Clinical/Basic Science Research Article

Expanded use of tranexamic acid is safe and decreases transfusion rates in patients with geriatric hip fractures

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Abstract

Objectives: To determine the effect of a standardized tranexamic acid (TXA) protocol on red blood cell transfusions and adverse events in fragility hip fracture patients.

Design: Retrospective cohort study.

Setting: Academic Tertiary Care Center.

Patients/Participants: Series of 209 patients with fragility hip fractures treated operatively from April 1, 2019 to September 30, 2019.

Intervention: Eligible patients received 4 intravenous doses of TXA. Some patients missed doses and only received between 1 and 3 doses of TXA: Ineligible patients received no TXA. Patients with medical conditions precluding the use of TXA were deemed ineligible: allergy to TXA; creatinine clearance <30 mL/min; active malignancy; vascular event in the past year; anticoagulant use; fracture > 48 hours prior to presentation.

Main Outcome Measures: Red blood cell transfusion; major adverse vascular events; minor drug related adverse events.

Results: Patients who received all 4 doses of TXA (n = 70) had a significantly lower transfusion rate compared to those who did not receive any TXA (7.1% vs 28.1%, $P = .003$). There were no significant differences in the number of major or minor adverse events between the 2 groups.

Conclusions: The use of a standardized TXA protocol of 4 doses significantly decreases transfusion rates in eligible patients undergoing operative intervention for fragility hip fracture without an increase in major or minor adverse events. These findings are even more pronounced in patients with decreased preoperative hemoglobin.

Level of Evidence: Prognostic Level III

Keywords: fragility hip fracture, red blood cell transfusion, tranexamic acid

1. Introduction

Allogenic blood transfusion is an established independent predictor of mortality in fragility hip fracture patients.[1] Red blood cell transfusion carries specific risks of transfusion reaction, infection transmission, increased length of hospital stay, and increased cost.[2–9] More recently, studies have demonstrated an association between allogenic transfusion and increased rates of surgical site infections in arthroplasty patients[10] and general surgical patients.[11]

Perioperative tranexamic acid (TXA) administration has been well established as a safe and effective means of reducing blood transfusion requirements in patients undergoing elective hip and knee arthroplasty.[12–16] These findings have been shown to be independent of dose, timing, type of anesthesia, and preoperative hemoglobin levels.[7,12,13] While dosing and route of administration may vary, most arthroplasty TXA administration protocols involve 1 dose at induction, frequently followed by a second dose postoperatively.[6]

Similarly, the role of TXA in trauma patients is now well accepted as a result of the sentinel CRASH-2 study.[17] In this study, trauma patients at 274 hospitals in 40 countries were randomized to IV TXA vs placebo. Patients were treated with TXA 1 g over 10 minutes starting within 8 hours of injury followed by an infusion of 1 g over 8 hours. Significant decreases were found in rates of overall death and death due to bleeding, without any difference in vascular events.

The literature on TXA use in fragility hip fracture patients is emerging now. Most studies use dosing regimens based on the arthroplasty literature, with 1 or 2 doses administered, the first typically prior to incision.[18,19] The clinical practice guideline from the American Association of Hip and Knee Surgeons notes no difference in single versus multiple doses of TXA;[20] however,

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there are likely differences in the clinical population of elective arthroplasty patients versus those who sustain a hip fracture. The first randomized controlled trial of TXA use in patients with hip fractures was published by Zufferey et al[21] in 2010. Here, 110 patients undergoing hip fracture surgery within 48 hours of their injury were randomized to IV TXA 15 mg/kg given at skin incision and again 3 hours later, similar to commonly used arthroplasty dosing regimens. With a primary outcome of transfusion up to 8 days postoperatively, a trend toward decreased transfusions within the TXA cohort was demonstrated. There was also a trend toward increased vascular events at 6 weeks, although neither outcome was statistically significant given the small sample size.

