Preliminary Results Suggest Tranexamic Acid is Safe and Effective in Arthroplasty Patients with Severe Comorbidities

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Abstract

Background Tranexamic acid (TXA) reduces blood loss and transfusion after total joint arthroplasty (TJA) but concerns remain that patients with severe medical comorbidities might be at increased risk for thromboembolic complications.

Questions/purposes Among patients undergoing primary TJA with severe systemic medical disease, (1) was TXA associated with increased symptomatic thromboembolic events; (2) was TXA associated with decreased blood transfusion rates; and (3) were there differences in symptomatic thromboembolism or transfusions in the subset of patients with a history of, or risk factors for; thromboembolic disease?

Methods We performed a retrospective review of 1131 primary TJAs in 1002 patients with American Society of Anesthesiologists score III or IV. Of these, 402 had at least one of seven risk factors for thromboembolic events and

were designated as high risk; 240 of those patients received TXA. Outcome measures included 30-day postoperative symptomatic thromboembolic events and postoperative transfusion.

Results There were no differences in symptomatic thromboembolic events within 30 days of surgery between patients who received TXA and those who did not (2.5% versus 2.6%, $p = 0.97$). Fewer patients treated with TXA received transfusions (11% with versus 41% without; $p < 0.0001$). In high-risk patients, TXA was not associated with an increase in symptomatic thromboembolic events (6.7% with versus 4.3% without; $p = 0.27$) and was associated with a decrease in transfusion rates (17% with versus 48% without; $p = 0.001$).

Conclusions Although TXA seemed safe and effective in this database review of patients with severe medical comorbidities, a larger prospective trial is warranted to confirm these results.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Introduction

Substantial blood loss is not uncommon after total joint arthroplasty (TJA; THA and TKA) and often results in postoperative blood transfusions [3, 22]. In recent years the use of antifibrinolytic medications such as tranexamic acid (TXA) to decrease blood loss and transfusion has slowly gained popularity in orthopaedics [9, 19]. Multiple prospective trials involving patients undergoing TJA have demonstrated a reduction in blood loss and transfusion rates with both TXA and ϵ -aminocaproic acid (EACA) [1, 2, 4, 8, 17, 20, 21, 25, 26, 28]. These results have been

further substantiated by multiple meta-analyses [5, 11, 13, 15, 18, 23], including a recent study examining the efficacy and safety of TXA in TKA [27].

Aprotinin, a nonlysine analog antifibrinolytic, was removed from the market in 2008 after studies demonstrated increased cardiovascular complications associated with its use [10]. No increase in the risk of cardiovascular or thromboembolic complications has been demonstrated in studies of TXA or EACA [7, 23, 24, 27], but those studies have typically excluded patients with multiple comorbidities or risk factors known to increase the risk of thromboembolic events. As a result of these exclusions, it remains unclear if TXA increases the risk for postoperative thromboembolic events in patients with severe systemic medical disease, particularly in those with additional risk factors for thromboembolism.

Tranexamic acid has been effective in reducing the prevalence of postoperative transfusion after primary TJA and we have shown its safety in broad groups of patients without known risk factors for thromboembolic events [12]. In the present study we specifically chose to examine patients with severe systemic medical disease (American Society of Anesthesiologists [ASA] physical status scores of III or IV) because we believed the clinical effects of any thromboembolic events in these patients would be poorly tolerated and, thus, unlikely to be overlooked.

With those concerns in mind, this study sought to determine, among patients undergoing primary TJA who have severe systemic medical disease, (1) was use of TXA associated with an increased likelihood of having a symptomatic thromboembolic event diagnosed within 30 days of surgery; (2) was use of TXA associated with a decreased likelihood of having a blood transfusion; and (3) were there differences in symptomatic thromboembolism or transfusions in the subset of those patients who had a history of, or risk factors for, thromboembolic disease?

Patients and Methods

This study was approved by our institutional review board. We retrospectively reviewed all patients undergoing hip or knee arthroplasty by three orthopaedic surgeons (RTT, MWP, RJS) at a single institution from January 2005 to May 2011 ($n = 5968$). We excluded all simultaneous bilateral, hip resurfacing, partial knee, and revision arthroplasties. Basic demographic data were obtained from the Mayo Clinic Joint Registry and then confirmed with a thorough review of individual medical records. During the individual record review, we confirmed the preoperative diagnoses, medical history, postoperative transfusion records, that all patients met the inclusion criteria, and then reviewed all postoperative visits and communications within 30 days of surgery.

