The Journal of Arthroplasty 30 (2015) 272–276

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Venous Thromboembolism and Mortality Associated With Tranexamic Acid Use During Total Hip and Knee Arthroplasty

Christopher M. Duncan, MD [a], Blake P. Gillette, MD [b], Adam K. Jacob, MD [a], Rafael J. Sierra, MD [c], Joaquin Sanchez-Sotelo, MD, PhD [c], Hugh M. Smith, MD, PhD [a]

[a] Department of Anesthesia, Mayo Clinic College of Medicine, Rochester, Minnesota
[b] Department of Orthopedic Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota
[c] Department of Orthopedics, Mayo Clinic College of Medicine, Rochester, Minnesota

ARTICLE INFO

Article history:
Received 5 June 2014
Accepted 27 August 2014

Keywords:
tranexamic acid
knee arthroplasty
venothromboembolism
hip arthroplasty
mortality

ABSTRACT

TKA and THA are associated with blood transfusion and risk for postoperative venothromboembolism (VTE). Reports show that tranexamic acid (TA) may be safe to use in high-risk orthopedic patients, but further data are needed to substantiate its use. All patients who underwent primary or revision TKA or THA in a five year period were retrospectively identified. In 13,262 elective TKA or THA procedures, neither the odds of VTE (OR = 0.98; 95% CI 0.67-1.45; $P = 0.939$) or adjusted odds of death (OR = 0.26; 95% CI 0.04-1.80; $P = 0.171$) were significant with TA administration. The major findings of this large, single center, retrospective cohort study show the odds of postoperative VTE and 30-day mortality were unchanged with TA administration.

There is compelling evidence demonstrating a beneficial blood-sparing effect of tranexamic acid (TA) administration in total joint arthroplasty, but unanswered questions remain regarding its potential safety [1–12]. It is well known that synthetic lysine antifibrinolytics such as tranexamic acid prevent clot breakdown by reducing fibrin degradation [13]. While this process reduces blood loss, there is concern that reduction in clot breakdown may increase the risk of postoperative venous thromboembolism (VTE) or death [14,15], especially in procedures associated with high risk for VTE (e.g., THA, TKA) or among "high risk" patients with pre-existing veno-occlusive diseases (e.g., myocardial infarction, stroke, previous VTE). Few studies have tried to directly address the question of TA use in these populations [16].

Total hip and knee arthroplasty have historically been associated with high transfusion rates. Approximately half of patients undergoing lower extremity joint arthroplasty required two units of packed red blood cells to maintain adequate hemoglobin levels [17]. Reported negative effects of blood transfusion include immunosuppression, transfusion reaction, and increased cost [15,18–21]. In addition, blood product transfusion may increase the risk of periprosthetic joint infection [22]. Tranexamic acid has the potential to reduce these transfusion-associated complications as well as decrease the cost of care. TA administration has been shown to reduce the direct hospital cost of joint arthroplasty in healthy patients, and may have an even greater impact in high morbidity patients [23].

While previous studies have reported the frequency of adverse thrombolic events in patients undergoing TKA and THA [24,25], no adequately powered prospective studies have specifically investigated the frequency of VTE in patients receiving TA. Studies examining the hemostatic role of TA have been powered to detect differences in blood loss and blood transfusion. These studies have not been adequately powered to detect frequencies of VTE and all-cause mortality in association with TA administration [1,2,4–6,8,10–12]. Another important limitation of previous investigations of TA in orthopedic surgery is that they have excluded patients with significant pre-existing cardiovascular and thromboembolic disease [2,3,26,27], leaving open the question of whether TA should be administered to high risk patients. Only a single preliminary study has evaluated the role of TA in high risk patients, showing a slight increase in the odds of postoperative VTE with TA administration [16]. Therefore, the objective of this large, single center, retrospective cohort study was to define the frequency of clinically-significant VTE and all-cause mortality within 30 days of surgery in patients who did and did not receive TA for primary and revision THA and TKA. We hypothesized that TA administration would not increase the frequency of VTE within 30 days of TKA or THA.