Further studies of TXA use in hip fracture patients, including 2 different meta-analyses, have demonstrated significant decreases in transfusion rates without an increase in vascular events. Baskaran et al[18] performed a metanalysis of 8 studies (6 randomized control trials and 2 cohort studies); Zhang et al[19] reviewed TXA use in 8 randomized controlled trials of patients undergoing hip fracture surgery (5 studies are also represented in Baskaran et al[18]). TXA dosing was either weight-based (10–20 mg/kg) or standardized (1 g) and included preoperative administration and/or a postoperative administration for a total of 1 or 2 doses. In 2 of the studies, patients were treated with an intraoperative weight-based infusion. Only 1 study administered TXA upon admission.[22] Overall, patients receiving TXA had reduced blood loss and reduced need for transfusion without an increase in VTE events as compared with placebo.[18,19] Although early and on ongoing, the published studies on TXA use in hip fracture patients have thus far shown that regardless of dosing regimen, TXA is safe and effective in this population.[18,19,21]

Unlike arthroplasty patients whose bleeding starts at the time of surgical incision, patients with hip fractures have onset of bleeding at the time of the fracture, before surgery. However, only 1 prior study has investigated the administration of TXA upon hospital admission for fragility hip fractures and was limited to 43 patients who underwent intertrochanteric fixation.[22]

The onset of bleeding in hip fracture patients can be likened to the trauma population. We therefore proposed using a hybrid TXA protocol drawing from both the arthroplasty and trauma literature. We hypothesized that a standardized TXA protocol of 4 doses starting at the time of admission and continuing through the operative intervention would significantly decrease transfusion rates in patients undergoing surgery for fragility hip fracture without an increase in the rate of adverse events.

2. Materials and methods

All patients admitted to the fragility hip fracture service from April 1, 2019 to September 30, 2019 were prospectively screened for inclusion in the study. Inclusion criteria included any fragility hip fracture admitted to the Yale New Haven Hospital St. Raphael Campus, the centralized campus of our fragility hip fracture service. Exclusion criteria included: allergy to TXA; creatinine clearance < 30 mL/min; active malignancy; vascular event in the past year (myocardial infarction, coronary stenting, stroke, peripheral vascular stenting, venous thromboembolism); anticoagulant use; and fracture > 48 hours prior to presentation. Eligible patients received a total of 4 intravenous doses of TXA: 1 g over 10 minutes followed by infusion of 1 g over 8 hours upon admission to the inpatient unit, typically within 1 hour; 1 g administered at surgical incision followed by 1 g 3 hours later. Ineligible patients received no TXA. If patients had not yet completed the 8-hour infusion by the time they arrived to the operating room, then the infusion was discontinued. If medically cleared, all patients were taken to the operating room the day after admission.

Exclusion criteria were determined by TXA contraindications in drug information literature.[23] In addition to patients with allergy to TXA and impaired renal function, patients at highest risk of venous or arterial thrombotic disease were excluded. This category includes patients with a history of a vascular event within the last year or active malignancy. Patients on long-term anticoagulation therapy were also considered to be in the high thrombosis risk category. Anticoagulation is prescribed, by definition, to prevent vascular events in a high-risk patient such as a patient with atrial fibrillation or recurrent venous thromboembolic disease. Unless contra-indicated, all patients received prophylactic dosing for venous thromboembolism, including heparin preoperatively, and enoxaparin postoperatively.

Demographic data, hemoglobin values, transfusions given, and timing of transfusion were recorded. Reasons for ineligibility were also tracked. Transfusion threshold was <7 g/dL or as determined by established blood management protocol. Major adverse events, including cerebrovascular event, myocardial infarction, and venous thromboembolic disease, were tracked in-hospital and for 3 months postdischarge. Minor adverse events associated with TXA, such as headache, abdominal pain, nasal symptoms, nausea, vomiting, and diarrhea, were tracked in hospital.

2.1. Statistical analysis

Statistical analysis using Chi-squared, Fisher exact, *t* tests, ANOVA, and multivariate analysis was performed to compare patient factors, TXA administration, and transfusion requirements. A multivariate analysis and intention to treat analysis was performed for analysis of nonrandomized intervention study designs.[24] All statistical analysis was performed using Stata 13.1 (StataCorp, College Station, Texas). Statistical significance was set as $P < .05$, 2-sided.

For outcome analysis, a group of patients who received all 4 doses of TXA (71 in total) were designated as the "All TXA" population and they were compared with those who did not receive any TXA (90 in total). Patients who received at least 1 dose of TXA but did not complete the protocol were analyzed as a separate cohort. A subset of patients who had admission hemoglobin of less than 11.5 g/dL were also analyzed separately in order to control for this important confounding variable.

