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Full Length Article

The effect of oral versus intravenous tranexamic acid in reducing blood loss after primary total hip arthroplasty: A randomized clinical trial

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ABSTRACT

Background: The purpose of this study was to determine whether the administration of multiple boluses of oral and intravenous tranexamic acid (TXA) postoperatively was equivalent in reducing blood loss in primary THA.
Methods: A total of 108 patients were randomized into two groups: oral TXA group (54 patients receiving 1 dose of 20 mg/kg intravenous TXA 5–10 min before skin incision and 3 doses of 2 g oral TXA 4 h, 10 h and 16 h postoperatively) and intravenous TXA group (54 patients receiving 1 dose of 20 mg/kg intravenous TXA 5–10 min before skin incision and 3 doses of 1 g intravenous TXA 6 h, 12 h and 18 h postoperatively). The primary outcomes were total blood loss, hidden blood loss, length of hospital stay, hemoglobin (Hb) and hematocrit (Hct) drop. The secondary outcomes were the level of inflammation markers and complications.
Results: There was no difference in the mean total blood loss or hidden blood loss [728.4 (645.8–806.9) mL vs 703.6 (576.9–832.8) mL, $p = 0.745$; 634.6 (552.0–715.7) mL vs 606.4 (480.1–734.5) mL, $p = 0.710$] and length of hospital stay was similar between the two groups. No patients received allogenic blood transfusion. The Hb and Hct drop on the first and second postoperative days were similar ($p > 0.05$). The level of inflammation markers did not reach statistical significance. The incidence of complications did not differ significantly between the two groups.
Conclusions: Multiple boluses of oral TXA and intravenous TXA postoperatively are equivalent in reducing blood loss, Hb and Hct drop in primary THA without increasing the risk of thromboembolic diseases and wound complications.

1. Introduction

Total hip arthroplasty (THA) is one of the most common orthopedic procedures to reduce pain and ameliorate function for end-stage hip diseases. However, the surgery is always associated with substantial perioperative blood loss, acute anemia and transfusion, delaying functional recovery and increase mortality [1–3]. Therefore, a number of strategies have been applied to reduce blood loss and need for transfusion, particularly the using of antifibrinolytic agents, such as tranexamic acid (TXA). TXA is a synthetic amino acid found to be effective to reduce blood loss and the risk of transfusion without increasing the risk of venous thrombus after THA [4–6].

TXA could be administered intravenously [7,8], topically [6,9] and orally [10,11]. Recent evidences showed that either single dose of intravenous (IV) or oral TXA was equivalent at reducing blood loss following THA and TKA [12,13]. However, oral TXA was only administered prior to 2 h preoperatively which was restricted to keep the plasma drug concentration for 6 h without covering the whole process of hyperfibrinolysis in previous studies [12,13]. Some studies had found that hyperfibrinolysis lasted 18–24 h postoperatively [14,15], so repeating application of TXA for 18–24 h could further inhibit fibrinolysis and reduce blood loss. Some literatures showed that multiple boluses of oral or IV TXA postoperatively were effective and safe [10,16,17]. To our best knowledge, few prospective studies compared the effect of multiple boluses of oral with that of IV TXA in reducing blood loss after THA. Thus, we conducted a randomized, controlled trial to investigate the efficacy and safety of multiple boluses of oral and IV TXA with proper dosing and timing after THA. The hypothesis of the current prospective study was that multiple boluses of IV TXA would be are equivalent to oral TXA in reducing blood loss after primary THA with

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proper dosing and timing.

2. Materials and methods

2.1. Study design and patients

This study was a single-center, prospective, double-blinded, randomized trial designed to test equivalence at reducing blood loss between multiple boluses of oral and IV TXA after primary THA. Our institutional review board approved the present study, and it was registered at www.chictr.org.cn (ChiCTR-INR-16009770). Written informed consent and research authorizations were obtained preoperatively from all participants. All patients to undergo primary unilateral THA for osteoarthritis, osteonecrosis of the femoral head and developmental dysplasia of hip (Crowe I/II) were considered eligible for enrollment. We excluded those patients with cardiovascular problems, history of deep venous thrombosis (DVT) or pulmonary embolism (PE), history of an arterial thromboembolic event, known allergy to TXA or renal insufficiency.

Enrolled patients were randomized into two study groups, oral TXA group or IV TXA group. Randomization was blind and performed with the use of sealed envelopes opened just prior to surgery. All patients were administered 1 bolus of 20 mg/kg IV TXA 5–10 min before skin incision, the oral TXA group received 2 g of oral TXA using 4 tablets of 500 mg approximately 4 h, 10 h, 16 h postoperatively, along with 100 mL of normal saline solution at the same time point and the IV TXA group received the standard dosing for our institution of 1 g TXA (diluted in 100 mL normal saline) 6 h, 12 h, 18 h postoperatively and 4 tablets of oral placebo at the same time point. A nurse not involved in the trial handed out the medications and implemented postoperative protocol. The patients, surgeons and data collector were blinded.

