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Combined Administration of Systemic and Topical Tranexamic Acid for Total Knee Arthroplasty: Can It Be a Better Regimen and Yet Safe? A Randomized Controlled Trial

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ABSTRACT

Background: Total knee arthroplasty (TKA) is associated with substantial blood loss in postoperative period. Tranexamic acid (TXA) is potent antifibrinolytic agent, routinely administered by intravenous (IV) and topical route, which can possibly interrupt cascade of events due to hemostatic irregularities close to source of bleeding. However, scientific evidence of combined administration of TXA in TKA is still meagre. The present study aimed to compare efficacy of combined IV and topical TXA with IV use alone in terms of blood loss, transfusion rate, and incidence of deep vein thrombosis and thromboembolism.

Patients and Methods: 119 patients undergoing unilateral TKA were randomized into IV alone and combined group. Patients assigned to IV group were given IV TXA as a preoperative and postoperative dose given 3 and 6 hours after surgery, whereas in combined group, topical TXA solution was applied intraarticularly about 5 minutes before closure of arthrotomy in addition to IV doses.

Results: Combined use of IV and topical TXA provided better results than IV use alone with mean calculated total blood loss (590.69 ± 191.1 vs 385.68 ± 182.5 , $P < .001$), blood transfusion rate (6.6% vs 1.6% , $P = .364$), hemoglobin drop (1.82 ± 0.6 vs 1.14 ± 0.5 , $P < .001$). No case of DVT or TE was noted among the 2 study groups.

Conclusion: Combined use of IV and intraarticular TXA provided significantly better results compared with IV use alone with respect to all variables related to post-operative blood loss in TKA. Moreover, TXA use is safe in terms of incidence of symptomatic DVT and TE.

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Total knee arthroplasty (TKA) is an excellent option for patients suffering from painful knee arthritis and is uniformly recognized as the most cost-effective surgery in current orthopedic practice. However, TKA is associated with substantial blood loss in the postoperative period [1]. Eventually, blood loss often leads to significant postoperative anemia [2], thereby increasing the risk for cardiopulmonary events, transfusion reactions, and increased health care costs [3]. Moreover, allogeneic blood transfusions may also increase the patient's risk for undesirable immunologic reaction, transmission of disease, and postoperative infection [4]. In addition, any surgery transiently activates the fibrinolytic system [5], and TKA is frequently associated with use of pneumatic tourniquet that further induces local fibrinolysis [6]. Thus, the resulting hyperfibrinolysis may lead to higher blood loss following TKA. Certainly, there is no substitute for good surgical technique and intraoperative local hemostasis. However, a surgeon may venture to lower the risk associated with blood loss by varied means like hypotensive anesthesia

[7], use of intramedullary femoral plug [8], drain clamping [9], preoperative autologous blood donation [10], and use of antifibrinolytic agents.

Tranexamic acid (TXA) is a potent antifibrinolytic agent, which can possibly interrupt the cascade of events due to hemostatic irregularities close to the source of bleeding. Tranexamic acid, a synthetic analogue of amino acid lysine, inhibits fibrinolysis by competitively blocking lysine-binding sites of plasminogen, resulting in decreased proteolytic action on the fibrin monomers and fibrinogen, which ultimately results in clot stabilization [11]. It reaches a concentration of 90%–100% in joints compared with its concentration in plasma [12]. A meta-analysis of the intravenous administration of TXA showed valid evidence that it significantly reduces the need for transfusion by 38% in cardiac, orthopedic, cranial and orthognathic, hepatic, gynecologic, and urologic surgery [13]. Besides, numerous randomized controlled trials (RCTs) [14–17] and several meta-analyses [18–20] have reported the efficacy of TXA in decreasing blood loss and blood transfusion rate without any increased incidence of deep vein thrombosis (DVT) and venous thromboembolism (TE). Furthermore, TXA concentrations up to 10 mg/mL of blood have no influence on the platelet count, the coagulation time, or various coagulation factors in whole blood or citrated blood from healthy subjects [21]. Nonetheless, theoretical concerns do exist because of a greater risk of thromboembolic complications with use of

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TXA due to its antifibrinolytic activity. However, a previous study reported that TXA does not influence the fibrinolytic activity in the vein walls [22]. Despite the evidence from several studies that shows no associated increased TE complications due to TXA, some concerns do remain about the symptomatic TE events [3,14,17,23,24]. Tranexamic acid is traditionally administered intravenously, in surgical settings, although the doses vary considerably without any standard set protocol [25–27]. In addition, multiple studies [28–30] including a meta-analysis [31] had demonstrated the potency of topical TXA to be similar to or even better than intravenous TXA. Furthermore, a recent study by Lin et al [32] had demonstrated the efficacy of combined administration of TXA to be better than topical use alone. Thus, it is imperative to say that a combined administration of TXA may prove to be more effective compared with intravenous or topical TXA use alone. However, the scientific evidence of combined administration of TXA in TKA is still meager.

