Can J Anesth/J Can Anesth (2015) 62:1179–1187
DOI 10.1007/s12630-015-0460-6

REPORTS OF ORIGINAL INVESTIGATIONS

Universal tranexamic acid therapy to minimize transfusion for major joint arthroplasty: a retrospective analysis of protocol implementation

Traitement universel à l'acide tranexamique pour minimiser les transfusions pendant toute arthroplastie majeure des articulations: une analyse rétrospective suivant la mise en œuvre d'un protocole

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Received: 2 October 2014 / Accepted: 13 August 2015 / Published online: 3 September 2015

Abstract

Purpose *Tranexamic acid (TXA) therapy can reduce red blood cell (RBC) transfusion; however, this therapy remains underutilized in many surgical patient populations. We assessed whether implementation of a protocol to facilitate universal administration of TXA in patients undergoing total hip or knee arthroplasty would reduce the incidence of RBC transfusion without increasing adverse clinical outcomes.*

Methods *We implemented a quality of care policy to provide universal administration of intravenous TXA at a dose of 20 mg·kg^{-1} iv to all eligible patients undergoing total hip or knee arthroplasty from October 21, 2013 to April 30, 2014. We compared data from an equal number*

The preliminary data were presented at the Society for Advancement of Blood Management (May 2014), won best abstract at the Symposium of the Centre for Quality Improvement and Patient Safety (C-QuIPS; October 2014), won the Jacques Duparc Award as one of the ten best e-posters at the 16th European Federation of National Associations of Orthopaedics and Traumatology (EFORT) Congress (Prague, May 2015), were accepted for podium presentation at the Canadian Orthopaedic Association and Canadian Orthopaedic Research Society Annual Meeting (COA/CORS, June 2015), and were presented at the Canadian Anesthesiologists' Society Meeting (CAS, Ottawa, June 2015).

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This article will be accompanied by an editorial. Please see Can J Anesth 2015; 62: this issue.

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of patients before and after protocol implementation (n = 422 per group). The primary outcome was RBC transfusion with secondary outcomes including postoperative hemoglobin concentration (Hb) and length of hospital stay. Adverse events were identified from the electronic medical records. Data were analyzed by a Chi square test and adjusted logistic and linear regression analysis.

Results *Implementation of the protocol resulted in an increase in TXA utilization from 45.8% to 95.3% [change 49.5%; 95% confidence interval (CI), 44.1 to 54.5; P < 0.001]. This change was associated with a reduction in the rate of RBC transfusion from 8.8% to 5.2%, (change −3.6%; 95% CI, −0.1 to −7.0; P = 0.043). Pre- and post-protocol mean [standard deviation (SD)] Hb values were similar, including the nadir Hb prior to RBC transfusion [72 (8) $g{\cdot}L^{-1}$ vs 70 (8) $g{\cdot}L^{-1}$, respectively; mean difference −1 $g{\cdot}L^{-1}$; 95% CI, −3 to 5; P = 0.569]. Length of stay was not altered, and no increase in adverse events was observed.*

Conclusions *Implementation of a perioperative TXA protocol was associated with both an increase in TXA use and a reduction in RBC transfusion following hip or knee arthroplasty. Adverse events and length of hospital stay were not influenced by the protocol.*

Résumé

Objectif *Le traitement à l'acide tranexamique (TXA) peut réduire les transfusions d'érythrocytes; toutefois, ce traitement demeure sous-utilisé dans de nombreuses populations chirurgicales. Nous avons évalué si la mise en œuvre d'un protocole qui faciliterait l'administration universelle de TXA chez les patients subissant une arthroplastie totale du genou ou de la hanche réduirait l'incidence de transfusion d'érythrocytes sans augmenter les complications cliniques.*

Méthode *Nous avons mis en œuvre une politique de qualité des soins afin de procéder à l'administration universelle de TXA par voie intraveineuse à une dose de 20 $mg{\cdot}kg^{-1}$ à tous les patients admissibles subissant une arthroplastie totale de la hanche ou du genou entre le 21 octobre 2013 et le 30 avril 2014. Nous avons comparé les données d'un nombre égal de patients avant et après la mise en œuvre du protocole (n = 422 par groupe). Le critère d'évaluation principal était la transfusion d'érythrocytes, les critères secondaires incluant la concentration d'hémoglobine (Hb) postopératoire et la durée d'hospitalisation. Les complications ont été identifiées à partir des dossiers médicaux électroniques. Les données ont été analysées à l'aide d'un test de chi carré et d'analyses de régression logistique et linéaire ajustées.*

