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Original Research

Is There a Synergistic Effect of Topical Plus Intravenous Tranexamic Acid Versus Intravenous Administration Alone on Blood Loss and Transfusions in Primary Total Hip and Knee Arthroplasties?

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ABSTRACT

Background: The optimal route and dosing regimen of tranexamic acid (TXA) in primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain unclear. As such, we sought to analyze if there was a synergistic effect of intravenous (IV) and topical TXA on blood loss and transfusions.

Methods: We retrospectively analyzed 6720 primary TKAs and 6559 THAs performed from February 1, 2016 to December 31, 2019 at a single institution in patients who received a double IV dose (6159 TKAs and 6276 THAs) compared with a combined single IV and topical dose (561 TKAs and 283 THAs) of TXA. Multivariate logistic regression models, adjusting for age, body mass index, American Society of Anesthesiologists class, preoperative hemoglobin, and TXA administration, were performed for significant variables from a univariate analysis.

Results: In the TKA cohort, the mean total blood loss was statistically similar for double IV (305 mL, 95% confidence interval [CI] = 301-310 mL) TXA compared with combined TXA (310 mL, 95% CI = 299-321 mL) ($P = .43$). Furthermore, there was no difference in the rate of transfusion (odds ratio = 1.23, 95% CI = 0.57-2.67, $P = .598$). In the THA cohort, there was statistically higher blood loss with double IV (328 mL, 95% CI = 323-333 mL) TXA than in the combined group (295 mL, 95% CI = 280-310 mL) ($P < .001$). The rate of transfusion was statistically similar at ~2% ($P = .970$).

Conclusions: A double IV TXA dose and a combined single IV and topical TXA dose were equally effective in minimizing blood transfusions (~2%) at primary TKA and THA. We did not find a synergistic effect when combining a systemic IV TXA with a topical TXA.

Level of Evidence: Level III.

Introduction

Perioperative blood management is an integral aspect of primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1]. Minimizing blood loss and blood transfusions reduces perioperative complications including transfusion reactions and periprosthetic joint infection [1-4]. Furthermore, limiting perioperative blood loss and proper fluid management also allows rapid rehabilitation protocols by minimizing delays in mobilization secondary to hypotension, orthostasis, and/or transfusion requirements [2,3].

The use of tranexamic acid (TXA), an antifibrinolytic that inhibits the plasminogen-mediated degradation of fibrin, has revolutionized perioperative blood management [1,5-11]. Furthermore, there is growing evidence that TXA has only antifibrinolytic properties without thrombogenic properties [5] and is clinically safe [12-15], even in higher-risk patients. However, although several dosages of intravenous (IV), topical, and oral administrations have been studied, there is currently no consensus on the optimal TXA administration or combination [6-8,16-19]. Although there have been some limited studies on the potential synergistic effect of the administration of both IV and topical TXA [20-23], the data remain mixed.

As such, the goal of the present study was to compare 2 doses of IV TXA with a combined single dose of topical and IV TXA each, to assess for a potential synergistic effect of this combination.

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Specifically, we analyzed (1) the total calculated blood loss, (2) blood transfusions, and (3) in-hospital thrombotic complications. We hypothesized that IV and topical TXA would have a synergistic effect of reducing blood loss in primary TKA and THA compared with IV TXA alone.

