



# Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial

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**Background:** Tranexamic acid (TXA) is an antifibrinolytic that has been shown to decrease blood loss and transfusion rates after hip and knee arthroplasty, with only limited evidence to support its use in shoulder arthroplasty. This study was conducted to determine whether intravenous (IV) TXA is more effective than placebo in reducing blood loss after primary total shoulder arthroplasty (TSA).

**Methods:** In this prospective, double-blind, placebo-controlled, randomized clinical trial, patients undergoing primary anatomic and reverse TSA were randomized to receive 1 g of intravenous TXA or a placebo of an equivalent volume of intravenous normal saline administered 10 minutes before the incision. The primary outcome measurement was calculated postoperative blood loss. Secondary outcomes included transfusion rates, weight of hemoglobin loss, hospital length of stay, and thromboembolic events.

**Results:** The study enrolled 110 patients, 2 of whom were excluded because they did not have a postoperative hemoglobin measurement, and the remaining 108 patients (52 for TXA, 56 for placebo) were analyzed. There were no significant differences between TXA and placebo groups in preoperative characteristics. For the primary outcome, the TXA group had significantly lower postoperative blood loss of  $1100.9 \pm 367.4$  mL compared with  $1274.5 \pm 460.0$  mL for the placebo group ( $P = .03$ ). For secondary outcomes, TXA had lower weight of hemoglobin loss compared with placebo ( $152.2 \pm 57.3$  g vs.  $178.0 \pm 65.8$  g;  $P = .03$ ). No patients in the TXA or placebo groups required a transfusion.

**Conclusions:** Intravenous TXA reduced blood loss after primary TSA compared with placebo.

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Anatomic and reverse total shoulder arthroplasty (TSA) is associated with the risk of moderate blood loss that can lead to transfusions. Average estimated intraoperative blood loss has been reported in the range of 354 mL to 361 mL, not accounting for additional blood loss postoperatively in soft tissues or surgical drains.<sup>4,15</sup> Transfusion rates of 2.4% to 9.5% have been reported for primary TSA.<sup>4,11,15,16</sup>

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that is an established method of reducing blood loss and transfusion re-

quirement for patients undergoing total hip and knee arthroplasty.<sup>2,3,7,13,22</sup> TXA can be administered intravenously (IV), topically (intra-articularly), or orally, with most available literature addressing IV and topical administration. Systematic reviews and meta-analyses of the total hip and knee arthroplasty literature demonstrate an approximately 30% decrease in blood loss and a 50% decrease in the transfusion rate with topical or IV administration of TXA compared with placebo.<sup>2,3,7,13,22</sup> Moreover, the literature demonstrates no increased rate of thromboembolic or other complications associated with TXA administration for hip and knee arthroplasty.<sup>7,22</sup> Several recent studies have begun to explore the use of TXA in TSA patients to potentially reduce blood loss and transfusion.<sup>1,6,8,14,19</sup>

This study was conducted to determine whether IV TXA is more effective than placebo in reducing blood loss after primary TSA. We hypothesized that IV TXA would significantly reduce blood loss after TSA.

The Rush University Medical Center Institutional Review Board approved this study on April 10, 2015 (ORA Number: 14102308-IRB01).

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## Materials and methods

### Study design and patients

This prospective, double-blind, placebo-controlled, randomized clinical trial of IV TXA compared with placebo was registered at [clinicaltrials.gov](http://clinicaltrials.gov) with registration number NCT02569658. The study was designed to determine the superiority of TXA over placebo by comparing 2 parallel groups: IV TXA and IV saline. A 1:1 allocation ratio of patients to TXA and placebo was used. There were no changes to the trial design during the study.

