Original Article

Effectiveness and Safety of the Combined Use of Tranexamic Acid: A Comparative Observational Study of 1909 Cases

Abstract

Background: Tranexamic acid (TA) use in lower-limb arthroplasty has been valued in these surgeries high-risk hemorrhagic due to its antifibrinolytic action. The objective of the present study was to determine the effectiveness of the combined intravenous (IV) and intraarticular (IA) administration of TA in lower-limb arthroplasty. **Methods:** We conduct a prospective observational study between January 1, 2014, and December 31, 2017, including all programmed lower-limb arthroplasties. Patients were divided into four groups: no TA, 15 mg/kg IV TA, 3 g IA TA, and 15 mg/kg IV and 3 g IA. The effect on calculated total blood loss (milliliter of red blood cell [RBC]), hemoglobin, transfusion, and duration of hospitalization was studied after adjustment on age, American Society of Anesthesiologists, surgery, and postoperative curative anticoagulation. Complications related to TA administration were systematically reported. **Results:** A total of 1909 patients were included – "no TA," n = 184; "IV," n = 1137; "IA," n = 214; and "IV + IA," n = 374. In the IV + IA group, a decrease in blood loss was observed compared to the no TA group (+220 ml 95% confidence interval [CI] [184; 255] of RBC $P < 0.001$) and in the IA group (+65 ml 95% CI [30; 99] of RBC $P < 0.001$). The length of hospital stay of the IV + IA group was shorter compared to the no TA group (hazard ratio [HR] 0.35, 95% CI [0.29; 0.43], $P < 0.001$) to the IA group (HR 0.57, 95% CI [0.48; 0.69], $P < 0.001$) and the IV group (HR 0.45, 95% CI [0.39; 0.50], $P < 0.001$). One case of deep vein thrombosis occurred in the group without TA. **Conclusion:** Administration of combined TA appears effective and safe; further studies are needed in order to establish a consensual protocol.

Keywords: *Blood loss, combined, intraarticular, intravenous, tranexamic acid*

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Introduction

Elective arthroplasty surgery of the lower limb (total knee arthroplasty [TKA], and total hip arthroplasty) is a surgical procedure widely performed for the treatment of terminal arthrosis. Prevalence is estimated between 2.3% and 4.5% in 2010 among adults aged 50 years or older,[1] and >2 million procedures per year are estimated to be performed by 2020 in the United States.[2] However, it is associated with a higher morbidity and mortality than would be expected for a functional surgery.[3] An increased perioperative blood loss is associated with increased transfusion rate, postoperative infections, poorer physical function and recovery, increased length of hospital stay, and mortality.[4] Furthermore, blood transfusion increases both morbidity and mortality[5] and is a source of cardiovascular, immunological, and viral complications.[6] Therefore, multiple means of reducing blood loss have been studied (for example, use of a tourniquet, autotransfusion, intraoperative blood salvage, and use of iron or erythropoietin) to avoid perioperative blood transfusion.[7,8]

The efficacy of intravenous (IV) tranexamic acid (TA) due do its antifibrinolytic action has been confirmed by meta-analyses.[9,10] Furthermore, its intraarticular (IA) use has been shown to reduce blood loss and the need for transfusion.[11] Since 2014, numerous randomized controlled trials[12-21] have studied the efficacy of combined IV and IA TA on blood loss as well as transfusion needs. These small studies reported contradictory results as to the efficacy of TA but no increase in the occurrence of adverse events. Three meta-analyses[22-24] have confirmed the benefits of the combined use of TA and its safety. However, none of these studies has formally quantified blood salvation related to the combined IV and IA administration of TA.

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In our center, which is a reference in lower-limb arthroplasty, we progressively (from 2014 to 2017) shifted from IV TA use to a combined strategy which allows us herein to quantify the effect of the combined strategy on the perioperative blood loss.