Material and Methods

After institutional review board approval, the Orthopedic Department Total Joint Registry (TJR) was searched to identify all patients

Financial Support: Mayo Clinic Departments of Anesthesiology and Orthopedic Surgery.
The Conflict of Interest statement associated with this article can be found at http://dx.doi.org/10.1016/j.arth.2014.08.022.
Reprint requests: Christopher M. Duncan, MD, 200 First Street, SW Rochester, MN 55905.

http://dx.doi.org/10.1016/j.arth.2014.08.022
0883-5403/

who underwent primary or revision TKA or THA at our institution between January 1, 2005 and January 1, 2010. The TJR is a previously validated and comprehensive repository of data collected for each joint arthroplasty surgery performed at our institution since 1969 [28]. Data included within the TJR have been prospectively defined; and are collected by manual chart review, written patient questionnaire, and follow-up telephone surveys by full-time research assistants unaware of the current study hypothesis. Patients denying access to their medical or administrative records for research purposes were excluded as per Minnesota statute. Patients undergoing simultaneous bilateral procedures were also excluded, as was one patient undergoing both knee and hip arthroplasty due to osteosarcoma. For patients who underwent two joint arthroplasty surgeries within a 30 day period, only the second surgery was included in the analysis.

Patient demographic data (age, gender, weight, and height), date of surgery, surgeon, joint (TKA or THA), side of surgery (right or left), VTE and mortality were collected from the TJR. Height and weight were confirmed by electronic data mining of the medical record. After manual record extraction for missing values, a BMI was calculated for all but four patients who had missing height or weight information. The American Society of Anesthesiology Physical Status (ASA-PS) data were identified by electronic query of the anesthesia record and medical record.

The primary outcome variable was presence of clinically significant VTE within 30 days of the date of surgery. Cases of clinically significant VTE were identified from the TJR. The TJR has a dedicated support staff that read all follow-up notes, including phone conversations and radiologic reports each time a patient returns for follow-up. Thromboembolic events are recorded in the TJR if: 1) DVT and/or PE was documented in the medical record by the primary surgeon or 2) if there was radiologic evidence (i.e., ultrasound or computed tomography report) in the medical record documenting the presence of a DVT or PE. Although the collection methods of the TJR have been previously validated for other outcomes [24,29,30], additional validation of the TJR was confirmed through manual chart review of 200 randomly selected patients (100 patients with VTE, 100 patients without VTE). In all 200 patients, the TJR diagnosis of VTE (positive or negative) was confirmed. Patients experiencing multiple events were only counted once.

Following identification of all primary or revision TKA or THA procedures during the 5-year study period, patients who received TA were identified by electronic query of the perioperative datamart. The Perioperative datamart is the access layer of an institutional data warehouse containing detailed information regarding aspects of a patient's surgical encounter (e.g., demographic information, procedural descriptions, locations, start and stop times, detailed physiologic information including vital signs, ventilator data, laboratory information, and fluid, transfusion and medication administration information) [31]. The decision to administer TA was based on surgeon request and judgment of the attending anesthesiologist. Per standard TA protocol, 1000 mg was infused prior to incision and 1000 mg was infused immediately prior to closure. The primary regimen of postoperative anticoagulation was determined using patient medication administration records and/or hospital discharge summaries. Patients were assigned to the following monotherapy anticoagulation groups: aspirin, heparin, low molecular weight heparin (LMWH), or warfarin. If a patient received LMWH as a bridge to warfarin anticoagulation, they were assigned to the warfarin group. A patient who received both warfarin and aspirin following surgery was assigned to the warfarin group. Patients receiving LMWH followed by aspirin were assigned to the LMWH group.

Statistical Analysis

The primary aim of this study was to calculate the frequency and risk of clinically-significant VTE in patients who received TA and in those patients who did not receive TA. Similarly, the secondary aim was to calculate the frequency and risk of all-cause mortality in both the TA cohort and non-TA cohort.

Because many patients (>15%) had more than one surgery included in the cohort, the analysis was performed using a generalized linear model framework utilizing generalized estimating equations to properly account for the within-patient correlation. Within this analysis framework, the association of TA use (as well as other risk factors including demographics, patient characteristics, and surgical factors) with the primary outcomes of (1) VTE within 30 days of surgery, and (2) all-cause death within 30 days of surgery were evaluated using logistic regression. Odds ratios are reported with 95% confidence intervals. Because of differences in the populations that received TA and did not receive TA, a propensity score was developed to estimate the probability that a patient received TA conditional on observed patient and surgical data. The propensity score was generated using a logistic regression model, with TA or no TA as the outcome variable, and demographic, clinical, and surgical data as the independent variables. The fitted values from this model represent the propensity that a patient received TA given the observed demographic, clinical, and surgical factors. This propensity score was included as an adjusting covariate in the final multivariable model for each outcome along with an indicator for TA to minimize the potential bias between the TA and no TA groups. Data were summarized as mean (standard deviation) for continuous variables, and count (percentage) for categorical outcomes, unless otherwise noted. All statistical tests were two-sided and *P*-values less than 0.05 were considered significant. All analysis was conducted in SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