This study was considered to be a quality improvement project and therefore exempt from Institutional Review Board approval by Yale University and Yale New Haven Hospital guidelines.

3. Results

There were 209 total patients admitted to the hip fracture service from April 1, 2019 to September 30, 2019. Patient demographics are shown in Table 1. In total, 70 patients received all 4 doses of TXA, 50 patients received between 1 and 3 doses of TXA, and 89 patients received no TXA. The most common procedure was an intramedullary nail (46%), followed by a hemiarthroplasty (34%). Sliding hip screw (9%), closed reduction and percutaneous pinning (8%), and total hip arthroplasty (3%) were the other procedures performed.

Table 1

Demographics

	All 4 doses of TXA	1–3 Doses of TXA	No TXA	Overall	*P* value		
Number	**70**	**50**	**89**	**209**	*	†	‡
Average Age (SD)	79.0 (11.5)	80.5 (11.1)	82.3 (12.1)	80.8 (11.7)	.779	.650	.186
Female	46 (66%)	33 (66%)	57 (64%)	136 (65%)	.999	.971	.974
Average BMI (SD)	24.4 (4.1)	23.5 (4.6)	24.6 (4.6)	24.3 (4.5)	.519	.326	.948
Procedure Type					.212	.286	.958
IMN	30 (43%)	23 (46%)	42 (47%)	95 (45%)			
Hemi	30 (43%)	13 (26%)	28 (31%)	71 (34%)			
DHS	4 (6%)	8 (16%)	8 (9%)	20 (10%)			
CRPP	3 (4%)	6 (12%)	7 (8%)	16 (8%)			
THA	3 (4%)	0 (0%)	4 (5%)	7 (3%)			

BMI = body mass index, CRPP = closed reduction percutaneous pinning, DHS = dynamic hip screw, hemi = hemiarthroplasty, IMN = intramedullary nail, THA = total hip arthroplasty, TXA = tranexamic acid.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Of the 209 patients admitted to the hip fracture service, 197 (93%) were appropriately screened for TXA eligibility with a total of 102 (48%) found to be eligible to receive TXA. Reasons for TXA ineligibility are illustrated in Table 2. Patients were most commonly excluded due creatine clearance < 30 mL/min (41 patients) and therapeutic anticoagulant use (32 patients). Of the eligible patients, over 90% received a 1-g admission dose of TXA, followed by a 1-g infusion dose of TXA given over the subsequent 8 hours. Eighty-three percent of eligible patients then received a 1-g incisional dose of TXA. Seventy-five percent of eligible patients received a subsequent 1-g of TXA in the recovery room. Overall, 70 (70%) of eligible patients received all 4 doses of TXA (Table 3).

In total, 25 of 209 (11%) patients were documented to have a minor adverse reaction. There was no difference in minor adverse event frequency between the 3 cohorts. There were a total of 2 documented major adverse events, but no statistically significant difference between the 3 cohorts (Table 4).

Overall, 19.9% of all patients admitted to the hip fracture service received a blood transfusion in the perioperative period. The transfusion rate of patients stratified by TXA administration is shown in Table 5. Patients who received all 4 doses of TXA had a significantly lower transfusion rate that those patients who did not receive any TXA (7.1% vs 28.1%, $P = .003$). Those who received 1 to 3 doses of TXA also had a lower transfusion rate of 22.0% although the p value was not statistically significant at 0.650.

As shown in Table 6, patients who underwent intramedullary nailing required more transfusions than patients who underwent a different procedure (31.6% vs 9.7%, $P < .001$).

Table 2

TXA screening and eligibility

Total number of patients	**209**
TXA Screening	197 (94%)
TXA Protocol	100 (48%)
Reasons patients did not meet TXA protocol	
Renal	41 (38%)
Vascular	13 (12%)
Screening Problems	4 (4%)
Oncology	21 (19%)
Anticoagulation	32 (29%)
> 48 h after injury	4 (3%)
Other	6 (6%)

Note that patients may have been excluded for multiple reasons. Therefore, total reasons patients did not meet TXA protocol exceeds number of patients.
TXA = tranexamic acid.

Table 3

TXA administration in patients who met criteria for TXA protocol

Total number of patients eligible for TXA protocol	**100**
Admission TXA	97 (97%)
Infusion TXA	96 (96%)
Incision TXA	85 (85%)
PACU TXA	78 (78%)
Total number of patients who completed TXA protocol when eligible	70 (70%)

This table shows the number of TXA-eligible patients receiving each one of the doses in the 4-dose protocol. Of eligible patients, 70% received all 4 TXA doses.
TXA = tranexamic acid.

