



# Intravenous tranexamic acid vs. topical thrombin in total shoulder arthroplasty: a comparative study

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**Background:** Blood loss and transfusions have been highlighted as a significant predictor of postoperative morbidity. Tranexamic acid (TXA) has been shown to decrease blood loss and transfusion in shoulder arthroplasty. However, the utility of topical thrombin in total shoulder arthroplasty (TSA) is unknown. The purpose of this study was to assess the utility of topical thrombin in TSA and compare the effectiveness of topical thrombin to intravenous (IV) TXA.

**Methods:** An institutional database was used to query shoulder arthroplasty patients from January 2017 to July 2019. Patients undergoing TSA were identified with CPT (Current Procedural Terminology) code (23742). After excluding reverse shoulder arthroplasty, arthroplasty for fracture or revision, the study groups were stratified based on intervention with IV TXA, topical thrombin, or neither. Patient demographics, American Society of Anesthesiologists (ASA) class, baseline coagulopathy, preoperative and postoperative hemoglobin levels, operative time, transfusion, length of stay, and 90-day readmission for each treatment group was obtained.

**Results:** A total of 283 TSA cases were included for final analysis. There was no statistically significant difference in the baseline characteristics with age, body mass index, or ASA class. The postoperative hemoglobin level (mg/dL) was higher in the group that received either IV TXA or thrombin compared with no hemostatic agents ( $P = .001$ ). Calculated blood loss in TSA was significantly higher in the group without hemostatic agents, 369.8 mL (standard deviation [SD] 59.5), compared with IV TXA or topical thrombin, 344.3 mL (SD 67.1) and 342.9 mL (SD 65.6) ( $P = .03$ ). Operative time was highest in the group that received no hemostatic agents, 2.3 hours (SD 0.6) ( $P = .01$ ). The transfusion rate for TSA treated with IV TXA or topical thrombin was equivalent (2.2%) but significantly lower than the no intervention group (12%) ( $P = .01$ ). The odds ratio for transfusion with IV TXA was 0.16 (95% confidence interval [CI] 0.07–0.40,  $P = .001$ ) and for topical thrombin, 0.1 (95% CI 0.02–0.42,  $P = .02$ ).

**Conclusion:** Topical thrombin is an effective adjunct to reduce blood loss and transfusion risk after TSA and a reasonable intraoperative alternative for TXA for patients with contraindication to IV TXA.

**Level of evidence:** Level III; Retrospective Cohort Comparison; Treatment Study

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**Keywords:** Transfusion; TXA; thrombin; shoulder arthroplasty

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There has been nearly a 60%–70% increase in the prevalence of total shoulder arthroplasty (TSA) in the last decade with expansion of indications, and an increasing elderly population.<sup>14</sup> In order to improve recovery and minimize surgical complications, perioperative

management of patients undergoing arthroplasty must be optimized. One such factor has been blood loss and transfusion, with reported rates between 4.5%-11% in shoulder arthroplasty.<sup>12,21</sup> Blood loss and risk of transfusion has been highlighted as a significant predictor of length of hospital stay, risk of infection, and cardiopulmonary complications, and reduction of blood loss and transfusion requirement may improve functional outcomes.<sup>13,19</sup>

In the last decade, tranexamic acid (TXA) has been extensively studied in the arthroplasty literature to reduce blood loss.<sup>6</sup> TXA is a synthetic antifibrinolytic that displaces plasminogen from fibrin, resulting in inhibition of fibrinolysis and clot breakdown. A review of 252 randomized controlled trials with more than 25,000 patients concluded that analogs such as TXA are effective in reducing blood loss during and after surgery and appear to be free of serious adverse effects.<sup>12</sup> Other modalities such as topical thrombin-based hemostatic agents have been rarely described in shoulder arthroplasty.<sup>7</sup> Studies in hip and knee arthroplasty literature suggest that it may be an effective option to reduce blood loss and not related to adverse reaction, particularly when patients have contraindications for intravenous (IV) TXA or additional hemostatic agents are needed for intraoperative management of blood loss.<sup>26</sup>

The purpose of this study was to first assess the role of topical thrombin in TSA compared with no intervention. To date, no studies have examined the effectiveness of topical thrombin to TXA. The second aim of our study was to compare the effectiveness of blood-conserving agents such as IV TXA and topical thrombin with a control group receiving no hemostatic agent to better delineate the utility of thrombin in shoulder arthroplasty.