During the study period, a total of 14,100 cases were initially identified. After exclusions, a total of 13,262 elective TKA or THA procedures in 11,175 unique patients were analyzed (Fig. 1). Patient demographic information is summarized in Table 1. At the time of surgery, 71% of subjects were over the age of 60 (median age 67 years). Tranexamic acid was administered intraoperatively in 2785 procedures (21%).

A total of 196 VTE events were identified for an overall frequency of 1.48%. Thirty-seven VTE events (1.3%) were identified among 2785 procedures in which patients received TA, while 159 VTE events (1.5%) were identified among 10,477 procedures in which patients did not re-

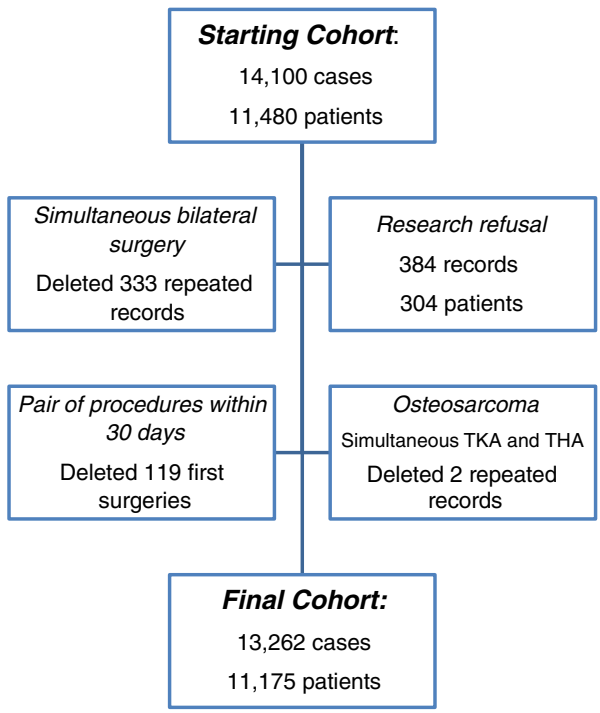

Fig. 1. Determination of final study cohort.

Table 1
Patient Characteristics.

Characteristic	Total		THA		TKA		*P*-Value[a]
	n	%	n	%	n	%	
Gender							<0.001
Female	7161	54.0%	3178	51.7%	3983	56.0%	
Male	6101	46.0%	2972	48.3%	3129	44.0%	
Age (yr)							
<50	1419	10.7%	1003	16.3%	416	5.8%	
50–59	2421	18.3%	1193	19.4%	1228	17.3%	<0.001
60–69	3791	28.6%	1545	25.1%	2246	31.6%	<0.001
70–79	4046	30.5%	1664	27.1%	2382	33.5%	<0.001
≥80	1585	12.0%	745	12.1%	840	11.8%	<0.001
BMI							
<30	6422	48.4%	3548	57.7%	2874	40.4%	
30–39.9	5514	41.6%	2186	35.6%	3328	46.8%	<0.001
≥40	1322	10.0%	413	6.7%	909	12.8%	<0.001
Missing	4	0.0%	3		1		
ASA-PS							0.124
I–II	8485	64.0%	3979	64.7%	4506	63.4%	
III–V	4777	36.0%	2171	35.3%	2606	36.6%	
Surgery type							<0.001
Primary	10,632	80.2%	4710	76.6%	5922	83.3%	
Revision	2630	19.8%	1440	23.4%	1190	16.7%	
Simultaneous bilateral							<0.001
Unilateral	12,931	97.5%	6102	99.2%	6829	96.0%	
Bilateral	331	2.5%	48	0.8%	283	4.0%	
Anticoagulation							
Aspirin	2501	18.9%	743	12.2%	1758	24.9%	
Warfarin	5211	39.3%	2539	41.6%	2672	37.8%	<0.001
LMWH	5453	41.1%	2819	46.2%	2634	37.3%	<0.001
Missing/other[a]	97	0.7%	49		48		

**THA = total hip arthroplasty, TKA = total knee arthroplasty, BMI = body mass index, ASA-PS = American Society of Anesthesiologists Physical Status, LMWH = low molecular weight heparin.
[a] *P*-values based on generalized linear models framework using GEE.

