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SHOULDER

Neer Award 2015: A randomized, prospective evaluation on the effectiveness of tranexamic acid in reducing blood loss after total shoulder arthroplasty



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Background: Tranexamic acid (TXA) is an antifibrinolytic agent that has been shown to significantly reduce blood loss and transfusion requirements after total knee and hip arthroplasty. The purpose of this study was to evaluate the effect of TXA on postoperative blood loss after shoulder arthroplasty.

Methods: A total of 111 patients (62 women; average age, 67 years) who underwent shoulder arthroplasty were prospectively randomized in double-blinded fashion to receive either 100 mL of normal saline or 100 mL of normal saline with 2 g TXA by topical application into the wound at the completion of the case. All patients received a postoperative drain. Drain output representing postoperative blood loss, transfusion requirements, and change in hemoglobin level were recorded. All postoperative complications were noted.

Results: The average blood loss recorded after surgery was 170 mL in the placebo group and 108 mL in the TXA group ($P = .017$). The average change in hemoglobin level was 2.6 g/dL in the placebo group and 1.7 g/dL in the TXA group ($P < .001$). There were no transfusion requirements or postoperative complications noted in either group.

Discussion: In this cohort of patients, those treated with TXA experienced a significantly lower amount of postoperative blood loss and a significantly smaller change in hemoglobin level compared with those treated with placebo. Further work is required to determine the effectiveness and clinical significance of TXA in reducing transfusion requirements in shoulder arthroplasty and, more specifically, shoulder arthroplasty performed for complicated patients or for trauma and fracture patients.

Level of evidence: Level I, Randomized Controlled Trial, Treatment Study.

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Keywords: Tranexamic acid; shoulder arthroplasty; postoperative blood loss; hemoglobin; hematocrit

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Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that prevents progression of the fibrinolytic pathway by competitively inhibiting the activation of plasminogen to plasmin, allowing more effective clot production.^{4,13} TXA has been used to reduce bleeding in surgical

patients for more than 40 years, and it has reduced blood transfusion requirements after a variety of surgical procedures.^{4,13} The use of allogeneic blood transfusions after major orthopedic surgery has been associated with an increased risk of surgical site infection,^{8,14} making reduction of blood loss of great interest to all orthopedic surgeons. Whereas TXA has been demonstrated to be effective in reducing blood transfusion requirements after hip and knee arthroplasty,^{2,5,9,10,12,15,17,24} no study has yet evaluated the safety and effectiveness of TXA in reducing blood loss and transfusion requirements after shoulder arthroplasty.

We have performed a prospective, randomized, double-blinded study of topical TXA applied intraoperatively during total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA) to determine whether topical TXA applied before wound closure after TSA and RTSA would reduce blood loss and reduce transfusion requirements. We hypothesized that the treatment group would experience less blood loss postoperatively through a surgical drain and would experience a smaller drop in hemoglobin values, therefore being less likely to meet criteria for transfusion.

Materials and methods

We designed a prospective, randomized, double-blinded study of TXA's effectiveness in reducing blood loss and transfusion requirements in shoulder arthroplasty. The primary outcome was postoperative blood loss, and the secondary outcome was postoperative hemoglobin level. On the basis of a prior study of TXA,³ in which the authors determined that 140 patients would be needed to show a difference in blood loss of 100 mL, which we considered to be clinically significant, we designed our study for inclusion of 140 patients. Participants were randomized using block randomization conducted by the pharmacology department for total enrollment of 140 subjects. Tables were created for each treatment site to reflect a randomization of 1:1 TXA to placebo in blocks of 6.

Participants were recruited on a volunteer basis and underwent primary TSA or primary RTSA between October 2012 and June 2014. Inclusion was discussed before the day of surgery, and all patients discontinued the use of aspirin and nonsteroidal anti-inflammatory medications 7 days before surgery. Exclusion criteria for this study were revision surgery, history of cardiac disease, liver disease, renal disease, preoperative hemoglobin level <11.5 g/dL or hematocrit <35%, severe joint deformity, history of joint infection, history of bleeding or metabolic disorder, history of peripheral vascular disease, history of prior deep venous thrombosis (DVT) or pulmonary embolism (PE), any patient unwilling to accept a blood transfusion, and any patient with a documented allergy to TXA. Each participant confirmed that he or she understood the benefits and risks of topical TXA use during open shoulder surgery and provided written consent to participate in the trial. Each patient had a hemoglobin level determined preoperatively.

