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Full Length Article

Efficacy and safety of multiple boluses of oral versus intravenous tranexamic acid at reducing blood loss after primary total knee arthroplasty without a tourniquet: A prospective randomized clinical trial

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ABSTRACT

Introduction: The aim of this study was to examine whether the administration of multiple boluses of oral or intravenous tranexamic acid (TXA) postoperatively were equivalent at reducing blood loss and the inflammatory and fibrinolytic responses in primary total knee arthroplasty (TKA) without a tourniquet.

Materials and methods: In this prospective, double-blinded, randomized trial, patients undergoing primary THA were randomized into either an oral or intravenous TXA group. All patients received 1 dose of 20 mg/kg intravenous TXA 5–10 min before skin incision. Patients in the oral TXA group then received 3 doses of 2 g oral TXA at 4, 10, and 16 h postoperatively, while patients in the intravenous TXA group received 3 doses of 1 g intravenous TXA at 6, 12, and 18 h after surgery.

Results: There was no significant difference in the hemoglobin (Hb) or hematocrit (Hct) drop on postoperative day 1 (14.7 ± 10.5 vs 14.4 ± 9.6 g/L, $p = 0.869$; 0.042 ± 0.032 vs 0.040 ± 0.028, $p = 0.781$) and 3 (22.6 ± 10.6 vs 20.5 ± 9.7 g/L, $p = 0.300$; 0.059 ± 0.031 vs 0.054 ± 0.031, $p = 0.332$). No patients needed an allogeneic blood transfusion. The mean total blood loss, hidden blood loss, length of hospital stay, the level of inflammatory and fibrinolytic markers on the first and third postoperative days, and the incidence of complications were not significantly different between the two groups ($p > 0.05$).

Conclusion: There was no difference in Hb and Hct drop, blood loss, inflammatory and fibrinolytic responses in primary TKA without a tourniquet between those who received multiple boluses of oral or intravenous TXA after surgery in current scheme.

1. Introduction

Total knee arthroplasty (TKA) is an effective treatment option to correct deformity, ameliorate pain, and improve quality of life for advanced osteoarthritis of the knee. With the increasing life expectancy in the population, the number of TKAs performed is growing annually [1,2]. However, the surgery is associated with significant perioperative blood loss, and postoperative anemia and need for allogeneic blood transfusions are common, which contribute to the high incidence of complications such as infection, venous thromboembolism, prolonged hospital stay, and increased mortality and cost [3,4]. Therefore, investigating appropriate blood management methods to reduce blood loss and minimize the rate of blood transfusions has long been an important goal for surgeons performing TKA.

It has been reported that surgical trauma and increased fibrinolysis after surgery lead to blood loss [3,5]. Therefore, as an antifibrinolytic agent, tranexamic acid (TXA) has received increasing attention, as it has been shown to effectively reduce blood loss following TKA without increasing complications [6–11]. Multiple methods of administration of TXA in TKA have been utilized, including intravenous (IV) [10,11], topical [12], oral [9], and a combination of these methods [7,8]. Fillingham et al. found that the application of oral TXA preoperatively provided equivalent reductions in blood loss compared with IV TXA following TKA [13]. Yuan et al. found that 2 doses of oral and IV TXA (preoperatively and 12 h after surgery) led to equivalent postoperative Hb loss and number of transfusions required [14]. However, studies

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reported that hyperfibrinolysis continued for 18–24 h after surgery and the duration that IV TXA or oral TXA maintained the hemostatic threshold was about 6 h [15–17]. One or 2 doses of TXA failed to cover the whole process of hyperfibrinolysis after TKA in previous studies [13,14]. In addition, some studies have found that multiple boluses of IV or oral TXA postoperatively further decreased the blood loss, inflammation, and fibrinolysis without increasing the risk of complications after TKA [6,9,11,18]. To our knowledge, no prospective study has compared the effect of multiple boluses of oral or IV TXA on blood loss after TKA. Thus, we performed a prospective, double-blinded, randomized study to evaluate the efficacy and safety of multiple boluses of oral versus IV TXA after TKA without a tourniquet. We hypothesized that with proper timing and dosing, oral TXA would be equivalent to IV TXA in reducing blood loss and inhibiting the inflammatory and fibrinolytic responses in the setting of primary TKA.

2. Materials and methods

2.1. Patients and design

This prospective, double-blinded, randomized trial was registered at www.chictr.org.cn (ChiCTR-INR-16009770) and approved by our institutional review board. Written informed consent and research authorizations were obtained before surgery from all participants. From January 2017 to May 2017, patients undergoing primary unilateral TKA for osteoarthritis or rheumatoid arthritis were eligible for the study. Patients were excluded if they presented with any of the following situations: cardiovascular problems, history of deep venous thrombosis (DVT) or pulmonary embolism (PE), flexion deformity $\geq 30^{\circ}$, varus/valgus deformity $\geq 30^{\circ}$, known allergy to TXA, or preoperative hepatic or renal dysfunction.

