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RESEARCH

Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety

Jashvant Poeran *assistant professor*[1], Rehana Rasul *biostatistician*[1], Suzuko Suzuki *fellow anesthesiology*[2], Thomas Danninger *research fellow anesthesiology*[2], Madhu Mazumdar *professor*[1], Mathias Opperer *research fellow anesthesiology*[2], Friedrich Boettner *attending orthopedic surgeon*[3], Stavros G Memtsoudis *attending anesthesiologist and senior scientist*[2] *clinical professor of anesthesiology and public health*[4]

[1]Institute of Healthcare Delivery Science, Mount Sinai Hospital System / Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Department of Anesthesiology, Hospital for Special Surgery, 535 East 70th Street, New York, NY, USA; [3]Department of Orthopedic Surgery, Hospital for Special Surgery, New York, NY, USA; [4]Department of Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, USA

Abstract

Objective To determine the effectiveness and safety of perioperative tranexamic acid use in patients undergoing total hip or knee arthroplasty in the United States.

Design Retrospective cohort study; multilevel multivariable logistic regression models measured the association between tranexamic acid use in the perioperative period and outcomes.

Setting 510 US hospitals from the claims based Premier Perspective database for 2006-12.

Participants 872 416 patients who had total hip or knee arthroplasty.

Intervention Perioperative intravenous tranexamic acid use by dose categories (none, ≤1000 mg, 2000 mg, and ≥3000 mg).

Main outcome measures Allogeneic or autologous transfusion, thromboembolic complications (pulmonary embolism, deep venous thrombosis), acute renal failure, and combined complications (thromboembolic complications, acute renal failure, cerebrovascular events, myocardial infarction, in-hospital mortality).

Results While comparable regarding average age and comorbidity index, patients receiving tranexamic acid (versus those who did not) showed lower rates of allogeneic or autologous transfusion (7.7% *v* 20.1%), thromboembolic complications (0.6% *v* 0.8%), acute renal failure (1.2% *v* 1.6%), and combined complications (1.9% *v* 2.6%); all P<0.01. In the multilevel models, tranexamic acid dose categories (versus no tranexamic acid use) were associated with significantly (P<0.001) decreased odds for allogeneic or autologous blood transfusions (odds ratio 0.31 to 0.38 by dose category) and no significantly increased risk for complications: thromboembolic complications (odds ratio 0.85 to 1.02), acute renal failure (0.70 to 1.11), and combined complications (0.75 to 0.98).

Conclusions Tranexamic acid was effective in reducing the need for blood transfusions while not increasing the risk of complications, including thromboembolic events and renal failure. Thus our data provide incremental evidence of the potential effectiveness and safety of tranexamic acid in patients requiring orthopedic surgery.

Introduction

Reducing blood loss and the need for blood transfusions surrounding orthopedic surgery remains a major concern among clinicians during the perioperative period. Many interventions have been developed over the past decades to achieve this goal, including controlled hypotensive anesthesia[1] and various blood salvage techniques. In addition, pharmacologic approaches have become more popular in recent years. Especially, tranexamic acid has seen a renaissance among patients requiring orthopedic surgery, with numerous publications showing clinical efficacy and cost effectiveness.[2-6] Indeed, a recent study found that the use of tranexamic acid may even make the use of blood salvage

Correspondence to: S G Memtsoudis memtsoudiss@hss.edu

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Supplementary tables 1-6

equipment unnecessary.[7] Despite these promising results, valid data on safety are lacking, as large sample sizes are needed to determine this outcome. Thus concerns about the routine use of tranexamic acid remain.[5 8 9] Data on perioperative outcomes, especially those related to thromboembolic events and renal complications, which have traditionally been of concern in the setting of antifibrinolytic use, are rare. Further, no population based data are available detailing outcomes in a large cohort outside of randomized controlled trials, which often only include selected patients based on stringent inclusion criteria and are thus not reflective of real world practice and are burdened by low external validity.[3]

Utilizing a large national database, we compared the characteristics and outcomes between patients receiving tranexamic acid and those that did not and analyzed if the use of tranexamic acid is independently associated with altered odds for blood transfusions and perioperative complications, particularly thromboembolic events and acute renal failure. We hypothesized that the characteristics associated with treated and untreated patients differed, and that tranexamic acid decreases the odds for blood transfusions while not increasing the risk of perioperative complications.