## Materials and methods

All patients  $\geq 18$  years of age who underwent primary shoulder arthroplasty (CPT [Current Procedural Terminology] 23472) at the investigating institution between June 2017 and December 2019 were retrospectively identified from an institutional database. All patients included in our cohort received IV TXA, topical thrombin, or neither. Topical thrombin was given during the time of surgery prior to IV TXA availability in shoulder arthroplasty at this institution. Patients who underwent reverse shoulder arthroplasty, revision TSA or shoulder arthroplasty, for fracture were excluded. All patients were treated by fellowship-trained surgeons at a tertiary referral center. Institutional review board approval was obtained before collecting any patient-related information. This is a retrospective comparative study between topical thrombin, IV TXA, and no hemostatic agent for blood loss and transfusion after shoulder arthroplasty.

Preoperative demographics including age, gender, height, weight, and body mass index (BMI) were collected. Medical comorbidities were represented with inclusion of American Society of Anesthesiologists class and presence of coagulopathy.

Preoperative hemoglobin obtained at preoperative anesthesia testing within 30 days of surgery was obtained, in addition to the hemoglobin from a complete blood count drawn on postoperative day 1, as well as the need for transfusion during their hospitalization. Transfusion was indicated if the hemoglobin level was lower than 8.0 g/dL for patients with oncologic or cardiac-related comorbidities or below 7.0 g/dL for all other patients. Additionally, perioperative data were collected to include duration of surgery and length of hospitalization.

After obtaining the final the cohort of TSA, the patients were stratified into intervention groups based on TXA, thrombin, or no hemostatic intervention. Groups were then compared by demographic characteristics, comorbidities, preoperative and postoperative hemoglobin, transfusion requirement, operative time, and length of stay (LOS). Hemoglobin loss ( $Hgb_{loss}$ ) was calculated by the following equation:  $(k1 \times height^3 + k2 \times weight + k3) \times (Hgb_{initial} - Hgb_{end}) \times 0.001 + Hgb_{transfused}$ , where  $k1 = 0.3669$  or  $0.3561$ ,  $k2 = 0.03219$  or  $0.03308$ , and  $k3 = 0.6041$  or  $0.1833$  for males and females, respectively. Total volume loss was calculated by the formula  $1000 \times (Hgb_{loss}/Hgb_{initial})$  as previously described.<sup>9</sup>

Univariate analysis was conducted with analysis of variance for continuous variables and Fischer exact test for categorical variables. A multivariable logistic regression analysis for transfusion was used to determine if TXA or thrombin use was significantly associated with a decrease in transfusion rate, while controlling for age, gender, BMI, American Society of Anesthesiologists class, coagulopathy, and duration of surgery. Controlling for these same variables, a multivariable linear regression analysis was performed for total volume loss. Wizard for Mac (E. Miller, Chicago, IL, USA) was used for statistical analysis and a  $P$  value  $< .05$  indicates statistical significance unless otherwise noted.<sup>22</sup>

## Results

A total of 434 procedures were screened with a final cohort of 283 TSA cases. In total, 135 (47.7%) of patients received IV TXA, 90 (31.8%) received topical thrombin, and 58 (20.5%) remaining patients did not receive any hemostatic agent. Demographic data for TSA groups are summarized in Table 1. A post hoc analysis revealed that the study was adequately powered to detect a difference for transfusion in the TSA group (84.9%).