Materials and Methods

A prospective observational study was conducted at the Lyon Sud Hospital (France) from January 1, 2014, to December 31, 2017. Patients aged 18 years or above who underwent elective primary or secondary arthroplasty of the knee or hip as well as acetabular revision were included; those with prosthesis ablation and unicompartmental knee arthroplasty as well as those who finally did not undergo surgery (contraindications or deceased) were excluded. Patients included successively at the preanesthesia consultation, during which information was given to the patient and his/her oral agreement for inclusion in the study was obtained. According to legislation in place at the time of the study, written informed consent was not required for this study; the database was registered with the national data protection agency (CNIL-HCL number: 18-105).

Demographic data (name, gender, age, height, weight, type of surgery expected, and ASA score) were collected during the preanesthesia consultation. Hemoglobin (Hb) and hematocrit levels the day before the surgery and the postoperative anticoagulant prescribed were collected during the operative time. Hb and hematocrit levels on the 5th day, the length of hospital stay, any blood transfusion, as well as complications (especially thromboembolic or seizures) were collected from the electronic patient medical files. Detection of thrombosis was based on clinical symptoms during hospital stay (daily medical visit) and during the surgical postoperative consultation that was scheduled between the 45th day and the 90th day.

TA (Exacyl®, Sanofi-Aventis® Gentilly, France) was administered during the perioperative period intravenously at a dose of 15 mg/kg, diluted in 100 mL of NaCl 0.9% as a bolus 20 min before incision, and intraarticularly as an injection of 3 g diluted in 100 ml of NaCl 0.9% at the end of the intervention. The route of administration depended on patient characteristics and surgical possibilities.

THA was performed using a posterior approach and TKA by a parapatellar approach; surgeries were conducted without tourniquet. Homologous blood transfusions were administered following national guidelines:[25] Hb threshold of 7.0 g/l, 8.0 g/l in case of cardiovascular history, and 10.0 g/l in case of chronic heart failure. Postoperative analgesia was provided by multimodal analgesia associating regional anesthesia (iliofascial block, femoral block, or a femoral catheter), a combination of step 1 and 2 painkillers (paracetamol, tramadol, nefopam, ketoprofen, and ketamine) and patient-controlled analgesia (morphine). Early mobilization was performed on postoperative day 0 with a protocoled fast-track pathway. A specialized team of physiotherapists was dedicated to the orthopedic department. Thromboprophylaxis was systematically introduced within the first 24 h for a duration of 35 days, either by rivaroxaban, dabigatran, apixaban, enoxaparin, fondaparinux, and unfractionated heparin depending on the patient's medical history. In case of anticoagulant use prior to surgery, it was reintroduced in the first 48 h. The thromboprophylaxis using an antithrombotic drug was associated with an early mobilization protocol.

Patients were separated into four groups depending on the administration of TA: IV + IA, IV, IA, or no TA.

The outcomes considered were blood loss, Hb level on the 5th day, postoperative transfusion, the length of hospital stay, and the occurrence of complications (thromboembolic or seizure). Hb and hematocrit levels were measured on the 5th day, which allowed the evaluation of the postoperative bleeding and the hidden loses while overcoming bias due to the blood regeneration. In the case of blood transfusion, pretransfusion parameters were taken into account. Blood loss was calculated by summing the compensated blood losses (blood recovered during surgery and blood transfusion) with the noncompensated blood loss estimated by the Mercuriali formula.[26] Blood loss was expressed in milliliter of red blood count (ml of red blood cell [RBC]). TA tolerance was evaluated by the occurrence of complications (thromboembolic or seizure) identified clinically during the duration of the hospital stay and during the postoperative consultation that was scheduled between the 45th day and the 90th day.

This article was drafted according to the STROBE statement.

Statistical analysis

Quantitative variables were presented using mean with standard deviation for descriptive variables and mean with associated 95% confidence interval [95% CI] for outcomes. Qualitative variables were presented using numbers and proportions. In univariate analyses, distributions of variables were compared between the four treatment groups (IV + IA, IV, IA, or no TA) using ANOVA (linear model) and qualitative models using Pearson's Chi-square tests.