Résultats *La mise en œuvre de ce protocole a entraîné une augmentation de l'utilisation de TXA de 45,8 % à 95,3 % [changement de 49,5 %; intervalle de confiance (IC) 95 %, 44,1 à 54,5; P < 0,001]. Ce changement a été associé à une réduction du taux de transfusion d'érythrocytes de 8,8 % à 5,2 % (changement -3,6 %; IC 95 %, -0,1 à -7,0; P = 0,043). Les valeurs Hb moyennes [écart type (ÉT)] pré- et post-protocole étaient semblables, y compris le Hb nadir avant la transfusion d'érythrocytes [72 (8) $g{\cdot}L^{-1}$ vs. 70 (8) $g{\cdot}L^{-1}$, respectivement; différence moyenne -1 $g{\cdot}L^{-1}$; IC 95 %, -3 à 5; P = 0,569]. La durée d'hospitalisation n'a pas changé, et aucune augmentation des complications n'a été observée.*

Conclusion *La mise en œuvre d'un protocole de TXA périopératoire a été associée à une augmentation de l'utilisation de TXA ainsi qu'à une réduction des transfusions d'érythrocytes après les arthroplasties de la hanche ou du genou. Les complications et la durée d'hospitalisation n'ont pas été influencées par le protocole.*

Administration of tranexamic acid (TXA) has been shown to reduce blood loss and allogeneic red blood cell (RBC) transfusion in cardiac and various noncardiac surgical procedures.[1] Many randomized controlled trials,[2–6]

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systematic reviews, and meta-analyses[7–11] have shown that systemic and topically administered TXA reduces allogeneic RBC transfusion in hip or knee arthroplasty surgery. Recent observational studies have also shown an association between TXA use and reduced RBC transfusion.[12,13] Despite this clear affirmation of efficacy by numerous randomized trials, concerns about associated adverse outcomes and safety have not been adequately addressed largely due to the uniformly small sample size of these studies. This concern was cited as one of the main reasons for the strikingly low percent utilization of TXA (11.2%) in the United States.[13] Despite the amount of supportive literature in favour of TXA utilization, a recent review from the Ontario Transfusion Coordinators (ONTraC) database revealed that 50.8% of patients undergoing primary hip or knee arthroplasty received TXA in 2013 (personal communication Dr. John Freedman). Review of our institutional practice revealed that our TXA utilization (45.8%) was low relative to other ONTraC centres.

To address this translational gap in patient care, we implemented a quality of care policy to provide universal administration of intravenous TXA perioperatively to all eligible patients undergoing hip or knee arthroplasty. We sought to evaluate institutional compliance with universal TXA use in arthroplasty and to document institutional transfusion outcomes before and after implementation. We intended to determine the impact of implementing a universal protocol directing TXA administration in eligible patients undergoing arthroplasty surgery. We assessed the impact of implementation on RBC transfusion, postoperative Hb, hospital length of stay, and adverse events.

Methods

Institutional research ethics approval was obtained from the St. Michael's Hospital Research Ethics Board on August 6, 2014. A retrospective observational study was then performed to assess the impact of implementation of a universal TXA protocol for hip or knee arthroplasty on quality of patient care. All patients undergoing total hip or knee arthroplasty from May 1, 2013 to April 30, 2014 were eligible for this retrospective quality of care chart review (Fig. 1). Patients undergoing elective primary or revision hip or knee arthroplasty at St. Michael's Hospital from October 21, 2013 to April 30, 2014 were subject to a protocol encouraging the use of TXA for hip or knee arthroplasty. Eligible patients received TXA 20 $mg \cdot kg^{-1}$ *iv* during surgery. Patients received TXA unless the attending physician judged them to be at an unacceptably high risk as defined by the occurrence of any the following conditions within the previous six months: evidence of a recent myocardial infarction (MI), stroke, pulmonary embolism (PE), deep vein thrombosis (DVT), seizure disorder, renal insufficiency, or placement of a bare metal coronary stent. Additional conditions included drug eluting stent within the previous 12 months, history of hypercoagulability, or an inability to receive standard DVT prophylaxis. A weight-based dosing schedule (20 $mg \cdot kg^{-1}$ *iv*) with a maximal dose of 2,400 mg was posted in the operating room to guide clinicians. In addition, a form outlining the indications and relative contraindications was posted in the operating room for review. Dose adjustments were not made for minor renal impairment, however dose adjustments were made or the drug was withheld in patients with severe renal insufficiency or dialysis dependence.

