A commentary by Richard Joel Friedman, MD, FRCSC, is linked to the online version of this article at jbjs.org.

The Michigan Experience with Safety and Effectiveness of Tranexamic Acid Use in Hip and Knee Arthroplasty

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Background: The efficacy of tranexamic acid (TXA) in reducing blood loss and transfusion requirements in total hip and knee arthroplasty has been well established in small controlled clinical trials and meta-analyses. The purpose of the current study was to determine the risks and benefits of TXA use in routine orthopaedic surgical practice on the basis of data from a large, statewide arthroplasty registry.

Methods: From April 18, 2013, to September 30, 2014, there were 23,236 primary total knee arthroplasty cases and 11,489 primary total hip arthroplasty cases completed and registered in the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI). We evaluated the association between TXA use and hemoglobin drop, transfusion, length of stay (LOS), venous thromboembolism (VTE), readmission, and cardiovascular events by fitting mixed-effects generalized linear and mixed-effects Cox models. We used inverse probability of treatment weighting to enhance causal inference.

Results: For total hip arthroplasty, TXA use was associated with a smaller drop in hemoglobin (mean difference = −0.65 g/dL; 95% confidence interval [CI] = −0.60 to −0.71 g/dL), decreased odds of blood transfusion (odds ratio [OR] = 0.72; 95% CI = 0.60 to 0.86), and decreased readmissions (OR = 0.77; 95% CI = 0.64 to 0.93) compared with no TXA use. There was no effect on VTE (hazard ratio [HR] = 0.91; 95% CI = 0.62 to 1.33), LOS (incident rate ratio [IRR] = 1.00; 95% CI = 0.97 to 1.03), or cardiovascular events (OR = 0.85; 95% CI = 0.47 to 1.52). For total knee arthroplasty, TXA was associated with a smaller drop in hemoglobin (mean difference = −0.68 g/dL; 95% CI = −0.64 to −0.71 g/dL) and one-fourth the odds of blood transfusion (OR = 0.26; 95% CI = 0.21 to 0.31). There was an association with decreased risk of VTE within 90 days after surgery (HR = 0.56; 95% CI = 0.42 to 0.73), slightly decreased LOS (IRR = 0.93; 95% CI = 0.92 to 0.95), and no association with readmissions (OR = 0.90; 95% CI = 0.79 to 1.04) or cardiovascular events (OR = 1.12; 95% CI = 0.74 to 1.71).

Conclusions: In routine orthopaedic surgery practice, TXA use was associated with decreased blood loss and transfusion risk for both total knee and total hip arthroplasty, without evidence of increased risk of complications. TXA use was also associated with reduced risk of readmission among total hip arthroplasty patients and reduced risk of VTE among total knee arthroplasty patients, and did not have an adverse effect on cardiovascular complications in either group.

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

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Blood transfusion can be accompanied by rare, life-threatening complications, including acute and delayed hemolytic reactions, acute lung injury, and disease transmission[1]. Several observational studies have raised concerns over the association of blood transfusion with poorer outcomes after surgery, including longer length of stay (LOS),

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higher hospital costs, and increased infections and mortality[2-10]. In a meta-analysis of randomized trials comparing liberal and conservative transfusion strategies, the conservative strategy (fewer transfusions) was associated with a decreased risk of serious infections (risk ratio [RR] = 0.83; 95% confidence interval [CI] = 0.69 to 0.99), including within the subgroup of patients undergoing orthopaedic surgery (RR = 0.72; 95% CI = 0.53 to 0.97)[11]. Blood transfusion is also expensive. Estimates for the cost of obtaining, storing, testing, and administering 1 unit of blood range from $700 to $1,130 (U.S.)[12,13]. Despite clinical trials showing the safety and effectiveness of restrictive transfusion practices, a reduction of unnecessary transfusions in elective joint arthroplasty has not yet been demonstrated. An analysis of data from the Nationwide Inpatient Sample showed an increase in the percentage of patients receiving allogeneic blood transfusions from 2000 to 2009 (total hip arthroplasty: 11% to 19%, $p < 0.001$; and total knee arthroplasty: 8% to 12%, $p < 0.001$)[14].

Tranexamic acid (TXA) is an antithrombolytic agent that inhibits the activation of plasminogen to plasmin. Recent meta-analyses of high-quality randomized controlled trials and several reviews of large cohorts have shown that TXA is effective in reducing blood loss and transfusion rates in total hip arthroplasty and total knee arthroplasty, with no evidence of increased risk of thrombogenic events[15-25]. However, a few reports have raised concerns about the risk of vascular complications, including venous thromboembolism (VTE), myocardial infarction, and stroke[26-28]. Because these complications are relatively rare in modern elective total joint replacement, they are difficult to study in clinical trials that may not be adequately powered to detect small but clinically important increased risk. In addition, the results of clinical trials and meta-analyses may not be completely generalizable to routine clinical practice.

We sought to determine the real-world effectiveness and safety of TXA across a broad spectrum of hospitals and providers through the use of a common total joint registry. To assess effectiveness, we asked whether the use of TXA is associated with a smaller drop in hemoglobin and a lower risk of transfusion of at least 1 unit of blood compared with cases in which TXA was not used. To evaluate safety, we compared the risk of VTE and readmission within 90 days of surgery; myocardial infarction, stroke, or transient ischemic attack within 7 days of surgery; and hospital LOS between patients receiving TXA and those not receiving it.