Patients and methods

Institutional review board approval was obtained before study initiation. Through a query of our electronic medical record, we identified patients who had undergone a unilateral primary THA or primary TKA and had received 2 perioperative doses of IV TXA or one topical and one IV dose of TXA from February 1, 2016 to December 31, 2019 at a single tertiary care academic center. For fairness in comparison of the total dose of TXA received, patients were excluded if they received only one IV or topical TXA dose. Patients undergoing bilateral procedures were also excluded. Patient- and surgery-specific factors were collected including age, sex, body mass index (BMI), preoperative hemoglobin (Hgb), postoperative day 1 (POD1 Hgb), American Society of Anesthesiologists (ASA) classification [24], which grades patients' physical health from 1 to 4, with 1 being the healthiest, in-hospital complications (namely thrombotic events including deep venous thrombosis and pulmonary embolism, myocardial infarction [MI], and cerebrovascular accidents [CVAs]), hospital length of stay (defined as the time of patient arrival to leaving the hospital), and blood transfusion. From this, we estimated the total calculated blood loss according to the Nadler formula [25], which analyzes preoperative day 1 and POD1 Hgb, factoring in patient sex, height, and weight for blood volume calculations. We included all patients who sustained a postoperative MI or CVA as having a potential thrombotic complication. To detect a difference of 100 mL in the total calculated blood loss, a power analysis revealed that we would need at least 35 patients in each cohort.

Institutional TXA administration

Although TXA utilization for elective primary THA and TKA is routine at our institution, the administration regimens are variable per surgeon and anesthesiologists' preferences for non–high-risk patients. However, per institutional policy, patients deemed higher risk, including those with a history of venous thromboembolism (VTE), atrial fibrillation or other cardiac arrhythmia, or prior thrombotic events, are routinely given topical TXA only.

For the double-dose IV regimen, 1 g of IV TXA is administered within 30 minutes of the skin incision and a second 1-g dose is administered postoperatively within 3 hours of the initial dose. For the combined IV and topical TXA dosing regimen, 1 g of IV TXA is administered within 30 minutes of the skin incision and 3 g of TXA diluted in 45 mL of the normal saline solution was applied locally to the open joint surfaces after irrigation and before closure. The solution was placed after the wound was irrigated and suctioned and left in contact with the tissues for 3 minutes.

For both primary THAs and primary TKAs, we routinely use neuraxial anesthesia and rapid recovery protocols at our institution. All surgeons routinely used tourniquets for primary TKAs. Our institutional triggers for a blood transfusion were consistent throughout the study period and are (1) any Hgb <7 g/dL, (2) symptomatic patients (ie, symptoms of hypotension or end-organ damage) and a Hgb <8 g/dL, or (3) a patient with a cardiac history and a Hgb <8 g/dL. We routinely check POD1 labs, including a complete blood count.

Patients

We identified 6720 TKAs in patients who underwent unilateral primary TKA who met inclusion criteria. A double IV dosing regimen was used in 6159 (92%) TKAs, whereas the combined IV and topical regimen was used in 561 (8%) TKAs. Baseline demographics were similar in the double IV and the topical plus IV dosing regimen groups, including age, sex, BMI, and preoperative Hgb (Table 1). There was a statistically significant, but not clinically significant, difference in the length of stay in hours (71.9 hours vs 71.4 hours, $P < .001$) between the 2 groups.

We identified 6559 THAs in patients who underwent unilateral primary THA who met inclusion criteria. The direct anterior approach was performed in 1472 (22%) patients, whereas a posterolateral approach was performed in 5087 (78%) patients. A double IV dosing regimen was used in 6276 (96%) THAs, whereas the combined IV and topical regimen was used in 283 (4%) THAs. Baseline patient demographics are listed in Table 2. There was a statistically significant, but unlikely clinically significant, difference in the patient age between the 2 groups (64.9 vs 66.9 years, $P < .001$), but otherwise, there was no difference in sex, BMI, ASA class, or preoperative Hgb level, or length of stay (Table 2).

Statistical analysis

Continuous variables are reported as means and ranges or standard deviations in the descriptive analysis. Frequencies and percentages are used to report descriptive statistics of dichotomous variables. Univariate analysis was then performed between study groups using independent samples t-tests for continuous data and chi-square tests for dichotomous variables. Analysis of covariance models was then used to adjust for known important confounders on the total calculated blood loss, adjusting for age, sex, BMI, ASA class, and preoperative Hgb level. Multivariate logistic regression analysis was performed for primary outcomes that were significant in the univariate analysis (blood transfusion for TKAs and thrombotic complications for THAs), adjusting for known potential confounders including age, BMI, ASA class, and preoperative Hgb level. Statistical significance was defined as $P \leq .05$. All analyses were performed with SPSS, version 23.0 (IBM Corp., Armonk, NY).