This study was conducted at 2 treatment centers, and all operations were performed by the 2 senior authors (R.G.G. and

R.J.G.), both of whom are fellowship trained in shoulder and elbow surgery. All patients underwent shoulder arthroplasty for treatment of degenerative joint disease of the shoulder, with the decision for TSA or RTSA based on the integrity of the rotator cuff at the time of the initial preoperative evaluation. All operations were performed through a deltopectoral approach in the beach chair position with use of a pneumatic arm holder. The use of TXA or placebo for each participant was determined by sealed envelope at the start of the case. Before closure of the deltopectoral interval, each patient in the treatment group had 100 mL of normal saline infused with 2 g of TXA poured into the surgical wound and left in place for 5 minutes. The control group had 100 mL of normal saline poured into the wound and left in place for the same duration. Neither the patient nor the surgeon had knowledge of whether TXA solution or placebo was being administered, and this blinding remained in place until analysis of data at completion of the study. Before closure of the deltopectoral interval, a standard Hemovac drain was placed deep to the deltoid muscle. The estimated blood loss (EBL) for the procedure was determined at this point, and all additional blood loss through the drain was recorded for the purposes of the study.

Each participant in the study had regular monitoring of the drain output at a prescribed interval of 8 hours. A postoperative hemoglobin level was determined on the morning of postoperative day 1. The protocol for blood transfusions called for these to be administered only for a hemoglobin level <7.0 g/dL or a hemoglobin level of >7.1 but <9.0 g/dL with accompanying signs and symptoms of acute blood loss anemia, as demonstrated by tachycardia (heart rate >100 beats/min), hypotension (systolic blood pressure <100 mm Hg), or subjective complaints of lightheadedness or dizziness that did not resolve after administration of intravenous fluids. The drain was removed on postoperative day 1, and the total drain output was calculated at the time of data analysis as the sum of the outputs recorded at the prescribed intervals. No measurement of hematoma size was attempted. All patients had the operative shoulder immobilized in a sling during the entire monitoring period, and patients were allowed to position themselves for comfort in bed as well as to move about the room unrestricted.

Statistical analysis

Comparisons between treatment group and placebo were made with the parametric Student *t* test to evaluate the null hypothesis of equality of means when data appeared to be normally distributed or otherwise, when the data appeared to be skewed or bimodal, by the nonparametric Mann-Whitney test to evaluate the null hypothesis of equivalent distributions. The mean was reported for normally distributed data, and the median was reported when nonparametric testing was necessary. A 2-sided *P* value of <.05 was considered significant.

Results

A total of 118 patients were randomized for inclusion in the study, with 57 randomized to the placebo group and 61 to the treatment group (Fig. 1). Two patients in the placebo group and 3 patients in the treatment group ultimately had

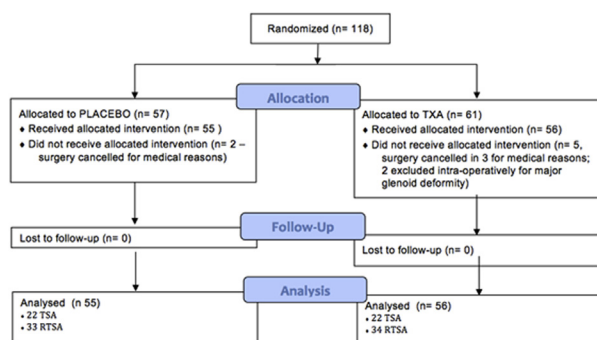


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of study. TXA, tranexamic acid; TSA, total shoulder arthroplasty; RTSA, reverse total shoulder arthroplasty.

their operations canceled for medical reasons. Two patients in the treatment group were also excluded from the analysis because of intraoperative findings of major glenoid deformity. Thus, a total of 111 patients were analyzed after randomization and surgery, with 55 patients receiving placebo and 56 patients receiving TXA. The mean age of participants in this study was 67 years (range, 41-86 years); 56% of participants were women, and 40% of procedures were left sided (Table I). The study groups were not different in terms of age ($P = .56$), sex ($P = .57$), or side of operation ($P = .44$). The same was true on subgroup analysis focusing separately on those undergoing RTSA or TSA. The degree of intraoperative blood loss (EBL) was also not different between the treatment and placebo groups ($P = .61$) or between the TSA and RTSA subgroups ($P = .35$).

The primary outcome of interest in this study was postoperative blood loss as measured by cumulative drain output. Postoperative blood loss was found to be significantly lower ($P = .017$) in the TXA group (median, 110 mL; range, 0-415 mL) compared with placebo (median, 170 mL; range, 30-540 mL). Subgroup analysis demonstrated that among participants who underwent TSA, there was a significant difference ($P = .014$) in postoperative blood loss between those receiving TXA (median, 120 mL; range, 22-415 mL) and those receiving placebo (median, 220 mL; range, 70-540 mL). In those undergoing RTSA, there was no significant difference ($P = .37$) in postoperative blood loss between those receiving TXA (median, 100 mL; range, 0-350 mL) and those receiving placebo (median, 150 mL; range, 30-350 mL) (Fig. 2).