Table 1. Demographic data for all patients with ASA class III or IV

Demographic	Value
Sex	
Female	510
Male	621
Age at surgery (years)	
Mean	69.5
Range	22–97
Body mass index (kg/m^2)	
Mean	33.0
Range	15.8–59.5
Joint	
Hip	498
Knee	633
ASA score	
III	1110
IV	21

ASA = American Society of Anesthesiologists.

This review was carried out between May and September 2012. No patients were lost during this 30-day followup period and three deaths occurred within 30 days of surgery.

Our inclusion criteria for this study included all patients aged 18 years or older classified as ASA score III or IV undergoing primary, unilateral TJA for a total of 1131 surgeries performed in 1002 patients (Table 1). We chose to include only those patients with ASA scores of III or IV because the presumed overall risk of thromboembolic events would be higher, thus allowing for a larger clinical effect to be expected among groups. Additionally, it was believed those patients with more severe medical comorbidities would be less tolerant of complications arising from postoperative thromboembolism and, thus, more likely to demonstrate symptoms of any such event that would require additional medical care. Finally, this was a patient population excluded from many prior studies that may gain the most benefit from antifibrinolytic therapy by avoiding the fluid shifts associated with surgical blood loss and subsequent transfusion.

Seven factors were presumed to increase the risk of postoperative thromboembolism including prior deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular accident (CVA), coronary artery stent placement, coronary artery bypass graft (CABG), or prothrombotic condition (Factor V Leiden deficiency, protein C deficiency, antiphospholipid syndrome, etc). All patients with ASA scores III or IV were divided into three groups: low-risk (no additional thromboembolic risk factors), $n = 729$; high-risk TXA (one or more thromboembolic risk factors and received TXA), $n = 240$; and high risk, no TXA (one or more thromboembolic risk

factors but did not receive TXA), $n = 162$. The overall mean age was 69.5 years (range, 22–97 years) at the time of surgery with an overall mean body mass index of 34.9 kg/m^2 (range, 15.8 – 59.5 kg/m^2).

All patients underwent primary unilateral TJA by one of three surgeons (RTT, MWP, RJS). One surgeon has used TXA on all patients undergoing TJA since 2000 except when anesthesia has strictly excluded the patient from receiving it (coronary artery stent placement or DVT within 6 weeks of surgery). The two other surgeons began using TXA in 2007. One of these two administers TXA in all patients undergoing TJA except when excluded by anesthesia. The third surgeon has been more conservative in the use of TXA in high-risk patients, generally excluding those with a history of CABG or stent and those with a DVT or PE within 6 months of surgery. Additionally, the final decision for administration was always under the purview of the anesthesiologist. Those receiving TXA had 1 g delivered intravenously at the time of incision and an additional gram intravenously at closure. Postoperatively all patients received comprehensive DVT prophylaxis with sequential compressive devices, early ambulation, regional anesthesia when appropriate, and chemoprophylaxis using aspirin, warfarin, or low-molecular-weight heparin as we have previously described [12].

The primary outcomes were symptomatic postoperative DVT, PE, MI, or CVA occurring within 30 days of surgery. Symptomatic events were chosen as the primary end point because these would be measurable events requiring additional medical intervention. As discussed previously, we believe that in this high-risk group with multiple medical comorbidities, the effects of any significant thromboembolic event would be poorly tolerated and thus become symptomatic. We also calculated the prevalence of postoperative blood transfusion with and without administration of TXA. Postoperative transfusion was chosen as the secondary end point because we believe this to be the clinically relevant manifestation of surgical blood loss because it is an additional medical treatment that carries its own risks. Transfusion is also important because it affects a patient's perception of their well-being, frequently interferes with early mobilization, and has an economic impact on both the patient and the medical system. All patients in this study were treated during the same time period with the same group of physicians making transfusion decisions regardless of TXA status. Our general transfusion guideline in this specific group is for symptomatic anemia with hemoglobin less than 10 g/dL , which differs from our standard transfusion guideline of hemoglobin $< 8 \text{ g/dL}$ in the general population.