For each clinical outcome of interest (perioperative blood loss, postoperative Hb, blood transfusion, and length of hospital stay), multivariate regression models were fitted to analyze the effect of TA on clinical outcome, systematically adjusted on age, ASA score, curative postoperative anticoagulant treatment, and surgical technique (complete model). Linear regression models were fitted to analyze total blood loss and postoperative Hb. A nonconditional logistic regression model was fitted to analyze the necessity of blood transfusion and a Cox proportional hazards model to analyze variables associated with the length of hospital stay. Nested models were compared to the complete model

using likelihood ratio tests, and Wald tests were performed for categorical variables. In all statistical tests (two-tailed), $P < 0.05$ was considered as statistically significant. The P values were not corrected according to the number of tests performed. Statistical analyses were performed using SPSS® statistics 25 (IBM, Armonk, NY, USA).

Results

A total of 1909 patients who underwent a lower-limb arthroplasty were included. Among them, 374 received a combined IV and IA administration (IV + IA group), 1137 received an IV bolus of TA (IV group), 214 received IA TA (IA group), and 184 patients did not receive any TA (no TA group). Patients underwent primary hip (n = 1170) or knee arthroplasty (n = 508), revision of hip (n = 149) or knee arthroplasty (n = 37), or for an acetabular revision (n = 45). There was no significant difference in Hb (P = 0.15) and hematocrit (P = 0.40) between the groups [Table 1]. There were 84 patients who were receiving curative anticoagulant treatment.

The mean blood loss was 299 ml of RBC (95% CI [280; 317]) in the IV + IA group, 313 ml of RBC (95% CI [302; 324]) in the IV group, 361 ml of RBC (95% CI [328; 393]) in the IA group, and 506 ml of RBC (95% CI [465; 547]) in the no TA group. The mean length of hospital stay was 4.8 days (95% CI [4.7; 5.0]) for the IV + IA group, 6.6 days (95% CI [6.5; 6.8]) for the IV group, 6.5 days (95% CI [6.2; 6.8]) for the IA group, and 7.9 days (95% CI [7.5; 8.3]) for the no TA group [Table 2].

After adjustment (covariates of the multivariate model are presented in Supplementary Data), the blood loss in the IV group was a mean 23 ml of RBC (95% CI [−0.1; 46]) greater than that found in the IV + IA group; this difference was not significant (P = 0.052). The blood loss in the IA and no TA groups were, respectively, a mean 65 ml of RBC (95% CI [30; 99], $P < 0.001$) and 220 ml of RBC (95% CI [185; 256], $P < 0.001$) significantly greater than that found in the IV + IA group. The postoperative Hb in the IV, IA, and no TA groups was significantly lower than that found in the IV + IA group (all $P < 0.001$). The transfusion rate for the no TA group was significantly greater than in the IV + IA group (OR 7.88, 95% CI [2.71; 22.93], $P < 0.001$). The hazard of the hospital discharge in the IV, IA, and no TA groups was significantly lower than that found in the IV + IA group (all $P < 0.001$) [Table 3]; the survival curves for these groups are presented in Figure 1.

No seizure occurred, and there was one case of deep vein thrombosis (no TA group) reported.

Table 1: Demographic characteristics and preoperative blood parameters according to tranexamic acid status

	IV + IA (*n*=374)	IV (*n*=1137)	IA (*n*=214)	No TA (*n*=184)	Total (*n*=1909)	Heterogeneity test*
Sex, *n* (%)						
Male	156 (42)	457 (40)	105 (49)	96 (52)	814 (44)	0.02
Female	215 (58)	650 (60)	101 (51)	83 (48)	1049 (56)	
Missing data					46 (3)	
Height, mean±SD	1.65±0.09	1.65±0.09	1.65±0.11	1.66±0.09	1.65±0.09	0.30
Weight, kg±SD	78±17.4	75.8±16.2	80.2±17.0	77.3±16.3	76.9±16.6	0.02
Age, mean±SD	67.4±12.2	66.1±12.5	71.8±10.2	70.5±10.5	67.4±12.2	<0.01
Missing data, *n* (%)					15 (1)	
Intervention, *n* (%)						
Acetabular revision	4 (1.1)	31 (2.7)	5 (2.3)	5 (2.7)	45 (2.4)	0.03
KA	121 (32.4)	270 (23.7)	70 (32.7)	47 (25.5)	508 (26.6)	
Revision of KA	13 (3.5)	18 (1.6)	3 (1.4)	3 (1.6)	37 (1.9)	
HA	213 (57)	730 (64.2)	120 (56.1)	107 (58.2)	1170 (61.3)	
Revision of HA	23 (6)	88 (7.8)	16 (7.5)	22 (12)	149 (7.8)	
ASA, *n* (%)						
1	55 (15)	220 (20)	3 (1)	10 (6)	288 (16)	<0.01
2	231 (62)	697 (62)	76 (37)	70 (39)	1074 (57)	
3	85 (23)	201 (18)	128 (61)	99 (55)	513 (27)	
4	0	1 (<0.1)	2 (<1)	0	3 (<1)	
Missing data					31 (2)	
Preoperative blood parameters						
Hb, g/dl, mean±SD	14.0±1.7	14.0±1.4	13.8±1.8	14.2±1.9	14.0±1.6	0.15
Hematocrit, %, mean±SD	42.3±3.6	42.0±3.7	41.9±3.8	42.3±4.4	42.1±3.8	0.40