Table 4

Adverse reactions

	All 4 doses of TXA	1–3 Doses of TXA	No TXA	Overall	*P* value		
Number	**70**	**50**	**89**	**209**	*	†	‡
Minor adverse events	11 (16%)	6 (12%)	9 (10%)	26 (12%)	.921	.856	.556
Major adverse event	1 (1.43%)	0 (0%)	1 (1.12%)	2 (0.96%)	.711	.793	.979

This table shows the number patients who reported symptoms that could possibly include an adverse reaction of TXA. There were no differences in both major and minor adverse reactions between the 2 cohorts of patients. Minor adverse events included headache, sinus congestion, hives, nausea, abdominal pain, diarrhea, a new musculoskeletal complaint, or a seizure. Major adverse events included pulmonary embolus, heart attack, or stroke.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Table 5

Transfusion rate in patients with and without TXA administration

	All 4 doses of TXA	1–3 Doses of TXA	No TXA	*P* value		
Number	**70**	**50**	**89**	*	†	‡
Transfusion Rate	7.1%	22.0%	28.1%	0.101	0.650	0.003

This table demonstrates that patients who received all 4 doses of TXA had a lower transfusion rate compared to patients who did not receive any TXA.
TXA = tranexamic acid.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Table 6

Transfusion rate stratified by procedure type

Transfusion	No transfusion	Transfusion rate	*P* value
Procedure Type			< .001
Intramedullary Nail	30 (32%)	65 (68%)	31.6%
No Intramedullary Nail	11 (10%)	103 (90%)	9.7%

This table demonstrates that patients who underwent an intramedullary nail required more transfusions than patients who underwent a different procedure.

A subgroup analysis of all patients who received a transfusion is shown in Table 7. Of patients requiring transfusions, there were no differences in procedure type, or the number of units transfused.

Admission and postoperative hemoglobin are shown in Table 8. Patients who were eligible for all 4 doses of TXA had a higher admission hemoglobin than those who were ineligible for TXA (12.5 vs 11.5, $P < .001$). However, multivariate linear regression demonstrated that only TXA administration and admission hemoglobin were significant in multivariable analysis to predict the need for transfusion, with intention to treat analysis (Table 9). This analysis demonstrates that TXA administration accounts for 70% of the decreased transfusion rate and the baseline difference in hemoglobin contributes to 30% of the effect.

Further subgroup analysis of all patients with admission hemoglobin less than 11.5 g/dL is shown in Table 10. These patients had no significant difference in admission hemoglobin between the 3 cohorts. However, in patients with an admission hemoglobin that was less than 11.5 g/dL, the difference in transfusion rate between the all TXA cohort and the no TXA cohort was even more pronounced (14.3% vs 46.7%, $P = .025$).

4. Discussion

Prior to initiation of this quality improvement project, 1 in 3 fragility hip fracture patients at our institution required an allogenic blood transfusion during their hospital stay despite adherence to a rigid blood management protocol. Further means of reducing blood loss in this patient population were required. Tranexamic acid (TXA) has been well established in the trauma and orthopaedic arthroplasty literature as both safe and effective.[6,25–29] Similarly, initial studies of TXA use in patients with hip fractures have confirmed safety and efficacy; however, there is wide variability in the timing of TXA administration, the dose, and the means of administration in this patient population.[18,19] This study demonstrates a novel 4-dose protocol that reduced transfusion requirements without an increase in vascular events in patients with fragility hip fractures. Our innovative hybrid TXA program drawn from both the trauma and

Table 7

Subgroup analysis of all patients who received a transfusion

	All 4 doses of TXA	1–3 Doses of TXA	No TXA	*P* value		
				*	†	‡
Procedure Type			0.986	.619	.663	
IMN	4 (80%)	10 (91%)	16 (64%)			
Hemi	1 (20%)	0	5 (20%)			
DHS	0	0	3 (12%)			
CRPP	0	1 (9%)	1 (4%)			
THA	0	0	0			
Number of units Transfused		0.953	0.841	.996		
1 unit	2 (40%)	7 (64%)	15 (60%)			
2 units	3 (60%)	3 (27%)	7 (28%)			
>2 units	0	1 (9%)	3 (12%)			