Table 2
Univariate Analysis of VTE Frequency With and Without TA Administration.

Characteristic	TA		No TA		*P*-Value[a]
	n	%	n	%	
Gender					0.52
Female	23	1.5%	90	1.6%	
Male	14	1.1%	69	1.4%	
Age (yr)					
<50	2	0.6%	14	1.3%	
50–59	7	1.2%	27	1.5%	0.43
60–69	7	0.9%	43	1.4%	0.69
70–79	16	2.1%	57	1.7%	0.21
80+	5	1.6%	18	1.4%	0.29
BMI					
<30	18	1.3%	66	1.3%	
30–39.9	19	1.6%	70	1.6%	0.98
40+	0	0.0%	23	2.0%	0.99
ASA-PS					0.76
I–II	23	1.2%	86	1.3%	
III–V	14	1.8%	73	1.8%	
Surgery type					0.91
TKA	26	1.7%	109	2.0%	
THA	11	0.9%	50	1.0%	
					0.94
Primary	35	1.4%	136	1.7%	
Revision	2	0.8%	23	1.0%	
Simultaneous bilateral					0.99
Unilateral	37	1.4%	149	1.5%	
Bilateral	0	0.0%	10	3.9%	
Anticoagulation					
Aspirin	16	1.6%	16	1.0%	0.07
Warfarin	16	1.5%	82	2.0%	0.5
LMWH	5	0.7%	59	1.3%	

[a] VTE = venous thromboembolism, TA = tranexamic acid, THA = total hip arthroplasty, TKA = total knee arthroplasty, BMI = body mass index, ASA-PS = American Society of Anesthesiologists Physical Status, LMWH = low molecular weight heparin.

ceive TA. There was no statistical difference in the adjusted odds of a clinically-significant VTE in patients that did and did not receive TA (OR = 0.98; 95% CI 0.67-1.45; $P = 0.939$). The odds of VTE within 30 days were significantly greater among simultaneous bilateral surgery (OR = 2.13; 95%CI 1.12-4.06; $P = 0.021$), primary joint arthroplasty (OR = 1.70; 95% CI 1.12-2.59; $P = 0.013$), patients undergoing TKA (OR = 1.93; 95% CI 1.43-2.61; $P < 0.001$), ASA 3-5 (OR = 1.43; 95% CI 1.07-1.90; $P = 0.015$) and patients receiving warfarin vs. LMWH (OR = 1.61; 95% CI 1.18-2.22; $P = 0.003$).

Overall, 30 deaths (0.2%) from any cause were identified within 30 days of surgery. One death occurred in a patient who received TA (0.04%), while the remaining 29 deaths were among patients who did not receive TA (0.28%). The cause of death in the patient receiving TA could not be determined and was reported as *unknown* in both the TJR and the medical record. Based on univariate analysis, patients who did not receive TA had a seven-fold higher risk than patients receiving TA (OR = 7.73; 95% CI 1.05-56.76; $P = 0.04$). However, after propensity score adjustment, the increased risk of death within 30-days of surgery among patients that did not receive TA was attenuated, and although still high, was no longer statistically significant (adjusted OR = 3.88; 95% CI 0.56-27.1; $P = 0.171$).

The odds of death within 30 days were significantly greater among males (OR = 2.74; 95%CI 1.26-6.00; $P = 0.01$), age ≥ 70 (OR = 2.35; 95% CI 1.12-4.93; $P = 0.03$), patients undergoing THA (OR = 2.70; 95% CI 1.24-5.91; $P = 0.01$), and ASA 3-5 (OR = 3.56; 95% CI 1.67-7.62; $P = 0.001$). The most frequent cause of death was a cardiovascular event (37%). Other causes included VTE (10%), respiratory (17%), and other (e.g., sepsis) or unknown (20%).

Univariate analysis was performed comparing VTE frequency with and without TA administration. No statistically significant difference in VTE frequency, TA use and gender, age, BMI, ASA PS, surgery type or the primary anticoagulants was used (Table 2).