Materials and Methods

Study Design and Data Source

This was a retrospective cohort study of cases enrolled in the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI), a statewide collaborative begun in 2011 to improve the quality of care for patients undergoing elective hip and knee arthroplasty. By the date of this study, MARCQI had 43 participating hospitals and 296 surgeons. At each participating institution, clinical, administrative, and medical-device data are collected on 100% of total hip and total knee arthroplasty cases. A probability sample of the data is audited annually. Additional administrative data are captured by linking MARCQI cases to a statewide database of hospital admissions, the Michigan Inpatient Database (MIDB). Further details regarding the collaborative data collection and management were previously reported[29].

We studied all registry cases of primary elective total hip and knee arthroplasty performed from April 18, 2013, when TXA use was added as a data element, to September 30, 2014. We also required that registry cases be matched to the MIDB so that subsequent hospitalizations could be identified. We excluded cases from 4 hospitals in which no TXA was used and cases for which no information regarding TXA use was recorded (Fig. 1).

Statistical Methods

Study Variables

The treatment variable of interest was perioperative use of TXA, including topical or intravenous routes. The outcome variables of interest were the drop in hemoglobin (measured as the difference between the preoperative hemoglobin level and the postoperative hemoglobin nadir), transfusion, LOS, readmission and VTE within 90 days of surgery, and the composite cardiovascular outcome of myocardial infarction, stroke, or transient ischemic attack within 7 days of surgery. The identification of at least 1 cardiovascular-complication diagnosis from the index encounter or a present-on-admission diagnosis from the matched readmission encounter was used to create the composite cardiovascular disease outcome using primary and secondary International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes from the MIDB. All other outcomes were routinely collected by MARCQI.

We controlled for numerous patient, surgical, and hospital-level variables that might have confounded the relationship between TXA and the outcomes of interest. Chart abstraction was used to obtain patient age, sex, race, and body mass index (BMI); preoperative values of hemoglobin, platelets, and creatinine; smoking history; preoperative treatment with antiplatelet agents and anticoagulants; American Society of Anesthesiologists (ASA) status; marital status; type of insurance; surgical approach; anesthesia type (general or other); bilateral cases; and type of VTE prophylaxis (aspirin or other chemoprophylaxis). VTE chemoprophylaxis was defined as treatment with an anticoagulant such as a low-molecular-weight heparin, vitamin K antagonist, factor Xa inhibitor, or direct thrombin inhibitor. Aspirin therapy was recorded separately (Tables I and II). Elixhauser comorbidity diagnoses[30] were obtained from the MIDB registry. We also controlled for the hospital's frequency of screening for VTE, calculated as the total number of venous ultrasound examinations

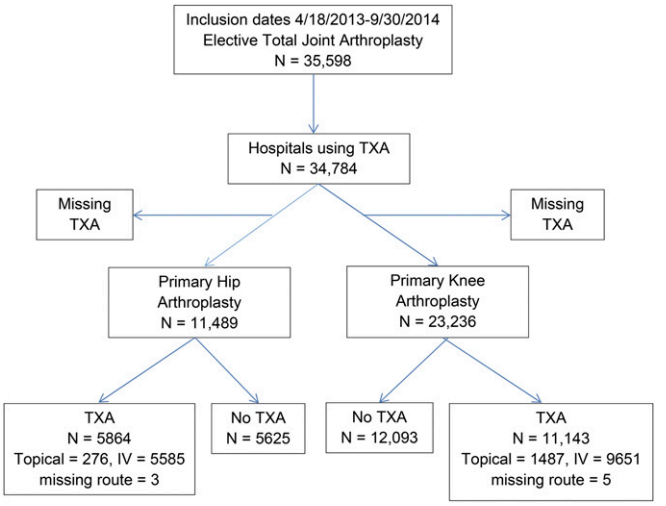

Fig. 1

Summary of registry cases of primary elective hip and knee arthroplasty that were available for study. IV = intravenous.

