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Full Length Article

# Comparison of three routes of administration of tranexamic acid in primary unilateral total knee arthroplasty: Analysis of a national database

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ABSTRACT

*Introduction:* The ideal route for the administration of tranexamic acid (TXA) remains undecided. This study aimed to compare the efficacy and safety of three routes of TXA following primary total knee arthroplasty (TKA).
*Materials and methods:* We prospectively collected patients' data through the National Health Database from January 2013 to September 2017. The patients were divided into a control group, intravenous group, topical group, and combined group according to the different routes of TXA. The primary outcome was the incidence of transfusion, and secondary outcomes were total blood loss, hemoglobin level and extent of hemoglobin decrease on postoperative day 3, and incidence of complications.
*Results:* Of the total of 7133 primary TKA procedures collected, 4201 employed TXA and 2932 did not. The transfusion rate was 19.8% in the control group and 7.5% in the topical group, significantly higher than that in the intravenous (4.0%, $p < 0.001$) and combined (4.2%, $p < 0.01$) groups. The topical group had higher blood loss (0.97 ± 0.47 L), greater reduction in hemoglobin level (31.2 ± 10.1 g/L), and lower hemoglobin level (102.6 ± 12.7 g/L) on postoperative day 3, compared with the intravenous and combined groups ($p < 0.05$ for all). The differences between the intravenous and combined groups were not significant ($p > 0.05$). The incidence of deep vein thrombosis in the topical group (1.1%) was significantly higher than that in the control (0.4%, $p = 0.007$) and intravenous groups (0.3%, $p = 0.003$).
*Conclusion:* Intravenous and combined administration of TXA was equivalent in reducing blood loss and transfusion requirement, and superior to topical routes.

## 1. Introduction

Total knee arthroplasty (TKA), one of the most effective orthopedic surgeries, can reconstruct joint alignment, alleviate pain, and improve joint function, but involves substantial blood loss and allogeneic blood transfusion [1–3], the direct outcomes of which include postoperative acute anemia and transfusion-associated complications such as disease transmission and immunologic reactions, which potentially increase the burden on the healthcare provider system [4–6]. Numerous strategies have been implemented to address this issue to reduce risks and enhance postoperative recovery [7,8], and the use of anti-fibrinolytic agents has gained popularity [9]. Tranexamic acid (TXA), a synthetic analog of amino acid lysine, can inhibit fibrinolysis by competitively blocking the lysine binding sites of plasminogen. Although TXA has been found to reduce perioperative blood loss in total knee or hip arthroplasty with no concomitant increase in thromboembolic complications [10,11], numerous issues persist regarding the best regimen and route of administration [12,13].

TXA can be administered intravenously [14], topically [15,16], orally, or by a combination of these methods. Intravenous application is a common practice, with evidence favoring its effectiveness in reducing blood loss and transfusion requirement in patients undergoing TKA [14]. Nevertheless, concerns regarding thromboembolic complications after systemic administration have led to a greater interest in topical application [15–17]. Some researchers have also explored the advantage of combined use [18]. However, to our knowledge little research has directly compared the efficacy and safety of the three major methods in primary TKA.

The purpose of our study was to compare the efficacy of TXA in patients undergoing primary unilateral TKA regarding allogeneic blood transfusion requirement and blood loss in relation to the three routes of TXA administration. In addition, we wanted to investigate the difference in safety between the three methods and a control group in terms of thromboembolic events and other complications.

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## 2. Patients and methods

### 2.1. Study design

This prospective cohort study was conducted between January 2013 and September 2017 in 27 large joint reconstruction centers within the framework of a Chinese National Health Ministry program (201302007). The study protocol was approved by the Institutional Review Board (2012-268). Written informed consent was obtained prospectively from all patients prior to surgery.