Patients were eligible for study inclusion if they were undergoing a unilateral primary anatomic or reverse TSA by the study authors at a single institution. Exclusion criteria were allergy to TXA, acquired disturbances of color vision, preoperative use of anticoagulant therapy within 5 days of surgery, history of arterial or venous thromboembolic disease (including deep venous thrombosis, pulmonary embolism, stroke, transient ischemic attack), ongoing pregnancy or breast-feeding, recent myocardial infarction (within 6 months before surgery), cardiac stent placement, renal impairment, hemophilia, refusal of blood products, revision TSA, TSA performed for the indications of acute proximal humeral fracture, or prior open shoulder surgery, including failed open reduction and internal fixation of proximal humeral fractures. Patients who underwent prior arthroscopic shoulder procedures were eligible to participate.

Patients who met eligibility criteria and consented to participate in the study by an informed consent process were randomized to receive 10 mL of IV normal saline placebo or 1 g of IV TXA diluted in 10 mL normal saline (X-Gen Pharmaceuticals, Inc., Horseheads, NY, USA). This dose of TXA was chosen because it is standard practice at our institution to administer 1 g IV TXA 10 minutes before the incision for total hip and knee arthroplasty.

A random number algorithm was used for the randomization process. The TXA or placebo was placed into an unlabeled 10-mL syringe by research pharmacy staff who were not involved in the patient's care to ensure identical appearance and blinding between TXA and placebo. A blinded research assistant delivered the syringe to the blinded anesthesiology staff, who administered the syringe was administered 10 minutes before the incision. All patients, surgeons, anesthesiologists, and clinical staff were blinded to the patient's study group allocation. Study group allocation remained blinded by the research pharmacists until the time of data analysis.

Data acquisition was performed by a research assistant blinded to patient study group allocation. Patient demographics and preoperative characteristics were recorded and compared between the TXA and placebo groups. Included were age, sex, American Society of Anesthesiologists (ASA) Physical Status Classification, body mass index, and preoperative hemoglobin.

### Surgical technique and postoperative care

Anatomic or reverse TSA was performed by 5 fellowship-trained attending surgeons. Anesthesia involved interscalene regional anesthesia combined with general anesthesia. A deltopectoral approach was used, followed by implantation of uncemented anatomic or reverse TSA implants, according to attending surgeon preference. Drains were used postoperatively based on surgeon preference and removed on postoperative day 1 in all patients.

Patients underwent standard postoperative care, including admission to the hospital for at least 1 night. Patients were monitored by a hospitalist while in the hospital and received occupational therapy. Patients had sequential compression devices for deep venous thrombosis prophylaxis during their hospital stay. The patients underwent daily complete blood count, including measurement of hemoglobin, for as long as they remained in the hospital. Patients underwent transfusion if their postoperative hemoglobin dropped

below 7.0 g/dL or for higher hemoglobin values only for specific medical indications specified by the consulting hospitalist attending.

### Outcomes

The primary outcome for this study was postoperative blood loss based on a formula accounting for initial patient hemoglobin, the lowest postoperative hemoglobin, and patient blood volume approximated based on patient sex, height, and weight.<sup>5,20</sup> This method of calculating blood loss is intended to account for intraoperative and postoperative losses, including bleeding into soft tissues. It is felt to be more accurate than methods such as estimated blood loss and surgical drain losses.<sup>5,20</sup> The blood loss calculation formulas are as follows:

$$\text{Hb(loss)} = \text{BV} \times [\text{Hb}(i) - \text{Hb}(e)] \times 0.001 + \text{Hb}(t)$$

$$\text{Blood loss} = 1000 \times \text{Hb(loss)} / \text{Hb}(i)$$

Where  $\text{Hb(loss)}$  is loss of hemoglobin in grams,  $\text{Hb}(i)$  is preoperative hemoglobin,  $\text{Hb}(e)$  is the lowest postoperative hemoglobin, and  $\text{Hb}(t)$  is total amount of transfused hemoglobin.  $\text{BV}$  is predicted blood volume, which is calculated as follows:

$$\text{BV (male)} = (0.3669 \times \text{Ht}^3) + (0.03219 \times \text{Wt}) + 0.6041$$

$$\text{BV (female)} = (0.3561 \times \text{Ht}^3) + (0.03308 \times \text{Wt}) + 0.1833$$

Where  $\text{Ht}$  is height in meters and  $\text{Wt}$  is weight in kilograms.