Methods

Data source and study design

For this retrospective cohort study we used the Premier Perspective database[10] (Premier, Charlotte, NC) containing information on surgical hospital discharges from January 2006 to October 2012. This database provides complete billing information on a patient's hospital stay as well as information on international classification of diseases-ninth revision clinical modification codes (ICD-9 CM) and current procedural terminology codes. Billed items are standardized by the database vendor after the hospital both reviews and consents to the items.

Study sample

We included cases if they had an indication of elective total hip or knee arthroplasty by the presence of ICD-9 CM codes 81.51 and 81.54, respectively. Cases were excluded if information on sex was unavailable (n=10), discharge status was unknown, patients were still listed as in-patients at the end of the data collection period (n=291), or patients had both a total hip and a total knee arthroplasty during the same hospital stay (n=193).

Study variables

The main intervention variable was the use of intravenous tranexamic acid on the day of surgery (further referred to as perioperative tranexamic acid use), which we categorized into four groups based on billing information retrieved dosing: none, ≤1000 mg, 2000 mg, and ≥3000 mg. Patient characteristics included age, sex, and race (white, black, Hispanic, other). Healthcare related variables included type of insurance (commercial, Medicaid, Medicare, uninsured, other), hospital location (rural, urban), hospital bed size (<300, 300-499, ≥500), hospital teaching status, and the mean annual number of total hip and knee arthroplasties per hospital. Procedure related variables included type of procedure (total hip or knee arthroplasty, unilateral or bilateral for both), type of anesthesia (general, neuraxial, general and neuraxial combined, other, unknown), use of peripheral nerve block, use of anticoagulants (antiplatelets (aspirin, other), warfarin, heparin, other), and year of procedure. Analogous to a previous report by our study group,[11] we used billed items to define type of anesthesia. The same applied to the definition of the use of anticoagulants (see supplementary appendix 1) for which we also took into account simultaneous use of multiple medications.

We used the Deyo adaptation of the Charlson comorbidity index to measure overall comorbidity burden.[12] Individual Elixhauser comorbidities,[13] and the presence of sleep apnea (not included in either index) were evaluated.

Primary outcome variables included transfusion (allogeneic or both allogeneic and autologous), thromboembolic complications (pulmonary embolism, deep venous thrombosis), and acute renal failure. In addition, we considered a combined complication variable, which included thromboembolic complications and acute renal failure as well as in-hospital mortality, cerebrovascular events, and acute myocardial infarction. Secondary outcome variables included mechanical ventilation, admission to an intensive care unit, length of hospital stay in days, and cost of hospital stay in US dollars. Supplementary appendix 2 gives an overview of the ICD-9 codes used.

Univariable analysis

The association between tranexamic acid use and study variables was assessed using χ^2 tests for categorical variables and *t* tests for continuous variables. Median and interquartile range were reported for length of hospitalization and cost of hospital stay due to their skewed distribution; significance between groups was measured using the Mann-Whitney rank sum test. To facilitate overall readability of the main manuscript text we chose to illustrate the univariable analyses by categorical "yes or no" tranexamic acid use instead of the more detailed categorization by dosage; the latter tables are provided in supplementary appendices 3 to 5.

Multilevel logistic regression analysis

We built separate multilevel multivariable logistic regression models to measure the association between use of tranexamic acid and the binary outcome variables. To account for correlation of patients within hospitals we included a random intercept term that varies at the level of each hospital. All hospitals (clusters) had sufficient patients (n>30) according to previously recommended sample sizes for this type of model to reduce bias.[14] We adjusted models using all available demographic, healthcare related, procedure related, and comorbidity variables that were significant (P<0.15[15]) in the univariable analysis. Odds ratios (95% confidence intervals) and P values are reported and used together as a measure of overall significance.