### 2.2. Patient cohort

Patients were included if they were (1) older than 18 years old undergoing primary unilateral TKA for end-stage knee joint disease such as osteoarthritis and rheumatoid arthritis; (2) had a normal preoperative level of platelets and normal coagulation; and (3) showed normal results on preoperative lower limb Doppler ultrasonography. Patients were excluded if they met any of the following criteria: (1) history of venous thromboembolism (deep vein thrombosis (DVT), pulmonary embolism (PE)); (2) clotting disorders; (3) cardio- or cerebrovascular conditions (history of myocardial infarction or stroke) within the previous 3 months; (4) known allergy to TXA; and (5) serious liver or kidney dysfunction. After exclusion of bilateral and revision arthroplasty and other contraindicated patients, a total of 7133 patients were included (Fig. 1). The patients were divided into a control group (n = 2932), topical group (n = 878), intravenous group (n = 2411), and combined group (n = 912) according to the different methods of TXA administration during knee arthroplasty. Their characteristics are described in Table 1.

### 2.3. TXA administration

In the topical group, a dose of 2–3 g of TXA was injected into the joint capsule via a drainage tube after closure or irrigated topically before deflation. In the intravenous group, a dose of 15–20 mg/kg TXA was injected 5–10 min prior to incision or tourniquet deflation. In the combined group, a dose of 15–20 mg/kg TXA was administered 5–10 min before incision or tourniquet deflation, and 1 g of TXA was topically applied during the operation according to the consensus for application of perioperative anti-fibrinolytic agents during total hip and knee arthroplasty as set by the Chinese Orthopedics Association (COA). No TXA was administered to the control group. The decision regarding TXA administration was made based on standard practices at the participating hospitals.

During surgery, anesthetists decided on whether blood transfusion was necessary; after surgery, attending physicians made these decisions. The criteria for blood transfusion were the same as those recommended by the Chinese National Ministry of Health: (1) hemoglobin < 70 g/L or (2) hemoglobin 70–100 g/L with symptomatic anemia, defined as lightheadedness, palpitations, fatigue precluding participation in therapy, or shortness of breath not due to other causes.

### 2.4. Surgical procedures and anesthesia

A fully cemented TKA was carried out in all patients. The medial para-patellar approach was used in 6705 of 7133 knees (94%), and the minimally invasive approach in 428 knees (6%). General anesthesia was used in 4763 of 7133 patients (67%), and spinal or combined spinal-epidural anesthesia (CSE) in the remaining 33%, depending on what the anesthesia team considered most appropriate for the individual patient. An intraoperative tourniquet was used in 81% of patients. Postoperative wound drainage was carried out in 5894 of 7133 patients (83%). Preoperative oral carbohydrate treatment and intraoperative goal-directed fluid therapy were adopted.

### 2.5. VTE prophylaxis

Physical prophylaxis and chemoprophylaxis were implemented to prevent venous thromboembolism (VTE). Exercises to strengthen dorsal and plantar flexion as well as the quadriceps muscle were initiated as soon as possible after admission. Postoperatively, 57% of all patients were placed on an intermittent foot slope pump system upon arrival in the recovery room, and ambulation was started on postoperative day (POD) 1. All patients received routine perioperative chemical prophylaxis against VTE according to the aforementioned consensus and guidelines for the prevention of VTE set by the COA. Doppler ultrasonography was not applied routinely. If DVT was clinically suspected, ultrasonography was performed immediately. PE was diagnosed based on clinical symptoms and enhanced computed tomography of the chest. All patients were followed up for 3 months postoperatively.