TABLE I Hip Arthroplasty: Variables by TXA Administration*

Variable	TXA, N = 5,864		No TXA, N = 5,625	
	N	Value	N	Value
Age *(yr)*	5,864	65.0 (11.2)	5,625	65.7 (11.2)
BMI *(kg/m^2)*	5,849	30.2 (6.1)	5,610	30.8 (6.5)
Preop. hemoglobin *(g/dL)*	5,791	13.7 (1.4)	5,512	13.6 (1.4)
Preop. platelets *(× 10^9/L)*	5,784	248.3 (66.5)	5,486	245.9 (65.4)
Preop. creatinine *(mg/dL)*	5,530	0.9 (0.4)	5,067	0.9 (0.5)
Comorbidity				
Congestive heart failure	5,864	143 (2.4)	5,625	190 (3.4)
Valvular disease	5,864	203 (3.5)	5,625	229 (4.1)
Pulmonary circulation disease	5,864	33 (0.6)	5,625	61 (1.1)
Peripheral vascular disease	5,864	154 (2.6)	5,625	170 (3.0)
Paralysis	5,864	13 (0.2)	5,625	14 (0.3)
Other neurologic disorder	5,864	209 (3.6)	5,625	223 (4.0)
Chronic pulmonary disease	5,864	777 (13.3)	5,625	871 (15.5)
Diabetes without chronic complications	5,864	764 (13.0)	5,625	837 (14.9)
Diabetes with chronic complications	5,864	70 (1.2)	5,625	86 (1.5)
Hypothyroidism	5,864	913 (15.6)	5,625	914 (16.3)
Renal failure	5,864	303 (5.2)	5,625	317 (5.6)
Liver disease	5,864	56 (1.0)	5,625	52 (0.9)
Peptic ulcer disease	5,864	0 (0.0)	5,625	1 (0.0)
Acquired immune deficiency syndrome	5,864	1 (0.0)	5,625	2 (0.0)
Lymphoma	5,864	17 (0.3)	5,625	18 (0.3)
Metastatic cancer	5,864	7 (0.1)	5,625	6 (0.1)
Solid tumor with or without metastasis	5,864	20 (0.3)	5,625	29 (0.5)
History of VTE	5,852	245 (4.2)	5,615	479 (8.5)
History of bleeding disorder	5,859	59 (1.0)	5,618	65 (1.2)
On antiplatelet agent before admission	5,864	2,205 (37.6)	5,625	2,264 (40.3)
On anticoagulant before admission	5,864	268 (4.6)	5,625	405 (7.2)
Male sex	5,863	2,581 (44.0)	5,615	2,517 (44.8)
ASA status	5,860		5,623	
I		174 (3.0)		145 (2.6)
II		3,425 (58.5)		2,977 (52.9)
III		2,194 (37.4)		2,403 (42.7)
IV		67 (1.1)		98 (1.7)
Smoking status	5,847		5,505	
Never		2,950 (50.5)		2,524 (45.9)
Former		2,199 (37.6)		2,256 (41.0)
Current		698 (11.9)		725 (13.2)
African-American	5,599	422 (7.5)	5,426	441 (8.1)
Married or partnered	5,863	3,905 (66.6)	5,614	3,555 (63.3)
Insurance	5,860		5,621	
Commercial		2,218 (37.9)		2,062 (36.7)
Medicare and other federal		3,053 (52.1)		3,127 (55.6)
Medicaid and other state/local		165 (2.8)		145 (2.6)
Self-pay		424 (7.2)		287 (5.1)
General anesthesia	5,864	2,520 (43.0)	5,625	2,559 (45.5)

continued

TABLE I (*continued*)

Variable	TXA, N = 5,864		No TXA, N = 5,625	
	N	Value	N	Value
Surgical approach	5,827		5,599	
Anterior		1,426 (24.5)		565 (10.1)
Anterolateral		1,213 (20.8)		1,917 (34.2)
Posterior		3,129 (53.7)		3,085 (55.1)
Transtrochanteric		59 (1.0)		32 (0.6)
VTE prophylaxis	5,864		5,625	
Aspirin only		1,316 (22.4)		1,108 (19.7)
Anticoagulant only		2,187 (37.3)		2,584 (45.9)
Both		2,341 (39.9)		1,908 (33.9)
Neither		20 (0.3)		25 (0.4)
Time period	5,864		5,625	
Apr. 18, 2013-Oct. 17, 2013		1,043 (17.8)		1,959 (34.8)
Oct. 18, 2013-Apr. 17, 2014		2,146 (36.6)		2,092 (37.2)
Apr. 18, 2014-Sept. 30, 2014		2,675 (45.6)		1,574 (28.0)

*The values for age, BMI, and preoperative hemoglobin, platelets, and creatinine are given as the mean and the standard deviation. All other values are given as the number of patients, with the percentage of the group in parentheses.

performed postoperatively divided by the number of cases performed at the hospital[31].

Inverse Probability of Treatment Weighting (IPTW) Analysis

There is the potential for serious bias by indication in observational studies of therapeutic interventions. In our case, the relationship between the motivation for TXA use and subsequent bleeding-related outcomes might have confounded any relationship between the actual effect of the drug and the outcomes of interest. In order to minimize the effect of differences between patients who did and did not receive TXA and to enhance causal inference, we created a series of IPT weights. IPTW has been shown to effectively balance identifiable risk factors between treatment groups[32]. The IPT weight was the inverse of the propensity score for patients receiving TXA, and the inverse of 1 minus the propensity score for patients not receiving TXA. The propensity score was the probability of receiving TXA treatment based on patient and hospital-related variables. Stabilized weights were used[33]. The adequacy of this approach for addressing confounding was checked by comparing standardized differences between patients receiving versus not receiving TXA in the weighted and unweighted samples[34].

Because of the hierarchical nature of the data, we addressed hospital-level clustering (covariance) in the propensity score model and surgeon-level clustering in the outcome model[35]. The propensity model predicting TXA use was fitted with a mixed-effects logistic regression model with a random effect for hospital. A different propensity model was fitted to derive weights for the VTE outcome analysis, because this analysis excluded patients using anticoagulants before admission. Also, a hospital-level variable reflecting the frequency of VTE screening was added.