Propensity score matching

To test the robustness of results and their sensitivity to the methodology chosen, we conducted a propensity score analysis. We calculated propensity scores from a multilevel logistic regression model with the outcome of tranexamic acid use (categorized into "yes or no" as opposed to the more detailed categorization used in the multilevel model) and the same covariates used in the primary analysis. A patient who received tranexamic acid (case) was matched with three patients who did not receive this drug (controls) by comparing their propensity scores.[16] We measured the balance between the groups by comparing standardized differences on the original study sample and the matched sample.[17] Although there is no consensus on a standard threshold to consider as an acceptable balance, a standardized difference of less than 10% or 0.1 to indicate negligible differences between groups has been suggested.[18] The Cochran-Mantel-Haenszel estimate of the common odds ratio to control for the three pairs of matches and 95%

confidence intervals were estimated on the matched sample to evaluate the effect of use of tranexamic acid on outcomes.

All analyses were performed in SAS v9.3 statistical software (SAS Institute, Cary, NC). The SAS procedure GLIMMIX was used for multilevel regression analyses. To match samples for propensity score analysis we used the SAS macro OneToManyMTCH with 8-digit to 1-digit match without replacement.

Results

The study sample consisted of 872 416 cases of elective total hip or knee arthroplasty from 510 hospitals.

Univariable results

Table 1⇓ lists the patient characteristics, healthcare related variables, and procedure related variables by tranexamic acid use. Except for average age (65.9 years for the tranexamic acid groups *v* 65.8 years for the no tranexamic acid group), all differences between the group of patients receiving tranexamic acid versus the group not receiving tranexamic acid were significant. Most notably, tranexamic acid was given more often to white patients (82.7% *v* 75.7%), in medium sized (300-499 beds) hospitals (57.7% *v* 37.4%), and in hospitals with a higher mean annual number of total hip or knee arthroplasties (776.6 *v* 731.2). Moreover, perioperative tranexamic acid use increased dramatically, from almost 0% in 2006 to 11.2% in 2012.

Table 2⇓ shows the comorbidity burden by tranexamic acid use. The mean Deyo-Charlson comorbidity index differed only slightly between the groups (0.72 for patients in the tranexamic acid group *v* 0.74 for patients in the no tranexamic acid group, P=0.0267). The incidence of individual comorbidities was similar in both groups for most comorbidities.

Primary and secondary outcome variables

Table 3⇓ shows the primary and secondary outcome variables by tranexamic acid use. Compared with patients who did not receive tranexamic acid, patients receiving tranexamic acid had lower rates of all binary outcomes: allogeneic or autologous transfusion (7.7% *v* 20.1%, P<0.001), thromboembolic complications (0.6% *v* 0.8%, P=0.0057), combined complications (1.9% *v* 2.6%, P<0.001), need for mechanical ventilation (0.1% *v* 0.2%, P=0.0003), and admission to an intensive care unit (3.1% *v* 7.5%, P<0.001). Median length of hospital stay was three days for both groups; median cost of hospital stay was $14 890 for the tranexamic acid group compared with $15 110 for the group not receiving tranexamic acid, P<0.001.

Multilevel logistic regression analysis

When controlling for covariates, the use of tranexamic acid was significantly associated with a decreased need for allogeneic or autologous blood transfusions (odds ratio varying from 0.31 to 0.38 by dose category), and allogeneic blood transfusions (odds ratio 0.29 to 0.37), with no significantly increased risk for complications: thromboembolic complications (0.85 to 1.02), acute renal failure (0.70 to 1.11), combined complications (0.75 to 0.98), and admission to an intensive care unit (0.73 to 1.01) (table 4⇓). For the dosage categories, 2000 mg tranexamic acid seemed to have the best effectiveness and safety profile. For all models, the C statistics were high (range 0.83 to 0.90).