Therefore, the present study was conducted (1) to compare the efficacy of combined use of intravenous and topical TXA with that of intravenous use alone in terms of total blood loss and the allogeneic transfusion rate and (2) to evaluate the safety profile of each regimen in terms of incidence of DVT and TE. As additional use of topical TXA increases the probability of enhanced antifibrinolytic activity, we hypothesized that there will be a significant difference between combined use of intravenous and topical TXA and intravenous use alone in terms of blood loss, allogeneic blood transfusion rate, and hemoglobin (Hb) drop.

Patients and Methods

Study Design and Subjects

A total of 130 consecutive patients scheduled for elective unilateral primary TKAs were assessed during the period between September 2014 and December 2014 for the eligibility of this study (Fig. 1). All patients with diagnosis of primary osteoarthritis (OA) posted for unilateral TKA were included in the study so as to obviate possible outcome confounders. Exclusion criteria were patients with a diagnosis other than primary OA, patients undergoing simultaneous bilateral TKA, patients diagnosed with coagulopathy (acquired or congenital), patients on current anticoagulation therapy, patients with history of thromboembolic disease, and those with hepatic or renal dysfunction or previous ischemic heart disease. Of the 130 patients assessed, 11 patients were excluded for the following reasons: 7 patients for diagnoses other than primary OA, 2 patients on anticoagulation therapy, and 2 patients with prior history of DVT. After meeting the inclusion and exclusion criteria, 119 patients undergoing unilateral TKA were enrolled and randomized into 2 groups—(1) intravenous TXA alone (IV) and (2) combined intravenous and intraarticular TXA (IV plus IA)—using a computer-generated randomization table with a permutation block of 6. Thus, 60 patients were assigned to the IV group and 59 to the combined IV and IA group. The patients and clinical investigators who prospectively