The secondary outcome of interest in this study was change in hemoglobin level. There was no significant difference in EBL between groups based on administration of TXA or placebo ($P = .61$), and therefore any difference in hemoglobin level between treatment groups was considered likely to result from postoperative blood loss. Patients who received TXA experienced a smaller drop in hemoglobin level from the preoperative level (median, 1.7 g/dL; range,

0.2-7.0 g/dL) compared with those who received placebo (median, 2.6 g/dL; range, -0.5 to 5.1 g/dL; $P < .001$). Subgroup analysis demonstrated that a difference in hemoglobin level change existed for patients undergoing RTSA ($P = .001$), but no significant difference was found in the subgroup of patients undergoing TSA ($P = .099$) (Fig. 3). None of the patients in this study met the aforementioned predetermined criteria for administration of a blood transfusion. There were no perioperative complications noted in any patient.

Discussion

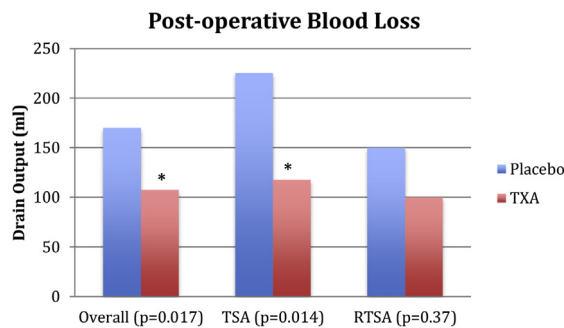
In this randomized, prospective study, we evaluated the effectiveness of TXA in reducing postoperative blood loss by comparing drain output and the change in hemoglobin level after TSA and RTSA. Compared with patients receiving placebo, the group of patients who were administered topical TXA experienced less postoperative blood loss ($P = .017$) through a surgical drain and demonstrated a smaller drop in hemoglobin level from baseline by postoperative day 1 ($P < .001$). No patient in either group required a blood transfusion, and no patient experienced a complication in the immediate postoperative period. These results suggest that the use of topical TXA at the conclusion of TSA and RTSA is safe and may be beneficial in certain situations.

This is the first study to evaluate TXA in the setting of shoulder surgery. TXA is now commonly used in lower extremity arthroplasty surgery, and there are data to support its use.^{1,3,6,11} In a retrospective chart review of 304 patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA), Gilbody et al found significant reductions in transfusion rates (19.3% vs. 2.3% for THA and 13.1% vs. 0% for TKA) and significant reductions in hemoglobin drop (8 g/L for THA, 15 g/L for TKA) when patients who were treated with topical TXA were compared against those who were not.⁶ König et al conducted a prospective comparative study comparing topical TXA with topical placebo in patients undergoing primary THA or TKA and demonstrated less postoperative bleeding and transfusion rates in patients receiving topical TXA.¹¹ In another prospective randomized controlled trial of 50 patients, Bidolegui et al found that intravenous TXA was associated with significantly reduced blood loss and need for transfusion in patients undergoing TKA.¹ A meta-analysis of 7 eligible studies on topical TXA use in TKA found TXA use to be associated with significant reductions in postoperative blood loss and blood transfusion requirements.¹⁵ Subgroup analysis in this study demonstrated a significant difference in postoperative blood loss with TXA use among patients undergoing TSA but no significant difference with TXA use among patients undergoing RTSA. However, there was a significant difference in hemoglobin level with TXA use among patients undergoing

Table I Baseline characteristic comparison across treatment groups

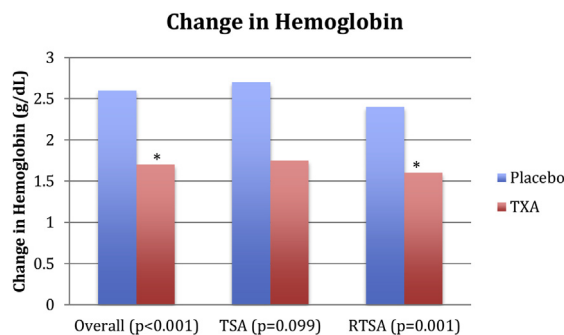
Characteristic	Overall	Overall			TSA			RTSA		
		Placebo	TXA	P value	Placebo	TXA	P value	Placebo	TXA	P value
Age (years)	67.03	66.45	67.59	.56	59.73	62.00	.45	70.94	71.21	.56
Female (%)	55.86	52.73	58.93	.57	27.27	40.91	.53	69.70	70.59	>.99
Left-sided surgery (%)	40.54	36.36	44.64	.44	45.45	36.36	.76	30.30	50.00	.14

There was no significant difference in average age between treatment groups (placebo or tranexamic acid [TXA]) or even between treatment groups subdivided by procedure type (total shoulder arthroplasty [TSA] or reverse total shoulder arthroplasty [RTSA]). There was no significant difference in the portion of patients who were female or had left-sided surgery between treatment groups or even between treatment groups subdivided by procedure type.