Discussion

The primary finding in our large, single institution, retrospective cohort study is that TA administration in TKA and THA did not affect the frequency of VTE within 30 days of surgery. This is consistent with multiple studies currently in the literature, including randomized trials, systematic reviews and meta-analysis [1,2,26,32–34]. Unfortunately, each of the randomized trials was significantly underpowered to detect a difference in the VTE rate. One recent letter to the editor suggested at least 5000 patients per arm would be needed to detect a 1% difference in the VTE rate [35]. Our investigation of 13,000+ patients is the largest series to date investigating the association of TA use and risk for 30-day VTE and mortality. Given the potential time and cost of conducting a large prospective study, a retrospective cohort study like ours may be the most feasible study design to evaluate the safety of TA administration in hypercoagulable TKA and THA patients.

One of the primary concerns regarding TA administration is patient selection, especially in patients with significant vascular occlusive comorbidity. Unlike prior investigations, our study included patients with significant comorbidities including vascular occlusive diseases [2–4,27]. The inclusion of the high morbidity patients improves the generalizability of our findings and is consistent with our preliminary study on high risk patients receiving TA for TKA [16].

The frequency of VTE (1.48%) in the present study is lower than the prior large retrospective studies [24,25] of TKA and THA procedures, but higher than more recent large, retrospective studies [36,37]. White et al [25] reported an overall VTE incidence of 2.8% in over 43,000 patients undergoing primary TKA or THA between 1991 and 1993. During a 10-year cohort study from 1986 to 1995, Mantilla et al [24] reported a clinically-significant VTE frequency of 2.2%. Wu et al [37] reported an overall VTE rate of 0.44% in 114,026 TKA and THA patients from 2002

to 2006. Similarly, Guijarro et al [36] reported a PE rate of 0.18% and 0.23% and DVT rate of 0.57% and 0.44% for patients undergoing TKA and THA, respectively, during a 2005-2006 study. Compared to older studies, the reduction in VTE frequency in the current investigation is likely due to numerous factors including early ambulation and physical therapy as well as advances in VTE prophylaxis regimens, and possibly TA administration.

There was no association between TA administration and all-cause 30-day mortality. Further, after propensity adjustment, there was a trend toward a protective effect of TA administration (OR = 3.88; $P = 0.171$). In the largest randomized trial of TA administration to date, trauma patients who received the TA experienced a significant reduction in all-cause postoperative mortality [38]. Since the current study was not a randomized trial, a selection bias for withholding TA administration in patients with severe cardiovascular comorbidities remains a possibility. While selection bias may explain the absence of association between TA and all-cause 30-day mortality, an actual protective effect cannot be discounted.

These are important findings given TKA and THA are two of the most commonly performed orthopedic operations and collectively constitute the single largest procedural expenditure in the United States Medicare budget. Moreover, up to half of all these patients may require blood product transfusion during the perioperative period [17,39]. Yet routine blood product administration is increasingly discouraged among surgical patient populations because of the growing list of recognized risks: transfusion reactions, acute lung injury, volume overload, impaired wound healing, and transfusion-associated infections [20]. Among orthopedic patients, blood administration has also been specifically associated with higher rates of postoperative joint infection [22,40,41]. Beyond medical sequelae, blood product administration increases health care expenditures at a rate of $1200/unit PRBC [42,43].

Tranexamic acid has been shown to reduce blood loss and blood transfusion requirements during total joint surgery [1–12]. The reduction in transfusion through the administration of TA has the potential to dramatically reduce the overall cost of TKA and THA. In healthy patients (ASA 1-2), TA was reported to reduce overall direct hospital costs by $879 per patient [23]. Our investigation reports no increased risk of VTE or death with TA administration, including higher risk patients. Widespread use of TA in TKA and THA could result in greater cost savings and may reduce transfusion-related complications in patients with higher morbidity (ASA 3-5).

A significant strength of our investigation was the large volume of TKA and THA operations performed per year. This allowed us to retrospectively include 13,262 cases over a five-year period. The relatively short time period increases the homogeneity in surgical techniques, anesthesia and analgesia, and postoperative recovery pathways. In addition, we were able to access and cross-reference multiple validated institutional databases. This included the ability to combine electronic patient data from our orthopedic department, electronic patient medical record, pharmacy administration record and the electronic anesthesia charting record. An additional strength is the large number of patients treated with a TA dosing strategy reported in previous studies as acceptable. There is no current standard for TA administration in TKA and THA, but multiple dosing strategies have been used successfully [5]. The current recommended dose is 10 to 20 mg/kg. Instead of using weight-based dosing, our practice elected to use two doses of 1000 mg. Our practice has been using the same dosing since 2000. Recently, investigations have failed to demonstrate any significant difference between dosing strategies [44,45].