Results

Total calculated blood loss

For primary TKAs, univariate analysis revealed a similar mean total calculated blood loss for the double IV group (mean = 299.8 mL, range, 142-1012 mL) compared with the combined group (mean = 299.4 mL, range, 138-1312 mL) ($P = .948$) (Table 3). For the multivariate analysis adjusting for age, BMI, ASA class, and preoperative Hgb, there was a similar total calculated blood loss for the double IV (305.2 mL, 95% confidence interval [CI] = 301.0-309.5 mL) and the combined groups (309.8 mL, 95% CI = 298.6-321.1 mL) ($P = .427$) (Table 5).

For primary THAs, univariate analysis showed a statistically significant higher total calculated blood loss for the double IV group (mean = 323.5 mL, range = 147-1218 mL) than the combined group (mean = 290.4 mL, range 152-1252 mL) ($P < .001$) (Table 4). For the multivariate analysis adjusting for age, BMI, ASA class, and preoperative Hgb, there was a significantly higher mean total calculated blood loss for the double IV group (mean = 328.3 mL, 95% CI = 323.3-333.4 mL) than the combined group (mean = 294.9 mL, 95% CI = 279.8-310.0 mL) ($P < .001$) (Table 5).

Table 1
Baseline demographics of patients undergoing primary TKA who received 2 doses of IV TXA (double IV) compared with one dose of IV and one dose of topical TXA (1 IV + 1 topical).

TKA										
Variable	Double IV			1 Topical +1 IV			Overall			*P*-value
	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	
Age	6159	68.0	9.1	561	69.9	9.0	6720	68.2	9.1	.000
ASA class	6105	2.2	0.4	551	2.2	0.4	6656	2.2	0.4	.983
Body mass index, kg/m^2	6159	31.2	6.5	560	31.0	6.5	6691	31.2	6.5	.550
Preoperative Hgb	6159	13.5	1.3	561	13.5	1.3	6720	13.5	1.3	.579
POD1 Hgb	6159	11.5	1.3	561	11.4	1.4	6720	11.5	1.3	.514
Change Hgb	6159	2.0	0.9	561	2.0	0.9	6720	2.0	0.9	.877
Length of stay (hours)	6159	71.9	33.6	561	66.1	29.3	6720	71.4	33.3	.000
ASA classification										
1	6105	165	3%	551	7	1%	6656	172	3%	.159
2	6105	4743	78%	551	444	81%	6656	5187	78%	
3	6105	1196	20%	551	100	18%	6656	1296	19%	
4	6105	1	0%	551	0	0%	6656	1	0%	
ASA class										
ASA 1 or 2	6105	4908	80%	551	451	82%	6656	5359	81%	.408
ASA 3 or 4	6105	1197	20%	551	100	18%	6656	1297	19%	
Sex										
M	6159	2166	35%	561	201	36%	6720	2367	35%	.754
F	6159	3993	65%	561	360	64%	6720	4353	65%	
Preoperative Hgb										
<10	6159	37	1%	561	6	1%	6720	43	1%	.183
10+	6159	6122	99%	561	555	99%	6720	6677	99%	
POD1 Hgb										
<10	6159	728	12%	561	76	14%	6720	804	12%	.228
10+	6159	5431	88%	561	485	86%	6720	5916	88%	

Blood transfusions

For primary TKAs, univariate analysis showed a statistically significant lower rate of blood transfusion for the double IV group (96/6,159, 2%) than the combined group (18/561, 3%) ($P = .004$) (Table 3). However, in the multivariate logistic regression analysis, adjusting for age, BMI, ASA class, and preoperative Hgb, the route of TXA administration was not a significant factor (odds ratio [OR] = 1.23, 95% CI = 0.57-2.67, $P = .598$) in blood transfusion rates. Furthermore, a higher ASA class of 3 or 4 (versus an ASA of 1 or 2) was a significant risk factor for higher transfusion rates (OR = 1.89, 95% CI = 1.16-3.09, $P = .011$), and a higher preoperative Hgb level had a protective effect for transfusion rates (OR = 0.36 per g/dL, 95% CI = 0.31-0.42, $P < .001$) (Table 6).