All outcome models were mixed-effects models with a random effect for surgeon, weighted using IPTW, and included the following surgical-level variables as covariates: general anesthesia, surgical approach, bilateral surgery, and type of VTE prophylaxis used. A linear model was fitted for the drop in hemoglobin. Logistic models were used for transfusion, readmission, and cardiovascular events. A negative binomial model was fitted for LOS. For VTE, a Cox proportional hazard model, with treatment with aspirin and/or anticoagulant agent included as a time-dependent covariate, was used. In the transfusion analysis, we included a covariate for the calendar time period (6-month intervals) in which the surgery was performed to account for quality-improvement initiatives during the study period that might have affected transfusion practices. The effect estimate in the LOS analysis was expressed as an incident rate ratio (IRR), comparing LOS in the TXA group with LOS in the no-TXA group. SAS software (version 9.4; SAS Institute) was used for all data analyses.

Power Analysis

A power analysis was performed using PASS 13 software (NCSS). TXA was used in approximately 51% of the hip cases and 48% of the knee cases. Cardiovascular events within 7 days of surgery occurred in approximately 0.8% of the hip cases and 0.6% of the knee cases in which TXA was not administered. With 11,489 hip cases and 23,236 knee cases, and an r^2 of approximately 0.03 for the association of the other surgical-level variables and the use of TXA, this study had 80% power to show a significant adverse cardiovascular effect of TXA if the true odds ratios (ORs) were at least 1.69 and 1.55 for total hip arthroplasty and total knee arthroplasty, respectively. Using the same logic, and given that the incidence of VTE within 90 days among patients not given TXA in this registry is approximately 0.8% in hip arthroplasty and 1.8% in knee arthroplasty, this study would have a power of 80% to show a significant adverse VTE effect if the true ORs were at least 1.58 and 1.30, respectively.

Results

The frequencies of baseline patient and surgical-level variables for hip and knee arthroplasty are shown in Tables I and II, respectively. Standardized differences before and after sample weighting with IPTW are shown in Table III. The closer the standardized differences are to 0, the less impact the risk factors have on the outcomes, making the calculated TXA effect less confounded. It has been suggested that a difference of <0.1 provides acceptable risk adjustment between groups[36]. Similarly, good risk adjustment or balance was achieved for the VTE data set.

TABLE II Knee Arthroplasty: Variables by TXA Administration*

Variable	TXA, N = 11,143		No TXA, N = 12,093	
	N	Value	N	Value
Age *(yr)*	11,143	66.0 (9.6)	12,093	66.1 (9.9)
BMI *(kg/m²)*	11,091	33.1 (7.0)	12,047	33.3 (7.1)
Preop. hemoglobin *(g/dL)*	10,976	13.6 (1.4)	11,848	13.6 (1.4)
Preop. platelets *(× 10^9/L)*	10,714	245.5 (66.0)	11,802	243.4 (65.0)
Preop. creatinine *(mg/dL)*	10,401	0.9 (0.3)	10,714	0.9 (0.4)
Comorbidity				
Congestive heart failure	11,143	233 (2.1)	12,092	402 (3.3)
Valvular disease	11,143	411 (3.7)	12,092	435 (3.6)
Pulmonary circulation disease	11,143	79 (0.7)	12,092	141 (1.2)
Peripheral vascular disease	11,143	227 (2.0)	12,092	347 (2.9)
Paralysis	11,143	18 (0.2)	12,092	29 (0.2)
Other neurologic disorder	11,143	518 (4.7)	12,092	563 (4.7)
Chronic pulmonary disease	11,143	1,660 (14.9)	12,092	2,101 (17.4)
Diabetes without chronic complications	11,143	2,217 (19.9)	12,092	2,470 (20.4)
Diabetes with chronic complications	11,143	201 (1.8)	12,092	221 (1.8)
Hypothyroidism	11,143	2,140 (19.2)	12,092	2,281 (18.9)
Renal failure	11,143	560 (5.0)	12,092	674 (5.6)
Liver disease	11,143	115 (1.0)	12,092	112 (0.9)
Peptic ulcer disease	11,143	5 (0.0)	12,092	6 (0.1)
Acquired immune deficiency syndrome	11,143	3 (0.0)	12,092	1 (0.0)
Lymphoma	11,143	27 (0.2)	12,092	39 (0.3)
Metastatic cancer	11,143	4 (0.0)	12,092	4 (0.0)
Solid tumor with or without metastasis	11,143	40 (0.4)	12,092	48 (0.4)
History of VTE	11,130	591 (5.3)	12,075	1,110 (9.2)
History of bleeding disorder	11,133	110 (1.0)	12,082	172 (1.4)
On antiplatelet agent before admission	11,143	4,742 (42.6)	12,093	5,227 (43.2)
On anticoagulants before admission	11,143	541 (4.9)	12,093	899 (7.4)
Male sex	11,143	4,065 (36.5)	12,063	4,554 (37.8)
ASA status	11,126		12,083	
I		179 (1.6)		191 (1.6)
II		6,086 (54.7)		6,018 (49.8)
III		4,760 (42.8)		5,684 (47.0)
IV		101 (0.9)		190 (1.6)
Smoking status	11,057		11,783	
Never		5,870 (53.1)		5,817 (49.4)
Former		4,276 (38.7)		4,790 (40.7)
Current		911 (8.2)		1,176 (10.0)
African-American	10,763	1,024 (9.5)	11,698	1,086 (9.3)
Married or partnered	11,138	7,599 (68.2)	12,062	8,069 (66.9)
Insurance	11,138		12,085	
Commercial		3,690 (33.1)		4,387 (36.3)
Medicare and other federal		6,199 (55.7)		6,840 (56.6)
Medicaid and other state/local		323 (2.9)		251 (2.1)
Self-pay		926 (8.3)		607 (5.0)
General anesthesia	11,143	3,089 (27.7)	12,093	4,502 (37.2)

continued

TABLE II (*continued*)