* - significant difference

Figure 2 Comparison of postoperative blood loss between treatment groups (placebo vs tranexamic acid [TXA]) in the overall sample population and in each subgroup based on procedure type (total shoulder arthroplasty [TSA] vs. reverse total shoulder arthroplasty [RTSA]).



* = significant difference

Figure 3 Comparison of hemoglobin change (from preoperative to postoperative) between treatment groups (placebo vs. tranexamic acid [TXA]) in the overall sample population and in each subgroup based on procedure type (total shoulder arthroplasty [TSA] vs. reverse total shoulder arthroplasty [RTSA]).

RTSA. One potential explanation for this may be due to the presence of a greater potential space after RTSA than after TSA, resulting in collection of blood that was not evacuated by drain output but still having an effect on postoperative hemoglobin levels.

The need for postoperative blood transfusions after lower extremity arthroplasty is well known as transfusion rates for THA and TKA during a 10-year period (2000-2009) were 25.5% and 17.9%, respectively.²³ The use of

TXA in this setting has been justified by the cost savings and by the likely reduction in postoperative infection rates due to the administration of fewer transfusions. In a retrospective cohort of 591 patients, Tuttle et al demonstrated a savings of \$83.73 per patient undergoing TKA or THA based on transfusion costs and after taking into account the cost of TXA.²⁰ Gillette et al demonstrated associated lower mean direct hospital total costs with TXA use in TKA and THA, given that the cost of TXA itself was more than offset by the cost savings in other expenses incurred with arthroplasty and postoperative care.⁷ Blood transfusion rates after shoulder arthroplasty are reported to be much lower at 8.1%, and transfusion need is highly associated with the complexity of surgery.¹⁸ This raises an important question: Is the cost of TXA justified by the degree of blood loss averted in uncomplicated TSA and RTSA?

The administration of TXA in this study was by topical application for 5 minutes near the end of the procedure. This administration method is cumbersome, adds time to the surgical case, and may discourage some surgeons from using TXA. Many lower extremity arthroplasty surgeons now use intravenous TXA. There is a theoretical risk of DVT or thromboembolic events when intravenous TXA is given because of its antifibrinolytic properties; however, a number of studies have shown no increased risk of these events with intravenous use. A meta-analysis by Sukeik et al examined 11 clinical trials that used intravenous TXA in THA and found no significant difference in DVT, PE, infection rates, or other complications among the study groups.¹⁹ In a meta-analysis of 15 trials studying intravenous TXA use in TKA, Yang et al found no significant difference in prothrombin time, activated partial thromboplastin time, DVT, or PE.²² Whereas intravenous administration of TXA is more convenient, the literature at present offers no consensus regarding superiority of topical vs. intravenous TXA application in joint arthroplasty. In a prospective randomized trial of 89 patients comparing topical and intravenous TXA administration during TKA, no significant difference was detected in the primary outcome of perioperative change in hemoglobin level, and no significant difference in total drain output was noted.¹⁶ Another prospective randomized trial of 417 patients undergoing THA found no significant difference in total blood

loss between patients treated with TXA intravenously and those treated with TXA topically.²¹

This study had some important limitations. The 2-surgeon design of this study produced outcomes that might not be applicable to every surgeon's practice, and in the future a multicenter trial that incorporates a larger number of surgeons may produce a different result. Also, we included only healthy patients undergoing primary TSA and RTSA in this trial. The inclusion of more complicated patients may have revealed a difference in transfusion requirements, although it may have produced some complications as well. Finally, the short-term nature of this study does not provide any information about whether TXA use in TSA and RTSA produces better outcomes or reduces prosthetic joint infection rates. In the future, addressing these limitations may provide more information about how TXA can benefit patients undergoing shoulder arthroplasty.

Conclusion

We have demonstrated that topical application of TXA near the end of TSA and RTSA procedures reduces blood loss and preserves a patient's hemoglobin level. However, we did not demonstrate a reduction in transfusion requirements, as no patient required transfusion in our study. Because the incidence of transfusion after primary TSA and RTSA is relatively low, it appears that the routine use of TXA in uncomplicated, primary TSA and RTSA may not be justified at this time. The use of topical or intravenous TXA may hold greater value for patients undergoing complex revision procedures and for patients in frail health who undergo shoulder arthroplasty for treatment of fracture. Further study of TXA in the setting of more complex shoulder arthroplasty is warranted on the basis of the encouraging results of this trial.

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Disclaimer

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