Secondary outcomes included transfusion rates, weight of hemoglobin loss, intraoperative estimated blood loss, and hospital length of stay. Postoperative complications, including thromboembolic events, were noted for a 90-day postoperative period. Complications were noted on routine postoperative follow-up examinations. A research assistant who was not involved in patient care and was blinded to patient study group allocation recorded data after patients were discharged from the hospital.

### Statistical analysis

Power analysis was performed before study initiation to determine sample size. Using estimated intraoperative blood loss averaging  $361 \pm 220$  mL for TSA from a recent report<sup>4</sup> and an estimated 30% reduction of blood loss based on total hip and knee arthroplasty literature,<sup>2,3,7,13,22</sup> we determined that a sample size of 110 patients (55 patients per group) was necessary to achieve power of 80% at an  $\alpha$  of 5%.

Descriptive statistics are presented with mean  $\pm$  standard deviation for continuous data and as frequency with percentages for categorical data. Data were tested for normality by Kolmogorov-Smirnov testing and found to be normally distributed, and therefore, parametric tests were used. Two-sample unpaired Student  $t$  tests were used to compare continuous variables, including calculated blood loss. The  $\chi^2$  and Fisher exact tests were used as appropriate based on expected values to compare categorical data. Significance was set at  $P < .05$ . Analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