*P value of the heterogeneity test (χ^2 or ANOVA). Missing data, if present, are expressed in n (%). Results are expressed into effective (%) or mean±SD. SD=Standard deviation, IV=Intravenous, IA=Intraarticular, ASA=American Society of Anesthesiologists, Hb=Hemoglobin, HA=Hip arthroplasty, KA=Knee arthroplasty

Table 2: Description of the outcome variables among the four study groups

	IV + IA	IV	IA	No TA
Mean blood loss, ml RBC (95% CI)	299 (280-317)	313 (302-324)	361 (328-393)	506 (465-547)
Mean postoperative, Hb, g/dl (95% CI)	11.86 (11.71-12.01)	11.47 (11.38-11.56)	11.12 (10.90-11.34)	10.48 (10.22-10.75)
Transfusion, *n* (%)	5 (1.3)	29 (2.6)	10 (4.7)	23 (12.5)
Mean length of hospital stay, days (95% CI)	4.8 (4.7-5.0)	6.6 (6.5-6.8)	6.5 (6.2-6.8)	7.9 (7.5-8.3)

IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, TA=Tranexamic acid, No TA=No TA group, ml RBC=Milliliter of red blood cell, 95% CI=Confidence interval 95%, Hb=Hemoglobin

Table 3: Comparison of the outcome variables among the four study group

	IV + IA	IV	IA	No TA
Mean Blood loss, ml RBC* (95% CI)	201 (162-242)	+23 (−0.1-46) *P*=0.052	+65 (30-99) *P*<0.001	+220 (185-256) *P*<0.001
Mean postoperative Hb, g/dl* (95%CI)	11.85 (11.55-12.14)	−0.51 (−0.68-−0.34) *P*<0.001	−0.55 (−0.81-−0.29) *P*<0.001	−1.28 (−1.55-−1.02) *P*<0.001
Transfusion, OR (95% CI)	1.00	2.02 (0.75-5.38) *P*=0.160	2.12 (0.63-7.09) *P*=0.222	7.88 (2.71-22.93) *P*<0.001
Length of hospital stay, HR (95% CI)	1.00	0.45 (0.39-0.50) *P*<0.001	0.57 (0.48-0.69) *P*<0.001	0.35 (0.29-0.43) *P*<0.001

*Predicted value for reference category of adjusted variables. Data are presented as mean, OR, and HR with (95% CI), associated with corresponding *P* values. HR <1 characterizes a longer length of hospital stay. TA=Tranexamic acid, IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, No TA=No TA group, ml RBC=Milliliter of red blood cell, 95% CI=95% confidence interval, Hb=Hemoglobin, OR=Odds ratio, HR=Hazard ratio