2.2. Surgical technique and postoperative care

The operations were performed by a senior surgeon through the posterolateral approach, the prosthesis was a cementless acetabular cup and a cementless femoral stem. All the THAs were conducted under general anesthesia without drains installed. Controlled hypotension was applied and mean arterial pressure (MAP) was reduced to 70–90 mmHg during surgery. All patients received IV prophylactic antibiotics for 24 h, physical prophylaxis and chemoprophylaxis for venous thromboembolism according to our previous study [16]. A half-dose of low-molecular-weight heparin (LMWH; 2000 IU in 0.2 ml; Clexane, Sanofi-Aventis, France) was injected percutaneously six hours postoperatively and repeated at 24-hour intervals until discharge, then 10 mg Rivaroxaban (Xarelto, Bayer, Germany) was taken orally once a day for ten days. Doppler ultrasound examinations were undergone routinely on POD2, in 2 weeks and 3 months to detect deep venous thrombosis (DVT). Transfusions were applied if the Hb level was < 70 g/L or 70–100 g/L with symptoms of anemia (defined as a bad mental status, palpitation or shortness of breath not due to other causes).

2.3. Outcome measurements

Demographic characteristics, including age, sex, American Society of Anesthesiologists (ASA) physical status classification, weight and height were collected. Inflammation markers (C-reactive protein [CRP], interleukin 6 [IL-6]), Hb and hematocrit (Hct) were tested preoperatively, on postoperative day 1 (POD1), POD2 and POD14. In addition, intraoperative blood loss, allogenic transfusion units and rate, length of hospital stay (LOH) and complications were carefully recorded.

The primary outcomes were total blood loss (TBL), hidden blood loss (HBL), transfusion requirements, length of hospital stay (LOH), Hb and Hct drop. TBL was calculated by the Gross and Nadel formula according to our previous study [6], which was TBL = patient's blood volume (PBV) × (Hct_{pre}-Hct_{post})/Hct_{ave} (Hct_{pre} = the initial preoperative Hct level, Hct_{post} = the Hct on the morning of the second postoperative day, 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 male; and $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$ for female, 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 [18]. Intraoperative blood loss was calculated using the difference between the weights of used gauze and the original unused gauze, in addition to the blood volume accumulated in suction bottles. HBL was defined as TBL minus intraoperative blood loss. The secondary outcomes were the level inflammation markers at different time points and complications.

2.4. Statistical analysis

Sample size calculations were performed using PASS 2011 (NCSS, LLC, Kaysville, UT, USA) software. Sample size requirements were determined on the primary outcome of reduction of hemoglobin concentration based on our previous data on the same measures. To detect a difference of 1.0 g/L of primary end point, with a power of 0.90 and an alpha of 0.05, 49 patients were needed for per group. The continuous variables were compared using the one-way analysis of variance, Wilcoxon Mann–Whitney *U* test or independent *t*-test. The categorical variables were compared using Pearson chi-square test or Fisher exact test. All analyses were compared by using SPSS version 22.0 (SPSS Inc. USA) and a p-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Demographics

From October 2016 to March 2017, totally 139 patients were scheduled to undergo primary THA in our center. However, 21 patients were ineligible because of the exclusion criteria and 10 patients declined to participate in the study. All 108 patients (54 oral TXA group and 54 IV TXA group) were observed and studied (Fig. 1). All patients were followed up for three months. The baseline characteristics of the two groups were comparable (Table 1).

3.2. Blood loss

The mean TBL was 728.4 (645.8–806.9) mL in oral TXA group versus 703.6 (576.9–832.8) mL in IV TXA group and HBL was 634.6 (552.0–715.7) mL in oral TXA group versus 606.4 (480.1–734.5) mL in IV TXA group, there was no statistical significant difference between the two groups ($p = 0.745$, $p = 0.710$, respectively). The Hct and Hb drop on POD1 and POD2 showed no significant difference as well ($p > 0.05$). In addition, no patient received allogeneic blood transfusion during hospitalization. The difference of LOH between the two groups was not significant. The comparison of blood loss was listed in Table 2.

3.3. Inflammation markers

As acute inflammation markers, CRP and IL-6 rose postoperatively in all patients. Significant differences were not detected between the two groups (Figs. 2 and 3).

3.4. Complications

All patients were followed up for three months. No PE, superficial or deep infection was observed in any group during a follow-up period of three months. Four patients in oral TXA group and six patients in IV TXA group developed calf muscular vein thrombosis. Two patients