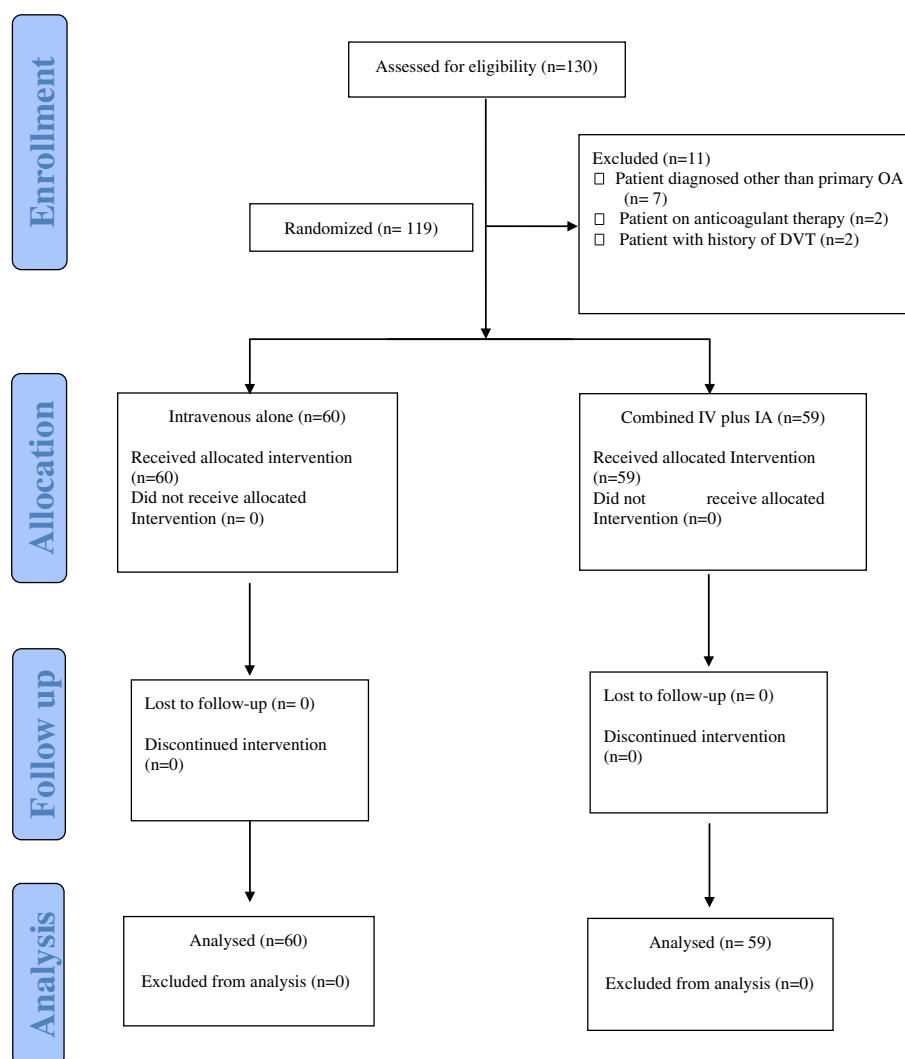


Fig. 1. Flow diagram showing patient selection and randomization.

collected all clinical information were unaware of the group identities until the final data analysis. All patients included in the study belong to same ethnic background; that is, all were Indians (Asians) who share common genetic pool and socioeconomic conditions. There were no significant differences in the demographic data, preoperative hematologic values, and operative time among the 2 groups (Table 1).

Administration of TXA

Patients assigned to the IV group were given intravenous TXA at 15 mg/kg of body weight 30 minutes before skin incision as a preoperative dose. A postoperative dose of 10 mg/kg was repeated 3 and 6 hours after surgery. Calculated dose of TXA was mixed in 100 mL of isotonic sodium chloride solution and given as a slow intravenous injection. Also, for patients in the IV-alone group, a mop soaked in isotonic sodium chloride solution was applied intraarticularly for 5 minutes before closure of arthrotomy. On the other hand, for patients in the combined group, in addition to intravenous preoperative and postoperative dose, 2 g of TXA diluted in 30 mL of isotonic sodium chloride solution was used as mop soaked in TXA solution and applied intraarticularly for about 5 minutes before closure of arthrotomy.

Surgical Procedure and Perioperative Management

All surgical procedures were done by the senior author using minimally invasive subvastus approach. All surgical procedures were performed without the use of a tourniquet. Moreover, no drain was applied in any patient following TKA. Cruciate-retaining implants were used in most of the cases, and the patella was resurfaced in selected group of patients. A continuous femoral nerve block technique was used for 24 hours postoperatively for pain control and early recovery. Intravenous analgesia was provided with injectable diclofenac sodium 75 mg in 100 mL normal saline 8 hourly if preoperative serum creatinine level was normal; otherwise, inj. paracetamol 1000-mg infusion was given 8 hourly. Also, inj. tramadol 50 mg was given for breakthrough pain if required. Additional analgesics consisted of oral acetaminophen 500 mg administered at 6-hour intervals starting 6 hours postoperatively. We followed standard set criteria for patients who require blood transfusion. Allogeneic blood transfusion was indicated if postoperative patient's Hb drops to less than 7.0 mg/dL or if any symptoms suggestive of anemia such as dyspnea or tachycardia persist in spite of volume replacement therapy in patients wherein Hb level falls between 7.0 and 8.0 mg/dL based on use of restrictive hematologic algorithm [33]. Accordingly, 1 U of packed red blood cells one at a time was administered so as to increase the Hb level to 8.0 g/dL. Postoperatively, mobilization was early and aggressive. Static quadriceps exercises and straight leg rising exercise were started from day 0, and range of motion

exercises began from day 1. Below-knee thromboembolic disease stockings for both lower limbs were used. Chemical prophylaxis for DVT was in the form of tablet aspirin 75 mg once a day for 6 weeks [34,35]. Patients were encouraged to get out of bed and walk as tolerated from day 1. Moreover, perioperative intravenous antibiotics were given to all patients for 24 hours.

Outcome Assessment

An independent investigator prospectively collected all the clinical information using predesigned protocol. The clinical information included demographic data, preoperative clinical status, and postoperative outcomes evaluated until 6 weeks postoperatively.

The primary outcomes measures were total blood loss and the allogeneic blood transfusion rate. Total blood loss was calculated from the difference between the preoperative Hb and the postoperative Hb level on the third postoperative day before the patient was routinely discharged from hospital or when the Hb level was lowest before blood transfusion. The total blood loss was calculated based on patient blood volume, Hb loss, and the formula described in previous studies [15,36].