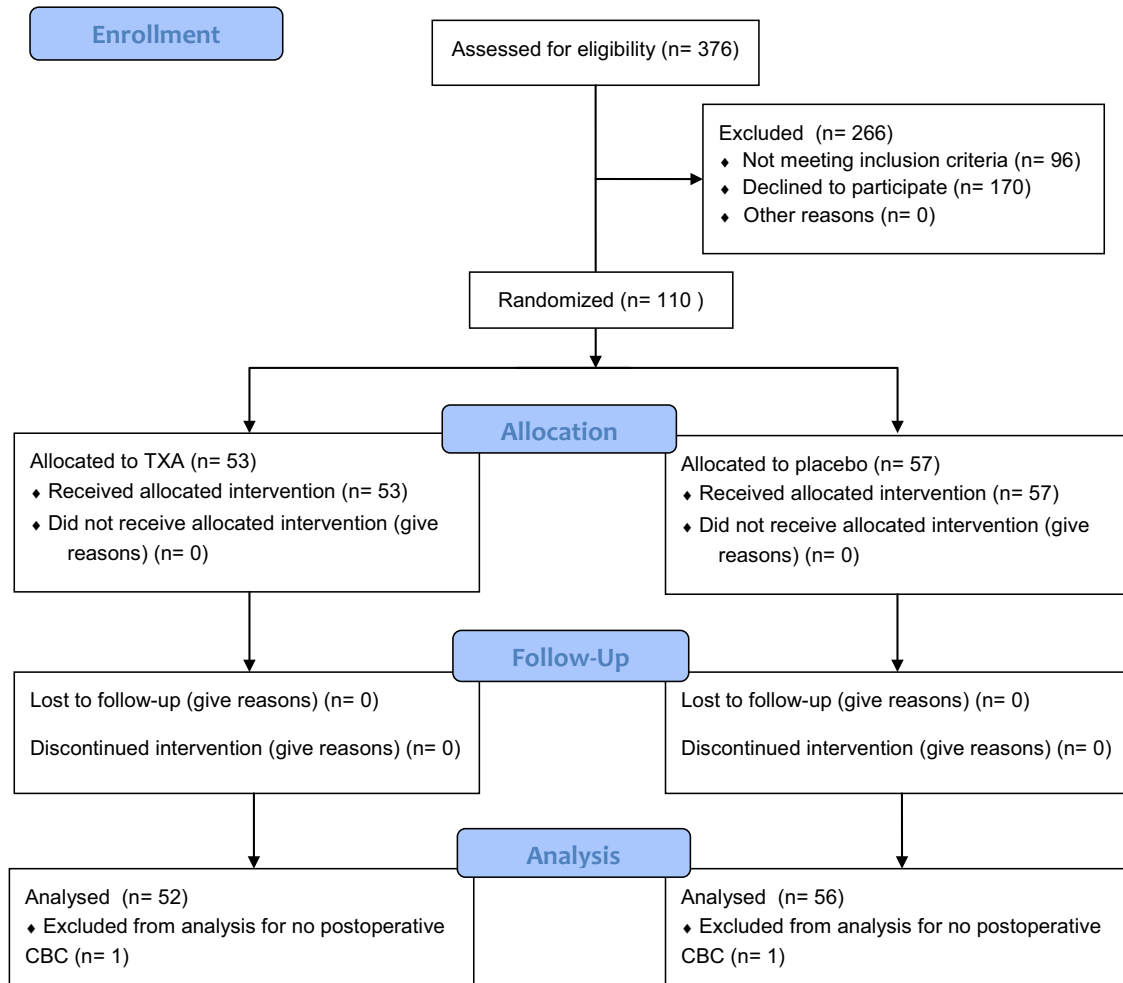
## Results

### Patient enrollment and baseline data

During the enrollment period from September 2015 to November 2016, 376 patients underwent primary anatomic or reverse TSA. A Consolidated Standards of Reporting Trials flow diagram is shown in [Fig. 1](#). Of these, 92 patients were ineligible based on exclusion



### CONSORT Flow Diagram



**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) flow diagram for patients in the study. (TXA, tranexamic acid; CBC, complete blood count.)

criteria, and 170 declined to participate. After randomization, there were 53 patients in the TXA group and 57 in the placebo group. All patients received the study drug according to their randomly assigned group. Postoperative hemoglobin values were not taken for 2 patients, and they could not be analyzed further. The remaining 108 patients (52 TXA and 56 placebo) were analyzed. No patients were lost to follow-up.

The enrolled patients were a mean age of  $66.4 \pm 10.1$  years, and 47.2% were male (51 of 108). Reverse TSA was performed in 54.6% of patients (59 of 108). Baseline preoperative data did not significantly differ between TXA and placebo (Table I). Operative time from incision to closure was  $101.9 \pm 21.4$  minutes (median, 99; range, 62–149 minutes), which did not differ between the TXA and placebo groups ( $P = .70$ ).

#### Primary outcome

The postoperative blood loss after TSA was significantly lower in the TXA group than in the placebo group ( $1100.9 \pm 367.4$  mL vs.  $1274.5 \pm 460.0$  mL;  $P = .03$ ; Table II). There was no statistically significant difference in blood loss by use of a drain ( $P = .34$ ) between the 5 attending surgeons ( $P = .25$ ) and between reverse and anatomic TSA ( $P = .30$ ). Increased surgical time was correlated with increased blood loss ( $P = .04$ ).

#### Secondary outcomes

The TXA group had lower total hemoglobin loss compared with placebo ( $152.2 \pm 57.3$  g vs.  $178.0 \pm 65.8$  g;  $P = .03$ ; Table II). There was

**Table I**  
Preoperative and intraoperative characteristics for total shoulder arthroplasty patients in placebo and tranexamic acid groups

Variable	Placebo (n = 56)	TXA (n = 52)	P value
Age, yr	65.2 ± 9.2	67.7 ± 10.9	.18
Male	28 (50.0)	23 (44.2)	.57
Weight, kg	88.4 ± 19.1	84.2 ± 19.6	.24
Height, m	1.7 ± 0.1	1.7 ± 0.1	.90
Body mass index, kg/m <sup>2</sup>	29.7 ± 5.2	29.0 ± 5.0	.47
Predicted blood volume, L	5.2 ± 1.0	4.9 ± 1.1	.23
Preoperative hemoglobin, g/dL	13.9 ± 1.2	13.7 ± 1.3	.20
Preoperative platelet count, ×10 <sup>9</sup> /L	234.8 ± 58.8	247.7 ± 62.1	.27
Operative time, min	102.7 ± 21.6	101.1 ± 21.4	.70
Reverse shoulder arthroplasty	30 (53.6)	29 (55.8)	.85
ASA score	2.8 (1.5)	2.8 (0.9)	.93