Data were described as mean (minimum-maximum) or count (percent) as appropriate. Univariate logistic regression with generalized estimating equations was performed;

odds ratios, 95% confidence intervals, and overall p values were reported. All analyses were performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, USA), all tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

In all patients with severe systemic medical disease (defined throughout as an ASA physical status score of III or IV), TXA was not associated with an increase in symptomatic thromboembolic events (30-day prevalence 2.6% without TXA versus 2.5% with TXA; $p = 0.97$; Table 2).

In all patients with severe systemic medical disease, TXA was associated with a decrease in postoperative transfusion rates (41% without TXA versus 11% with TXA; $p < 0.0001$; Table 3).

Within patients with severe systemic medical disease, the subset with a history of, or risk factors for, thromboembolic disease had an increase in symptomatic thromboembolic events when compared with those without

Table 2. Postoperative symptomatic thromboembolic events in all patients with ASA class III or IV based on risk factors (history of prior DVT, PE, MI, CVA, CABG, coronary artery stent, or pro-thrombotic condition)

Event	Low risk	High risk
Total patients	729	402
Symptomatic thromboembolism	6 (0.8%)	23 (5.7%)
Odds ratio	1	7.5
p value		< 0.0001
95% confidence interval		3.1–18

ASA = American Society of Anesthesiologists; DVT = deep vein thrombosis; PE = pulmonary embolus; MI = myocardial infarction; CVA = cerebrovascular accident; CABG = coronary artery bypass graft.

Table 3. Postoperative symptomatic thromboembolic events in all patients with ASA class III or IV based on tranexamic acid (TXA) administration

Event	No TXA	TXA
Total patients	343	788
Symptomatic thromboembolism	9 (2.6%)	20 (2.5%)
Odds ratio	1	0.99
p value		0.97
95% confidence interval		0.4–2.2

ASA = American Society of Anesthesiologists.

Table 4. Postoperative transfusion in all patients with ASA class III or IV based on tranexamic acid (TXA) administration

Event	No TXA	TXA
Total patients	343	788
Total receiving transfusion	141 (41%)	90 (11%)
Odds ratio	5.8	1
p value	< 0.0001	
95% confidence interval	4.1–8.1	

ASA = American Society of Anesthesiologists.

Table 5. Postoperative symptomatic thromboembolic events in patients with ASA class III or IV with additional risk factors for thromboembolic disease based on tranexamic acid (TXA) administration

Event	No TXA	TXA
Total high-risk patients	162	240
Symptomatic thromboembolism	7 (4.3%)	16 (6.7%)
Odds ratio	1	1.7
p value		0.27
95% confidence interval		0.7–4.0

ASA = American Society of Anesthesiologists.

Table 6. Postoperative transfusion in patients with ASA class III or IV with additional risk factors for thromboembolic disease based on tranexamic acid (TXA) administration

Event	No TXA	TXA
Total high-risk patients	162	240
Total receiving transfusion	77 (48%)	41 (17%)
Odds ratio	4.6	1
p value	0.001	
95% confidence interval	2.8–7.3	

ASA = American Society of Anesthesiologists.

that previous history or risk factors (30-day prevalence 5.7% versus 0.8%; $p < 0.0001$; Table 4). The use of TXA in this subset, however, was not associated with an increase in the 30-day prevalence of thromboembolic events (4.3% without TXA versus 6.7% with TXA; $p = 0.27$; Table 5). A post hoc power analysis demonstrated that for the difference observed in this group to be statistically significant, the group would need to have 3158 high-risk patients with the same proportions of them receiving or not receiving TXA. In this subset of high-risk patients, there was also a decrease in postoperative transfusion rates when TXA was used (48% without TXA versus 17% with TXA; $p = 0.001$; Table 6).

