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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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A B S T R A C T

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 postoperative 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 of 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

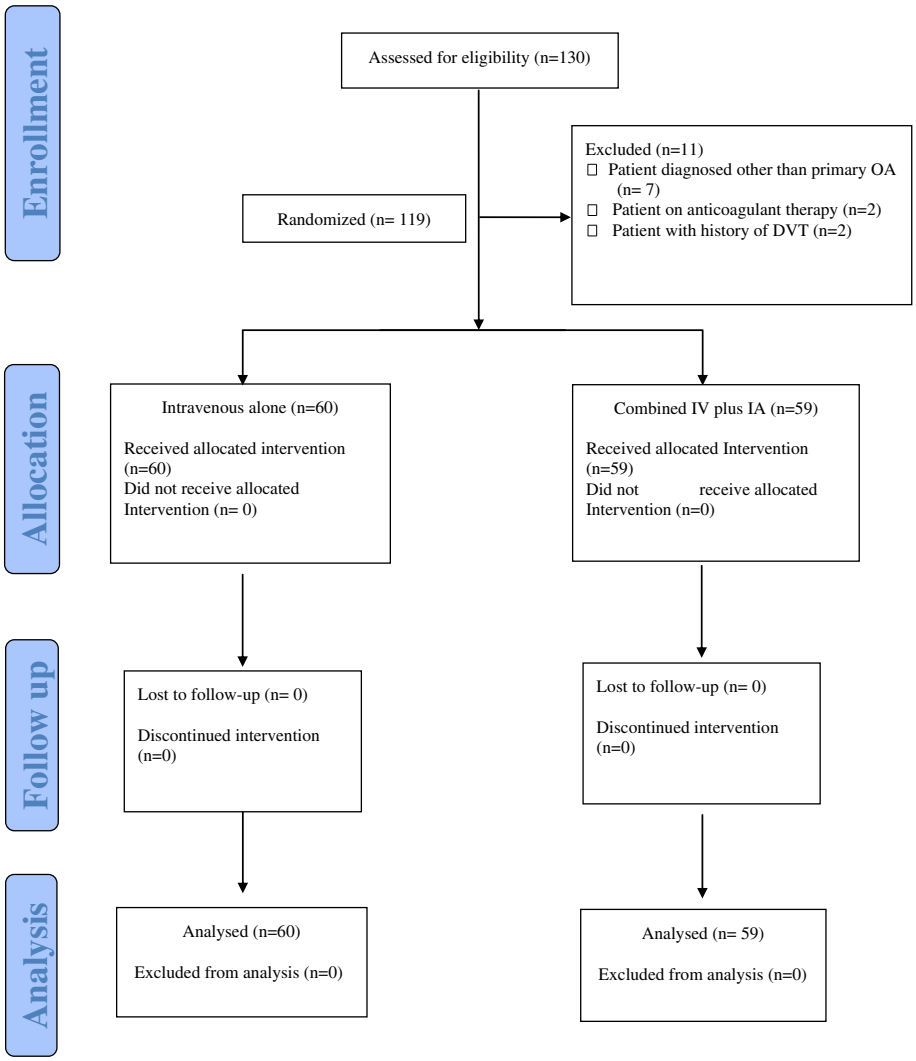

Fig. 1. Flow diagram showing patient selection and randomization.