Inconsistent administration of TA during the study period is the greatest limitation of the present study. During the study period, limited data were available regarding the safety of TA, especially in patients with significant comorbidities. Additionally, during our data collection period, the practice evolved from a few surgeons ordering TA, to all surgeons ordering TA on most patients, resulting in no "standard" for TA administration. Changes in ordering practices by surgeons and selective administration by covering anesthesiologists potentially lead to a selection bias in the administration of TA. However, this limitation is likely minimized in the data by three factors. First, during the majority of the study period only two surgeons ordered TA and it was uniformly ordered regardless of patient comorbidity. Secondly, in the absence of evidence demonstrating increased VTE risks, the majority of anesthesiologists administered the TA regardless of patient comorbidity. Thirdly, a propensity model was developed to correct for TA administration patterns, including differences in anticoagulation regiments. The collection of VTE events was limited to clinically significant VTE. The retrospective nature of our study prevented active VTE screening, resulting in an inability to account for subclinical VTE. In addition, despite extensive validation to try and ensure accurate database information, the retrospective nature of data collection introduces the possibility of missing transient, yet clinically significant events that may not be have been documented. Therefore, even trained abstractors will not be able to identify those events that were 1) clinically present and *not* documented; or 2) documented >30 days after surgery but occurring during the immediate postoperative period.

Conclusions

This study demonstrates that the overall frequency of clinically-significant VTE was *lower* when TA was administered, and the odds of postoperative VTE were unchanged. Equally important, no statistically significant change was seen in 30-day mortality, although a trend toward reduced mortality with TA administration was observed. Although these results are encouraging, the exact risks of TA administration for patients undergoing THA and TKA remain unclear and our understanding of the safety of antifibrinolytic administration, including TA, remains incomplete. A large prospective, randomized trial is necessary to provide more definitive results to define the risks of TA administration for patients undergoing THA and TKA.

Acknowledgments

We would like to acknowledge the contributions of Dirk Larson (Mayo Department of Biostatistics) for his assistance with the statistical analysis and preparation of the statistical methods and results sections of manuscript.

References

1. Lozano M, Basora M, Peidro L, et al. Effectiveness and safety of tranexamic acid administration during total knee arthroplasty. Vox Sang 2008;95(1):39.
2. Alvarez JC, Santiveri FX, Ramos I, et al. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion 2008;48(3):519.
3. Molloy DO, Archbold HA, Ogonda L, et al. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. J Bone Joint Surg Br 2007;89(3):306.
4. Claeys MA, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg 2007;107(4):397.
5. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology 2006;105(5):1034.
6. Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces blood loss after cementless total hip arthroplasty-prospective randomized study in 40 cases. Int Orthop 2004;28(2):69.
7. Hynes M, Calder P, Scott G. The use of tranexamic acid to reduce blood loss during total knee arthroplasty. Knee 2003;10(4):375.
8. Husted H, Blond L, Sonne-Holm S, et al. 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;74(6):665.
9. Veien M, Sorensen JV, Madsen F, et al. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. Acta Anaesthesiol Scand 2002;46(10):1206.
10. Ekback G, Axelsson K, Ryttberg L, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000;91(5):1124.
11. Howes JP, Sharma V, Cohen AT. Tranexamic acid reduces blood loss after knee arthroplasty. J Bone Joint Surg Br 1996;78(6):995.
12. Hiippala S, Strid L, Wennerstrand M, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 1995;74(5):534.