The secondary outcomes were postoperative Hb drop and the incidences of symptomatic DVT and TE. If patients were transfused, the lowest Hb level before transfusion was taken for the calculation. The number of patients that presented with symptomatic DVT or TE was noted. Routine screening for DVT was not performed, and ultrasonographic study was done for patients with suspicious symptoms including pain, swelling, and tenderness in the thigh or calf.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 20.0; IBM, Chicago, IL). The nature of the hypothesis testing was 2-tailed, and a *P* value of less than .05 was considered statistically significant for all comparisons. The Kolmogorov-Smirnov test was used to determine whether measured and calculated parameters were normally distributed. The Student *t* test was used to determine the significances of group differences in continuous variables. The χ^2 or Fisher exact test was used to analyze categorical variables.

Sample size estimation was done based on the total blood loss calculated in the pilot study before initiation of the present study between the 2 groups, namely, intravenous TXA alone and combined IV and IA TXA. A reduction of total blood loss of more than 200 mL, the half volume of allogeneic blood transfusion unit, was regarded as clinically meaningful. Total blood loss was calculated in 75 patients who underwent unilateral TKA during pilot study, and we found a mean blood loss and standard deviation of 620 ± 190 mL and 438 ± 186 mL in the IV-alone and combined IV and IA group, respectively. The sample size estimation thus calculated with an α of .05 and power of 80% to discern a difference of 200 mL with Student *t* test showed that a sample of 33 and 36 patients would be required for the IV-alone and combined IV and IA group, respectively. Thus, a sample size 60 patients in each group was considered as deemed appropriate.

Results

Combined administration of intravenous and topical TXA provided better results in terms of total blood loss and allogeneic transfusion rate (Table 2). Moreover, the degree of Hb drop was lesser with combined IV and IA TXA use as compared with IV TXA use alone. Mean calculated total blood loss was higher with intravenous TXA use alone compared with combined IV and IA TXA use (590.69 ± 191.1 vs 385.68 ± 182.5 , *P* value < .001). Also, the rate of allogeneic blood transfusion was greater in the IV-alone group compared with the combined IV and IA group but without any statistical significance (6.6% vs 1.6%, *P* = .364). Likewise, the amount of Hb drop (Table 2) was lesser with combined IV and IA TXA use (1.82 ± 0.6 vs 1.14 ± 0.5 , *P* value < .001).

Table 1
Demographic Variables and Hematological Values Between the Study Groups.

Variables	IV Group Only (n = 60)	Combined IV and IA Group (n = 59)	P Value
Gender (female) ^a	36 (60)	39 (66.1)	.570
Age (y)	70.0 (6.56)	68.27 (8.66)	.223
Height (cm)	154.8 (9.9)	156.6 (9.9)	.311
Weight (kg)	71.88 (10.8)	71.21 (15.6)	.788
BMI (kg/m ²)	30.12 (4.7)	29.14 (6.5)	.351
Knee type (CR) ^a	58 (96.6)	56 (94.9)	.679
Patella (%) ^a	14 (23.3)	13 (22.0)	.959
Operation time (min)	68.48 (5.2)	69.12 (4.9)	.191
Preoperative Hb (g/dL)	12.39 (1.46)	12.11 (1.19)	.251
Prothrombin time	13.03 (0.41)	12.98 (0.32)	.438
aPTT	31.29 (3.54)	30.68 (2.99)	.310

Data are presented as mean with standard deviation in parentheses. IV, intravenous; IA, intraarticular; BMI, body mass index; CR, cruciate retaining; Hb, haemoglobin; aPTT, activated partial thromboplastin time.

^a Data are presented as number of patients with percentage in parentheses.

Table 2
Comparison of Outcome Variables Among the 2 Study Groups.

Variables	IV Group only (n = 60)	Combined IV and IA Group (n = 59)	P Value
Calculated total blood loss (mL)	590.69 (191.1)	385.68 (182.5)	.001
Hb drop (g/dL)	1.82 (0.61)	1.14 (0.50)	.001
Allogeneic transfusion rate (%) ^a	4 (6.6)	1 (1.6)	.364
Symptomatic DVT (no. of patients) ^a	1 (1.6)	0	NA
Symptomatic TE (no. of patients) ^a	0	0	NA

Data are presented as mean with standard deviation in parentheses for calculated total blood loss and Hb drop. IV, intravenous; IA, intraarticular; DVT, deep venous thrombosis; TE, thromboembolism; NA, not applicable.