For primary THAs, univariate analysis did not show any significant difference between the rate of blood transfusions in the double

Table 2
Baseline demographics of patients undergoing primary THA who received 2 doses of IV TXA (double IV) compared with one dose of IV and one dose of topical TXA (1 IV + 1 topical).

Variable	Double IV			1 Topical +1 IV			Overall			*P*-value
	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	
Age	6276	64.9	10.9	283	66.9	11.5	6559	65.0	10.9	.003
ASA class	6210	2.1	0.4	279	2.1	0.3	6489	2.1	0.4	.677
Body mass index, kg/m^2	6254	28.4	6.1	283	28.8	5.8	6537	28.4	6.1	.244
Preoperative Hgb	6276	13.6	1.3	283	13.6	1.4	6559	13.6	1.3	.851
POD1 Hgb	6276	11.3	1.4	283	11.6	1.4	6559	11.3	1.4	.001
Change Hgb	6276	2.3	0.9	283	2.0	0.8	6559	2.3	0.9	.000
Length of stay (hours)	6276	57.3	28.6	283	54.7	26.0	6559	57.2	28.5	.137
ASA class										
1	6210	309	5%	279	7	3%	6489	316	5%	.220
2	6210	5193	84%	279	244	87%	6489	5437	84%	
3	6210	703	11%	279	28	10%	6489	731	11%	
4	6210	5	0%	279	0	0%	6489	5	0%	
ASA class										
ASA 1 or 2	6210	5502	89%	279	251	90%	6489	5753	89%	.482
ASA 3 or 4	6210	708	11%	279	28	10%	6489	736	11%	
Female										
M	6275	2382	38%	283	114	40%	6558	2496	38%	.431
F	6275	3893	62%	283	169	60%	6558	4062	62%	
Preoperative Hgb										
<10	6276	30	0%	283	3	1%	6559	33	1%	.176
10+	6276	6246	100%	283	280	99%	6559	6526	99%	
POD1 Hgb										
<10	6276	983	16%	283	34	12%	6559	1017	16%	.097
10+	6276	5293	84%	283	249	88%	6559	5542	84%	

Table 3
Univariate analysis of total calculated blood loss, blood transfusions, and complications in patients undergoing primary TKA who received 2 doses of IV TXA (double IV) compared with one dose of IV and one dose of topical TXA (1 IV + 1 topical).

Total knee arthroplasty										
Variable	Double IV			1 Topical +1 IV			Overall			*P*-value
	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	
Total calculated blood loss (mL)	6159	299.8	150.2	560	299.4	146.1	6720	299.8	149.8	.948
Transfusion? (0 = no, 1 = yes)										
N	6159	6063	98%	561	543	97%	6720	6606	98%	.004
Y	6159	96	2%	561	18	3%	6720	114	2%	
In-hospital deep venous thrombosis (DVT)										
N	6159	6132	100%	561	557	99%	6720	6689	100%	.358
Y	6159	27	0%	561	4	1%	6720	31	0%	
In-hospital pulmonary embolism (PE)										
N	6159	6139	100%	561	558	99%	6720	6697	100%	.415
Y	6159	20	0%	561	3	1%	6720	23	0%	
In-hospital myocardial infarction (MI)										
N	6159	6158	100%	561	560	100%	6720	6718	100%	.033
Y	6159	1	0%	561	1	0%	6720	2	0%	
In-hospital cerebrovascular accident (CVA)										
N	6159	6159	100%	561	561	100%	6720	6720	100%	NA
Y	6159	0	0%	561	0	0%	6720	0	0%	
In-hospital complication (DVT/PE, MI, CVA)										
N	6159	6114	99%	561	554	99%	6720	6668	99%	.181
Y	6159	45	1%	561	7	1%	6720	52	1%	

IV group (109/6,276, 2%) compared with the combined IV and topical group (5/278, 2%) ($P = .970$) (Table 4).