Propensity score matching

Out of the 20 051 patients who received tranexamic acid (cases), 5486 were successfully matched to patients who did not receive tranexamic acid (controls). The matched sample was well balanced (standardized differences <10%) for almost all variables (see supplementary appendix 3). Similar to the multilevel models, the propensity score analyses showed decreased odds for allogeneic or autologous transfusion (odds ratio 0.50, 95% confidence interval 0.45 to 0.55) and allogeneic transfusion (0.47, 0.42 to 0.53) in patients given tranexamic acid. In this model too, we found no increased risk for complications: thromboembolic complications (0.86, 0.59 to 1.25), acute renal failure (0.74, 0.57 to 0.96), combined complications (0.75, 0.61 to 0.92), and admission to an intensive care unit (0.85, 0.74 to 0.99).

Discussion

In this population based study of 872 416 total hip and knee arthroplasty procedures, the use of tranexamic acid was significantly associated with an up to 69% reduction in the need for allogeneic or autologous blood transfusions. Further, irrespective of the use of anticoagulants, tranexamic acid use was not associated with an increased risk for perioperative complications, including thromboembolic events and acute renal failure. In a univariable context, we also found the use of tranexamic acid to be associated with reduced healthcare utilization: lower rates of advanced care need, lower length of hospital stay, and lower costs of hospital stay.

Strengths and limitations of this study

The main strengths of our study are the large sample size, use of data from actual, everyday practice (establishing generalizability), and the multivariable multilevel analysis controlling not only for individual level factors but also for hospital clusters. In particular, the ability to control for the use of anticoagulants and type of anesthesia—both important determinants of transfusion risk—is unique for population based databases. Further, the large sample size allows for the study of safety concerns regarding the incidence of rare complications such as pulmonary embolism or deep venous thrombosis. Meta-analyses are limited in their utility to assess generalizable safety concerns about perioperative tranexamic acid use, as patients with, for example, a history of cardiovascular disease or those taking warfarin or low molecular weight heparin, are often excluded from these trials.[3]

Our study has several limitations. First, our analysis utilized data from an administrative database, and detailed clinical information was missing, including hemoglobin levels or other transfusion triggers. We expect the multilevel model to account in part for this limitation as it adjusts for practice variations among hospitals (of which transfusion practices are a part). In addition, our outcome is the actual transfusion being administered regardless of the existence of triggers. As in all other guidelines, transfusion triggers are not static and, especially in the perioperative period, may be dynamic and only partially dependent on hemoglobin levels, as rapidly changing variables such as patients' symptoms and expected trajectory may also play important roles. Thus, lack of detailed clinical data will remain a problem for studies that use retrospective data. Furthermore, having detailed clinical information still would not guarantee perfect validity of data as there will always be unmeasured factors influencing decisions and outcomes. This problem is dealt with in a randomized clinical trial setting, but then again at the cost of loss of generalizability to more general

populations. Another important facet of the lack of detailed clinical data refers to the selective use of tranexamic acid in patients with arterial stents or a history of thromboembolic events, both considered relative contraindications for tranexamic acid use by some practitioners. However, the pseudorandomized approach of the propensity score analysis showed the same results as the multilevel analysis. Moreover, although the Elixhauser comorbidities (but also other patient characteristics) do not specifically capture these contraindications, they might act as a partial proxy, thus reducing the effect of this limitation. Another limitation refers to residual confounding. Although we included many important covariates in our analytic models while also accounting for correlation of patients within hospitals, residual confounding might remain. However, the multilevel models showed high C statistics (up to 0.90) indicating good model discrimination between subjects for each level of the outcome. The use of ICD-9 codes and billing data may also be associated with (registration) bias. However, this bias should be equally distributed between our treatment groups, thus reducing its impact. Although we did have information on the dose of tranexamic acid using billing data, we do not know with complete certainty how much of the billed medication was actually administered to the patients as this is a topic of major controversy. We therefore have limited our statements to the categorical ("yes or no") use of tranexamic acid. Finally, in respect to the safety of tranexamic acid we were only able to study complications that occurred during the patients' hospital stay, which is an inherent limitation of our data source. This may cause an underestimation of the actual incidence of complications. However, one study showed that more than 90% of complications in unilateral arthroplasties occur within four days after surgery, suggesting that most complications should be encompassed within our dataset.[19]