In the TSA group, there were no statistically significant differences for age, BMI, and American Society of Anesthesiologists class preoperative values (Table 1). This study used an evidence-based formula to calculate hemoglobin loss and total blood volume loss based on height and weight.<sup>9</sup> Postoperative hemoglobin was lower for patients who did not receive either hemostatic agent (10.1 mg/dL) compared with IV TXA (11.3 mg/dL) or topical thrombin (11.5 mg/dL), which was significant ( $P = .001$ ). There was a statistically significantly lower rate of transfusion of 2% for both the IV TXA and thrombin group, compared with the group without any hemostatic agent (12%) ( $P = .01$ ). In the TSA group, the LOS was similar for all groups without

**Table I** Baseline characteristics for TSA following treatment with and without hemostatic agents

Characteristic	Hemostatic agents			P value
	None (n = 58)	IV TXA (n = 135)	Topical thrombin (n = 90)	
Sex, n (%)				.2
Male	26 (44.8)	67 (49.6)	45 (50)	
Female	32 (55.2)	69 (50.4)	45 (50)	
Age°	68.8 (9.1)	65.7 (10.1)	68.2 (8.2)	.2
BMI	31.6 (5.9)	30.4 (6.9)	30.8 (6.2)	.3
ASA class	2.4 (0.6)	2.6 (0.6)	2.5 (0.6)	.1
Coagulopathy, total (%)	1/58 (2)	1/135 (1)	4/90 (4)	.2
Preoperative Hgb (mg/dL)	13.0 (1.8)	13.5 (1.8)	13.7 (1.4)	.05

TSA, total shoulder arthroplasty; BMI, body mass index; ASA, American Society of Anesthesiologists; Hgb, hemoglobin; IV TXA, tranexamic acid. Unless otherwise noted, values are mean (standard deviation).

significant differences: 2.3 days for IV TXA and 2.4 for both thrombin and neither ( $P = .8$ ) (Table II).

Overall, the odds ratio for transfusion with IV TXA was 0.16 (95% confidence interval 0.07-0.40,  $P = .001$ ), and thrombin was 0.1 (95% confidence interval 0.02-0.42,  $P = .02$ ). For total blood volume loss in the TSA cohort, with a multivariable linear regression model to control for age, gender, BMI, presence of coagulopathy, and duration of the operation, IV TXA and topical thrombin use was statistically significant for a reduction in the total blood volume loss (coefficient 5.2,  $P = .02$ , and coefficient 3.2,  $P = .04$ ).

## Discussion

IV TXA has been shown to be an effective agent to reduce blood loss and transfusion in shoulder arthroplasty.<sup>1,8,16,17,24</sup> There are common contraindications to IV TXA such as history of thromboembolic or ischemic events such as pulmonary embolism, deep vein thrombosis, ischemic cerebrovascular accident, and myocardial infarction.<sup>5</sup> For these patients, there has been debate about effective hemostatic agent use including avoiding TXA altogether or use of topical agents such as topical thrombin.<sup>3,6,10,16,17,20,25</sup> Additionally, the use of topical agents such as thrombin may provide surgeons an option for intraoperative hemostasis.<sup>7</sup> Studies in total knee arthroplasty and use of thrombin have supported significant reduction in blood loss without added risk for adverse reaction such as pulmonary embolism, deep vein thrombosis, or complications.<sup>26</sup> However, no studies currently exist to compare topical thrombin to IV TXA in shoulder arthroplasty. In this study, we first aim to assess the role of topical thrombin in shoulder arthroplasty. Second, we aim to compare the effect of topical thrombin to a well-studied intervention (IV TXA) and a control group (no hemostatic agent). As such, topical thrombin may be an effective adjunct modality to improve intraoperative hemostasis in

shoulder arthroplasty and reduce the risk of postoperative transfusion.

Previous studies relating to TXA or thrombin have used direct difference of hemoglobin level or estimated blood loss, both of which have significant inherent bias and error.<sup>11</sup> This study used a validated formula in hip and knee arthroplasty literature to calculate blood volume loss taking into account patient weight, height, and pre- and postoperative hemoglobin levels. In this study, the calculated blood volume loss was consistently higher in the group that did not receive either TXA or thrombin. Postoperative hemoglobin was consistently lower for the group that did not receive any hemostatic agent and was statistically significant. This finding is supported by current studies that evaluate the effect of TXA on blood loss.<sup>6,8,18</sup>