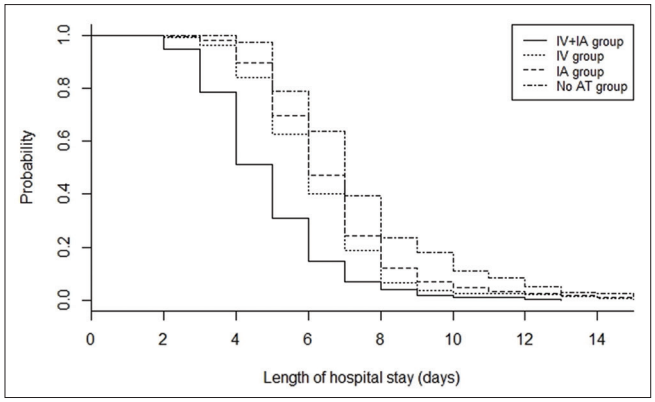

Figure 1: Survival curve of hospital stay of the four tranexamic acid groups

Discussion

The present study found an association between the use of the IV + IA strategy of TA and the reduction of perioperative blood loss, the rise of the postoperative Hb level, and the reduction of postoperative length of hospital stay.

To the best of our knowledge, the study reported herein is the first to have included a large number of patients and to have quantified the amount of blood loss avoided by the combined strategy. It is of note that only a trend toward greater amount of blood loss avoided by the combined strategy with respect to the IV strategy. RCTs have generally found a reduction of total blood loss,[12-21] but only a minority have found this to be significant; however, meta-analyses concord as to the better efficacy of the combined strategy compared to the use of IV-only strategy.[22-24] The results are expressed as milliliters of RBC because the Mercuriali formula to evaluate blood loss was used,[26] which differs from the Gross formula. The latter is subject to bias related to postoperative hemoconcentration and hemodilution, and therefore, the Mercuriali formula is the most suitable formula for studies regarding blood loss in surgery.[27] A general consideration when interpreting the results concerns the doses of TA used. There is currently no consensus, but in the literature, IV doses vary from 10 to 15 mg/kg, and IA doses fluctuate from 1 to 3 g.[22] In our center, we use highest reported doses of both IV and IA TA. This was chosen because the antifibrinolytic efficacy increases in function of dose; a TA concentration of 10 μg/ml is necessary to block 80% of fibrinolysis, and a concentration of 100 μg/ml is needed for a total nullification of fibrinolysis.[28] Such doses are unlikely to be particularly toxic as TA has a wide therapeutic index, which is illustrated by the doses used in cardiac surgery that can be up to 150 mg/kg intravenously.[29]

Preoperative and postoperative Hb levels were higher compared to the majority of studies on lower-limb arthroplasty.[4] This is likely to be, at least in part, due to the preoperative patient pathway that we introduced in our center, where the patient receives an anesthetic consultation more than 30 days before surgery, and Hb/hematocrit is prescribed during the surgical consultation. This individualizes the protocol in order to reach a sufficient preoperative Hb level and thus avoid blood transfusion. This explains why the transfusion rates (from 1.3% to 12.5% herein) were much lower than that reported in elsewhere, ranging from 18% to 68%.[5] This may also

explain why the OR for transfusion was not significant owing to the low number of events.

The duration of hospital stay was significantly reduced in the TA IV + IA group compared to the four other groups. Although postoperative anemia is associated with increased length of hospital stay,[4] this does not seem to be the only factor explaining such a difference in length of stay. For instance, the IA administration of TA leads to a higher IA concentration of TA than IV administration, reducing the postoperative IA bleeding and therefore allowing a faster rehabilitation.[30] Another explanation could be related to the antiinflammatory effect attributed to TA which could reduce the postoperative swelling due to the local inflammation allowing early rehabilitation and a faster discharge compared to placebo. For instance, Huang *et al*. also have reported reduced postoperative pain and swelling at the climax of inflammation (day 2–day 3) compared to its use intravenously.[19] Krauss *et al*. studied the influence of IA use of TA on early rehabilitation and proved the efficacy for a shorter mobilization, the 1st and 2nd days.[31] The pathophysiology of the antiinflammatory effect of the TA has been well documented and reviewed by Levy *et al*. in 2018.[32] TA administered intraarticularly has certainly an effect on postoperative rehabilitation and early discharge, but published studies are small number and the results need confirmation in a larger population.

The only thromboembolic event occurred into the No TA group. Despite its antifibrinolytic activity, TA is probably not associated with an increase of thromboembolic events. Indeed, since the CRASH-2 study has shown a reduction of thromboembolic and cardiovascular events in the group treated by TA,[33] a number of studies including a Cochrane meta-analysis[34] have not shown an association between TA administration and thromboembolic events (arterial or venous).