Comparison with existing literature

The use of tranexamic acid has been shown to be effective in reducing blood transfusions both in small, randomized controlled trials and in meta-analytic publications.[2-7 9] Our study validates these findings, by providing data on effectiveness from information gathered in a wide range of settings representing actual, "real world" practice. This is important, as the information gathered from randomized controlled trials conducted in single institutional—often academic—settings frequently lacks external validity, as participants tend to be highly selected. The effect size, as measured by the reduction in the odds for the need of allogeneic or autologous blood transfusions by up to 69% was large even by conservative standards. This finding has significant implications for two reasons: firstly, total hip and knee arthroplasty are common procedures, with over one million interventions annually in the United States alone,[20] and the utilization is expected to increase dramatically in the future.[21] Secondly, joint arthroplasties are associated with significant blood loss with relatively high transfusion rates compared with other elective surgeries.[22] In this context, the use of tranexamic acid in patients undergoing total joint arthroplasty may have a profound clinical and economic impact if used in appropriate candidates—that is, those at high risk for requiring blood transfusions.[23 24]

When analyzing the impact of tranexamic acid use on complications we found no increased risk for adverse outcomes in general, and for thromboembolic events and acute renal failure in particular. In fact, the multilevel model showed significantly decreased risks for some complications. These complications have been put forward by several clinicians as major reasons for a conservative use of tranexamic acid given previously published concerns with agents of this category.[25] As tranexamic acid inhibits fibrinolysis, safety concerns are based on the fact that interference with the coagulation cascade may promote a procoagulable state and thus increase the risk for complications such as pulmonary embolism, deep venous thrombosis, myocardial infarctions, and cerebrovascular events.[25] This is of particular concern as patients who require joint arthroplasty have been identified as an especially vulnerable group for clotting based complications as the source of major morbidity and mortality.[26] Further, previous publications have identified the use of certain antifibrinolytics to be associated with increased mortality in surgical patients, leading to the withdrawal of aprotinin from the US market.[27] Renal failure was identified as a major contributor to this outcome and has since been the focus of many outcome studies related to antifibrinolytics.[28] Although comparative evaluations between aprotinin and other agents such as tranexamic acid have been published showing improved safety profiles with tranexamic acid, such studies are scarce for the population of patients requiring orthopedic procedures.[28] Even though a meta-analysis showed efficacy of either agent in patients requiring orthopedic surgery, the authors concluded that safety data are needed before recommending the use of these agents in this patient population.[29] Despite encouraging results derived from our analysis regarding the safety of tranexamic acid, we cannot provide support for the ubiquitous use of tranexamic acid in all patients requiring joint arthroplasty as the differential impact on complications among patient subpopulations remains to be studied. In this context, studies with aprotinin have suggested that the use of this antifibrinolytic agent among low to intermediate risk patients requiring cardiac surgery may increase mortality risk, while not having the same effect in high risk patients.[30] Thus, a conservative approach taking into account appropriate stratification strategies for bleeding risk seems prudent when deciding to use any antifibrinolytic perioperatively. Future studies might focus on this subgroup specific effectiveness and safety of tranexamic acid.

Conclusions and implications

Utilizing population based data we found that tranexamic acid was effective in reducing the need for blood transfusions while not increasing the risk of complications, including thromboembolic events and renal failure. Although our data provide incremental evidence of the potential effectiveness and safety of tranexamic acid in patients requiring orthopedic surgery, this study has limitations inherent to observational analyses. Moreover, outcome data in subpopulations of patients remain to be studied. Therefore, the prudent identification of patients most likely to benefit from tranexamic acid—that is, those at increased risk of bleeding—is warranted. Additional studies focusing not only on subgroup specific effectiveness and safety but also on optimal dosing schemes are needed.

Contributors: JP, RR, MM, and SGM designed the study and attained the Premier Perspective database. RR and JP analyzed data under guidance of SGM and MM. All authors contributed to the interpretation of the results, particularly TD, MO, SS, and FB with their clinical viewpoints. All authors reviewed and approved the final manuscript. All authors, particularly JP and RR, had full access to all of the data in the study. All authors gave their final approval of the submitted manuscript and agreed to be accountable for all aspects of the work. JP and RR take responsibility for the integrity of the data and the accuracy of the data analysis. SGM is the guarantor.