Variable	TXA, N = 11,143		No TXA, N = 12,093	
	N	Value	N	Value
Surgical approach	11,066		12,026	
Medial parapatellar		9,074 (82.0)		9,757 (81.1)
Lateral parapatellar		33 (0.2)		37 (0.3)
Midvastus		1,748 (15.8)		1,704 (14.2)
Subvastus		174 (1.6)		509 (4.2)
Other		37 (0.3)		19 (0.2)
VTE prophylaxis	11,143		12,093	
Aspirin only		2,283 (20.5)		2,299 (19.0)
Anticoagulant only		4,392 (39.4)		5,600 (46.3)
Both		4,430 (39.8)		4,140 (34.2)
Neither		38 (0.3)		54 (0.5)
Time period	11,143		12,093	
Apr. 18, 2013-Oct. 17, 2013		1,854 (16.6)		4,548 (37.6)
Oct. 18, 2013-Apr. 17, 2014		4,197 (37.7)		4,383 (36.2)
Apr. 18, 2014-Sept. 30, 2014		5,092 (45.7)		3,162 (26.2)

*The values for age, BMI, and preoperative hemoglobin, platelets, and creatinine are given as the mean and the standard deviation. All other values are given as the number of patients, with the percentage of the group in parentheses.

The results of the adjusted outcome analyses are summarized in Figure 2. In primary elective hip arthroplasty, the use of TXA was associated with a smaller drop in hemoglobin (mean difference = −0.65 g/dL; 95% CI = −0.60 to −0.71 g/dL; $p < 0.0001$) and decreased odds of transfusion (OR = 0.72; 95% CI = 0.60 to 0.86; $p = 0.0004$). At the same time, there was no evidence of increased relative LOS (IRR = 1.00; 95% CI = 0.97 to 1.03; $p = 0.9825$), risk of VTE within 90 days of surgery (hazard ratio [HR] = 0.91; 95% CI = 0.62 to 1.33; $p = 0.5586$), or risk of composite cardiovascular outcomes by 7 days after surgery (OR = 0.85; 95% CI = 0.47 to 1.52; $p = 0.5761$). Use of TXA was associated with decreased odds of readmission (OR = 0.77; 95% CI = 0.64 to 0.93; $p = 0.0080$).

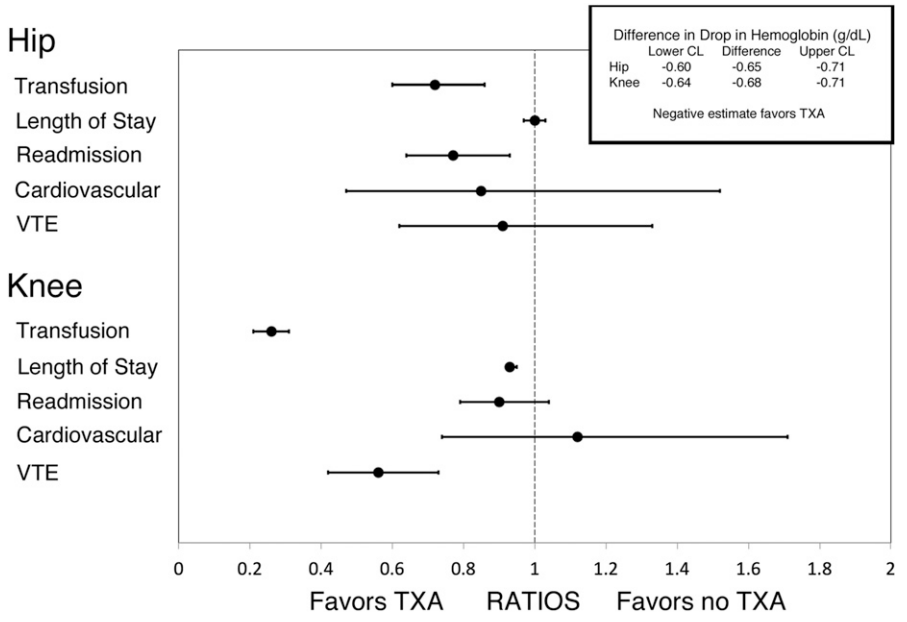

Fig. 2

Adjusted outcomes of perioperative use of TXA in primary elective hip or knee arthroplasty. CL = confidence limit.