^a Data are presented as the number of patients with percentage in parentheses for allogeneic transfusion rate and symptomatic DVT and TE.

There was no significant difference observed in terms of any adverse complications among the 2 groups. One patient in the IV-alone group had clinical suspicion of DVT; however, he was found to be negative on duplex Doppler study. No other patient in the 2 study groups had such symptoms. Moreover, there was no case of clinical thromboembolic event among the 2 study groups.

Discussion

Tranexamic acid, a potent antifibrinolytic agent, has proved to be effective in reduction of surgical blood loss. Moreover, numerous studies showed the efficacy of systemic as well as topical use of TXA for TKA [2,3,14,16–18,30]. Also, a recent study [32] has demonstrated the better efficacy of combined intravenous and topical TXA compared with topical TXA use alone. We therefore performed this study to compare the efficacy of intravenous administration of TXA alone and combined use of IV and IA TXA use as well as their safety profile for TKA.

Tranexamic acid can be administered by several routes including intravenous, intramuscular, intraarticular, and oral. Moreover, to achieve maximum plasma concentration, TXA takes about 2 hours for oral, 30 minutes for intramuscular, and 5–15 minutes for intravenous administration [37,38]. Thus, for patients undergoing TKA, the best suitable method for rapidly increasing and maintaining the therapeutic concentration of TXA is by the intravenous route. Also, the elimination half-life of TXA is 120 minutes, with majority of TXA excreted in urine [39]. Besides, TXA enters the extravascular space and accumulates in tissues for up to 17 hours; the basis for its mechanism of action is thought to be inhibition of tissue fibrinolysis and consequent stabilization of clots [40]. However, on intraarticular administration, TXA is rapidly absorbed and maintains a biological half-life of approximately 3 hours within joint fluid [3]. Furthermore, pharmacokinetic studies in the recent past reported that an intravenous dose of 20 mg/kg of TXA is suitable for TKA because therapeutic levels can be maintained for approximately 8 hours after operation, which covers the period of postoperative hyperfibrinolysis [41]. The regimen of TXA used in the present study included single preoperative intravenous dose followed by 2 postoperative intravenous doses in the intravenous group, whereas in the combined group, in addition to IV TXA use, topical solution of TXA soaked in the mop was kept in the joint for 5 minutes, just before closure. A study by Maniar et al [29] has demonstrated that a regimen with preoperative and postoperative intravenous doses was most effective in reducing the blood loss. Furthermore, they described that preoperative dose made a difference and must be a part of any regimen of TXA, as giving TXA preoperatively and before tourniquet application, if used, would deactivate the fibrinolysis as soon as it starts. Also, fibrinolysis is best inhibited at its initial stages, being best achieved by a preoperative dose [42]. Topical application of TXA has many conceptual as well as realistic advantages. Firstly, it inhibits local activation of fibrinolysis as well as systemic activation from local mediators after tourniquet release [43]. Also, high concentration of local TXA in the knee joint should result in greater thrombus formation and lower time to vascular occlusion [44]. In addition, topical TXA has very low systemic absorption [45]. Besides, few studies in the recent past have reported the dose-dependent effect of TXA and that higher topical TXA dose gives better

results [2]. All these formed the basis for the intravenous regimen as well as combined intravenous and intraarticular TXA administration in the present study.

The findings of the present study support the hypothesis that combined administration of IV and IA TXA is more effective than IV TXA administration alone in terms of calculated total blood loss and allogeneic transfusion rate following TKA. Blood loss is associated with significant postoperative anemia [2], thereby increasing the risk for cardiopulmonary events, transfusion reactions, and increased health care costs [3]. Also, complications after allogeneic blood transfusion including undesirable immunologic reaction, transmission of disease, and postoperative infection have been well reported in the literature [4]. The administration of TXA, whether systemic or topical, has been found to reduce the blood loss and the transfusion rate post-TKA and thus the associated complications. Several clinical trials have reported the efficacy of systemic use of TXA [3,14,16–18]. Moreover, in the recent past, there has been an increasing trend of topical use of TXA during TKA to obviate the adverse effects associated with its systemic use. Furthermore, multiple studies have evidently described the effectiveness of topical TXA for reducing blood loss post-TKA [2,30]. Also, numerous studies comparing the efficacy of systemic and topical TXA administration had demonstrated that the results of intraarticular TXA use are similar [29] to or better [30] than those of its intravenous use. In addition, a recently published study [32] has reported the better efficacy of combined TXA administration compared with topical use alone and the control group. Likewise, the most important finding of the present study is that combined use of TXA has provided better results with regard to total calculated blood loss ($P < .001$) and the degree of Hb drop ($P < .001$) than the intravenous group alone. The use of allogeneic blood transfusion (Table 2) was lesser in the combined group, although it did not reach statistical significance ($P = .364$).