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What is already known on this topic

Tranexamic acid has been shown to reduce perioperative blood loss and blood transfusions in orthopedic surgery

Safety concerns remain, however, as small and highly selective populations were studied

Large scale effectiveness studies are lacking

What this study adds

Tranexamic acid is associated with a decreased risk for blood transfusions, while not increasing the risk of complications, including thromboembolic events and renal failure

Our data provide incremental evidence of the potential effectiveness and safety of tranexamic acid in patients requiring orthopedic surgery

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: These data meet the requirements of deidentification as defined by the Health Insurance Portability and Accountability Act and were exempt from consent requirements of the Hospital for Special Surgery institutional review board (No 2012-050-CR2).

Data sharing: Data were purchased from Premier and as such are restricted for this project and cannot be shared because of these restrictions on use of data. Syntax is available from the corresponding author (memtsoudiss@hss.edu).

Transparency: The senior author, SGMemtsoudis (the manuscript's guarantor), affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Tables

Table 1| Patient characteristics and healthcare and procedure related variables by tranexamic acid use. Values are numbers (percentages) unless stated otherwise

Variables	Tranexamic acid (n=20 051)	No tranexamic acid (n=852 365)	P value*
Tranexamic acid dose (mg):			
None	—	852 365 (100.0)	
≤1000	7041 (35.1)	—	—
2000	8992 (44.9)	—	
≥3000	4018 (20)	—	
Patient characteristics			
Mean (SD) age	65.9 (10.6)	65.8 (11)	0.2554
Age category (years):			
<45	513 (2.6)	24 584 (2.9)	<0.001
45-54	2334 (11.6)	107 604 (12.6)	
55-64	5834 (29.1)	244 809 (28.7)	
65-74	6973 (34.8)	276 301 (32.4)	
≥75	4397 (21.9)	199 067 (23.4)	
Female	12 358 (61.6)	518 978 (60.9)	0.0324
Male	7693 (38.4)	333 387 (39.1)	
Race:			
White	16 578 (82.7)	645 157 (75.7)	<0.001
Black	1920 (9.6)	58 628 (6.9)	
Hispanic	32 (0.2)	14 572 (1.7)	
Other	1521 (7.6)	134 008 (15.7)	
Healthcare related			
Insurance type:			
Commercial	7614 (38)	326 811 (38.3)	<0.001
Medicaid	390 (1.9)	21 894 (2.6)	
Medicare	11 302 (56.4)	471 430 (55.3)	
Uninsured	126 (0.6)	4551 (0.5)	
Other	619 (3.1)	27 679 (3.2)	
Hospital location			
Rural	3215 (16)	93 594 (11)	<0.001
Urban	16 836 (84)	758 771 (89)	
Hospital bed size:			
<300	5582 (27.8)	299 687 (35.2)	<0.001
300-499	11 567 (57.7)	318 544 (37.4)	
≥500	2902 (14.5)	234 134 (27.5)	
Hospital teaching status:			
Non-teaching	13 662 (68.1)	520 228 (61)	<0.001
Teaching	6389 (31.9)	332 137 (39)	
Mean (SD) annual No of total hip and knee arthroplasties per hospital	776.55 (382)	731.21 (672.8)	<0.001
Procedure related			
Type of arthroplasty:			
Unilateral knee	12 310 (61.4)	545 422 (64)	<0.001
Bilateral knee	882 (4.4)	34 798 (4.1)	
Unilateral hip	6785 (33.8)	26 9467 (31.6)	
Bilateral hip	74 (0.4)	2678 (0.3)	
Type of anesthesia:			

Table 1 (continued)