Complications

For primary TKAs, there was not a significant difference in the rate of in-hospital thrombotic complications between the double IV (45/6,159, 1%) and the combined groups (7/561, 1%) ($P = .181$) (Table 3).

For primary THAs, there was a lower rate of in-hospital thrombotic complications in the double IV group (15/6,261, 0.2%) than in the combined group (3/277, 1%) ($P = .04$) (Table 4). For the multivariate logistic regression analysis, adjusting for age, BMI, ASA class, and preoperative Hgb, the combined IV and topical group had a statistically significant higher risk of in-hospital thrombotic complications than the double IV group (OR = 5.80, 95% CI = 1.62-20.79) ($P = .007$) (Table 7).

Discussion

With the growing data on the efficacy and safety of TXA, the routine use of TXA in primary and revision procedures has been widely adopted by arthroplasty surgeons [19]. However, there is little to no consensus on the most effective and safest route and dosage of perioperative TXA [6,16-23,26]. In one of the largest single-institution studies analyzing the efficacy and safety of TXA utilization in elective primary THA and TKA, the present study shows that both a double IV TXA and a combined single IV and topical TXA dose result in a similarly low total blood loss of ~300 mL and drop in Hgb of ~2 g/dL, low transfusion rate of ~2%, and low in-

Table 4
Univariate analysis of total calculated blood loss, blood transfusions, and complications in patients undergoing primary THA who received 2 doses of IV TXA (double IV) compared with one dose of IV and one dose of topical TXA (1 IV + 1 topical).

Total hip arthroplasty										
Variable	Double IV			1 top +1 IV			Overall			*P*-value
	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	Total N	Mean or N	SD or %	
Total calculated blood loss (mL)	6276	323.5	144.6	283	290.4	143.7	6559	322.1	144.7	.000
Transfusion? (0 = no, 1 = yes)										
N	6276	6167	98%	283	278	98%	6559	6445	98%	.970
Y	6276	109	2%	283	5	2%	6559	114	2%	
In-hospital deep venous thrombosis (DVT)										
N	6276	6267	100%	280	278	99%	6556	6545	100%	.022
Y	6276	9	0%	280	2	1%	6556	11	0%	
In-hospital pulmonary embolism (PE)										
N	6276	6272	100%	280	278	99%	6556	6550	100%	.000
Y	6276	4	0%	280	2	1%	6556	6	0%	
In-hospital myocardial infarction (MI)										
N	6276	6274	100%	280	280	100%	6556	6554	100%	.765
Y	6276	2	0%	280	0	0%	6556	2	0%	
In-hospital cerebrovascular accident (CVA)										
N	6276	6276	100%	280	280	100%	6556	6556	100%	NA
Y	6276	0	0%	280	0	0%	6556	0	0%	
In-hospital DVT/PE, MI, or CVA										
N	6276	6261	100%	280	277	99%	6556	6538	100%	.039
Y	6276	15	0%	280	3	1%	6556	18	0%	

Table 5
Multivariate analysis analyzing total calculated blood loss in patients undergoing primary THA and TKA who received either 2 doses of IV TXA (double IV) or one dose of IV and one dose of topical TXA (1 IV + 1 topical).

THA or TKA	IV group	Mean	SEM	95% CI		*P*-value
				Lower	Upper	
THA	Double IV	328.3	2.6	323.3	333.4	.000
	1 Topical + 1 IV	294.9	7.7	279.8	310.0	
TKA	Double IV	305.2	2.2	301.0	309.5	.427
	1 Topical + 1 IV	309.8	5.7	298.6	321.1	

The model adjusted for age, BMI, ASA class, and preoperative Hgb level.

hospital thrombotic (VTE, MI, and CVA) complication rate of ~1%. Furthermore, there does not appear to be a clinically significant positive or negative synergistic effect of IV and topical TXA.