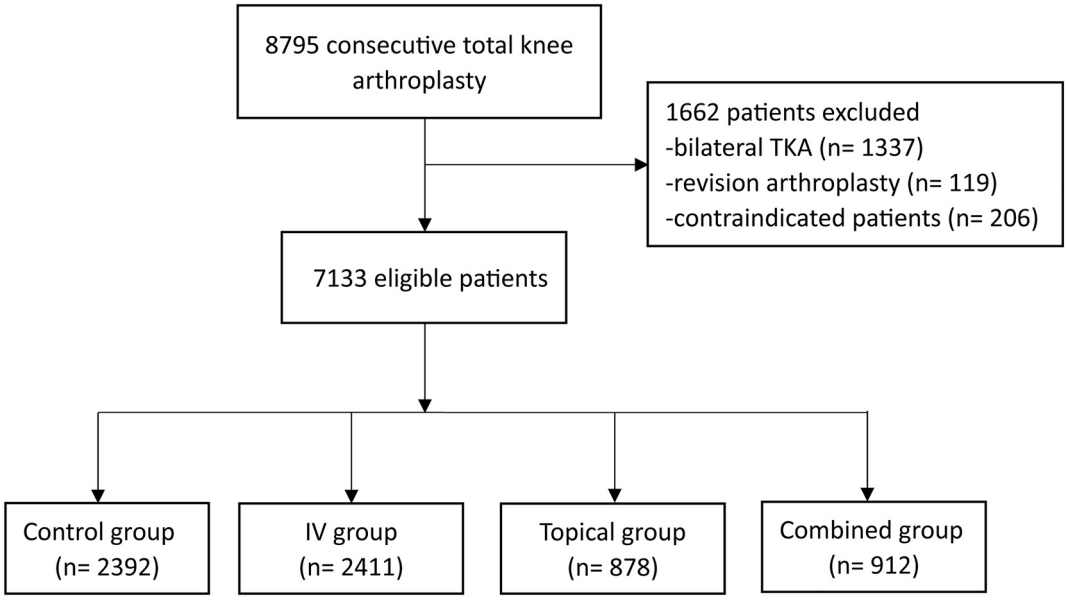


**Fig. 1.** Flow chart of patient selection.

**Table 1**
Details of the patients in both groups.

| | Control (n = 2932) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value |
|---|---|---|---|---|---|
| Age (yrs) | 67.1 (8.5) | 66.8 (8.8) | 66.1 (8.6) | 66.1 (9.0) | **0.553** |
| Female (n, %) | 2058 (70.2%) | 588 (67.0%) | 1726 (71.6%) | 640 (70.2%) | **0.086** |
| Height (cm) | 160.7 (8.1) | 161.0 (7.4) | 158.6 (7.1) | 157.7 (6.9) | **0.064** |
| Weight (kg) | 66.6 (18.2) | 66.7 (10.8) | 65.2 (11.4) | 64.5 (8.9) | **0.270** |
| BMI ($kg/m^2$) | 25.9 (10.8) | 25.8 (3.8) | 25.9 (4.0) | 25.3 (3.5) | **0.382** |
| Diagnosis | | | | | **0.371** |
| OA | 2692 (91.8%) | 792 (90.2%) | 2207 (91.5%) | 659 (92.6%) | |
| RA | 160 (5.5%) | 51 (5.8%) | 141 (5.8%) | 33 (4.6%) | |
| Others | 80 (2.7%) | 35 (4.0%) | 63 (2.6%) | 20 (2.8%) | |
| ASA | | | | | **0.118** |
| I | 978 (33.4%) | 297 (33.8%) | 865 (35.9%) | 318 (34.9%) | |
| II | 1642 (56.0%) | 495 (56.4%) | 1342 (55.7%) | 515 (56.5%) | |
| III | 312 (10.6%) | 86 (9.8%) | 204 (8.5%) | 79 (8.7%) | |
| Anesthesia | | | | | **0.658** |
| General | 1949 (66.5%) | 575 (65.5%) | 1618 (67.1%) | 621 (68.1%) | |
| Spinal + CSE | 983 (33.5%) | 303 (34.5%) | 793 (32.9%) | 291 (31.9%) | |
| Drainage (n, %) | 2396 (81.7%) | 741 (84.4%) | 2007 (83.2%) | 750 (82.2%) | **0.228** |
| Tourniquet (n, %) | 2347 (80.0%) | 709 (80.8%) | 1978 (82.0%) | 725 (79.5%) | **0.218** |
| Physical prophylaxis | 1694 (57.8%) | 499 (56.8%) | 1358 (56.3%) | 532 (58.3%) | **0.643** |
| Chemical prophylaxis | | | | | **0.102** |
| LMWH | 1622 (55.3%) | 479 (54.6%) | 1344 (55.7%) | 507 (55.6%) | |
| Xa inhibitor | 1042 (35.5%) | 323 (36.8%) | 901 (37.4%) | 337 (37.0%) | |
| None | 268 (9.1%) | 76 (8.7%) | 166 (6.9%) | 68 (7.5%) | |
| Operation time (min) | 84.6 (24.6) | 82.7 (23.0) | 83.1 (23.4) | 84.7 (22.8) | **0.191** |
| Crystalloid fluid (ml) | 883.2 (381.6) | 894.6 (298.6) | 884.0 (425.0) | 848.6 (335.2) | **0.180** |
| Hb level (g/L) | 129.1 (13.8) | 130.5 (12.9) | 130.0 (14.1) | 129.8 (14.9) | **0.073** |