Table 7. Thromboembolism risk factors and 30-day postoperative symptomatic thromboembolic events for individual patients (all risk factor events occurred greater than 1 year before surgery unless otherwise noted)

Patient group	Patient risk factor	Patient thromboembolic event
Low risk n = 729 Events = 6 Rate = 0.8%		DVT
		DVT
		PE
		PE
		PE
		PE
High risk, no TXA n = 162 Events = 7 Rate = 4.3%		Death with no known thromboembolic event
	CVA	DVT
	DVT 6–12 months preoperatively	DVT
	MI	DVT
	DVT 3–6 months preoperatively	PE/MI, death
	MI, CABG	MI, death
	CVA 3–6 months preoperatively, antiphospholipid antibody	MI
	DVT, MI, CVA	CVA
High risk TXA n = 240 Events = 16 Rate = 6.7%	DVT	DVT
	DVT	DVT
	MI, CABG	DVT
	MI, coronary stent	DVT
	DVT	DVT/PE
	MI, CABG	DVT/PE
	DVT, PE	PE
	MI	PE
	MI	PE
	MI, CABG, coronary stent	PE
	CVA	PE
	CVA	PE
	MI, CABG, coronary stent	MI
	CVA < 3 months preoperatively, coronary stent	MI
	Coronary stent	CVA
	CVA	CVA

DVT = deep vein thrombosis; PE = pulmonary embolus; CVA = cerebrovascular accident; MI = myocardial infarction; CABG = coronary artery bypass graft.

In all patients with ASA class III or IV, there were three deaths within 30 days of surgery. None of these patients received TXA. One patient was low risk without a known symptomatic thromboembolism and the two remaining patients were in the high-risk, no TXA group (Table 7).

Discussion

In recent years, the use of antifibrinolytic medications to limit blood loss and transfusion after hip and knee arthroplasty has grown in popularity but some questions regarding safety have remained. Multiple prospective trials and subsequent meta-analyses have shown decreased blood loss and transfusion rates with the use of TXA in TJA. However, those studies have typically excluded patients with severe systemic medical disease or a history of, or risk factors for, thromboembolic complications [1, 2, 4, 5, 8, 11, 13–15, 17, 18, 20, 21, 23, 25–28]. We sought to determine whether administering TXA to patients undergoing primary TJA with severe systemic medical disease (ASA class III or IV) was associated with increased thromboembolic complications or decreased transfusion rates. We were especially interested in its association with these outcomes in those patients with a history of, or risk factors for, thromboembolism. Our data suggest that for patients with severe systemic medical disease, TXA use was not associated with an increase in symptomatic thromboembolic events but was associated with fewer blood transfusions. In patients with severe systemic disease, an additional history of, or risk factors for, thromboembolism was associated with an increase in postoperative symptomatic thromboembolic events regardless of TXA use.

This study has several limitations. First, there is a possibility for selection bias to have affected which patients did or did not receive TXA. Two of the surgeons administer TXA in all patients except when prohibited by the anesthesiologist. This typically does not occur unless the patient has had a significant event such as placement of a coronary artery stent or DVT within 6 weeks of surgery but could potentially occur for other reasons not accounted for in our analysis. The third surgeon is more conservative in his administration of TXA in these high-risk patients, excluding those with any prior CABG or coronary artery stent as well as those with a DVT or PE within 6 months of surgery. This third surgeon did not begin using TXA until 2007, accounting for some of the high-risk patients not receiving TXA. Sixty-eight of the 162 high-risk patients who did not receive TXA were operated on by this third surgeon before 2007. Despite the three surgeons' consistent personal administration guidelines, the possibility remains for this selection bias to have influenced our results. Additionally, there could be other factors increasing the

risk for postoperative thromboembolic events that were not studied. We chose to examine seven risk factors routinely considered by both our surgical and anesthesia teams when deciding whether to administer TXA during TJA and our data show a significant association between these historical factors and postoperative symptomatic thromboembolism regardless of TXA administration (Table 4). In future studies, this potential selection bias and unforeseen factors affecting thromboembolism could be protected against through a prospective, randomized controlled trial involving all high-risk patients.

The second significant limitation is that the power of the statistical analysis is limited by the relative rarity of the primary outcomes. Our post hoc power analysis showed that the high-risk group would need 3158 patients to state if the difference we observed in symptomatic thromboembolic events was statistically significant (Table 5). In an attempt to provide a more sound analysis, we chose to report all symptomatic thromboembolic events together instead of individual rates for each outcome. We chose symptomatic events as the primary end point because in these patients with more severe medical comorbidities, we felt any significant event would be poorly tolerated and become symptomatic. Additionally, symptomatic events are considered significant because they require additional medical treatment, which would carry its own risks. Although all patients had documented followup beyond the 30-day postoperative period, it is possible that some patients had a complication of interest, which was not recorded in the medical record. Patients typically return to our institution at 8 weeks postoperatively and report complications that are then extracted from the medical record and tabulated into the joint registry, making it unlikely that the type of thromboembolic complications that were of interest in this study would be missed.