Enrolled patients were randomized into two study groups using computer-generated random numbers: an oral TXA group and an IV TXA group. All patients were administered 1 bolus of 20 mg/kg IV TXA 5–10 min before skin incision. In addition to this, the oral TXA group received 2 g of oral TXA using 4 tablets of 500 mg approximately 4, 10, and 16 h after surgery, along with 100 mL of normal saline solution at 6, 12, and 18 h postoperatively, while the IV TXA group received 4 tablets of oral placebo at 4, 10, and 16 h after surgery, along with 1 g IV TXA (diluted in 100 mL of normal saline solution) at 6, 12, and 18 h postoperatively. A nurse who was not involved in the trial handed out the medications and implemented the postoperative protocol. The patients, surgeons, and data collector were blinded.

2.2. Surgical technique

All of the TKAs were performed by the same senior surgeon under general anesthesia. The operations were conducted via a midline skin incision, medial parapatellar approach, and a measured resection technique. All patients received a cemented posterior-stabilized prosthetic design with patellar resurfacing. A dose of 60 mL normal saline solution containing 200 mg ropivacaine (Naropin; AstraZeneca, Cambridge, United Kingdom) was injected percutaneously around the incision when the deep fascia was sutured. Wound vacuum drainage and tourniquet were not used in any cases. Controlled hypotension was induced, with the blood pressure being maintained between 90 and 110 mmHg/60–70 mmHg during surgery. In addition, no nerve block, intravenous patient-controlled analgesia, or blood salvage system were used. The operative time and intraoperative blood loss were recorded carefully.

2.3. Postoperative care protocol

All patients received prophylactic IV antibiotics for 24 h after surgery. A combination of physical prophylaxis and chemoprophylaxis for venous thromboembolism were used in all patients. A half-dose of low-molecular-weight heparin (LMWH; 2000 IU in 0.2 ml; Clexane, Sanofi-Aventis, France) was injected percutaneously 6–8 h postoperatively, then repeated every 24 h after the first dose. After discharge, 10 mg of rivaroxaban (Xarelto, Bayer, Germany) was administered orally for 10 days. Cold pack and intermittent foot slope pump systems were given to all patients before walking. Doppler ultrasound examinations were performed routinely to detect DVT on the third postoperative day, as well as at 2 weeks and 3 months after surgery. The diagnosis of PE was made based on clinical symptoms and enhanced chest computed tomography scans.

All patients received oral Celecoxib (200 mg twice a day, Celebrex; Pfizer, New York) preoperatively and oral enteric-coated diclofenac sodium (50 mg twice a day, Voltaren; Novartis, Basel, Switzerland) postoperatively for 2 weeks after surgery. Transfusions were applied if the hemoglobin (Hb) level was < 70 g/L or 70–100 g/L with symptoms of anemia, such as altered mental status, palpitations, or decreased exercise tolerance.

2.4. Outcome measurements

Demographic characteristics, medical histories, and concomitant medication were collected before surgery. Inflammation markers (C-reactive protein [CRP], interleukin 6 [IL-6]), fibrinolysis markers (fibrin degradation products [FDP], D-dimer), Hb and hematocrit (Hct) were tested preoperatively, on postoperative day 1 (POD1) and POD3. The primary outcomes were Hb and Hct drop. The secondary outcomes were mean total blood loss (TBL), mean hidden blood loss (HBL), transfusion rate, length of hospital stay (LOH), level of inflammation markers, fibrinolysis markers and complications.

TBL and intraoperative blood loss was calculated according to our previous study [18]. TBL = patient's blood volume (PBV) $\times$ ($Hct_{pre} - Hct_{post}$) / Hct_{ave} (Hct_{pre} = the initial preoperative Hct level, Hct_{post} = the Hct on the morning of POD3. PBV = $k_1 \times$ height $(m)^3 + k_2 \times$ weight (kg) + k_3 ($k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$ for men; and $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$ for women, Hct_{ave} = the average of the Hct_{pre} and Hct_{post}). If either reinfusion or allogeneic transfusion was performed, the TBL was equal to the loss calculated from the change in Hct plus the volume transfused. HBL was defined as TBL minus intraoperative blood loss.

2.5. Statistical analysis

PASS 2011 (NCSS, LLC, Kaysville, UT, USA) software were used to calculate sample size, which was determined on the outcome of reduction of Hb concentration and on our preliminary data. Based on our previous data on the same measures. To detect a difference of 10 g/L of primary end point, with a power of 0.90 and an alpha of 0.05, 49 patients were needed per group. All analyses were compared by SPSS version 22.0(SPSS Inc. USA) and a p-value < 0.05 was regarded as significant difference.

3. Results

3.1. Patients' demographics

From January 2017 to May 2017, a total of 146 patients were scheduled to receive primary TKA in our institution. However, 19 patients were eliminated because of exclusion criteria and nine patients declined to participate in the study. The remaining 118 patients were included in the study (Fig. 1). The baseline characteristics of the patients in the two groups were comparable (Table 1).

3.2. Blood loss

There was no significant difference in the hemoglobin (Hb) or hematocrit (Hct) drop on POD1 (14.7 ± 10.5 vs 14.4 ± 9.6 g/L,

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