As the most clinically relevant aspect of blood loss, transfusion rates have decreased with increased utilization of IV TXA in current literature.<sup>2,6</sup> This study supports such findings, as a significant reduction was detected in the total blood volume loss and transfusion rates for TSA. Uniquely, this study also found that topical thrombin in TSA patients resulted in significant reduction of transfusion rates, similar to TXA. In lower extremity arthroplasty, Suarez et al<sup>23</sup> found statistically significant reduction in calculated blood loss after TKA in the thrombin-treated group. This study is the first to identify an association between topical thrombin administration in TSA and a significant reduction in transfusion compared to the group without hemostatic agents. As highlighted by Box et al,<sup>3</sup> there is a paucity of literature that compares route of administration of hemostatic agents. This study demonstrates a significant difference in TSA patients for calculated blood loss, and transfusion for both the IV TXA and the topical thrombin groups, compared with no intervention. Topical thrombin also demonstrated a larger reduction in blood loss and higher postoperative hemoglobin compared with IV TXA, which has not been previously identified.

Despite the effectiveness of IV TXA or topical thrombin in the context of minimizing blood loss and subsequent

**Table II** Postoperative outcomes for TSA comparing hemostatic agent use (IV TXA vs. topical thrombin vs. none)

Outcome	Hemostatic agents			P value
	None (n = 58)	IV TXA (n = 135)	Topical thrombin (n = 90)	
Postop Hgb, mg/dL	10.1 (1.8)	11.3 (1.4)	11.5 (1.4)	<.001
Operative time, h	2.3 (0.6)	2.0 (0.6)	2.1 (0.5)	.001
Total blood loss, mL	369.8 (59.5)	344.3 (69.5)	342.9 (65.6)	.03
Transfusion, total (%)	7/58 (12%)	3/135 (3%)	2/90 (2%)	.01
Length of stay, d	2.4 (0.9)	2.3 (1.2)	2.4 (1.6)	.8
Readmission (90 d), total (%)	5/58 (10%)	6/135 (4.2%)	4/90 (4.2%)	.5

TSA, total shoulder arthroplasty; IV, intravenous; TXA, tranexamic acid; Postop Hgb, postoperative hemoglobin level.

Unless otherwise noted, values are mean (standard deviation).

rates of transfusion, the same benefits do not always translate to a decrease in LOS. Kuo et al<sup>17</sup> demonstrate no difference in length of hospitalization after total shoulder replacements regardless of TXA exposure. Anthony et al<sup>2</sup> reviewed claims data of more than 80,000 patients and found a significant decrease in hospital stay, but Budge et al<sup>4</sup> reported no significant change in LOS. This study was consistent with Budge et al in showing no significant reduction in LOS with use of IV TXA or topical thrombin vs. no intervention. Future studies may be directed at studying a different population such as reverse shoulder arthroplasty, which may have a higher reported overall LOS, to detect a difference in hospitalization related to transfusion. For readmission, we found no significant difference in the number of readmissions between either of the intervention groups, which is consistent with other studies that show no increase in readmission rates after TXA or thrombin use.<sup>2,4,8,15,23</sup> This indicates a satisfactory safety profile for these hemostatic agents, as they were not found to be associated with any adverse events such as blood clots leading to increased readmission. As dosage and administration of hemostatic agents are refined moving forward, we may see future studies aimed at identifying the cost-effective dosage to reduce the overall medical expenditure of shoulder arthroplasty.

Although IV TXA has been studied with randomized trials, this is the first study to compare TXA and topical thrombin directly in TSA. The findings from this study may be relevant for surgeons considering additional hemostatic agents for TSA patients who have poorly controlled intraoperative bleeding or that may have contraindication for TXA altogether in TSA. This was suggested by the significantly lower operative time for patients who received either IV TXA or topical thrombin compared with no intervention. However, this study is not without limitations. As a retrospective study, there is an inherent selection bias that may be based on factors such as presentation and medical history or other variables not captured in the study. As transfusion is the most clinically relevant outcome for blood loss, this study was adequately powered to detect a significant difference for it. However, this study was not

powered to detect a difference for other outcomes such as readmission. Future prospective studies can be directed to identify the effective dosage of topical thrombin, topical TXA, and IV TXA in shoulder arthroplasty.

## Conclusion

Both IV TXA and topical thrombin are effective at reducing blood loss and transfusion after TSA. Topical thrombin may be a reasonable adjunct for intraoperative hemostasis or an alternative option for patients with contraindication for TXA in TSA.

## Disclaimer

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