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Original Article

Multiple Boluses of Intravenous Tranexamic Acid to Reduce Hidden Blood Loss After Primary Total Knee Arthroplasty Without Tourniquet: A Randomized Clinical Trial

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ABSTRACT

Background: The optimal dosage and timing of tranexamic acid (TXA) in total knee arthroplasty (TKA) are undetermined. The purpose of this study was to explore the effect of multiple boluses of intravenous TXA on hidden blood loss (HBL), inflammatory response, and knee function after primary TKA without tourniquet.

Methods: A total of 151 patients were randomly divided into 3 groups to receive single bolus of 20 mg/kg IV-TXA before skin incision (group A), or another bolus of 10 mg/kg IV-TXA 3 hours later (group B), or another 2 boluses of 10 mg/kg IV-TXA 3 hours and 6 hours later (group C). TKAs without tourniquet were operated by 1 single surgeon. The primary outcomes were HBL and maximum hemoglobin drop. Other outcome measurements such as total blood loss, transfusion rate, inflammation markers (C-reactive protein, interleukin 6), visual analog scale pain score, limb swelling ratio, Hospital for Surgery Score, range of motion, length of hospital stay (LOH), and deep venous thrombosis were also compared.

Results: The mean HBL and maximum Hb drop in group C (467.6 ± 305.9 and 20.9 ± 9.3) was lower than those in group A (763.0 ± 373.3, $P < .001$; 28.7 ± 12.2, $P < .001$) and group B (637.5 ± 303.5, $P = .010$; 25.2 ± 8.4, $P = .036$). However, such differences were not detected between groups A and B ($P = .058$ and $P = .080$, respectively). The mean value of total blood loss in the groups A, B, and C were 967.2 ± 380.1, 803.7 ± 321.8, and 677.6 ± 326.0 mL, respectively, with a significant intergroup difference ($P < .001$). The mean serum level of C-reactive protein and interleukin 6 in group C were lower than those in group A and group B on postoperative days 1 and 2. The visual analog scale pain score and swelling ratio were also lower in group C than in the other 2 groups with statistical significance on POD 1-3. Moreover, the Hospital for Surgery Score, range of motion, and LOH were better in group C. No episodes of transfusion or deep venous thrombosis had occurred.

Conclusion: Multiple boluses of IV-TXA can effectively reduce HBL after primary TKA without tourniquet. What is the most important is that, by adding another bolus of IV-TXA, patients can gain a smaller decline of Hb, less postoperative inflammatory response, less pain, less knee swelling, better knee function, and shorter LOH.

Total knee arthroplasty (TKA), as one of the most common surgeries in orthopedics, can effectively alleviate pain, ameliorate function, and improve the quality of patients' life [1]. With the development of aging population, the demand of TKA is increasing. It is estimated that the demand for primary TKA will grow by 673% to 3.48 million procedures by 2030 in the United States [2]. However, the substantial intraoperative and postoperative blood loss and the consequential acute anemia and transfusion are the major concerns for joint surgeons. To reduce blood loss and allogeneic blood transfusion requirement, while speeding function recovery, a lot of patient blood management alternatives have been introduced. According to the literature, the perioperative blood loss results from surgical trauma and hyperfibrinolysis enhanced by the application of tourniquet [3,4]. Thus, the application of

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antifibrinolytic drugs, such as tranexamic acid (TXA), has been put into the spotlight with promising results [5-8].

TXA is an analog of the amino acid lysine, which can competitively inhibit plasminogen activation and plasmin binding to fibrin, thus inhibiting the fibrinolysis. There are 3 major regimens of TXA in TKA: intravenous [5,6], topical [7], and combined application [8]. Although a large amount of level I evidences has confirmed that the application of TXA can significantly decrease blood loss and transfusion requirement without increasing the risk of venous thrombosis events (VTEs), the hidden blood loss (HBL) has not been reduced [9,10]. Furthermore, in most of the studies referred to, tourniquet was used.

The HBL, caused by postoperative hyperfibrinolysis, accumulated in anatomic third space, which will lead to the postoperative inflammation, lower limb swelling, and pain [11]. According to a kinetics study [12], hyperfibrinolysis peaked at 6 hours postoperatively, which would last for 18 hours. In our pilot study, we tested D-Dimer and fibrin degenerated products at 6, 12, 24, and 48 hours postoperatively in 40 TKAs. The preliminary results indicated that the fibrinolysis peaked at 6 hours postoperatively and lasted for 24 hours at least. To inhibit the fibrinolysis completely, single dose of TXA is not enough. So, we made the hypothesis that repeated dose of IV-TXA for 18-24 hours could inhibit postoperative fibrinolysis, reducing HBL. Therefore, we conducted this prospective randomized controlled clinical trial, which is expected to answer the following 3 questions: (1) Can the multiple boluses of IV-TXA reduce HBL and the maximum hemoglobin drop further? (2) Are there any other benefits, such as the mitigation of limb swelling, inflammation response, and postoperative pain, patients can gain from the repeated administration? (3) Is this regimen safe?