13. Slaughter TF, Greenberg CS. Antifibrinolytic drugs and perioperative hemostasis. Am J Hematol 1997;56(1):32.
14. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57(6):1005.
15. Lange M, Van Aken H, Westphal M. Prevention and treatment of major blood loss. N Engl J Med 2007;357(12):1260 [author reply 1261].
16. Whiting DR, Gillette BP, Duncan C, et al. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res 2014;472(1):66.
17. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):381S.
18. Fraser IS, Porte RJ, Kouides PA, et al. A benefit-risk review of systemic haemostatic agents: part 1: in major surgery. Drug Saf 2008;31(3):217.
19. Ramsey EZ, Smith KM, Flynn JD. Prophylaxis of perioperative blood loss. Orthopedics 2006;29(8):689.
20. Tobias JD. Strategies for minimizing blood loss in orthopedic surgery. Semin Hematol 2004;41(1 Suppl 1):145.
21. Levy JH. Novel pharmacologic approaches to reduce bleeding. Can J Anaesth 2003;50 (6 Suppl):S26.
22. Pulido L, Ghanem E, Joshi A, et al. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res 2008;466(7):1710.
23. Gillette BP, Maradit Kremers H, Duncan CM, et al. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):137.
24. Mantilla CB, Horlocker TT, Schroeder DR, et al. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 2002;96(5):1140.
25. White RH, Romano PS, Zhou H, et al. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Arch Intern Med 1998;158(14): 1525.
26. Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces postoperative blood loss in cementless total hip arthroplasty. J Bone Joint Surg Am 2005;87(4):766.
27. Alipour M, Tabari M, Keramati M, et al. Effectiveness of oral tranexamic acid administration on blood loss after knee artroplasty: a randomized clinical trial. Transfus Apher Sci 2013;49(3):574.
28. Berry DJ, Kessler M, Morrey BF. Maintaining a hip registry for 25 years. Mayo Clinic experience. Clin Orthop Relat Res 1997(344):61.
29. Jacob AK, Mantilla CB, Sviggum HP, et al. Perioperative nerve injury after total hip arthroplasty: regional anesthesia risk during a 20-year cohort study. Anesthesiology 2011;115(6):1172.
30. Jacob AK, Mantilla CB, Sviggum HP, et al. Perioperative nerve injury after total knee arthroplasty: regional anesthesia risk during a 20-year cohort study. Anesthesiology 2011;114(2):311.
31. Holtby H, Skowno JJ, Kor DJ, et al. New technologies in pediatric anesthesia. Paediatr Anaesth 2012;22(10):952.
32. Kagoma YK, Crowther MA, Douketis J, et al. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb Res 2009;123(5):687.
33. Panteli M, Papakostidis C, Dahabreh Z, et al. Topical tranexamic acid in total knee replacement: a systematic review and meta-analysis. Knee 2013;20(5):300.
34. Tan J, Chen H, Liu Q, et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res 2013;184 (2):880.
35. Munoz M, Paramo JA. Antifibrinolytic agents in current anaesthetic practice: use of tranexamic acid in lower limb arthroplasty. Br J Anaesth 2014;112(4):766.
36. Guijarro R, Montes J, San Roman C, et al. Venous thromboembolism and bleeding after total knee and hip arthroplasty. Findings from the Spanish National Discharge Database. Thromb Haemost 2011;105(4):610.
37. Wu PK, Chen CF, Chung LH, et al. Population-based epidemiology of postoperative venous thromboembolism in Taiwanese patients receiving hip or knee arthroplasty without pharmacological thromboprophylaxis. Thromb Res 2014;133(5):719.
38. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23.
39. Bozic KJ, Katz P, Cisternas M, et al. Hospital resource utilization for primary and revision total hip arthroplasty. J Bone Joint Surg Am 2005;87(3):570.
40. Schwarzkopf R, Chung C, Park JJ, et al. Effects of perioperative blood product use on surgical site infection following thoracic and lumbar spinal surgery. Spine (Phila Pa 1976) 2010;35(3):340.
41. Steinitz D, Harvey EJ, Leighton RK, et al. Is homologous blood transfusion a risk factor for infection after hip replacement? Can J Surg 2001;44(5):355.
42. Blumberg N. Allogeneic transfusion and infection: economic and clinical implications. Semin Hematol 1997;34(3 Suppl. 2):34.
43. Shander A, Hofmann A, Gombotz H, et al. Estimating the cost of blood: past, present, and future directions. Best Pract Res Clin Anaesthesiol 2007;21(2):271.
44. Hourlier H, Fennema P. Single tranexamic acid dose to reduce perioperative morbidity in primary total hip replacement: a randomised clinical trial. Hip Int 2014;24(1): 63.
45. Levine BR, Haughom BD, Belkin MN, et al. Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29(9 Suppl):186.