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Full Length Article

Blood loss and cost-effectiveness of oral vs intravenous tranexamic acid in primary total hip arthroplasty: A randomized clinical trial

Yuangang Wu[1], Yi Zeng[1], Qinsheng Hu, Mingyang Li, Xianchao Bao, Jian Zhong, Bin Shen*

Department of Orthopaedic Surgery, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan Province 610041, China

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ABSTRACT

Background: To assess the blood loss and cost-effectiveness of the oral and intravenous (IV) administration of tranexamic acid (TXA) for the treatment of primary total hip arthroplasty (THA).

Methods: From January 2017 to August 2017, 100 patients undergoing primary THA were enrolled and randomly divided into two groups. In the oral TXA group (N = 50), 1 g of TXA (2 tablets of 500 mg) was given 2 h before the incision, and the same dose was repeated 3 h and 6 h postoperatively. In the IV TXA group (N = 50), 1 g of TXA was administered 10 min before the incision, and the same dose was repeated 3 h and 6 h postoperatively. The total follow-up period was 6 months.

Results: There were no statistically significant differences in total blood loss (863.3 ± 272.5 mL and 886.1 ± 200.2 mL, P = 0.66), maximum Hb drop (2.9 ± 0.6 g/dl and 3.1 ± 0.8 g/dl, P = 0.17), maximum Hct drop (7.4 ± 2.1% and 7.7 ± 1.8%, P = 0.48), transfusion rates (1 and 2, P = 1.00) and transfusion units (1.5 u and 3 u, P = 0.56) between the two groups. However, the costs of TXA in the oral group were significantly lower than those in the IV TXA group (¥600 and ¥3150, P < 0.01). There was no difference in the Hb levels on postoperative days 1 and 3. No significant differences were found for operating time, hospital length of stay, DVT and/or PE, and wound complications in the postoperative follow-up.

Conclusions: The study demonstrated that the oral and IV administration of TXA in patients undergoing THA was proved to be an equivalent and effective method in reducing blood loss and transfusion rates. However, oral TXA is more cost-effectiveness than IV TXA, and it may be an alternative to the IV form.

1. Introduction

Total hip arthroplasty (THA) is a common treatment for severe hip disease [1–3]. However, THA is associated with substantial complications, such as infections, periprosthetic fractures and blood loss necessitating transfusion [4–8]. Of these complications, bleeding is the most unpredictable and frightening, and blood transfusion can lead to serious morbidity [9,10], including hemolytic reactions, immunological reactions, acute lung injuries and transfusion-related infections [11–13].

Tissue plasminogen activator is released during tissue trauma; it is the main enzyme that induces the conversion of plasminogen to plasmin [14,15]. Having established efficacy in reducing blood loss, tranexamic acid (TXA), a competitive plasminogen inhibitor, has been used for the treatment of perioperative bleeding associated with THA for several decades [15–17]. As previously reported, TXA can be administered intravenously [16,18,19], locally [18,19] or orally [20]. Although intravenous (IV) use of TXA in THA can significantly reduce blood loss and blood transfusion rates, it may also be associated with systemic side effects, such as nausea, intraoperative hypotension, and thromboembolism [21–23]. Oral TXA is easy to use, low in cost and does not require specific equipment for administration [20,24,25].

However, it is still unclear if oral TXA has similar benefits in reducing blood loss and transfusion rates compared with those of IV TXA following THA. Therefore, the aim of this study is to evaluate the efficacy of preoperative administration of oral TXA and IV TXA on perioperative blood loss, cost-effectiveness, and transfusion requirements during THA.

2. Material and methods

2.1. Study design and patients

After institutional ethics committee approval, this study was

* Corresponding author at: Department of Orthopaedics, West China hospital, Sichuan University, 37# Guoxue Road, Chengdu, 610041, China.
E-mail address: shenbin_1971@163.com (B. Shen).

[1] Yuangang Wu and Yi Zeng contributed equally to this work and should be considered as equal first authors.

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conducted in our hospital. Written informed consent was obtained from each patient. The study was registered in the Chinese Clinical Trial Registry (ChiCTR1800015265). All evaluated patients with a diagnosis of osteoarthritis (OA) or osteonecrosis of the femoral head (ONFH) undergoing unilateral THA were eligible for inclusion in the study. The exclusion criteria were as follows: developmental dysplasia of the hip, rheumatoid arthritis, revision surgery, a history of thrombosis, patients with infection, allergy to TXA, uncontrolled hypertension, body mass index (BMI) > 35 kg/m^2, and preoperative anaemia (hemoglobin [Hb] level < 12 g/dL for women and < 13 g/dL for men). Patients were allocated randomly into oral TXA or IV TXA groups, and randomization was blinded and performed with the use of sealed envelopes at a ratio of 1:1 to be opened just prior to surgery. Computer-generated random number tables were used to generate the stratified randomization schedule.

2.2. TXA administrations

In the oral TXA group, 1 g of TXA (2 tablets of 500 mg) was given 2 h before the incision, and the same dose was repeated 3 h and 6 h postoperatively. In the IV TXA group, 1 g of TXA was administered 10 min before the incision, and the same dose was repeated 3 h and 6 h postoperatively. Additionally, to support this double-blind study, patients in the oral TXA group were given 100 mL of normal saline solution intravenously 10 min before the incision, and the same dose was repeated 3 h and 6 h postoperatively. Patients in the IV TXA group were given 2 placebo tablets (with no active component) orally 2 h before the incision, and the same dose was repeated 3 h and 6 h postoperatively. All drugs were administered by a nurse who was not involved in the study. The patients, investigators, and statisticians were blind during the study.