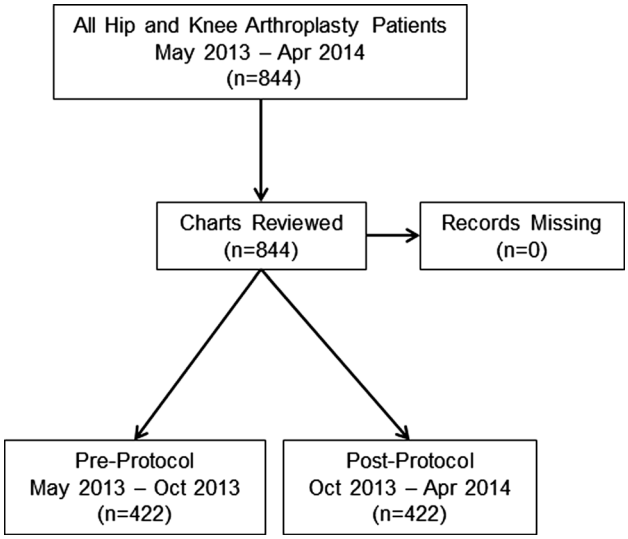

Fig. 1 Flow diagram of patients and data included within this retrospective study

The primary outcome was the proportion (percentage) of patients receiving an RBC transfusion in the perioperative period. Secondary outcomes included perioperative Hb, length of hospital stay, and adverse events, including death, MI, stroke, seizure, PE, DVT, and acute kidney injury (AKI).

We assessed an equal number of patients (n = 422) immediately before and after implementing the universal protocol. Four hundred twenty-two patients were included sequentially after the October 21, 2014 initiation date (Post-Protocol). Outcomes from these patients were compared with the most recent 422 patients operated on prior to initiation of the protocol (Pre-Protocol).

Patient records were confidentially assessed (G.H., R.A.P., A.W., R.P.) one month following surgery to determine: 1) RBC transfusion; 2) Hb before surgery and on postoperative days 1 and 3; 3) length of hospital stay;

and 4) adverse events. The adverse events assessed were death, MI (elevated troponin and clinical correlate for myocardial ischemia), stroke (new clinical deficit with evidence of brain injury on imaging), seizure, PE (clinical diagnosis with positive imaging), DVT (clinical diagnosis with positive imaging), and AKI (an increase in serum creatinine by > 50% of the preoperative value). The World Health Organization definition of anemia was used to determine incidence of preoperative anemia (Hb < 120 $g{\cdot}L^{-1}$ for females, Hb < 130 $g{\cdot}L^{-1}$ for males). For comparison purposes, anemia was defined as an Hb level of < 120 $g{\cdot}L^{-1}$ for both males and females to enable comparison of transfusion rates in anemic (Hb < 120 $g{\cdot}L^{-1}$) and non-anemic patients (Hb ≥120 $g{\cdot}L^{-1}$) before and after protocol implementation. For all outcomes, several elements of the hospital's internal electronic database (Soarian Clinicals) were reviewed (G.H., R.A.P., A.W., R.P.), including the operative record, anesthesia record, doctor's notes and orders, nursing notes, and blood bank records, to ensure completeness and accuracy of record collection. Transfusion events were confirmed in both the main hospital and transfusion medicine databases (G.H., R.P.). The data collection involved a retrospective chart review and subsequent data entry. The data collected from the chart included the patient's sex, date of birth, height, weight, body mass index (BMI), admitting diagnosis, procedure, date of operation, type of anesthesia, TXA dose, volume of crystalloid and/or colloid infused, estimated blood loss (EBL), preoperative and postoperative Hb, intraoperative and postoperative transfusion data, occurrence of serious adverse events, and date of discharge.

No transfusion algorithm was used in this study. The decision for transfusion was made by the anesthesiologist and surgeon within the operating room, postanesthesia care unit staff, and the surgical team on the ward. The transfusion threshold for patients on the ward has been near 75 $g{\cdot}L^{-1}$ during 2012-2014, but the decision to transfuse RBCs was left to the discretion of the surgical team based on the clinical assessment and comorbidities of each individual patient.

