The Journal of Arthroplasty 30 (2015) 1354–1358

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Topical Administration of Tranexamic Acid Plus Diluted-Epinephrine in Primary Total Knee Arthroplasty: A Randomized Double-Blinded Controlled Trial

Fuqiang Gao, MD, Wei Sun, MD, Wanshou Guo, MD, Zirong Li, MD, Weiguo Wang, MD, Liming Cheng, MD

Osteonecrosis and Joint-Preserving and Reconstruction Center, Beijing, China
Department of Orthopedic Surgery, Beijing, China
Beijing Key Laboratory of Arthritic and Rheumatic Diseases, Beijing, China
China-Japan Friendship Hospital, National Health and Family Planning Commission of the People's Republic of China, Beijing, China

ARTICLE INFO

Article history:
Received 13 January 2015
Accepted 9 March 2015

Keywords:
topical
tranexamic acid
epinephrine
transfusion
blood loss
TKA

ABSTRACT

The aim of this trial was to evaluate the efficacy and safety of intra-articular administration of tranexamic acid (TXA) plus diluted-epinephrine (DEP) on perioperative blood loss and transfusion in primary unilateral total knee arthroplasty (TKA) without drainage. One hundred patients scheduled to undergo TKA were randomized into two groups: 50 patients received intra-articular 3 g TXA plus 0.25 mg DEP (1:200,000), and 50 patients received 3 g topical TXA alone. The results showed that topical combined administration significantly reduced total blood loss ($P = 0.006$), hidden blood loss ($P = 0.000$) and transfusion rate (0% vs. 4%), without increasing the risk of thromboembolic and hemodynamic complications ($P > 0.05$). Therefore, topical TXA plus DEP was effective and safe in reducing blood loss and transfusion following TKA, without substantial complications.

Blood loss is inevitable after total knee arthroplasty (TKA) [1–9]. Extensive blood loss after TKA is often associated with cardiovascular complications, and a high rate of allogeneic blood transfusions (ABT) [1,3,4,8,10]. ABTs may lead to serious adverse effects in patients, including postoperative infections and disease transmission [2,5,9,11]. Therefore, there is a need to identify an efficient and safe method to minimize blood loss in TKA.

Various measures to reduce blood loss, such as preoperative autologous blood donations [12], postoperative autotransfusion [13], and the use of a femoral intramedullary plug [14] have been proposed. However, these procedures are associated with cumbersome administrative tasks, high medical costs, and limited storage period. As a strategy for reducing blood loss, drain clamping has been combined with intravenous or intra-articular administration of tranexamic acid (TXA) and intra-articular injection of diluted-epinephrine (DEP) since 1995, and the preventive effect on blood loss is well documented [1–9,15]. Recent meta-analyses of intravenous or topical administration of TXA during TKA suggest that it can be safely administered in the perioperative period with significant reduction in blood loss and transfusion rates, and no increase in rates of venous thromboembolism (VTE) [6,16]. Topical infusion of epinephrine solution has been advocated in recent studies to reduce postoperative blood loss [1,3,4,17]. However, the complications associated with this agent, such as delayed wound healing with skin-edge necrosis, hematomata, elevated blood pressure and deep venous thrombosis (DVT) are worrisome [3,4].

In this study, we focused on developing a new intra-surgical procedure based on the local infusion of TXA combined with DEP without drainage clamping for eligible patients undergoing TKA. The hypothesis was that topical administration of TXA plus DEP into the joint space immediately prior to surgical closure in TKA would result in maximum decline in postoperative blood loss than in patients who received topical TXA alone. In addition, we compared the rate of blood transfusions and complications, including the rate of thromboembolic events.

Materials and Methods

The study was approved by the Institutional Review Board on Human Studies of the Ethical Committee of our hospital, and the study procedures adhered to the 1975 Declaration of Helsinki. This prospective, randomized, double-blind, controlled trial was conducted at a single hospital. All patients were required to sign an informed consent prior to their participation in the study. The written consents provided

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to http://dx.doi.org/10.1016/j.arth.2015.03.003.