2.3. Surgical technique and postoperative care

All patients underwent general anaesthesia, which was administered by the same anaesthetist. All surgeries were performed by 1 senior orthopaedic surgeon through a posterolateral surgical approach; the prosthesis was a cementless acetabular cup and femoral stem (DePuy, Warsaw, IN). All patients received antibiotics to prevent infection during the perioperative period. No drainage tube was used. After surgery, the patients were transferred to the anaesthesia recovery unit for 2 h and then sent to the inpatient ward for further nursing. A cold pack was applied to the surgical site for 1–2 days. A daily gait rehabilitation programme and full weight-bearing were conducted the first day after surgery as tolerated.

2.4. Thrombosis prevention and screening

All patients were given low molecular-weight heparin (0.2 mL, 2000 IU; Clexane, Sanofi-Aventis, France) subcutaneously 6 h postoperatively, and it was repeated with a full dose at 24-hour intervals (0.4 mL, 4000 IU) until discharge. After discharge, rivaroxaban (10 mg QD; Xarelto, Bayer, Germany) was administered orally for 15 days to prevent thrombosis if there was no bleeding. An intermittent pneumatic compression device was routinely applied on the calves of patients until walking. Doppler ultrasound examination was routinely used to detect deep vein thrombosis (DVT) at the time of discharge and at 1- and 6-month follow-up assessments or at any time there was clinically suspected DVT. Pulmonary embolism (PE) was diagnosed on the basis of chest computed tomography (CT) scans.

2.5. Blood transfusions

Blood transfusions were applied using the guidelines of the Chinese Ministry of Health if the Hb level was < 70 g/L or 70–100 g/L with symptoms of anaemia (e.g., change in mental status and palpitations).

2.6. Outcome Measurements

The primary outcomes were evaluated, including total blood loss, maximum Hb drop, TXA cost (¥, RMB), transfusion rates and transfusion units. Hb and hematocrit (Hct) levels were examined on postoperative days 1 and 3. The total blood loss was calculated by the Gross formula [26]. Maximum Hb/Hct drop was defined as the difference between the preoperative Hb/Hct level and the lowest postoperative Hb/Hct level, as well as the lowest pre-transfusion Hb/Hct level. In our hospital, the oral TXA cost was ¥ 4 per dose (1 g), while the IV TXA was ¥ 21 (1 g). Consequently, the cost of the oral form of TXA was cheaper than the IV form in similar doses, and its cost was relatively low. The secondary outcomes were the Hb level on postoperative days 1 and 3, operating time, hospital length of stay, DVT and/or PE, and wound complications.

2.7. Statistical analysis

Sample size calculations were performed using PASS 2011 software (NCSS, LLC, Kaysville, UT, USA). As previously described by Xie et al. [27], the total blood loss was 677.6 ± 326.0 mL, with a dosage of 20 mg/kg TXA before skin incision and 10 mg/kg IV TXA 3 h and 6 h postoperatively. To detect a difference of 200 mL in the primary endpoint, which was chosen as the primary outcome to be examined because it is considered a hallmark of success for TXA during primary THA (with a power of 0.90 and a significance level of 0.05), 43 patients per arm were required. Therefore, we included 50 subjects for each group in the trial, assuming a 10% loss to follow-up.

Continuous variables were given as 95% confidence intervals and mean ± standard deviation (SD). If the numerical variables were of a non-normal distribution or unequal variance, the Wilcoxon Mann-Whitney *U* test was used. The categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

From January 2017 to August 2017, a total of 113 patients with OA or ONFH requiring unilateral primary TKA were enrolled. A total of 13 patients were excluded, including 1 patient with a history of DVT, 3 patients with infection, and 5 patients with anaemia, and 4 patients declined to participate. Finally, 100 patients were eligible to participate in this study, with 50 patients (OA, 23; ONFH, 27) randomly assigned to the oral TXA group and 50 patients (OA, 25; ONFH, 25) to the IV TXA group. No patient was lost or excluded during follow-up (Fig. 1). All patients in the two groups were similar with regard to baseline demographics (Table 1).

3.2. Primary outcomes

No significant differences were observed in the total blood loss (863.3 ± 272.5 mL and 886.1 ± 200.2 mL, P = 0.66), maximum Hb drop (2.9 ± 0.6 g/dl and 3.1 ± 0.8 g/dl, P = 0.17), maximum Hct drop (7.4 ± 2.1% and 7.7 ± 1.8%, P = 0.48), transfusion rates (1 and 2, P = 1.00) and transfusion units (1.5 u and 3 u, P = 0.56) between the oral and IV TXA groups. However, the total TXA cost in the oral TXA group was significantly less compared to that in the IV TXA group (¥600 and ¥ 3150, P < 0.01) (Table 2).

3.3. Secondary outcomes

There was no difference in the Hb levels on postoperative days 1 and 3 (Fig. 2). No significant differences were observed in the operating