TXA, tranexamic acid; ASA, American Society of Anesthesiologists.  
Data are presented as mean ± standard deviation for continuous data and as frequency (%) for categorical data.

no difference in length of stay ( $1.8 \pm 1.0$  days for TXA vs.  $1.8 \pm 1.2$  days for placebo;  $P = .95$ ; Table II), estimated blood loss as recorded in the operative report ( $208.2 \pm 122.2$  mL for TXA vs.  $221.6 \pm 139.2$  mL for placebo;  $P = .59$ ; Table II), or in operative time between reverse ( $105.8 \pm 21.0$  minutes) and anatomic TSA ( $98.7 \pm 21.4$  minutes;  $P = .09$ ). No patients in the TXA or placebo groups required a transfusion or experienced infection, readmission, or return to the operating room by 90 days postoperatively (Table II). A postoperative deep venous thrombosis occurred in 1 patient in the placebo group, but there were no other thromboembolic complications.

## Discussion

TXA is widely used in total hip and knee arthroplasty due to multiple studies suggesting that it reduces postoperative blood loss and transfusion rate without increasing rates of complications.<sup>2,3,7,13,22</sup> In recent years, there has been emerging interest in translating TXA to TSA patients because transfusion rates of 2.4% to 9.5% have been reported for primary TSA.<sup>4,11,15,16</sup> We report results of a prospective, double-blind, placebo-controlled randomized clinical trial of TXA vs. placebo for primary TSA, finding that TXA reduces blood loss after TSA.

Several studies addressed TXA in TSA with retrospective study designs.<sup>16</sup> Abildgaard et al<sup>1</sup> retrospectively compared cohorts of primary TSA patients who received 1 g IV TXA before incision (during years 2014–2015) with a prior group of patients that did not receive TXA (during year 2013). They found that the TXA group had lower blood loss, drain output, and change in hemoglobin for primary an-

**Table II**  
Primary and secondary outcomes for total shoulder arthroplasty patients in placebo and tranexamic acid groups

Variable	Placebo (n = 56)	TXA (n = 52)	P value
Primary outcome			
Postoperative blood loss, mL	1274.5 ± 460.0	1100.9 ± 367.4	.03
Secondary outcomes			
Total hemoglobin loss, g	178.0 ± 65.8	152.2 ± 57.3	.03
Estimated blood loss, mL	221.6 ± 139.2	208.2 ± 122.2	.59
Hospital length of stay, d	1.8 ± 1.2	1.8 ± 1.0	.95
Transfusion	0 (0)	0 (0)	1.0
Thromboembolic complications	1 (1.8)*	0 (0)	1.0
Reoperation and readmission	0 (0)	0 (0)	1.0

TXA, tranexamic acid.  
Data are presented as mean ± standard deviation for continuous variables and as frequency (%) for categorical variables.

\* One patient in the placebo group experienced a deep venous thrombosis.

atomic and reverse TSA. Similarly, Friedman et al<sup>6</sup> retrospectively compared patients receiving 20 mg/kg IV TXA before incision for primary anatomic and reverse TSA (years 2009–2012) with a prior group of patients that did not receive TXA (years 2007–2009). They found that the TXA group had reduced blood loss, 21% shorter recovery room time, and 16% shorter hospitalization. These retrospective studies suffer from limitations inherent in their design that could bias results, including lack of blinding, lack of randomization, and importantly, changes in surgical and postoperative procedures between an earlier cohort and a more recent cohort that are major confounding variables in their conclusions.