In this study, the double IV and the combined IV/topical dosing regimens had similarly low total calculated blood loss of ~300 mL and transfusion rates at ~2% in patients undergoing primary THA and TKA. Although the combined dosing regimen had a statistically lower total calculated blood loss than the double IV group, the difference of 30 mL is unlikely to be clinically significant. Furthermore, multivariate analysis revealed that lower preoperative Hgb and higher ASA classes were independent risk factors for a postoperative blood transfusion rather than TXA dosing regimen, risk factors well outlined in the literature [27,28]. The studies that show a positive synergistic effect of combined IV and topical TXA compare only a single dose of either IV or topical TXA to the combined dosing regimen [20-23]. A prospective study of patients undergoing primary TKA with either topical or IV TXA administration showed no significant difference of systemic or wound TXA levels, suggesting that both routes are systemically effective [5]. Furthermore, a meta-analysis of IV TXA only compared with IV plus topical TXA showing lower blood loss with IV plus topical TXA also included mainly patients who received only a single dose of IV TXA [29]. Therefore, to better answer this question, we elected to compare a double IV dose to a combined IV and topical dose, a more fair comparison. Two meta-analyses of TXA in primary TKA [7] and THA [8] had similar conclusions to the present study: although it is clear that TXA is an important aspect of minimizing blood loss and transfusions, the ideal dosing regimen remains unclear.

Interestingly, there was a similar rate of the total calculated blood loss in a randomized controlled trial (RCT) by Abdel et al [6]. In 640 patients randomized to a single IV or topical TXA dose in primary TKA, the mean total blood loss, calculated via the same method as in the present study, and transfusion rate was similar in each cohort at ~300 mL and ~2%, respectively [6]. We can speculate that a single dose of TXA is approaching, if not reaching, the plateau in which TXA can effectively minimize perioperative blood loss. Data in further support of this include a multicenter RCT by Fillingham et al [17] analyzing various dosing regimens of TXA in

Table 6
Multivariate binary logistic regression model, taking into account the route of TXA administration, ASA classification, age, BMI, and preoperative hemoglobin, analyzing the risk for transfusion for those undergoing primary TKA.

Outcome	Factor	Odds ratio	95% CI		*P*-value
			Lower	Upper	
Any transfusion	1 Topical +1 IV (vs. double IV)	1.23	0.57	2.67	.598
	ASA 3 or 4 (vs. ASA 1 or 2)	1.89	1.16	3.09	.011
	Age	1.02	1.00	1.05	.051
	BMI	0.97	0.94	1.00	.053
	Preoperative Hgb	0.36	0.31	0.42	.000

Table 7
Multivariate binary logistic regression model, taking into account the route of TXA administration, ASA classification, age, BMI and preoperative hemoglobin, analyzing the risk for any in-hospital complication (DVT/PE, CVA, and/or MI) for those undergoing primary THA.

Outcome	Factor	Odds ratio	95% CI		*P*-value
			Lower	Upper	
Any complication	1 Topical +1 IV (vs. Double IV)	5.80	1.62	20.79	.007
	ASA 3 or 4 (vs. ASA 1 or 2)	1.75	0.35	8.84	.499
	Age	0.99	0.95	1.03	.705
	BMI	0.96	0.88	1.05	.378
	Preoperative Hgb	0.96	0.66	1.39	.811

patients undergoing revision TKA (single IV, double IV, combined IV/topical, and oral), which did not show a difference in change in Hgb, calculated blood loss, or transfusion rates for any of these dosing regimens. Finally, in a double-blinded RCT of 100 patients undergoing primary TKA with combined IV and topical TXA administration, Tsukada et al [26] did not find any further reduction in the total blood loss in patients randomized to 3 additional postoperative doses of 1-g IV TXA compared with those who received 3 additional doses of saline. In summary, additional TXA administration did not have a significant additive effect in these studies. Perhaps, further research into the ideal TXA dosing regimens should focus on high-risk groups with higher expected blood loss, including revision and bilateral procedures and in patients with bleeding disorders.