Previous studies have used various techniques such as drain output and pre- and postoperative hemoglobin levels to quantify tranexamic acid's ability to decrease absolute blood loss during TJA [2, 14, 18]. Given this well-established information, we chose to assess whether the use of TXA had an effect on postoperative transfusion rates in this high-risk population because we believe this to be the clinically relevant manifestation of surgical blood loss. In this particular patient population, our transfusion guideline is for symptomatic anemia with hemoglobin less than 10 g/dL. Transfusion is a clinically important event because it affects a patient's perception of their well-being, frequently interferes with early mobilization, and has an economic impact on both the patient and the medical system. Also, transfusion is an additional medical treatment that carries its own risks. All patients in this study were treated during the same time period with the same group of physicians making transfusion decisions regardless of TXA status.

Approximately 95% of TXA is excreted in urine unchanged by the kidneys and as such, there is concern that renal insufficiency may allow for prolonged exposure to increased levels of TXA [7, 24]. The product information states that renal insufficiency is a precaution for TXA administration and may require dose adjustment [6]. Previous studies discussing renal insufficiency as a result of antifibrinolytic therapy are mainly from the cardiothoracic arena where much higher doses are given over multiple days [16, 24]. Our protocol of 1 g intravenously before incision and an additional gram at the time of closure generally provides a total dose of 10 to 30 mg/kg. Given this low overall dose, we did not directly assess renal function for this study.

Patients with severe systemic medical disease, as indicated by an ASA class of III or IV, may be the group of patients who would benefit most from avoiding the substantial fluid shifts and changes in oxygen-carrying capacity that occur with typical blood loss after contemporary TJA. These patients have often been excluded from prior studies, which have well established TXA's effects on blood loss and transfusion rates [7, 15, 23, 27]. Within our larger group of all patients with ASA class III or IV, TXA was not associated with an increase in postoperative symptomatic thromboembolic events with nearly equal rates between the two groups (Table 2). This is in agreement with previous studies that have demonstrated no increase in thromboembolism risk with TXA use in a healthier population [11–13, 15, 27].

Within our larger group of all patients with ASA class III or IV, TXA was associated with a significant decrease in transfusion rates (Table 3). This is also in agreement with the current literature regarding the effect of TXA on postoperative transfusion in TJA [11, 13, 15, 18, 27].

The main focus of this article is the smaller group of patients with ASA class III or IV with a history of, or risk factors for, thromboembolism, because the effects of TXA in these patients has not been previously reported. Within our larger group of all patients with ASA class III or IV, the seven historical factors used to identify high-risk patients in this study were associated with a significant increase in postoperative symptomatic thromboembolic events (Table 4). However, within this smaller high-risk group, TXA was not associated with a significant increase in postoperative symptomatic thromboembolism (Table 5). The absolute percentages demonstrate a trend toward slightly higher risk with the administration of TXA, but the statistical power is lacking to make a definitive statement and our post hoc power analysis shows that a very sizeable group would be required to do so. Within this high-risk group, TXA again had a significant association with decreased postoperative transfusion rates (Table 6) as was also shown in our larger group and previous studies with

healthier patients [11, 13, 15, 18, 27]. It is of substantial interest that in this large group of 1002 patients, none of the three early postoperative deaths occurred in a patient who received TXA (Table 7).

As the population ages and medical advances allow patients with severe comorbidities to survive longer, the demand for these sicker patients to undergo TJA for improved quality of life will continue to increase. It is in these patients that TXA's ability to decrease blood loss and subsequent transfusion may be of the most benefit. The data from this study are valuable in assisting orthopedic surgeons and anesthesiologists to manage this group of patients who are by definition at higher risk for perioperative morbidity and mortality. Again seen is an association with TXA and decreased blood loss and transfusion rates. However, this benefit must be balanced against concern for a possible trend toward a slight increase in postoperative symptomatic thromboembolism. This population with additional risk factors requires further study to provide the best perioperative management as their demand for surgery increases.

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