Funding: This study was supported by the National Natural Science Foundation of China (81372013), the Research Fund of China–Japan Friendship Hospital (2013-MS-27), and China–Japan Friendship Hospital Youth Science and Technology Excellence Project (2014-QNYC-A-06).

Reprint requests: Wei Sun, MD, Department of Orthopedic Surgery, China-Japan Friendship Hospital, Beijing 100029, China.

http://dx.doi.org/10.1016/j.arth.2015.03.003
0883-5403/

by the patients were stored in the hospital database, and used for clinical research.

From May 2013 to August 2014, a primary, unilateral, cemented TKA was performed on 100 eligible patients with primary osteoarthritis of the knee. Exclusion criteria included revisions, bilateral joint arthroplasty, known hypersensitivity to TXA or its ingredients, active intravascular clotting disorders, and acute subarachnoid hemorrhage. Patients with a history of DVT or PE were not excluded, as the current literature does not indicate that TXA has an increased risk for thromboembolic events. Patients were randomly divided into the TXA + DEP group (50 patients received intra-articular injection of 50 mL normal saline mixed with 3 g TXA plus 0.25 mg DEP (1:200,000) after surgical closure of articular capsule without drain insertion) and the TXA group (50 patients received intra-articular injection of 50 mL normal saline mixed with 3 g TXA alone after surgical closure of articular capsule without drain insertion). Age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Hospital for Special Surgery knee score (HSS), preoperative hemoglobin (Hb) and hematocrit (Hct) levels, thigh and calf girths and comorbidities were evaluated by two surgeons who were not involved in the evaluation of the results. The preoperative demographic characteristics of the two groups are listed in Table 1.

All surgeries were performed with cemented prostheses (NexGen, posterior stabilized type, manufactured by Zimmer, USA), by or under the supervision of a fellowship-trained arthroplasty surgeon. TKA are routinely performed on an exsanguinated limb under tourniquet pressure, using a medial parapatellar arthrotomy and cement fixation. Prophylaxis against DVT with anticoagulants (10 mg oral rivaroxaban) and anti-embolic stockings were given. All patients underwent the same rehabilitative protocol. After the effects of the anesthesia were lost, lower limb muscle contraction exercises were immediately performed. Leg and knee exercises were also performed gradually. Patients were mobilized early post-surgery, and encouraged to ambulate with assistive devices, 2–3 days after the operation. Vascular Doppler ultrasonography was used to examine any lower extremity pain or swelling.

Calculation of Hidden Blood Loss

The volumes of intra-operative blood loss, postoperative blood loss, blood transfusion, and hidden blood loss were recorded. The increased weight of the gauze pads plus the volume in the aspirator bottle, excluding the rinse, equated to the intra-operative blood loss. The amounts of postoperative visible blood loss equaled the increased weight of the gauze pads, which were removed after the surgery.

Hct and Hb levels were determined preoperatively, and on the first, third and fifth days after surgery. Hidden blood loss was calculated according to the formula of Gross [2,18–20], based on the Hct levels measured on the fifth day post-surgery. Blood volume of each patient was calculated according to Nadler et al [19] formula based on the weight, height and gender of the patient.

Patient's blood volume (PBV) was calculated [18–20] as follows:

$$\text{PBL} = \text{k1} \times \text{height}\left(\text{m}^3\right) + \text{k2} \times \text{weight(kg)} + \text{k3}$$

(where k1 = 0.3669, k2 = 0.03219, k3 = 0.6041 for men, and k1 = 0.3561, k2 = 0.03308, k3 = 0.1833 for women)

$$\text{Total blood loss} = \text{PBL} \times (\text{preoperative Hct} - \text{postoperative Hct})$$

$$\text{Hidden blood loss} = \text{Total blood loss} - \text{Dominant blood loss} + \text{ABT}$$

The hidden loss can be determined by subtracting the visible loss from the calculated loss. The results were converted to whole blood volume for each patient, using their average Hct [20]. Patients received blood transfusions according to the following protocol [2]: (1) patients with Hb levels less than 70 g/L received a homologous blood transfusion until the level reached or exceeded 80 g/L; and (2) patients with Hb levels between 70–100 g/L received a transfusion determined by the specific circumstances of the patients. Data on the number of patients requiring blood transfusions and the amount of transfused blood were documented in both groups. The staff evaluating the results was blinded to the patient allocation.