Importantly, 2 doses of TXA, regardless of the administration route, result in a low rate of overall in-hospital thrombotic complications of 1% or less in patients undergoing primary THA and TKA. Although the combined group undergoing primary THA statistically had more overall complications than the double IV group, even with multivariate analysis, this difference of less than 1% is unlikely to be clinically significant and is likely driven by the very low rate (0.2%) in the double IV group. Furthermore, this is likely secondary to the large numbers and difference of sample sizes between the cohorts that can lead to statistical fragility of rare complications in the smaller group (ie, the combined TXA group). There are a number of studies reporting the overall safety of TXA in total joint arthroplasty [12-15]. Similar to the present study in which the ASA class was not associated with an increase in thrombotic complications, several studies have not found multiple comorbidities, a history of VTE, or a higher ASA class had increased complications with the routine use of TXA [12-15]. This consistent finding in the literature is likely secondary to TXA's mechanism of action as an antifibrinolytic rather than a thrombotic agent. In a study analyzing systemic levels of TXA, thrombogenic markers, and antifibrinolytic markers in 76 patients undergoing primary TKA with either IV or topical TXA administration, Jules-Elysee et al [5] did not find any significant increase in thrombogenic markers. There is a plethora of combined data suggesting that TXA is nonthrombogenic and safe for routine use in total joint arthroplasty [5,12-16,19].

We acknowledge several limitations of the present study. First, TXA administration was largely surgeon and anesthesiologist dependent without strict standardization; however, higher-risk patients, including those with prior thrombotic disorders or events and cardiac arrhythmias, receive only one dose of topical TXA perioperatively. This may affect the study's generalizability; however, with 10%-20% of the patient population in this study being ASA class 3 or 4, there was a wide range of patient health statuses captured in this study and the underlying demographics are typical for an arthroplasty cohort. We attempted to mitigate all

of these factors by performing a robust univariate and multivariate analysis of factors that have been shown to affect blood loss and transfusion and complication rates (age, BMI, ASA class, and preoperative Hgb). As this was a retrospective study design, we did not prospectively track patients to analyze complications that occurred after hospital discharge. With the short-acting half-life of TXA [5] and the variability of institutions in which patient's present for these complications, we did not believe that posthospital complications would significantly differ between dosing regimens. Finally, as it can be difficult to definitively characterize, we considered all MIs and CVAs as potentially thrombotic and therefore counted them as complications here to be as inclusive as possible; as such, this study may slightly overestimate these complications.

In the present study, both a double IV and a combined dose of IV and topical TXA were effective in minimizing blood loss. Furthermore, both regimens had a low rate of blood transfusions (~2%) and did not confer a significant risk of potential in-hospital thrombotic complications (~1%). Although both of these dosing regimens are similarly effective and safe, there does not appear to be a synergistic effect of IV and topical TXA administration in primary THA and TKA. Although further study of dosing and administration of TXA to maximize its efficacy is warranted, both dosing regimens may be reaching a plateau at which there will not be a further significant reduction in blood loss during primary THA and TKA with the administration of additional TXA.

Conflict of interests

G.H. Westrich receives royalties from Exactech and Stryker Orthopaedics, is a member of the speakers' bureau for Exactech, Stryker Orthopaedics, and Mallinckrodt Pharmaceuticals, is paid consultant for Exactech and Stryker Orthopaedics, receives research support from Exactech and Stryker Orthopaedics, and is a board member of the Eastern Orthopaedic Association and P.K. Sculco is a member of the speakers' bureau for EOS imaging, Intellijoint Surgical, and DePuy Synthes, is paid consultant for EOS imaging, Intellijoint Surgical, and DePuy Synthes, holds stock ownership in Intellijoint surgical and Parvizi Surgical Innovation, and receives research support from Intellijoint surgical; all other authors declare no potential conflicts of interest.

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