Variables	Tranexamic acid (n=20 051)	No tranexamic acid (n=852 365)	P value*
General	9232 (46)	491 388 (57.7)	<0.001
Neuraxial	1876 (9.4)	94 201 (11.1)	
General/neuraxial combined	2761 (13.8)	101 368 (11.9)	
Other	2093 (10.4)	116 924 (13.7)	
Unknown	4089 (20.4)	48 484 (5.7)	
Use of peripheral nerve block:			
No	17 235 (86)	704 493 (82.7)	<0.001
Yes	2816 (14)	147 872 (17.3)	
Use of anticoagulants:			
Antiplatelets: aspirin	2602 (13)	43 046 (5.1)	<0.001
Antiplatelets: other	3591 (17.9)	97 608 (11.5)	
Anticoagulants: warfarin	5293 (26.4)	219 407 (25.7)	
Anticoagulants: heparin	3142 (15.7)	225 168 (26.4)	
>1 of above	5075 (25.3)	243 520 (28.6)	
None	348 (1.7)	23 616 (2.8)	
Year of procedure:			
2006	2 (0.01)	103 532 (12.1)	<0.001
2007	22 (0.1)	111 168 (13)	
2008	167 (0.8)	116 739 (13.7)	
2009	240 (1.2)	130 532 (15.3)	
2010	1074 (5.4)	143 319 (16.8)	
2011	5643 (28.1)	144 357 (16.9)	
2012	12 903 (64.4)	102 718 (12.1)	

*χ^2 test for categorical variables, *t* test for continuous variables.

Table 2| **Comorbidities by tranexamic acid use. Values are numbers (percentages) unless stated otherwise**

Comorbidities	Tranexamic acid (n=20 051)	No tranexamic acid (n=852 365)	P value*
Mean (SD) Deyo-Charlson comorbidity index	0.72 (1.05)	0.74 (1.05)	0.0267
Elixhauser comorbidity grouping:			
Congestive heart failure	520 (2.6)	27 663 (3.2)	<0.001
Valvular disease	906 (4.5)	43 238 (5.1)	0.0004
Pulmonary circulation disease	240 (1.2)	12 010 (1.4)	0.0117
Peripheral vascular disease	615 (3.1)	26 030 (3.1)	0.9137
Paralysis	64 (0.3)	3327 (0.4)	0.1096
Other neurological disorders	894 (4.5)	37 166 (4.4)	0.5006
Chronic pulmonary disease	3261 (16.3)	139 304 (16.3)	0.7629
Diabetes, no chronic complications	3703 (18.5)	162 615 (19.1)	0.0297
Diabetes, chronic complications	335 (1.7)	15 726 (1.8)	0.0696
Hypothyroidism	3463 (17.3)	134 721 (15.8)	<0.001
Renal compromise	918 (4.6)	35 215 (4.1)	0.0017
Hypertension, uncomplicated	12 866 (64.2)	548 962 (64.4)	0.4863
Hypertension, complicated	1055 (5.3)	44 037 (5.2)	0.5476
Liver disease	256 (1.3)	9871 (1.2)	0.1210
Chronic peptic ulcer disease	7 (0.0)	482 (0.1)	0.2007
HIV/AIDS	11 (0.1)	516 (0.1)	0.7464
Lymphoma	69 (0.3)	2916 (0.3)	0.9615
Metastatic cancer	45 (0.2)	2063 (0.2)	0.6158
Solid tumor without metastasis	327 (1.6)	12 777 (1.5)	0.1293
Rheumatoid arthritis/collagen vascular disease	1050 (5.2)	41 586 (4.9)	0.0202
Coagulopathy	848 (4.2)	22 997 (2.7)	<0.001
Obesity	5381 (26.8)	190 198 (22.3)	<0.001
Weight loss	158 (0.8)	6614 (0.8)	0.8478
Fluid and electrolyte disorders	2318 (11.6)	94 965 (11.1)	0.0623
Chronic blood loss anemia	334 (1.7)	21 980 (2.6)	<0.001
Deficiency anemia	4030 (20.1)	167 718 (19.7)	0.1375
Alcohol misuse	118 (0.6)	5122 (0.6)	0.8220
Drug misuse	133 (0.7)	5727 (0.7)	0.8830
Psychosis	433 (2.2)	18 257 (2.1)	0.8651
Depression	3145 (15.7)	118 380 (13.9)	<0.001
Other:			
Sleep apnea	2730 (13.6)	89 923 (10.6)	<0.001

*χ^2 test for categorical variables, *t* test for continuous variables.