Tranexamic acid is a potent antifibrinolytic agent, and therefore, there is an apprehension over its use and the related increased incidence of TE complications following TKA. All patients were Asians (Indians), and multiple studies including a meta-analysis [46] had reported lower incidence of VTE in Asians compared with Western populations. Also, patients in the study underwent a TKA using the subvastus approach without the use of a tourniquet, which does allow an earlier recovery, thereby further reducing the DVT rate [47]. Furthermore, numerous previous studies [2,15–17,29,30] along with a recent systemic review [48] have reported the safety profile of TXA administration for TKA without any increased incidence of symptomatic DVT or TE using different doses, routes, and timings of TXA administration. Moreover, a dose-related study has recommended that a dose of TXA up to 100 mg/kg in cardiac surgery is safe [49]. Similarly, a study showed that a high dose of TXA across the range of about 61 to 259 mg/kg had no adverse effects [50]. Although it is an accepted fact that TXA does not inhibit fibrinolytic activity in the vein wall [22], its real impact on disrupted endothelium remains unknown. Moreover, local venous endothelial injury/disruption during TKA (dissection, manipulation, use of power tools in close proximity of vessels) may have influence on the DVT incidence post-TKA. Also, in the present study, 1 patient in the intravenous group had clinical suspicion of DVT based on clinical observation including calf swelling and tenderness; however, he was found to be negative on duplex Doppler study. Thus, the findings of

our RCT with extremely low incidence of DVT or TE may reflect the safety profile of TXA use, both intravenous as well as combined (IV plus IA) regimen, during TKA. Likewise, the findings of our RCT on safety findings are evidently echoed by several meta-analysis studies [18–20].

Several limitations of this RCT study need to be considered before its interpretation. First, the present study is performed at a single institute and is not free from the usual shortcomings of an original study. The surgical techniques and complexity of surgical procedures, particularly the extent of soft tissue release, which may be unique to the operating surgeon as evidenced by use of the minisubvastus approach, without the use of tourniquet and not using closed suction drain in the postoperative period, in this study, may influence the calculated total blood loss post TKA. The present study had not evaluated the variables relating to these aspects. However, patients were randomly distributed, and no significant differences were found between the groups in any demographic data, preoperative status, and operation time (Table 1), which indicate that the confounding effects of these issues may be negligible. Second, we did not include patients who underwent simultaneous bilateral TKA in the present study, and therefore, our conclusions may not apply to these patients. Third, we have also not included a control group (with no TXA use) in the present study because it would be unethical and inappropriate to bereave patients in the RCT from the accepted benefits of TXA use and thereby subject them to increased blood loss and transfusion and, thus, their complications. Fourth, no blood studies have been carried out to estimate serum TXA levels following TKA, and thus no information regarding the toxicity related to TXA can be retrieved. Fifth, in this study, we did not evaluate and monitor plasminogen levels, D-dimer, fibrin degradation products, and thromboelastography, as it would have provided us with the objective and conclusive evidence of hyperfibrinolysis and the resultant antifibrinolytic activity. Sixth, the power analysis was done based on the blood loss; however, we did not take the incidence of VTE as a basis for power analysis, which is much more infrequent and may require a larger sample size. Finally, the present study has not addressed the subjective knee function score and objective clinical examination findings of the patients after TKA, as the main purpose of this study was to evaluate the effects of combined use of TXA as compared with intravenous TXA use alone, so as to minimize the postoperative blood loss in patients who undergo TKA.

In conclusion, the combined use of intravenous and intraarticular TXA has provided significantly better results compared with intravenous TXA use alone with respect to all variables related to postoperative blood loss in TKA. Besides, our RCT study has reported the safe nature of TXA use including the combined IV and IA administration in terms of incidence of symptomatic DVT and TE. However, the variable effect of TXA use combined and/or topical at varying doses and timings is a matter for future studies.

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