This table demonstrates that of those patients requiring perioperative transfusions, there was no difference in number of units transfused in patients between the 2 cohorts. There was no difference between transfusion rate and procedure type between the 2 cohorts.
CRPP = closed reduction percutaneous pinning, DHS = dynamic hip screw, hemi = hemiarthroplasty, IMN = intramedullary nail, POD = postoperative day, THA = total hip arthroplasty, TXA = tranexamic acid.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Table 8

Outcomes of hip fracture patients by TXA cohort

Characteristics	All 4 doses of TXA	1–3 Doses of TXA	No TXA	*P* value		
Total N	**70**	**50**	**89**	*	†	‡
Baseline Labs						
Admission Hemoglobin (SD)	12.5 (1.61)	12.0 (1.67)	11.5 (1.66)	.217	.184	<.001
Admission Hematocrit % (SD)	38.3 (4.55)	36.9 (4.75)	35.6 (5.02)	.281	.233	.001
Outcomes						
Transfusion %	7.1%	22.0%	28.1%	.101	.650	.003
Estimated Blood Loss (SD)	137 (82)	138 (125)	168 (121)	1.000	.276	.201
POD1 Hemoglobin (SD)	10.2 (1.90)	9.9 (1.95)	9.2 (1.58)	.460	.073	.001
Change in POD1 Hemoglobin (SD)	2.29 (1.22)	2.37 (2.00)	2.39 (1.38)	.866	.619	.896
POD2 Hemoglobin (SD)	9.8 (1.71)	9.4 (1.88)	8.6 (1.38)	.405	.017	<.001
Change POD2 Hemoglobin (SD)	2.76 (1.39)	2.54 (1.53)	2.95 (1.42)	.714	.255	.666

This table demonstrates outcome characteristics of hip fracture patients by TXA cohort. The 4 dose TXA cohort had a higher average admission hemoglobin and hematocrit, higher postoperative day 1 and day 2 hemoglobin values, and a shorter hospital length of stay, compared to the cohort that did not receive TXA. There were no differences between the 1 and 3 dose TXA cohort and the other cohorts.
POD = postoperative day.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Table 9

Multivariable linear regression of variables that predict need for transfusion

	Coefficient	Std Error	*P* value
TXA protocol	**−0.235**	0.110	**.034**
> 48 h after injury	−0.034	0.112	.763
Admission Hgb	**−0.112**	0.015	**.001**
Anticoagulation	−0.167	0.191	.383
Malignancy	−0.093	0.120	.436
Renal	−0.038	0.114	.740
Vascular	0.097	0.140	.491

This table shows a multivariable linear regression analysis with an intention to treat analysis that predicts need for transfusion. Only TXA administration and admission hemoglobin were significant factors to predict need for transfusion, accounting for 70% and 30% of the effect respectively.
Bold means $P < 0.05$, highlighting statistical significance.

arthroplasty literature resulted in a significant reduction in transfusion rate (7.1%) in those patients who receive a standardized 4-dose TXA protocol compared to those who received 1 to 3 TXA doses (22.0%) or those who did not receive any TXA (28.1%).

Prior studies comparing TXA administration and transfusion rates in fragility hip fractures had a range of transfusion rates, but none exceeding the efficacy of our protocol of 4 doses. Transfusion rates of fragility hip fractures in the literature with and without TXA range from 5% to 85% in the TXA cohort and 18% to 82% in the control group.[21,30–37] Our decrease in transfusion rates with TXA exceeded all of these studies except one. Lee et al[37] followed 271 consecutive patients who underwent hip hemiarthroplasty for fracture where 31% received 1 g of TXA at induction, without any inclusion or exclusion criteria. In those patients who received TXA, only 6% received a transfusion, compared to 18% of those who did not receive TXA.

In this study, we demonstrate that a hybrid protocol of admission and perioperative TXA dosing is safe and effective in decreasing rates of red blood cell transfusions. Overall, our control cohort (no TXA) had an admission hemoglobin nearly 1 g/dL less than the TXA group, demonstrating increased risk for possible transfusion. However, intention to treat analysis demonstrated that TXA administration accounts for 70% of the decreased transfusion rate and the baseline difference in hemoglobin contributes to 30% of the effect.