Data were presented as mean values with stand deviation or number with frequency.
BMI, body mass index, OA, osteoarthritis, RA, rheumatoid arthritis, ASA, America anesthesia association, Hb, hemoglobin.
Bold values indicate statistically significance at $p < 0.05$.

### 2.6. Outcome measures

The study was conducted within the framework of a National Health Ministry program. Professional staff was in charge of data collection and recording utilizing Microsoft Surface. All data in the system is transported to a central server. The following patient data were collected: age, gender, weight, height, body mass index, American Society of Anesthesiologists rating, anesthetic type, comorbidities, operation time, intraoperative fluids, drainage, anticoagulation, hemoglobin and hematocrit levels (preoperative, on admission, and on PODs 1 and 3), transfusion, DVT, PE, and adverse events such as mortality, stroke, and myocardial infarction.

The primary outcome was transfusion requirement before discharge. Secondary outcomes were hemoglobin level, total blood loss, DVT, PE, and other adverse events. Total blood loss was calculated using the Gross formula and *Nadel* formula according to previous studies [19].

### 2.7. Statistical analysis

All data were analyzed using SPSS 21.0 (IBM, Chicago, IL, USA) with a significance threshold of $p < 0.05$. For continuous, normally distributed data (e.g., total blood loss and hemoglobin level), one-way ANOVA with post hoc Tukey test was performed. For categorical data (e.g., transfusion rate and VTE), these variables were analyzed using the chi-squared or Fisher's exact test, followed by the Bonferroni corrected post hoc test. A multivariable logistic regression model was used to elucidate the impact of confounding factors. The factors such as age, gender, BMI, diagnosis, ASA score, anesthesia, drainage, tourniquet, thromboprophylaxis, preoperative hemoglobin level, and hospital district were included. And the transfusion was set as dependent variable, other factors as covariates.

## 3. Results

No significant differences were found between the groups regarding their baseline characteristics, including demographic data and operation information (Table 1).

A total of 582 patients (19.8%) in the control group received allogeneic blood transfusion, which was significantly higher compared with the topical group (7.5%, $p < 0.001$), intravenous group (4.0%, $p < 0.001$), and combined group (4.2%, $p < 0.001$; Table 2). The

**Table 2**
Transfusion requirement compared among groups.

| | Control (n = 2932) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value |
|---|---|---|---|---|---|
| Transfusion | 582 (19.8%) | 66 (7.5%) | 97 (4.0%) | 38 (4.2%) | < **0.001** |
| p value* | | | | | |
| Topical TXA | < **0.001** | | | | |
| IV-TXA | < **0.001** | < **0.001** | | | |
| Combined TXA | < **0.001** | 0.002 | 0.850 | | |

Values are presented as number with frequency.
Bold values indicate statistically significance at $p < 0.05$.
* Adjust p value by Bonferroni method $p' = 0.008$.