Statistical analysis

Utilizing our 2012 transfusion data, we observed a baseline transfusion rate of 16% (138 patients were transfused *vs* 735 patients were not transfused). Assuming the effect of universal TXA therapy would reduce the absolute incidence of transfusion to 7% (a 50% relative reduction), we estimated a sample size of at least 393 patients would be required. With a case load of about 1,000 patients per year, we further estimated that a significant treatment effect should be observed within six months of initiating the protocol. Limiting the time to assess the implementation of the protocol in this observational study would have the advantage of diminishing the likelihood that additional independent factors might have influenced the transfusion rate.

An independent statistical analysis was performed by statisticians at the Dalla Lana School of Public Health, University of Toronto. The primary analysis was a comparison of the proportion of patients receiving TXA and RBC transfusion before and after protocol initiation (Pre-Protocol *vs* Post-Protocol) using a Chi square analysis. For RBC transfusion and length of stay, logistic regression analysis was performed before and after adjustment for age, sex, body mass index (BMI), and type of anesthesia (regional *vs* general).The proportion of transfused RBC units and creatinine values were compared using the Mann-Whitney Rank Sum test. All *P* values reflect use of adjusted analysis unless indicated. Subgroup analyses stratified by Hb < 120 $g{\cdot}L^{-1}$ and Hb ≥ 120 $g{\cdot}L^{-1}$ were pre-specified. All reported *P* values are two sided.

Results

Patient demographics showed an equal Pre- and Post-Protocol proportion of males and females with comparable age, BMI, and administered TXA dose (Table 1).

Utilization of TXA increased from 45.8% in the Pre-Protocol group to 95.3% in the Post-Protocol group [change 49.5%; 95% confidence interval (CI), 44.1 to 54.5; $P < 0.001$; Fig. 2]. Reasons for not administering TXA therapy in 20 (4.7%) of 422 patients included a history of: 1) transient cerebral ischemic event or stroke ($n = 4$); severe carotid stenosis ($n = 1$); PE, DVT, or hypercoagulability ($n = 5$); coronary stent, coronary artery disease, atrial fibrillation, or valvular heart disease ($n = 4$); ischemic bowel (n = 1); and no reason identified or missed dose ($n = 5$). Several patients with relative contraindications to TXA use were given TXA in the dose specified by the protocol. This included nine patients with known atrial fibrillation, two patients with a remote

Table 1 Patient characteristics

	Pre-Protocol $n = 422$	Post-Protocol $n = 422$
Female	252 (59.7)	240 (56.9)
Age (yr)	65 (12)	63 (13)
Body Mass Index ($kg{\cdot}m^{-2}$)	30.2 (7.4)	30.2 (7.0)
Treated with TXA	193 (45.8)	402 (95.3)
TXA Dose ($mg{\cdot}kg^{-1}$)	19.8 (1.6)	20.0 (1.5)

Data presented as number (%) or mean (standard deviation)

TXA = tranexamic acid

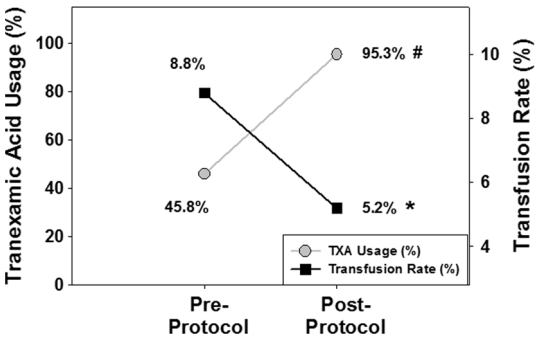

Fig. 2 Rate of tranexamic acid (TXA) utilization (grey circles) and red blood cell transfusion (black squares) before and after initiating the TXA protocol (black symbols, Pre-Protocol *vs* Post-Protocol, n = 422 per group). There was a significant increase in the proportion of patients receiving TXA and a reduction in the proportion of patients receiving a transfusion after implementation of the protocol (*P = 0.043 and #$P < 0.001$, Chi square analysis)

Table 2 Perioperative hemoglobin concentrations

Perioperative Hemoglobin ($g{\cdot}L^{-1}$)	Pre-Protocol n = 422	Post-Protocol n = 422
Preoperative	133 (14)	135 (14)
Postoperative Day 1	108 (13)	112 (13)*
Postoperative Day 3	97 (15)	101 (14)*
Transfused Patients	**Pre-Protocol n = 37**	**Post-Protocol n = 22**
Nadir Hemoglobin Prior to Transfusion	72 (8)	70 (8)

Data presented as mean (standard deviation)

*Comparison of pre and post values by logistic regression: $P < 0.001$

history of stroke, one patient with a remote history of pulmonary embolus, and two patients with a history of coronary artery disease, including one patient who had received a stent 15 months prior to surgery. None of these patients experienced an adverse event postoperatively.