Our work is a prospective observational study, leading to the absence of randomization. In order to minimize bias, we adjusted the results on the main confounding factors (age, intervention, ASA, and curative anticoagulation). The absence of blind administration of TA could lead to a bias; however, the main outcome measures were objective with very little possibility of interpretation bias. However, our study is still subjected to an important temporal bias: Indeed, in 2014, a large majority of patients received IV therapy, whereas in 2017, the combined administration was predominant. In 4 years, surgeons have gained in experience and have probably decreased their perioperative blood losses. As regards the length of hospital stay, the progress of postoperative rehabilitation and economic considerations is leading to shorter hospitalization, which may explain the significant reduction of hospital stay.

Conclusion

The administration of combined TA appears effective and safe. Further studies are needed in order to investigate the optimal doses so as to establish a consensual protocol.

Implication statement

We report the interest of the combined use of tranexamic acid (intravenous and intraarticular) during knee and hip arthroplasty on a large cohort of patients for blood salvage and postoperative length of hospital stay.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Data

Table A: Blood loss (milliliter of red blood cell) for the intervention

Intervention	Primary THA	Primary TKA	Revision THA	Revision TKA	Acetabular revision
Mean blood loss, ml RBC (95% CI)	296 (284-307)	387.42 (370-405)	429 (385-473)	439 (371-508)	318 (255-380)

Result are express in mean (CI 95%). ml RBC=Milliliter of red blood cell, CI=Confidence interval, KA=Knee arthroplasty, TKA=Total KA, HA=Hip arthroplasty, THA=Total HA

Table B: Multivariate regression analysis of the total blood loss adjusted on the type of tranexamic acid, age, intervention, American Society of Anesthesiologists, and curative anticoagulation status

	Mean blood loss, ml RBC	95% CI	*P*†
Intercept*	201	162-242	
TA			**<0.001**
IV + IA	0		
IV	+23	−0.1-46	*0.052*
IA	+65	30-99	*<0.001*
No TA	+220	185-256	*<0.001*
Age			**<0.001**
>80	0		
71-80	+32	3-61	*0.032*
61-70	+46	17-75	*0.002*
51-60	+97	64-131	*<0.001*
41-50	+156	108-204	*<0.001*
<40	+114	59-169	*<0.001*
Intervention			**<0.001**
HA	0.00		
KA	+108	87-129	*<0.001*
Revision HA	+126	93-159	*<0.001*
Revision KA	+162	98-227	*<0.001*
Acetabular revision	+10	−48-67	*0.742*
ASA			**0.764**
1	0		
2	−4	−30-22	*0.763*
3-4	−11	−43-21	*0.495*
Curative anticoagulation			**0.002**
No	0		
Yes	+71	26-116	*0.002*

*Predicted value for reference categories of adjusted variables, †Likelihood ratio test (bold) and Wald test (italic). IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, TA=Tranexamic acid, No TA=No TA group, ml RBC=Milliliter of red blood cell, HA=Hip arthroplasty, KA=Knee arthroplasty, CI=Confidence interval, ASA=American Society of Anesthesiologists, ml RBC=Milliliter of red blood cell

Table C: Multivariate regression analysis of the postoperative hemoglobin adjusted on the type of tranexamic acid, age, intervention, American Society of Anesthesiologists, and curative anticoagulation status

	Mean Hb, g/dl	95% CI	*P*
Intercept*	11.85	11.55-12.14	
TA			**<0.001**
IV + IA	0.00		
IV	−0.51	−0.68-−0.34	*<0.001*
IA	−0.55	−0.81-−0.29	*<0.001*
No TA	−1.28	−1.55-−1.02	*<0.001*
Age			**<0.001**
>80	0.00		
71-80	+0.44	0.22-0.65	*<0.001*
61-70	+0.65	0.43-0.87	*<0.001*
51-60	+0.41	0.16-0.66	*0.001*
41-50	+0.62	0.26-0.97	*0.001*
<40	+0.36	−0.04-0.77	*0.081*
Intervention			**0.001**
HA	0.00		
KA	−1.06	−1.21-−0.90	*0.001*
Revision HA	−0.93	−1.18-−0.69	*0.001*
Revision KA	−1.31	−1.78-−0.84	*0.001*
Acetabular revision	−0.44	−0.86-−0.01	*0.043*
ASA			**0.051**
1	0.00		
2	+0.65	−0.13-0.26	*0.516*
3-4	−0.14	−0.37-0.9	*0.243*
Curative anticoagulation			**0.142**
No	0.00		
Yes	−0.25	−0.59-0.08	*0.142*