**Table 3**
Total blood loss compared among groups.

| | Control (n = 2932) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value* |
|---|---|---|---|---|---|
| TBL (L) | 1.20 (0.64) | 0.97 (0.47) | 0.83 (0.41) | 0.80 (0.39) | < **0.001** |
| p value† | | | | | |
| Topical TXA | < **0.001** | | | | |
| IV-TXA | < **0.001** | **0.002** | | | |
| Combined TXA | < **0.001** | **0.001** | **0.854** | | |

Values are presented as mean, with standard deviation in parentheses.
Bold values indicate statistically significance at $p < 0.05$.
* Using one-way ANOVA for comparison among groups.
† Using Tukey's test for pairwise comparison; TBL, total blood loss.

difference between the topical and intravenous groups was statistically significant ($p < 0.001$), as was the difference between the topical and combined groups ($p = 0.002$). However, no significant difference was detected between the intravenous group and the combined group ($p = 0.850$). The results of binary logistic regression analysis also revealed an equivalent efficacy between intravenous TXA and combined TXA (odds ratio (OR) = 1.33, 95% confidence interval (CI) 0.98–1.81) and superior to topical TXA (OR = 0.47, 95% CI 0.42–0.55; OR = 0.43, 95% CI 0.28–0.64, respectively).

The total blood loss in each study group was significantly lower than that in the control group ($p < 0.001$ for all, Table 3). Among the study groups, the mean total blood loss was greatest in the topical group (970 mL), as compared with the intravenous group (0.83 ± 0.41 L, $p = 0.002$) and combined group (0.80 ± 0.39 L, $p = 0.001$). However, the difference between the intravenous and combined groups was not significant ($p = 0.854$).

The hemoglobin level on POD 3 in each study group was significantly higher than in the control group ($p < 0.001$ for all, Table 4). In the study groups, the mean hemoglobin level on POD 3 was the least (102.6 ± 12.7 g/L) in the topical group and greatest (104.8 ± 13.0 g/L) in the combined group, although the difference between them was not significant.

The mean decrease in hemoglobin level on POD 3 was 33.8 ± 12.1 g/L in the control group, which was higher than in the topical (31.2 ± 10.1 g/L, $p = 0.030$), intravenous (26.0 ± 11.9 g/L, $p < 0.001$), and combined groups (24.9 ± 12.3 g/L, $p < 0.001$, Table 5). Among the study groups, the topical group showed the largest decrease in hemoglobin level on POD 3 ($p < 0.001$ for all). Comparing the effect of intravenous group versus combined group, the combined group had less reduction of hemoglobin level although the difference was not significant ($p = 0.400$).

The results of postoperative complications are shown in Table 6. There was more DVT in the study groups (0.6%) than in the control group (0.4%), but this was not statistically significant ($p = 0.243$). However, the incidence of DVT in the topical group was higher than in the control and intravenous groups ($p = 0.007$ and $p = 0.003$, respectively). Although the frequency of DVT in the combined group was higher than in the control and intravenous groups, the difference was not statistically significant ($p = 0.025$ and $p = 0.010$, respectively). No significant differences between groups were found with respect to the other complications and total number of complications.

**Table 4**
Hb level on postoperative day 3 compared among groups.

| | Control (n = 2932) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value* |
|---|---|---|---|---|---|
| Hb on POD 3 (g/L) | 95.4 (15.2) | 102.6 (12.7) | 103.8 (15.1) | 104.8 (13.0) | < **0.001** |
| p value† | | | | | |
| Topical TXA | < **0.001** | | | | |
| IV-TXA | < **0.001** | **0.673** | | | |
| Combined TXA | < **0.001** | **0.298** | **0.665** | | |

Values are presented as mean, with standard deviation in parentheses.
Bold values indicate statistically significance at $p < 0.05$.
* Using one-way ANOVA for comparison among groups.
† Using Tukey's test for pairwise comparison; Hb, hemoglobin.

## 4. Discussion

The efficacy of TXA in reducing blood loss and transfusion requirement following primary TKA has been confirmed in numerous studies, but there has been debate concerning the ideal route of administration [13–16,20]. Nevertheless, concern still exists regarding the safety profile of TXA in primary TKA, which hinders its widespread use [14,20]. The current study was performed to compare the efficacy of TXA in terms of transfusion rate, blood loss, postoperative hemoglobin level, and the safety of TXA in terms of thromboembolic events and other adverse events, when administered by topically, intravenously alone, or by combining the two methods. Although there have been numerous randomized clinical trials [21,22] or meta-analyses [23,24] to compare the three routes of TXA administration in primary TKA, these have been limited by small sample size [21,22] and indirect comparisons [23,24]. The current study was more specific as we attempted to directly compare three different methods of TXA administration within a larger sample.