With respect to RBC transfusion, TXA therapy per protocol was associated with an overall reduction in RBC transfusion from 8.8% to 5.2% (change −3.6%; 95% CI, −0.1 to −7.0; P = 0.043; Fig. 2). Hemoglobin concentration (Hb) levels were recorded for each patient preoperatively and on postoperative days 1 and 3 (Table 2). There were no differences in preoperative hemoglobin when assessed by time period (Table 2, P = 0.073). There was a slight statistical increase in postoperative days 1 and 3 hemoglobin values after initiation of the universal TXA protocol (Table 2, $P < 0.001$ for both). The mean [standard deviation (SD)] nadir hemoglobin concentration prior to transfusion of RBCs was not different before and after protocol implementation [72 (8) $g{\cdot}L^{-1}$ *vs* 70 (8) $g{\cdot}L^{-1}$, respectively; mean difference −1 $g{\cdot}L^{-1}$; 95% CI, −3 to 5; P = 0.569; Table 2].

The overall incidence of anemia (Hb < 120 $g{\cdot}L^{-1}$) and hemoglobin values are presented in Table 3. Analysis of RBC transfusion was performed by stratification of patients with preoperative hemoglobin levels < 120 $g{\cdot}L^{-1}$ (anemic patients) *vs* those with a preoperative Hb ≥ 120 $g{\cdot}L^{-1}$ (non-anemic patients) before and after protocol implementation. This analysis suggested fewer transfusions following protocol implementation in both anemic (18.6% *vs* 28.6%, P = 0.242) and non-anemic patients (3.7% *vs* 5.3%, P = 0.294); however, neither of these differences reached statistical significance (Table 3, Fig. 3).

Estimates of mean blood loss and infused crystalloid volumes were collected when data were available on the medical record. The mean (SD) estimates of blood loss for the Pre-Protocol and Post-Protocol groups were [261 (49) mL, n = 143 *vs* 268 (238) mL, n = 322, respectively], with a mean difference of −7.0 mL (95% CI, −42.7 to 28.7). The mean recorded estimates of crystalloid administration for the Pre-Protocol and Post-Protocol groups were [1,458 (490) mL, n = 284 *vs* 1,464 (490) mL, n = 378, respectively], with a mean difference of −6.0 mL (95% CI, −81.4 to 69.4).

The mean (SD) hospital length of stay (LOS) before initiating the protocol was 3.93 (1.93) days, which was not

Table 3 Impact of anemia on red blood cell transfusion

Preoperative Hemoglobin ($g{\cdot}L^{-1}$)	Pre-Protocol (n = 422)			Post-Protocol (n = 422)		
	n (%)	Patients Transfused n (%)	Units Transfused	n (%)	Patients Transfused n (%)	Units Transfused
< 120	63 (14.9)	18 (28.6)	30	43 (10.2)	8 (18.6)	17[A]
≥ 120	359 (85.1)	19 (5.3)	32	379 (89.8)	14 (3.7)	30[B]
Total	422	37 (8.8)	62	422	22 (5.2)	47[C]

Protocol implementation had the largest impact on red blood cell (RBC) transfusion in anemic patients. The observed difference proportion transfusion did not reach statistical significance in anemic and non-anemic patients (P = 0.242 and 0.294, respectively)

Comparison of pre and post values by Mann-Whitney Rank Sum Test: [A] P = 0.128; [B] P = 0.335; [C] P = 0.074

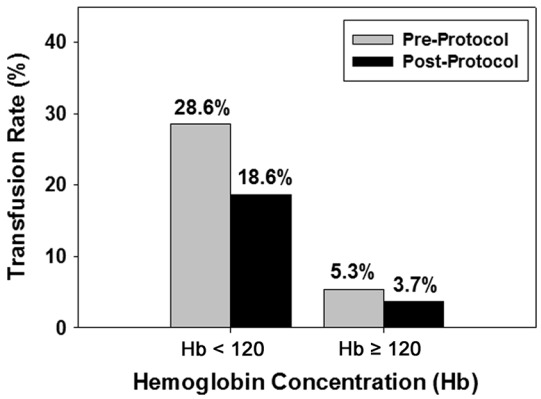

Fig. 3 The impact of protocol implementation in anemic (Hb < 120 g·L^{-1}) and non-anemic patients (Hb > 120 g·L^{-1}) is demonstrated. Protocol implementation had the largest impact on red blood cell transfusion in anemic patients

different from the mean LOS after protocol implementation 3.87 (2.16) days ($P = 0.652$).