Table 10

Transfusion rate in patients with and without TXA administration in patients with admission Hgb < 11.5

	All 4 doses of TXA	1–3 Doses of TXA	No TXA	*P* value		
Number	**21**	**20**	**45**	*	†	‡
Average Admission Hgb	10.74	10.72	10.69	.610	.610	.106
Transfusion Rate	14.3%	40%	46.7%	.237	.723	.025

It demonstrates a subgroup analysis of transfusion rates with and without TXA administration in patients with an admission hemoglobin less than 11.5 g/dL. The difference in transfusion rate was even more pronounced in these patients as compared to the larger cohort.
TXA = tranexamic acid.
* Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received between 1 and 3 doses of TXA.
† Denotes the *P* value derived from a comparison between the group who received between 1 and 3 doses of TXA and the group who received no TXA.
‡ Denotes the *P* value derived from a comparison between the group who received all 4 doses of TXA and the group who received no TXA.

Our study is not without limitations. With the strict exclusion criteria we used, we preselected healthier patients into our TXA cohort. However, multivariate analysis did not demonstrate that renal, vascular, or oncologic disease contributed to transfusion rate. Patients on therapeutic anticoagulation at admission were considered high risk for vascular events and excluded from the TXA protocol. These patients would be expected to have higher rates of blood loss and transfusions; however, multivariate analysis again showed that preoperative anticoagulant was not an independent contributor to transfusion rate. The subtype of hip fracture likely also influences the rate of transfusion and other outcomes, but was not analyzed in this study due to insufficient numbers. We were able to demonstrate that patients undergoing IMN required higher rates of transfusion, but did not have the power to further analyze the differences between other types of procedures. Further analysis will need to clarify how the subtype of hip fracture should influence TXA administration protocols. Finally, while we do have 3-month follow-up data, it is possible that our patients presented to other institutions with vascular complications that are not captured in our data analysis. However, because we are a tertiary care center with a large catchment area and a shared medical record with our partner hospitals within the YNHH system, losses to follow up are minimized.

To address the selection bias associated with the TXA protocol eligibility criteria, we performed a matched analysis of patients who presented with an admission hemoglobin less than 11.5 g/dL. This group of patients had no significant difference in admission hemoglobin but a pronounced difference in transfusion rate, which we believe supports the conclusions drawn from the overall population. Multivariable analysis also shows that both TXA protocol and admission hemoglobin were significant predictors for needing transfusion, though the study is underpowered to exclude the possibility of contributions from other factors such as use of anticoagulation, which may have resulted in a type II statistical error during analysis. Further analysis in a truly randomized fashion is needed to validate these observations.

In conclusion, we demonstrate that use of a standardized 4 dose TXA protocol significantly decreases transfusion rates in patients undergoing operative intervention for fragility hip fracture without an increase in the rate of adverse events. This study advances our understanding of the safety and efficacy of TXA in fragility hip fracture patients. Future studies examining the optimal dosing of TXA should be explored.