TABLE III Unweighted and Weighted Standardized Differences Between Patients Treated and Not Treated with TXA

Variable	Hip		Knee	
	Unweighted	Weighted	Unweighted	Weighted
Age	−0.0672	−0.0165	−0.0061	0.0085
BMI	−0.0981	0.0436	−0.0183	−0.0099
Preop. hemoglobin	0.0177	−0.0495	0.0198	0.0053
Preop. platelets	0.0358	−0.0306	0.0388	−0.0032
Preop. creatinine	−0.1018	−0.0510	−0.0401	−0.0099
Congestive heart failure	−0.0618	0.0660	−0.0733	0.0017
Valvular disease	−0.0342	−0.0267	0.0068	0.0045
Pulmonary circulation disease	−0.0498	0.0047	−0.0489	0.0000
Peripheral vascular disease	−0.0259	0.0026	−0.0564	0.0100
Paralysis	−0.0058	0.0134	−0.0208	0.0144
Other neurologic disorder	−0.0257	0.0023	−0.0068	−0.0022
Chronic pulmonary disease	−0.0608	0.0120	−0.0716	0.0030
Diabetes without chronic complications	−0.0480	−0.0153	−0.0118	0.0091
Diabetes with chronic complications	−0.0282	0.0703	0.0013	0.0059
Hypothyroidism	−0.0316	0.0557	0.0036	0.0104
Renal failure	−0.0121	0.0369	−0.0263	0.0090
Liver disease	0.0036	−0.0047	0.0110	0.0645
Peptic ulcer disease	0	0	−0.0031	−0.0047
Acquired immune deficiency syndrome	−0.0016	−0.0032	0.0141	−0.0044
Lymphoma	0.0077	0.0110	−0.0130	−0.0105
Metastatic cancer	0.0012	0.0230	0.0009	−0.0097
Solid tumor with or without metastasis	−0.0219	−0.0006	−0.0003	−0.0048
Sex	0.0160	−0.0031	0.0324	0.0105
ASA status	0.1096	0.0481	0.1113	0.0212
Smoking	0.0948	0.0167	0.0880	0.0126
Married or partnered	0.0633	0.0086	0.0244	−0.0098
Insurance	0.1070	0.0426	0.1580	0.0538
African-American	0.0031	0.0327	0.1580	0.0280
History of VTE	−0.1856	0.0250	−0.1544	0.0443
History of bleeding disorder	−0.0161	−0.0214	−0.0423	0.0116
On antiplatelet agents before admission	−0.0161	0.0392	−0.0423	0.0365
On anticoagulants before admission	−0.0718	0.0158	−0.0230	0.0015

In primary elective knee arthroplasty, perioperative TXA use was associated with a smaller drop in hemoglobin (mean difference = −0.68 g/dL; 95% CI = −0.64 to −0.71 g/dL; $p < 0.0001$) and decreased odds of transfusion (OR = 0.26; 95% CI = 0.21 to 0.31; $p < 0.0001$). This beneficial outcome associated with TXA was accompanied by a slightly decreased relative LOS (IRR = 0.93; 95% CI = 0.92 to 0.95; $p < 0.0001$) and decreased risk of VTE within 90 days after surgery (HR = 0.56; 95% CI = 0.42 to 0.73; $p < 0.0001$). We found no evidence of increased odds of readmission (OR = 0.90; 95% CI = 0.79 to 1.04; $p = 0.1511$) or cardiovascular outcomes (OR = 1.12; 95% CI = 0.74 to 1.71; $p = 0.5715$).

Discussion

We found a significant reduction in the risk of transfusion with the use of TXA in primary total hip and total knee replacement surgery in the clinical practice setting. Hip and knee patients were three-fourths and one-fourth as likely, respectively, to receive transfusions if TXA was administered. Additionally, TXA was associated with a reduction in the drop in hemoglobin by an average of 0.6 g/dL per case. These findings are consistent with those of several randomized controlled clinical trials and meta-analyses of the use of TXA in arthroplasty patients[16,19-25].

However, clinical trials have inclusion and exclusion criteria that may not represent all contemporary patients

undergoing total joint replacement in the United States. Rare thrombogenic events such as myocardial infarction, transient ischemic attack, or stroke are hard to detect in clinical trials because of the relatively small number of cases. For example, Sukeik et al. performed a meta-analysis of 11 randomized controlled trials investigating the use of TXA in total hip arthroplasty[23]; 10 of the studies had <50 cases and the other had 100, for a total of 505 cases. They reported that there was no significant difference in deep-vein thrombosis (DVT) or pulmonary embolism (PE) between TXA and no-TXA groups, but they did not report on the absolute numbers of DVTs, and there were only 3 cases with PE. Aguilera et al. randomized 150 patients to intravenous or topical administration of TXA or to placebo[15]. Exclusion criteria were an allergy to TXA, a history of coagulopathy or VTE events, previous bypass surgery, use of anticoagulant or contraceptive treatment, and a cardiovascular prosthesis. They did not attempt to identify thromboembolic complications because they excluded cases "with possible TXA related complications." Our study was designed specifically to have sufficient statistical power to test the relationship of TXA and these untoward events. A study such as ours provides reassurance that the results of randomized controlled trials are relevant and generalizable to the broader, unselected population.

We showed a significantly decreased risk of VTE within 90 days of total knee arthroplasty associated with TXA, and we did not find an increase in VTE events in total hip arthroplasty. This is consistent with the findings of 1 study involving a large administrative database and 2 meta-analyses in which no increased risks of DVT or PE were identified[37-39]. Our finding of the association of TXA with a significantly decreased risk of VTE in total knee arthroplasty is preliminary and may be due to residual confounding not accounted for in the propensity model. As demonstrated in Table II, patients with more comorbidities may not be treated with TXA as often and may be at higher risk for VTE at baseline, biasing the results. Alternately, a possible physiologic explanation for this observation might be that decreased bleeding in and around the knee leads to decreased swelling and less venous obstruction. The key clinical point is that TXA was not associated with an increased risk.