We observed 13 adverse events (1 MI, 3 PEs and 9 AKIs) in the pre-protocol cohort and 19 adverse events in the post-protocol cohort (1 MI, 1 DVT, 1 PE, 16 AKIs) (Table 4, $P = 0.368$ for all events and $P = 0.223$ for all AKI events). The diagnostic criteria for both MIs were clinical symptoms, an elevated troponin level and electrocardiogram changes consistent with myocardial ischemia. The patient in the pre-protocol group did not receive TXA and underwent percutaneous coronary revascularization. The patient in the post-protocol group did receive TXA and was managed with medical therapy. There was one patient in the pre-protocol group who did not receive TXA and experienced a sustained rise in creatinine from a baseline creatinine of 72 umol·L^{-1} to a peak value of 196 uMol·L^{-1} on postoperative day 2. No dialysis was required and the creatinine returned to baseline within 1 year. With respect to the transient AKIs, the baseline, peak and recovery creatinine values were similar before and after protocol implementation (Table 5, $P = 0.830$ for baseline, $P = 0.603$ for peak and $P = 0.359$ for recovery creatinine values). The mean time to recovery was 1.9 (SD 0.3) *vs* 1.8 (SD 0.8) days (Table 5, $P = 0.786$). For transient AKI, the mean differences in peak creatinine and time to recovery to baseline creatinine were 3.1 uMol·L^{-1}(95% CI −28.8 to 35.0) and 0.1 days (95% CI −0.3 to 0.5), respectively.

Discussion

Our data showed that a programmatic approach to initiating universal TXA therapy was associated with an absolute increase of 49.5% (95% CI, 44.1 to 54.5) in TXA administration. Introduction of the protocol resulted in 95% of arthroplasty patients receiving this blood conservation measure and was associated with an absolute reduction of 3.6% (95% CI, 0.1 to 7.0) in the proportion of patients transfused. Postoperative Hb levels did not decrease in the Post-Protocol cohort. In addition, the pre-transfusion Hb threshold values were not different in the post *vs* pre-protocol period, suggesting that the reduction in transfusion rate was not a result of a change in transfusion practice or reduced hemoglobin threshold for transfusion. We did not observe an increase in hospital length of stay after implementing this program. In addition, we did not observe an increase in adverse events post-protocol implementation. We conclude that protocol-driven use of TXA in orthopedic surgery reduced RBC transfusion rates in patients undergoing total hip or knee arthroplasty without an increase in adverse events.

Despite the availability of strong evidence that utilization of TXA therapy will reduce blood loss and RBC transfusion in patients undergoing total hip or knee arthroplasty surgery,[1–21] published data from an American administrative database showed that only 11.2% of patients were receiving this therapy in 2012.[13] This was mirrored by our relatively low provincial and institutional use of TXA at the time of protocol implementation. The discrepancy between the available data for efficacy of TXA therapy and our actual practice of administering TXA suggested that a translational gap existed at our institution. Clinicians may have discounted the results of more than 33 randomized trials (24 of which are double-blinded) because of the uniformly small sample size of these studies (maximum 96 treated patients), thus leaving unresolved questions regarding safety. A large retrospective administrative database (872,416 patients) showed low TXA utilization;[13] therefore, any conclusions about the safety of this therapy may not translate to our patient population. In this study, only 11.2% of patients were treated, raising the possibility that confounding by indication may have biased the results. Our initiative examined the impact of using TXA in all eligible patients. Implementation of this universal protocol resulted in an absolute reduction in RBC transfusion without a significant increase in thrombotic adverse outcomes. While the number of patients experiencing an acute peak in creatinine $> 50\%$ above baseline increased numerically, this change did not achieve statistical significance and creatinine values returned to baseline in all patients within an average of two days without evidence of prolonged renal failure. Further ongoing surveillance of adverse effects of TXA therapy is required to ensure that this therapy is not associated with increased adverse outcomes. While we are underpowered to determine safety, our results add to the literature in support of utilizing TXA as an important blood management initiative for patients undergoing total hip or knee arthroplasty.