Table 3| **Outcome variables by tranexamic acid use. Values are numbers (percentages) unless stated otherwise**

Variables	Tranexamic acid (n=20 051)	No tranexamic acid (n=852 365)	P value*
Primary outcome variables			
Allogeneic or autologous transfusion	1549 (7.7)	171 423 (20.1)	<0.001
Allogeneic transfusion only	1202 (6.0)	123 764 (14.5)	<0.001
Thromboembolic complications:			
Deep venous thrombosis	85 (0.4)	3993 (0.5)	0.3607
Pulmonary embolism	49 (0.2)	3169 (0.4)	0.0033
Other:			
Acute renal failure	250 (1.2)	13 383 (1.6)	0.0003
In-hospital mortality	7 (0.04)	672 (0.1)	0.0275
Cerebrovascular events	13 (0.1)	853 (0.1)	0.1173
Acute myocardial infarction	20 (0.1)	1945 (0.2)	0.0002
Combined complications†	382 (1.9)	22 041 (2.6)	<0.001
Secondary outcome variables			
Mechanical ventilation	11 (0.1)	1344 (0.2)	0.0003
Admission to intensive care unit	628 (3.1)	63 828 (7.5)	<0.001
Median(interquartile range) length of hospital stay (days)‡	3 (2-4)	3 (3-4)	<0.001
Median (interquartile range) cost of hospital stay ($)‡	14 890 (12 508-17 483)	15 110 (12 409-18 740)	<0.001

*χ^2 test for categorical variables.

†Thromboembolic and "other" complications combined.

‡Mann-Whitney rank sum test.

Table 4| Results from multilevel logistic regression model and propensity score analysis for primary outcomes. Values are odds ratios† (95% confidence intervals) unless stated otherwise

	Multilevel logistic regression‡				Propensity score analysis
Outcomes	Tranexamic acid ≤1000 mg	Tranexamic acid 2000 mg	Tranexamic acid ≥3000 mg	C statistic	Tranexamic acid *v* no tranexamic acid
Allogeneic or autologous transfusion	0.38 (0.35 to 0.42)*	0.31 (0.28 to 0.34)*	0.31 (0.27 to 0.36)*	0.83	0.50 (0.45 to 0.55)*
Allogeneic transfusion only	0.37 (0.33 to 0.41)*	0.29 (0.26 to 0.32)*	0.31 (0.27 to 0.37)*	0.83	0.47 (0.42 to 0.53)*
Thromboembolic complications	1.02 (0.71 to 1.45)	0.99 (0.70 to 1.39)	0.85 (0.53 to 1.35)	0.90	0.86 (0.59 to 1.25)
Acute renal failure	0.80 (0.63 to 1.02)	0.70 (0.55 to 0.88)*	1.11 (0.84 to 1.45)	0.89	0.74 (0.57 to 0.96)*
Combined complications	0.79 (0.65 to 0.96)*	0.75 (0.62 to 0.91)*	0.98 (0.78 to 1.24)	0.86	0.75 (0.61 to 0.92)*
Admission to intensive care unit	0.73 (0.63 to 0.86)*	1.01 (0.88 to 1.16)	0.89 (0.72 to 1.10)	0.89	0.85 (0.74 to 0.99)*

*P<0.05.

†In multilevel logistic regression analysis adjusted for age, sex, race, insurance type, hospital location, hospital size, hospital teaching status, mean annual number of total hip and knee arthroplasties per hospital, type of anesthesia, use of peripheral nerve block, use of anticoagulants, year of procedure, type of procedure (2006 to 2008 combined owing to low frequencies), congestive heart failure, valvular disease, pulmonary circulation disease, paralysis, diabetes with no chronic complications, hypothyroidism, renal compromise, liver disease, rheumatoid arthritis or collagen vascular disease, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, chronic blood loss anemia, deficiency anemia, drug misuse, depression, and sleep apnea.

‡Reference group was no tranexamic acid.