Our major finding is that TXA is associated with less blood loss and allogeneic blood transfusion requirement, regardless of topical, intravenous, or combined route. Furthermore, intravenous or combined use was equivalent in hemostatic effect but superior to topical use alone. Our results also indicated that intravenous and combined administration was safe, while topical administration of TXA might increase the risk of venous thrombotic events.

Intravenous administration of TXA is the most common practice for patients undergoing primary TKA, and the clinical results are promising. A large number of clinical trials and meta-analyses have confirmed its effectiveness in primary TKA [14,25,26]. Alshryda and colleagues [14] conducted a systematic review and meta-analysis of intravenous TXA in primary TKA, which involved 18 clinical trials of 971 patients. The results indicated a lower transfusion rate (risk ratio (RR) = 2.56, 95% CI 2.1–3.1) and lower blood loss (mean difference (MD) = 591 mL, 95% CI 535–647 mL). Our study findings are consistent with these results (Tables 2 and 3).

Despite the available evidence, the concern about the risk of thromboembolic events after systemic administration has hindered its wider application. In light of the safety concerns with intravenous TXA, topical use of TXA has gained popularity because it can prevent bleeding in lower limb arthroplasty [27]. In another meta-analysis of 14 clinical trials by Alshryda et al. [28], the authors found that the incidence of transfusion was lower with the use of topical TXA, while the incidence of thromboembolic events was similar to that found with a

**Table 5**
Decrease in hemoglobin level on POD 3 compared among groups.

| | Control (n = 2932) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value* |
|---|---|---|---|---|---|
| Hb drop (g/L) | 33.8 (12.1) | 31.2 (10.1) | 26.0 (11.9) | 24.9 (12.3) | < **0.001** |
| p value† | | | | | |
| Topical TXA | **0.030** | | | | |
| IV-TXA | < **0.001** | < **0.001** | | | |
| Combined TXA | < **0.001** | < **0.001** | 0.400 | | |

Values are presented as mean, with standard deviation in parentheses.
Bold values indicate statistically significance at $p < 0.05$.
* Using one-way ANOVA for comparison among groups.
† Using Tukey's test for pairwise comparison; Hb, hemoglobin.

placebo. In addition, they concluded that topical TXA was superior to intravenous TXA through indirect comparison. In our previous study [29] we included 18 trials involving 1720 patients who underwent primary TKA, the results of which showed that topical TXA was non-inferior to intravenous TXA in terms of transfusion rate (RR = 1.12, 95% CI 0.82–1.52), but inferior to intravenous TXA in terms of maximum hemoglobin decrease (MD = 0.3 g/dL, 95% CI 0.02–0.59 g/dL). In the current study, more patients were involved (n = 3289) and the results revealed reduced blood loss, transfusion, and hemoglobin with the use of intravenous TXA.

The advantage of intravenous TXA is its wide distribution throughout the extracellular and intracellular compartments, and its rapid reach of maximum plasma concentration in 5–15 min, while topical TXA is able to maintain maximum local level to induce partial microvascular hemostasis by stopping fibrin clots breaking down [30]. However, when combining these two routes the duration of action would be longer than with intravenous or topical use alone. Theoretically, combined use of TXA is superior to intravenous or topical use alone. However, our results showed that combined TXA had a transfusion rate, blood loss, and hemoglobin drop similar to those of intravenous TXA, for the following possible reasons. First, in the current study 81% of all patients had a tourniquet applied during surgery (Table 1), with intraoperative electric coagulation hemostasis also being performed, thus limiting the hemostasis effect of topical TXA. Second, the hidden blood loss caused by postoperative hyperfibrinolysis accounts for appropriately 60% of total blood loss [31], and this would last for 18–24 h [32]. As topical TXA always was injected into the joint capsule through a drainage tube, the short contact time might explain the incompatible results between the theory and clinical application.