As has been previously shown, preoperative anemia is a risk for RBC transfusion and serious adverse events.[22–34] Our data confirm that patients in the Pre-Protocol group with

Table 4 Complications in hip and knee arthroplasty surgery

Sex	Age	Body Mass Index	Received TXA	Received RBC Transfusion	Preoperative Hb < 120	Procedure	Timing of Complication	Complication
Pre-Protocol (n = 422)								
M	77	21.2	No	Yes	No	Primary TKA	Inpatient	MI
F	79	26.0	No	No	No	Primary TKA	Inpatient	PE
F	74	27.6	Yes	No	Yes	Bilateral TKA	Inpatient	PE
F	92	28.3	Yes	No	No	Primary TKA	Outpatient	PE
M	66	37.5	No	Yes	Yes	Revision TKA	Inpatient	AKI (Sustained)
M	54	55.9	No	No	No	Primary TKA	Inpatient	AKI (Transient)
F	68	26.0	No	No	No	Primary TKA	Inpatient	AKI (Transient)
M	59	29.3	No	Yes	No	Primary THA	Inpatient	AKI (Transient)
M	68	23.3	No	No	No	Primary TKA	Inpatient	AKI (Transient)
M	52	38.4	No	No	No	Primary THA	Inpatient	AKI (Transient)
M	68	31.4	No	No	No	Primary TKA	Inpatient	AKI (Transient)
M	80	25.5	No	Yes	Yes	Primary TKA	Inpatient	AKI (Transient)
F	76	29.7	Yes	No	Yes	Primary THA	Inpatient	AKI (Transient)
Post-Protocol (n = 422)								
M	83	30.7	Yes	No	No	Primary THA	Inpatient	MI
F	66	29.0	Yes	No	No	Primary TKA	Inpatient	PE
M	50	24.7	Yes	No	No	Primary THA	Outpatient	DVT
F	54	60.6	No	No	Yes	Revision TKA	Inpatient	AKI (Transient)
F	78	49.8	Yes	No	No	Primary THA	Inpatient	AKI (Transient)
M	86	33.0	Yes	No	No	Primary TKA	Inpatient	AKI (Transient)
F	71	33.7	Yes	No	Yes	Revision TKA	Inpatient	AKI (Transient)
F	62	28.3	Yes	No	Yes	Primary TKA	Inpatient	AKI (Transient)
F	48	42.8	Yes	Yes	Yes	Primary TKA	Inpatient	AKI (Transient)
F	44	26.3	Yes	No	Yes	Primary THA	Inpatient	AKI (Transient)
F	59	32.6	Yes	No	No	Primary THA	Inpatient	AKI (Transient)
M	56	34.2	Yes	No	No	Revision THA	Inpatient	AKI (Transient)
M	74	–	No	Yes	Yes	Revision THA	Inpatient	AKI (Transient)
M	73	25.1	No	Yes	Yes	Revision THA	Inpatient	AKI (Transient)
F	74	35.1	Yes	No	No	Primary THA	Inpatient	AKI (Transient)
F	39	45.9	Yes	No	Yes	Primary TKA	Inpatient	AKI (Transient)
M	80	36.2	Yes	No	No	Primary TKA	Inpatient	AKI (Transient)
F	46	23.5	Yes	No	No	Primary TKA	Inpatient	AKI (Transient)
M	44	37.1	Yes	No	No	Primary THA	Inpatient	AKI (Transient)

AKI = acute kidney injury; DVT = deep vein thrombosis; Hb = hemoglobin concentration; MI = myocardial infarction; PE = pulmonary embolism; RBC = red blood cells; THA = total hip arthroplasty; TKA = total knee arthroplasty; TXA = tranexamic acid

a preoperative Hb level < 120 $g{\cdot}L^{-1}$ have a higher transfusion rate (28.6%) relative to non-anemic patients with a transfusion rate of 5.3%. Post-protocol transfusion rates for both anemic and non-anemic patients tended to decrease after implementation of the TXA protocol, suggesting that TXA reduced transfusion rate independent of hemoglobin level.