Materials and Methods

Study Design

This prospective, randomized, clinical trial was performed on adult patients who were scheduled for primary unilateral TKA from March 2015 to October 2015. Before starting this trial, the study protocol was approved by the institutional review board. Written informed consent and research authorizations were obtained before surgery from all participants.

Patients' Cohort

All patients, aged 18 years or older, who were scheduled to have primary unilateral TKA for osteoarthritis or rheumatoid arthritis were considered eligible for being included in the trial. Exclusion criteria for both the groups included patients with anemia (<120 g/L for female, <130 g/L for male), cardiovascular problems (history of myocardial infraction, angina, and atrial fibrillation), cerebrovascular conditions (history of previous stroke), thromboembolic disorders (history of deep vein thrombosis [DVT] or pulmonary embolism [PE]), clotting disorders, known allergy to TXA, and flexion deformity $\geq 30^{\circ}$, varus and/or valgus deformity $\geq 30^{\circ}$.

The recruited patients in this double-blinded study were randomized into 1 of 3 groups and received TXA by the following ways, which are confidential in the opaque sealed envelopes only opened before surgery. The three groups are: (1) group A: the patients received 1 bolus of 20 mg/kg IV-TXA before skin incision, and 10 mg/kg of normal saline was intravenously injected 3 and 6 hours later; (2) group B: a dosage of 20 mg/kg IV-TXA was administered 5-10 minutes before skin incision, and 10 mg/kg of TXA was administered 3 hours later, another 10 mg/kg of normal saline was administered 6 hours later; and (3) group C: a dosage of 20 mg/kg of IV-TXA was administered 5-10 minutes before skin incision, and 10 mg/kg of TXA was administered 3 and 6 hours later. All the patients received 1-g topical TXA intraoperatively according to our previous study [13]. The postoperative protocol was implemented by a nurse who was not involved in this trial. The patients, surgeons, data collector, and analyst were blinded.

Surgical Procedures

All the TKAs were operated under general anesthesia or spinal anesthesia, depending on what techniques were considered most appropriate for the individual patient by the anesthetic team. All the operations were performed by the senior author in the same laminar air flow operation room. A midline skin incision, medial parapatellar approach, and a measured resection technique were used in all cases. Intramedullary guides were used for all femoral preparation, and extramedullary guides were used for tibial preparation. Autologous bone was used to fill the femoral medullary canal before implant cementation. All patients received a surgeon-selected cemented posterior-stabilized prosthetic design with patellar resurfacing, and all TKAs were conducted without tourniquet. Vacuum wound drainage was used in every patient and removed 24 hours postoperatively. Besides, no blood salvage system was used, and electrocautery and routine hemostasis were performed during surgery routinely. The surgery time, intraoperative blood loss, and drainage volume were recorded carefully.

Postoperative Care Protocol

After the surgery, patients were first transferred to the post-anesthesia care unit for 2 hours, then to the inpatient unit. Immediately after they arrived at the inpatients unit, cold pack was used on the surgical sites for 12 hours. Diclofenac sodium enteric–coated tablets were administered orally with a regular dose of 50 mg bid for postoperative pain management except the intraoperative periarticular injection with ropivacaine. Daily functional training, including quadriceps strength training, active range of motion (ROM) training, and walking training were performed under the supervision and assistance of a physiotherapist.

A combination of physical prophylaxis and chemoprophylaxis was adopted to prevent venous thromboembolism. An intermittent foot slope pump system was used as a routine practice to prevent DVT before walking. Besides, half dose of enoxaparin (0.2 mL 2000 IU; Clexane; Sanofi-Aventis, France) was subcutaneously administered 6 hours postoperatively and repeated at 24-hour intervals with a full dose (0.4 mL 4000 IU) on the subsequent days. After discharge, 10 mg of rivaroxaban was administered orally to the patients for 10 days, if no bleeding events happened. Doppler ultrasound was applied routinely to detect DVT at the time of discharge and 1-month follow-up. If clinically suspended DVT was found, ultrasound would be performed immediately. PE was diagnosed by clinical symptoms and enhanced chest computed tomography scan.

The criterion for a blood transfusion was set as a hemoglobin level of <70 g/L or 70-100 g/L with symptomatic anemia (defined as light-headedness, fatigue precluding participation in the therapy, palpitations, or shortness of breath not due to other causes) according to the guidelines by the National Ministry of Health.

Outcome Measurements

Measurements were completed during the inpatient hospital stay. Preoperatively, patient demographics, medical history, and