*Predicted value for reference categories of adjusted variables, †Likelihood ratio test (bold) and Wald test (italic). IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, TA=Tranexamic acid, No TA=No TA group, HA=Hip arthroplasty, KA=Knee arthroplasty, CI=Confidence interval, ASA=American Society of Anesthesiologists, Hb=Hemoglobin

Table D: Multivariate regression analysis of the probability of transfusion adjusted on the type of tranexamic acid, age, intervention, American Society of Anesthesiologists, and curative anticoagulation status

	OR	95% CI	*P*†
TA			**0.122**
IV + IA	1.00		
IV	2.02	0.75-5.38	*0.160*
IA	2.12	0.63-7.09	*0.222*
No TA	7.88	2.71-22.93	*<0.001*
Age			**0.026**
>80	1.00		
71-80	0.39	0.18-0.82	*0.014*
61-70	0.30	0.13-0.69	*0.004*
51-60	0.82	0.36-1.86	*0.648*
41-50	0.72	0.18-2.89	*0.647*
<40	-	-	-
Intervention			**0.001**
HA	1.00		
KA	4.18	2.10-8.33	*<0.001*
Revision HA	11.57	5.57-24.05	*<0.001*
Revision KA	20.34	6.77-61.08	*<0.001*
Acetabular revision	3.02	0.63-14.49	*0.166*
ASA			**0.621**
1	1.00		
2	0.62	0.26-1.49	*0.291*
3-4	0.73	0.27-1.96	*0.738*
Curative anticoagulation			**<0.001**
No	1.00		
Yes	6.98	3.02-16.12	*<0.001*

Logistic regression model. †Likelihood ratio test (bold) and Wald test (italic). IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, TA=Tranexamic acid, No TA=No TA group, HA=Hip arthroplasty, KA=Knee arthroplasty, OR=Odds ratio, CI=Confidence interval, ASA=American Society of Anesthesiologists

Table E: Multivariate regression analysis of the length of hospital stay adjusted on the type of tranexamic acid, age, intervention, American Society of Anesthesiologists, and curative anticoagulation status

	HR	95% CI	*P*†
TA			**<0.001**
IV + IA	1.00		
IV	0.45	0.39-0.50	*<0.001*
IA	0.57	0.48-0.69	*<0.001*
No TA	0.35	0.29-0.43	*<0.001*
Age			**0.003**
>80	1.00		
71-80	1.20	1.03-1.40	*0.015*
61-70	1.25	1.07-1.45	*0.004*
51-60	1.42	1.20-1.70	*<0.001*
41-50	1.32	1.02-1.70	*0.031*
<40	1.43	1.07-1.90	*0.014*
Intervention			**<0.001**
HA	1.00		
KA	0.80	0.72-0.90	*<0.001*
Revision HA	0.64	0.54-0.76	*<0.001*
Revision KA	0.58	0.41-0.83	*0.003*
Acetabular revision	0.67	0.49-0.90	*0.010*
ASA			**0.071**
1	1.00		
2	0.91	0.79-1.05	*0.204*
3-4	0.75	0.63-0.88	*0.001*
Curative anticoagulation			**0.025**
No	1.00		
Yes	0.75	0.59-0.96	*0.025*

Cox regression model. †Likelihood ratio test (bold) and Wald test (italic). IV + IA=Intravenous and intraarticular group, IV=Intravenous group, IA=Intraarticular group, TA=Tranexamic acid, No TA=No TA group, HA=Hip arthroplasty, KA=Knee arthroplasty, HR=Hazard ratio, CI=Confidence interval, ASA=American Society of Anesthesiologists