The current study has a number of limitations. This is a retrospective observational trial to initiate a protocol for universal TXA therapy. This trial is therefore subject to confounding and bias in the quality of health records, incomplete diagnostic information, and secular trends in transfusion behaviour. We endeavoured to minimize the impact of additional influences on RBC transfusion by assessing a rapid change in practice over a short period of time (six months). In addition, no difference in nadir pre-transfusion Hb was observed between groups, suggesting that comparable transfusion thresholds were used. To minimize practice variation, our protocol defined a standardized 20 $mg{\cdot}kg^{-1}$ dose of TXA. The rationale for

Table 5 Transient acute kidney injury following hip and knee arthroplasty

	Pre-Protocol (n = 8)	Post-Protocol (n = 16)	P Value
Age	65 (9)	62 (15)	
Baseline Creatinine $\mu Mol \cdot L^{-1}$	81.1 (17.4)	82.3 (33.4)	0.830
Peak Creatinine $\mu Mol \cdot L^{-1}$	172.9 (36.6)	173.0 (64.4)	0.603
Recovery Creatinine $\mu Mol \cdot L^{-1}$	71.3 (11.0)	87.7 (41.9)	0.359
Days to Recovery	1.9 (0.3)	1.8 (0.8)	0.796

Data presented as mean (standard deviation)

Comparison of pre and post values by Mann-Whitney Rank Sum Test

utilizing the TXA dose was established independently in 2012 prior to initiation of the protocol following an extensive review of available literature by the Pharmacy and Therapeutics Committee.[2–6,9–11,14–17] It was determined that, from the highly variable dosing reported, this 20 $mg \cdot kg^{-1}$ dose provided a balance between reducing perioperative blood loss and RBC transfusion while limiting the incidence of potential adverse events. Nevertheless, this study did not incorporate a well-defined *a priori* standardized intraoperative fluid management strategy with strictly defined transfusion triggers, which limited the interpretation of our data. Use of TXA and other transfusion reduction strategies is a concern among many anesthesiologists. The 45.8% rate of TXA use in our own institution spurred the development of the protocol. This information was probably known to department members and may have influenced clinician practice. We informally sought a secular trend in blood conservation behaviour by evaluating additional data on 422 arthroplasty patients from our database that predated the "before:after" study periods. In this group whose surgeries occurred during January to May 2013, we found use of TXA and transfusion rates of 29.9% and 10.3%, respectively (data not shown). Similarly, the finding that postoperative Hb levels in the Post-Protocol group remained above pre-protocol levels suggests that the observed reduction in RBC transfusion rate was not due to concurrent lowering of the transfusion threshold. The similar nadir pre-transfusion Hb levels in the Pre- and Post-Protocol groups support this conclusion. In this context, we suspect that, while a change in practice was occurring, the protocol accelerated both use of TXA and a reduction in transfusion. We assessed the complication rates based on the available data on the electronic chart. We observed no deaths and one MI in the pre- and post-protocol groups. There was one patient in the pre-protocol group that had a sustained increase in creatinine. This patient did not receive TXA. There were 8 patients in the pre-protocol groups and 16 patients in the post-protocol group who experienced a transient (>50%) rise in the creatinine level. In all cases of transient AKI, creatinine values returned to baseline within an average of two days. In addition, 14 of these 24 cases received TXA, while only five received a blood transfusion. Further assessment will be required to determine if TXA contributed to these transient rises in creatinine level. Despite these measures, a number of postoperative adverse events may not have been recorded. We are continuing to develop quality-based initiatives to capture the occurrence of adverse outcomes following elective surgery.

In summary, our data support implementation of a program of universal TXA therapy to reduce the RBC transfusion rate in a large number of eligible patients undergoing total hip or knee arthroplasty. This positive treatment effect was obtained without evidence of an increase in adverse events.

Acknowledgements The authors gratefully acknowledge: Vas Georgiou, Catherine Hogan, Ella Ferris, and Douglas Sinclair for their support of the TXA initiative and the St. Michael's Centre of Excellence for Patient Blood Management; Departments of Anesthesia, Surgery and Laboratory Medicine, St. Michael's Hospital, University of Toronto; the Transfusion Coordinators within the network of Ontario Transfusion Coordinators (ONTraC); Frank Garcea for information technology support; Operating room nurses for clinical support and documentation; Alvina Joseph, Andrew Bagrin, and Marc Lalonde for clinical care; Tom Mickus and Kiran Saini for assistance in data acquisition; Yunke (Kelly) Guo for assistance in preparation of the formulary review; Clarence Chant for pharmacy administration; and Francis Tungcol for assistance in data analysis. Drs Hare, Lo, Ho, and Pronovost were supported by AHSC AFP Innovation Fund Grants. Dr. Hare has received funding from Forest Research Inc. for basic science studies and salary support from Johnson & Johnson Inc. for his role in the St. Michael's Hospital Centre of Excellence for Patient Blood Management. Drs Hare and Mazer are supported by University of Toronto, Department of Anesthesia Merit Awards.

Conflicts of interest None declared.

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