Other postoperative clinical examination data including rehabilitative activity, hemodynamic changes and complications were also collected. Two staff members who judged the results were blinded to group assignment. Incidence of symptomatic DVT and pulmonary embolism was assessed until the 90th day. Clinical symptoms including pain and swelling of the limb, calf tenderness, superficial venous engorgement, and Homan's sign were evaluated daily in the postoperative period, until the patient was discharged. Dyspnea and/or chest pain, which can be indicative of pulmonary embolism, were also evaluated. Patients were followed up on the 30th and 90th days post-surgery, and instructed to report any signs of DVT.

Statistical Analysis

Quantitative variables are reported as mean (M) and standard deviation (SD), and were compared by analysis of variance (ANOVA). Pearson's chi-squared test or Fisher's exact test was used to assess the differences between qualitative variables. Changes in Hb levels, Hct, volume of blood loss, volume of allogenic transfusion, and the circumferential measurements were compared using paired t-tests. All data analyses were performed using SPSS version 16.0.0 software (SPSS Inc., USA). The level of significance was set at $P < 0.05$.

Table 1
Preoperative Demographic Characteristics for Patients.

Variables	TXA + DEP Group ($n = 50$)	TXA Group ($n = 50$)	*P* Value
Gender (male:female)	11:39	13:37	0.640
Age (years)	68.5 ± 8.1	67.4 ± 9.8	0.628
Height (cm)	162.6 ± 14.7	167.2 ± 12.5	0.261
Weight (kg)	72.5 ± 10.2	73.9 ± 9.4	0.117
BMI (kg/m^2)	27.3 ± 3.6	27.8 ± 4.1	0.467
Operated side (Right%)	23 (46%)	21 (42%)	0.687
Preoperative comorbidities			
Hypertension	16	13	0.509
Diabetes mellitus (type 2)	7	9	0.585
Coronary heart disease	4	2	0.339
Cerebrovascular Disease	1	2	0.500
Blood volume (l)	5.0 ± 0.9	5.1 ± 0.8	0.754
Preoperative Hb (g/dl)	135.9 ± 12.9	134.3 ± 15.7	0.659
Preoperative Hct (%)	38.5 ± 7.5	38.4 ± 5.4	0.597
Preoperative thigh girth (cm)	45.1 ± 7.3	45.4 ± 5.7	0.811
Preoperative calf girth (cm)	34.5 ± 3.8	34.9 ± 4.3	0.498
Preoperative knee flexion (°)	105.3 ± 25.7	101.9 ± 27.2	0.196
Preoperative HSS	41.6 ± 11.2	38.9 ± 13.6	0.337
ASA grade 0–I/II–III	45/5	47/3	0.357

BMI, body mass index; Hb, hemoglobin; Hct, hematocrit; ASA, American Society of Anesthesiologists score; HSS, hospital for special surgery knee score; Thigh girth, circumference at the thigh, 10 cm proximal portion from the top of the patella; Calf girth, the maximum circumference of the calf. Data reported as mean ± SD or total sum.

Results

From May 2013 through August 2014, 139 patients scheduled for a primary TKA with a single group of surgeons were screened and assessed for eligibility. Twenty-nine patients were eliminated by exclusion criteria, and 36 patients due to refusal for enrollment. A total of 103 patients were randomized to receive the study drug using a block randomization technique. After randomization, three patients withdrew consent prior to surgery. Therefore, 100 patients (50 patients in the TXA + DEP group and 50 patients in the TXA group) were included in our trial (Fig. 1).

There were no statistically significant differences in the baseline demographic and clinical characteristics between the two groups