Three randomized studies have been performed in TSA patients using TXA to date.<sup>8,14,19</sup> Gillespie et al<sup>8</sup> compared TSA patients receiving 100 mL saline placebo vs. 2 g TXA in 100 mL saline solution administered by topical application into the surgical wound at the end of the case for 5 minutes. The topical TXA group had reduced blood loss (108 mL vs. 170 mL) as determined by estimated intraoperative blood loss plus loss occurring in surgical drains. This study also noted that TXA decreased changes in hemoglobin, with no transfusions or complications noted. Although the authors demonstrated the effectiveness of topical TXA, their method of blood loss calculation did not account for additional blood loss in the soft tissues that was not evacuated by the postoperative drain. The authors therefore likely underestimated the true total blood loss, and we believe our method of calculating blood loss more accurately represents postoperative blood loss.

Pautzenberger et al<sup>14</sup> recently randomized patients to 1 g IV TXA or saline, finding reduced drainage, estimated blood loss, early postoperative pain by visual analog scale, and hematoma formation. Similarly, Vara et al<sup>19</sup> reported that IV TXA reduced blood loss in primary reverse TSA. Our study confirms these results, also finding Level I evidence that TXA reduces blood loss after primary shoulder arthroplasty, although none of our patients required a transfusion compared with the 9.8% transfusion rate reported by Vara et al.<sup>19</sup> Surgeons can therefore consider using TXA to reduce blood loss during TSA by whichever route of administration is best for their practice based on the available literature showing significant decreases in blood loss from IV as well as topical administration.

The present study has limitations. Although we found statistically significant decreases in blood loss for patients receiving TXA for TSA compared with placebo, our results do not establish that TXA provides a benefit to patients or health systems in improved outcomes, reduced transfusion rates, shorter lengths of stay, or cost savings. The use of TXA in hip and knee arthroplasty has demonstrated cost savings of as much as \$83.73 per patient based on transfusion costs alone.<sup>9,12,18</sup> After accounting for reduction in operating room, laboratory, blood, and room and board costs, Gillette et al<sup>9</sup> was able to show \$879 of cost savings per patient in the setting of a primary hip or knee arthroplasty. The transfusion rates in the groups not being treated with TXA were much higher, at 17.5% to 43%.<sup>12,18</sup> Transfusion rates are lower for TSA compared with hip and knee arthroplasty, so demonstrating cost-effectiveness may be more challenging.

Next, calculations for blood loss and change in hemoglobin before postoperative day 5 are at risk of inaccuracy due to hemodilution.<sup>10</sup> Nevertheless, this is routinely performed in hip and knee arthroplasty and is unlikely to alter the significance of the study conclusions because the same methodology was applied to both groups and the hospital length of stay was equivalent between the two.<sup>10</sup> Calculated blood losses for hip and knee arthroplasty have included values closer to 1300 mL compared with 1100 mL for TSA in our study group.<sup>5,20</sup> In addition, the lack of transfusions and complications in the study population makes our study underpowered to assess differences for these uncommon secondary study outcomes.<sup>17,21,22</sup>

Finally, the study's inclusion and exclusion criteria may limit generalizability of study findings to other scenarios. The exclusion



criteria generally included medical contraindications for TXA and patients not undergoing primary TSA, including prior open shoulder surgery and revision TSA. The latter was used to achieve the necessary sample size of relatively uniform patient populations for the TXA and placebo groups. Future studies investigating TXA in revision TSA will be necessary, particularly because these patients may experience greater blood loss than primary TSA and might derive greater benefit from TXA.<sup>4,11,15,16</sup>

## Conclusion

IV TXA reduced blood loss after primary TSA compared with placebo.

## Disclaimer

The TXA used in this study was donated by X-Gen Pharmaceuticals, Inc. (Horseheads, NY, USA), which had no other role in the study including no role in study design, patient enrollment, data collection, data analysis, and manuscript preparation.

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