The main concern about TXA was the incidence of venous thromboembolic events, which was observed in hip fracture surgery [33]. In line with other studies [10,11], we also found no difference in DVT or other adverse events between intravenous TXA and control groups (0.3% vs. 0.4%, p = 0.594). However, the incidence of DVT in the topical and combined groups was higher than that in the control group. This might be due to the use of a tourniquet and fixed concentration of TXA (10 mg/mL), which would lead to swelling of the lower limb, especially when reaching a high dose of TXA. Such swelling of the joint would influence early mobility, thus increasing the possibility of DVT. By contrast, when TXA is used to inhibit fibrinolysis, anticoagulation therapy should be initiated early to maintain balance between coagulation and fibrinolysis.

Our findings need to be interpreted in light of the following shortcomings. First, the patients' allocation was not randomized, which might have increased the risk of selection bias. However, the decision on the route of TXA administration was made according to standard practice under the guidance of consensus, and the baseline characteristics were comparable among all groups. In our opinion, therefore, the results of our study would not be influenced by the non-randomization. Second, we excluded patients who underwent simultaneous or staged bilateral TKA or revision knee arthroplasty; therefore, the results may not be applicable to these patients, and further studies are warranted to investigate the difference in efficacy in these subpopulations. Third, as the patients with high risk of thromboembolic events were also excluded, the findings were restricted in this subgroup. However, the literature has provided evidence of safety of TXA regarding the issue [34]. Forth, in our study ultrasonography was not routinely performed postoperatively; consequently the incidence of DVT and PE, especially asymptomatic DVT and non-fatal PE, would have been underestimated.

In addition to the aforementioned shortcomings, other limitations

**Table 6**
Postoperative complications.

| | Control (n = 2932) | TXA (n = 4201) | Topical TXA (n = 878) | IV TXA (n = 2411) | Combined (n = 912) | p value* |
|---|---|---|---|---|---|---|
| DVT | 11 (0.4%) | **24 (0.6%)** | 10 (1.1%)† | 7 (0.3%) | 7 (1.0%) | **0.003** |
| PE | 0 | **1** | 0 | 1 | 0 | **0.594** |
| Death | 0 | **0** | 0 | 0 | 0 | **NA** |
| Stroke | 0 | **1** | 1 | 0 | 0 | **0.124** |
| AMI | 0 | **0** | 0 | 0 | 0 | **NA** |
| AHF | 3 | **2** | 0 | 2 | 0 | **1.00** |
| UTI | 1 | **2** | 0 | 1 | 1 | **0.690** |
| PI | 1 | **1** | 0 | 1 | 0 | **1.00** |
| SSI | 4 | **3** | 0 | 1 | 2 | **0.295** |
| oozing | 1 | **4** | 0 | 2 | 2 | **0.280** |
| Total | 21 (0.7%) | **38 (0.9%)** | 11 (1.3%) | 15 (0.6%) | 12 (1.3%) | **0.099** |

Values were expressed as number with frequency.
DVT, deep venous thrombosis; PE, pulmonary embolism; AMI, acute myocardial infarction; AHF, acute heart failure; UTI, urinary tract infection; PI, pulmonary infection; SSI, surgical site infection.
Bold values indicate statistically significance at $p < 0.05$.
* Using chi-squire test or Fisher's exact test.
† Using chi-squire test for pairwise comparison, p value was corrected with Bonferroni method, significant threshold was $p < 0.008$.

should be taken into consideration. First, this study included patients who underwent primary unilateral TKA in 27 centers, and the operations were performed by at least 27 surgeons, which might represent another confounding factor, although it also increases the external objective reality and applicability of the study. Second, each center made a different decision regarding the route of TXA under the guidance of consensus. Finally, herein the term “topical” has two different connotations: intra-articular after wound closure, and topical irrigation before tourniquet deflation.

## 5. Conclusion

In summary, according to our results intravenous and combined administration of TXA was equivalent in reducing blood loss and transfusion requirement, while being superior to the topical route.

## Declaration of conflicts of interest

None of the authors has financial or personal relationships with other people or organizations that would inappropriately influence this work.

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