2%) and 15 total transfusions in control patients (4.8%). Sensitivity analysis of pooled transfusion outcomes from RCTs only was nonsignificant because of the low event rates in the groups (RR, 0.4; 95% CI, 0.11 to 1.45; $p = 0.16$).

Complications

The overall rate of complications was low. One patient who received TXA had a complication—syncopal fall, managed successfully with fluid resuscitation[55]. Three patients who did not receive TXA had reported complications, including 1 patient who required reoperation secondary to a postoperative hematoma[42]. Additionally, 1 patient in the control group had a non-ST-segment-elevation myocardial infarction (NSTEMI) after receiving a transfusion of 1 unit of packed red blood cells[55].

Discussion

We found a significant reduction in the amount of perioperative blood loss as measured by the mean change in hemoglobin and by the drain output associated with the use of TXA in primary shoulder arthroplasty. The risk of blood transfusion strongly approached a meaningful difference, with a point estimate favoring TXA use; however, because of low overall event rates in the groups, this was not significant. Overall complications occurred at a very low rate, and no thromboembolic events were associated with TXA use.

The results of this study are similar to findings in the literature regarding the effects of TXA following lower extremity arthroplasty and orthopaedic spine surgery[29,31-37,56-59]. A recent meta-analysis of 46 RCTs, including almost 3,000 patients undergoing lower extremity arthroplasty and orthopaedic spine surgery,

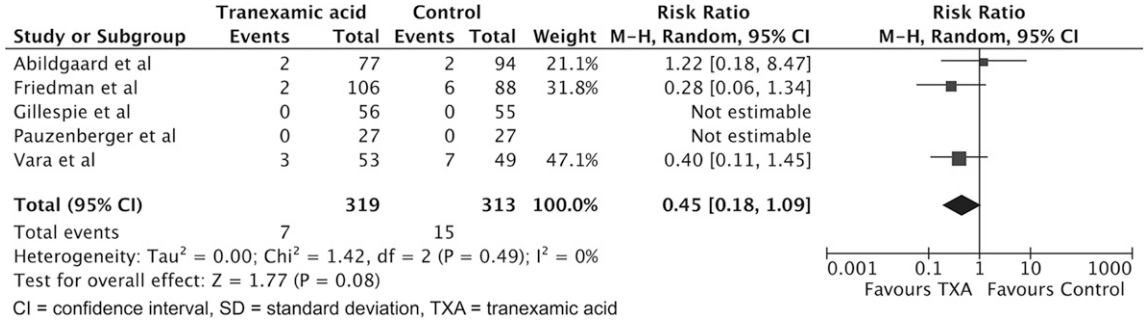


Fig. 5

Pooled change in blood transfusions with TXA compared with controls after primary shoulder arthroplasty. M-H = Mantel-Haenszel, and df = degrees of freedom.

demonstrated a reduction in mean intraoperative and postoperative blood loss by 125.65 mL (95% CI, 68.72 to 182.58 mL) and 214.58 mL (95% CI, 154.52 to 274.63 mL), respectively[29]. Another recent high-quality meta-analysis of 29 RCTs including over 2,600 patients by Ker et al.[30] demonstrated that topical TXA decreased bleeding by 29% (RR, 0.71; 95% CI, 0.69 to 0.72). Twelve of the trials involved orthopaedic studies; however, the results were consistent among all studies represented in the meta-analysis. In our study, administration of TXA significantly decreased blood loss compared with controls as measured by the mean difference in hemoglobin change, with low heterogeneity across all 5 trials[42-44,54,55].

Several studies from the adult lower extremity reconstruction literature have demonstrated significant reduction in postoperative drain output associated with TXA use[36,60-62]. In our study, although there was a significant association in favor of decreased drain output with TXA, the heterogeneity was high ($I^2 = 76\%$). Only Gillespie et al.[44] used topical TXA, and when that study was removed during the sensitivity analysis, the significant effect favoring TXA for reducing blood transfusions remained but heterogeneity became low ($p = 0.38$, $I^2 = 3\%$). Therefore, it is certainly possible that the topical use of TXA[44] accounted for the variability among trials.

The association between TXA and reduced transfusion requirements is well established[29-31,35,40]. Rates of allogeneic blood transfusion following shoulder arthroplasty have ranged considerably in the literature (4% to 43%)[15-24]. Our analysis of the effect of TXA on transfusion rates approached a meaningful difference; however, it did not reach significance, while having low heterogeneity. The overall event rate in our study was relatively low (22 of 632), and therefore is associated with a high risk of fragility[63]. A larger sample size might have produced a significant difference.

The low overall transfusion rate in this study can be explained by several factors. Previous studies often included both primary and revision arthroplasties[17,19,20] and adhered to older, less restrictive transfusion guidelines. More recent blood transfusion guidelines[64] advocate for a lower, more restrictive transfusion threshold. Furthermore, when evaluating data from the last 5 years, transfusion rates following shoulder arthroplasty have ranged from 4.5% to 11.3%[15,16,18,21,24], even when both primary and revision arthroplasties have been included. A recent Cochrane review demonstrated that use of a more restrictive transfusion threshold decreased rates of blood transfusion by 43%, with no effect on 30-day morbidity or mortality[65]. The decision to administer a blood transfusion is often multifaceted and subject to both individual and institutional criteria, which make it difficult to reliably standardize across studies.