We found no association between TXA and an increased risk of myocardial infarction, stroke, or transient ischemic attack in either hip or knee arthroplasty. In a meta-analysis of surgery trials, Ker et al. also found no difference in myocardial infarction or stroke events associated with the use of TXA[38]. In our study, 58 (0.5%) of the hip cases and 108 (0.5%) of the knee cases experienced cardiovascular events within 7 days of surgery. Because the outcomes are rare, the CIs around our estimates are wide enough to allow for a 50% to 70% increase in cardiovascular outcomes associated with treatment. We also found a decreased risk of readmission among the hip patients treated with TXA, along with strong evidence of no increase in LOS. Those outcomes were not investigated in other large studies, to our knowledge.

The current study had several limitations. We did not assess the effect of intravenous versus topical administration or TXA dosage on outcomes. We focused on the potential impact of TXA use on thrombogenic events and readmissions but did not explore relationships with all adverse events associated with total joint replacement. Patients were not randomly assigned to treatment, and bias by indication is a possibility. We also found that surgeons changed practice over time: the percentage of surgeons using TXA in <10% of their cases went from 76% in the first 3 months to 30% in the last 3 months of this study, while the percentage of surgeons using it in >90% of their cases went from 12% to 41% (Fig. 3). The change in TXA utilization at the surgeon level creates the potential for patient selection bias, resulting

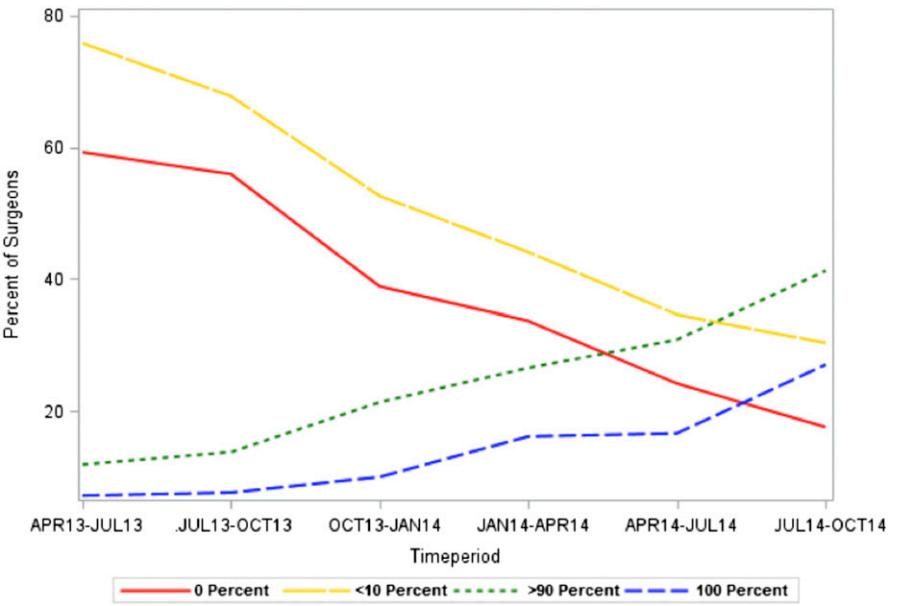

Fig. 3
Percentage of surgeons by levels of TXA usage over time.

in an exaggerated benefit attributable to TXA. Our strategies to delineate the TXA effect more clearly given this potential selection bias were to balance patient-level variables using IPTW based on the patients' propensity to receive TXA given their characteristics and to account for the potential correlation of outcomes among patients cared for in the same hospital or by the same surgeon. We were reassured because we were able to achieve excellent balance on covariates, indicating that we were able to adequately control for identified confounders.

Even with these efforts, there could still be other unidentified confounders responsible for the apparent lack of thrombogenic events with TXA use. For example, a surgeon may choose to withhold TXA from patients with cardiovascular risk factors that we did not measure, which in turn could obscure a true underlying increased risk of myocardial infarction or stroke. Although some level of uncertainty remains, techniques exist to estimate how strong the impact of such unmeasured confounders would need to be to overturn our conclusions[40]. Given reasonable assumptions about the differential prevalence of the unmeasured confounder, this seems unlikely. For example, a confounder would have to have an RR of close to 6 to reverse our conclusions about cardiovascular outcomes.

In summary, our registry-based study adds to the evidence that the use of TXA in primary total hip and knee arthroplasty patients is a safe and effective adjunct to reduce blood loss and the need for transfusion. Additionally, TXA was associated with reduced readmissions among total hip arthroplasty patients and reduced risk of VTE among total knee arthroplasty patients. ■

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References

1. Bolton-Maggs PH, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol. 2013 Nov;163(3):303-14. Epub 2013 Sep 14.

2. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg. 2009 May;208(5):931-7: 937.e1-2, discussion :938-9. Epub 2009 Mar 26.

3. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med. 2004 Jan;32(1):39-52.

4. Frisch NB, Wessell NM, Charters MA, Yu S, Jeffries JJ, Silverton CD. Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplasty. 2014 Sep;29(9)(Suppl):189-92. Epub 2014 May 24.

5. Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty-day complication rates. J Bone Joint Surg Am. 2014 Dec 3;96(23):1945-51.

6. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma. 2003 May;54(5):908-14.

7. Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion. 2005 Jan;45(1):103-10.

8. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg. 2006 May;81(5):1650-7.

9. McAlister FA, Clark HD, Wells PS, Laupacis A. Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies. Br J Surg. 1998 Feb;85(2):171-8.

10. Weber WP, Zwahlen M, Reck S, Misteli H, Rosenthal R, Buser AS, Kaufmann M, Oertli D, Widmer AF, Marti WR. The association of preoperative anemia and perioperative allogeneic blood transfusion with the risk of surgical site infection. Transfusion. 2009 Sep;49(9):1964-70. Epub 2009 May 11.

11. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, Hickner A, Rogers MA. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA. 2014 Apr 2;311(13):1317-26.

12. Harris RN, Moskal JT, Capps SG. Does tranexamic acid reduce blood transfusion cost for primary total hip arthroplasty? A case-control study. J Arthroplasty. 2015 Feb;30(2):192-5. Epub 2014 Sep 06.

13. Tuttle JR, Ritterman SA, Cassidy DB, Anazonwu WA, Froehlich JA, Rubin LE. Cost benefit analysis of topical tranexamic acid in primary total hip and knee arthroplasty. J Arthroplasty. 2014 Aug;29(8):1512-5. Epub 2014 Feb 03.

14. Yoshihara H, Yoneoka D. National trends in the utilization of blood transfusions in total hip and knee arthroplasty. J Arthroplasty. 2014 Oct;29(10):1932-7. Epub 2014 Apr 26.

15. Aguilera X, Martínez-Zapata MJ, Hinarejos P, Jordán M, Leal J, González JC, Monllau JC, Celaya F, Rodríguez-Arias A, Fernández JA, Pelfort X, Puig-Verdie LI. Topical and intravenous tranexamic acid reduce blood loss compared to routine hemostasis in total knee arthroplasty: a multicenter, randomized, controlled trial. Arch Orthop Trauma Surg. 2015 Jul;135(7):1017-25. Epub 2015 May 07.

16. Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J. 2014 Aug;96-B(8):1005-15.

17. Charoencholvanich K, Siriwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. Clin Orthop Relat Res. 2011 Oct;469(10):2874-80. Epub 2011 Apr 22.

18. Gomez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, Pérez-Chrzanowska H, Figueredo-Zalve R. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. J Bone Joint Surg Am. 2014 Dec 3;96(23):1937-44.

19. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemelä HM, Mäntylä SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg. 1997 Apr;84(4):839-44.

20. Huang F, Wu D, Ma G, Yin Z, Wang Q. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. J Surg Res. 2014 Jan;186(1):318-27. Epub 2013 Sep 13.

21. Husted H, Blønd L, Sonne-Holm S, Holm G, Jacobsen TW, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. Acta Orthop Scand. 2003 Dec;74(6):665-9.

22. Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013 Aug;21(8):1869-74. Epub 2012 Jun 24.

23. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br. 2011 Jan;93(1):39-46.

24. Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res. 2014 Jan;472(1):66-72.

25. Wu Q, Zhang HA, Liu SL, Meng T, Zhou X, Wang P. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. Eur J Orthop Surg Traumatol. 2015 Apr;25(3):525-41. Epub 2014 Nov 28.

26. Bruce-Brand R, Dragomir R, Baker J, Harty J. Cerebrovascular infarction following bilateral total knee arthroplasty and tranexamic acid administration. Acta Orthop Belg. 2013 Jun;79(3):351-4.

27. Gupta PN, Mullamalla UR, Sabin P, Vellappan P. Acute MI in a young hypertensive woman: could it be due to tranexamic acid? BMJ Case Rep. 2013;2013. Epub 2013 May 27.

28. Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. BJOG. 2009 Jan;116(1):91-7. Epub 2008 Nov 11.

29. Hughes R, Hallstrom B, Cowen M, Igrisan R, Singal B, Share D. Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI) as a model for regional registries in the United States. Orthop Res Rev. 2015 Jun 8;7:47-56.

30. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998 Jan;36(1):8-27.

31. Bilimoria KY, Chung J, Ju MH, Haut ER, Bentrem DJ, Ko CY, Baker DW. Evaluation of surveillance bias and the validity of the venous thromboembolism quality measure. JAMA. 2013 Oct 9;310(14):1482-9.

32. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med. 2004 Oct 15;23(19):2937-60.

33. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010 Mar-Apr;13(2):273-7. Epub 2009 Nov 12.

34. Austin PC, Mamdani MM, van Walraven C, Tu JV. Quantifying the impact of survivor treatment bias in observational studies. J Eval Clin Pract. 2006 Dec;12(6):601-12.

35. Li F, Zaslavsky AM, Landrum MB. Propensity score weighting with multilevel data. Stat Med. 2013 Aug 30;32(19):3373-87. Epub 2013 Mar 24.

36. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol. 2001 Apr;54(4):387-98.

37. Gandhi R, Evans HMK, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes. 2013;6:184. Epub 2013 May 07.

38. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ. 2012;344:e3054. Epub 2012 May 17.

39. Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG. 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. Epub 2014 Aug 12.

40. Vanderweele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. Epidemiology. 2011 Jan;22(1):42-52.