References

1. Lemaire R. Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg Br. 2008;90:1128–1136.
2. Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg. 1997;84:839–844.
3. Tobias JD. Strategies for minimizing blood loss in orthopedic surgery. Semin Hematol. 2004;41 (1 suppl 1):145–156.
4. Bursi F, Barbieri A, Politi L, et al. Perioperative red blood cell transfusion and outcome in stable patients after elective major vascular surgery. Eur J Vasc Endovasc Surg. 2009;37:311–318.
5. Gao F, Sun W, Guo W, et al. Topical application of tranexamic acid plus diluted epinephrine reduces postoperative hidden blood loss in total hip arthroplasty. J Arthroplasty. 2015;30:2196–2200.
6. Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. Transfus Med. 2015;25:151–162.
7. Jennings JD, Solarz MK, Haydel C. Application of tranexamic acid in trauma and orthopedic surgery. Orthop Clin North Am. 2016;47:137–143.
8. Hill GE, Frawley WH, Griffith KE, et al. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma. 2003;54:908–914.
9. Edna TH, Bjerkeset T. Association between blood transfusion and infection in injured patients. J Trauma. 1992;33:659–661.
10. Kim JL, Park JH, Han SB, et al. Allogeneic blood transfusion is a significant risk factor for surgical-site infection following total hip and knee arthroplasty: a meta-analysis. J Arthroplasty. 2017;32:320–325.
11. Tang R, Chen HH, Wang YL, et al. Risk factors for surgical site infection after elective resection of the colon and rectum: a single-center prospective study of 2,809 consecutive patients. Ann Surg. 2001;234:181–189.
12. Whiting DR, Duncan CM, Sierra RJ, et al. Tranexamic acid benefits total joint arthroplasty patients regardless of preoperative hemoglobin value. J Arthroplasty. 2015;30:2098–2101.
13. Sukeik M, Alshryda S, Haddad FS, et al. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br. 2011;93:39–46.
14. Benoni G, Lethagen S, Fredin H. The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. Thromb Res. 1997;85:195–206.
15. Benoni G, Carlsson A, Petersson C, et al. Does tranexamic acid reduce blood loss in knee arthroplasty? Am J Knee Surg. 1995;8:88–92.
16. Hiippala S, Strid L, Wennerstrand M, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth. 1995;74:534–537.
17. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17:1–79.
18. Baskaran D, Rahman S, Salmasi Y, et al. Effect of tranexamic acid use on blood loss and thromboembolic risk in hip fracture surgery: systematic review and meta-analysis. Hip Int. 2018;28:3–10.
19. Zhang P, He J, Fang Y, et al. Efficacy and safety of intravenous tranexamic acid administration in patients undergoing hip fracture surgery for hemostasis: a meta-analysis. Medicine (Baltimore). 2017;96:e6940.
20. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic acid in total joint arthroplasty: the endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. Reg Anesth Pain Med. 2019;44:7–11.
21. Zufferey PJ, Miquet M, Quenet S, et al. Tranexamic acid in hip fracture surgery: a randomized controlled trial. Br J Anaesth. 2010;104:23–30.
22. Zhu YSJC, Li J. Effect of tranexamic acid on perioperative hidden blood loss in aged patients receiving intramedullary fixation for treatment of intertrochanteric fractures. J Trad Chin Orthop Trauma. 2015;27:16–18.
23. Tranexamic Acid. In: MicroMedEx (Database). From Greenwood Village (CO): Truven Health Analytics. 2020 [cited 2020 January 10], Available at: www.micromedexsolutions.com. Accessed February 1, 2020.
24. Axelrod D, Hayward R. Penson D, Wei J. Nonrandomized Interventional Study Designs (Quasi-Experimental Designs). Clinical Research Methods for Surgeons. Totowa, NJ: Humana Press; 2007;63–76.
25. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ. 2014;349:g4829.
26. Oremus K. Tranexamic acid for the reduction of blood loss in total knee arthroplasty. Ann Transl Med. 2015;3 (suppl 1):S40.
27. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am. 2012;94:1153–1159.
28. Tan J, Chen H, Liu Q, et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res. 2013;184:880–887.
29. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) Study. Arch Surg. 2012;147:113–119.
30. Sadeghi MM-AA. Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A

prospective randomized double blind study in 67 patients. Acta Medica Iranica. 2007;45:437–442.
31. Lei J, Zhang B, Cong Y, et al. Clinical research of tranexamic acid on the hidden blood Ioss after the treatment of intertrochanteric fractures with proximal femoral nail anti-rotation (PFNA). Med Res Educ. 2013; 30:51–54.
32. Emara WM, Moez KK, Elkhouly AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesth Essays Res. 2014; 8:48–53.
33. Tian S, Shen Z, Liu Y, et al. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. Injury. 2018;49:680–684.
34. Mohib Y, Rashid RH, Ali M, et al. Does tranexamic acid reduce blood transfusion following surgery for inter-trochanteric fracture? A randomized control trial. J Pak Med Assoc. 2015;65 (11 suppl 3): S17–20.
35. Tengberg PT, Foss NB, Palm H, et al. Tranexamic acid reduces blood loss in patients with extracapsular fractures of the hip: results of a randomised controlled trial. Bone Joint J. 2016;98-B:747–753.
36. Vijay BS, Bedi V, Mitra S, et al. Role of tranexamic acid in reducing postoperative blood loss and transfusion requirement in patients undergoing hip and femoral surgeries. Saudi J Anaesth. 2013;7:29–32.
37. Lee C, Freeman R, Edmondson M, et al. The efficacy of tranexamic acid in hip hemiarthroplasty surgery: an observational cohort study. Injury. 2015;46:1978–1982.