TXA is associated with important economic implications for patients and health-care systems. In addition to the potential adverse health risks, including increased risk of postoperative infection, associated with blood transfusions[8-10,66], the mean cost per unit of blood can exceed $1,000[13,14]. Use of TXA has been associated with both direct cost savings for patients and indirect savings in post-discharge costs[39,67]. TXA is relatively inexpensive, with a mean cost of $58 to $68[43,67]. Tuttle et al.[67] highlighted the economic benefits of TXA, reporting a savings of $8,000 per 100 patients undergoing hip and knee arthroplasty treated with TXA. Furthermore, the use of TXA significantly reduced the number of patients going to a subacute nursing facility postoperatively[66], which may cost over 3 times more than home care following lower extremity total joint arthroplasty[68].

Regarding hospital costs[20-22], Kandil et al.[21] performed a recent large study utilizing the National Inpatient Sample database consisting of almost 52,000 patients undergoing total shoulder arthroplasty, and reported that blood transfusion was associated with a longer hospital stay and higher total cost. Similar findings were reported by Gruson et al.[20], who found longer inpatient hospital stays for patients receiving a transfusion following shoulder arthroplasty. Ricchetti et al.[22] reported that patients over 80 years of age undergoing shoulder arthroplasty had transfusion requirements that were 8 times greater, in addition to significantly increased inpatient hospital stays and fewer discharges directly to home.

Recent literature regarding the safety of TXA has demonstrated a favorable profile, with no increased risk of thromboembolic events compared with controls[30,31,35,37-41,56]. In a recent registry-based study by Hallstrom et al.[40], including almost 35,000 patients undergoing total hip and knee arthroplasty, TXA was associated with a decreased risk of venous thromboembolism in patients undergoing total knee arthroplasty. Furthermore, those authors found no association between TXA and an increased risk of thromboembolic events such as stroke, transient ischemic attack, or myocardial infarction[40]. Although the overall rates of complications reported in our study were too low for adequate statistical comparison, 2 of the 3 reported complications in the control group were related to bleeding: 1 patient required reoperation for a hematoma and another had an NSTEMI following a blood transfusion.

This study has several limitations. Most notably, the administration of TXA varied among studies. As there is no clearly established dosing regimen for TXA in shoulder arthroplasty, this reflects current clinical practice as TXA is increasingly utilized in shoulder arthroplasty. Postoperative blood management strategies also varied. Four of the 5 studies reported using a postoperative drain[42,44,54,55], which was removed on the first postoperative day in 3 studies and on the second postoperative day in 1 study[55]. Three of those 4 studies[42,44,55] had similar transfusion guidelines, which were hemoglobin

of <7 g/mL, or 7 to 9 g/mL in the presence of symptomatic anemia, whereas 1 study[54] used hemoglobin of <8 g/mL as the transfusion threshold. In contrast, Friedman et al.[43] did not report defined criteria for transfusion. Additionally, the postoperative measurement of hemoglobin was performed on postoperative day 1 in 3 studies[42-44] and on postoperative day 2 in 1 study[55], and it was determined from the lowest measurement throughout the duration of the patient's hospital stay in 1 study[54]. Lastly, our overall rate of blood transfusion of 3.5% is lower than that previously reported in the literature[15-24]. This is likely attributable in part to the use of more restrictive transfusion guidelines compared with historical studies. Interestingly, the control group (no TXA) had a transfusion rate of 4.8%, which is comparable with the most recent literature on transfusion rates following shoulder arthroplasty (4.26% to 6.1%)[15,21,24]. Although the TXA cohort had an overall transfusion rate of only 2.2%, the low overall event rate predisposes this result to a high risk of fragility.

This study has numerous strengths. It is an exhaustive review of very recent studies and therefore represents the most current literature on the use of TXA in shoulder arthroplasty. The findings were robust when sensitivity analyses for studies at high and at low risk of bias were performed, supporting our findings for a true effect of TXA in shoulder arthroplasty. Although the efficacy of TXA in lower limb arthroplasty has been reviewed extensively, a meta-analysis of the efficacy in the setting of shoulder arthroplasty has been lacking. The strengths of this study also include broad search terms, duplicate assessment of study eligibility, and a methodological quality assessment of included studies. The agreement between reviewers regarding study eligibility and methodological assessment was high. Although the small sample size limited robust interpretation, funnel plot analysis suggested a low risk of publication bias (see Appendix).

In conclusion, this systematic review and meta-analysis provides moderate-strength evidence supporting the use of TXA for decreasing blood loss in primary shoulder arthroplasty. There was a strong trend toward decreased transfusion requirements with TXA, and use of TXA was not associated with any thromboembolic events. Further research is necessary to evaluate the efficacy of TXA for shoulder arthroplasty in the revision and acute trauma settings. Additionally, identifying the optimal dosing and route of administration will provide clinicians with a standardized approach to TXA utilization in shoulder arthroplasty.

Appendix

Tables showing the search strategy and a summary of the results including the quality of evidence, as well as a figure showing the funnel plot for possible publication bias, are available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSREV/A258).

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Update

This article was updated on September 26, 2017, because of a previous error that occurred during production. On page 6, in Figure 2, the author of the first article had been listed as "Friedman et al." That text now reads "Gillespie et al."