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Topical Application of Tranexamic Acid Plus Diluted Epinephrine Reduces Postoperative Hidden Blood Loss in Total Hip Arthroplasty

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ABSTRACT

We evaluated the efficacy and safety of topical application of tranexamic acid (TXA) plus diluted epinephrine (DEP) and its effect on perioperative hidden blood loss and transfusion requirement in primary unilateral total hip arthroplasty (THA). We randomized 107 patients undergoing THA into two groups: 53 received intra-articular TXA 3 g plus 1:200,000 DEP 0.25 mg; 54 received topical TXA 3 g alone. Results showed that combined administration significantly reduced total blood loss ($P = 0.009$), hidden blood loss ($P = 0.001$) and transfusion rate (1.9 vs. 9.3%) compared with TXA alone, without increasing the risks of thromboembolic and hemodynamic complications. Topical TXA plus DEP in THA can decrease postoperative hidden blood loss and avoid homologous transfusion without substantial complications.

Postoperative blood loss, especially hidden blood loss is an inevitable complication of total hip arthroplasty (THA) [1–7]. Extensive blood loss after THA is often associated with cardiovascular complications and a high rate of allogeneic blood transfusion (ABT) [4,7], and about half of the patients with total joint arthroplasty have received more than 2 U of blood postoperatively [8,9]. ABT following THA is common but not without risk. Potential problems include disease transmission, anaphylactic and hemolytic reactions, immunomodulation, availability and cost, and prolonged hospital stay [1,6,7,10]. Therefore, there is a need to identify a safe, effective method of reducing blood loss and rate of ABT after THA.

Several techniques for minimizing blood loss are available. These include autologous blood transfusion, intraoperative blood salvage, and hypotensive anesthesia [4,6,11,12]. Recent studies have suggested that a relatively new strategy, intravenous [4,12,13] or topical [1–7] tranexamic acid (TXA) or topical infusion of diluted epinephrine (DEP) [10,14,15], can reduce postoperative blood loss or hidden blood loss after THA and total knee arthroplasty (TKA). Recent meta-analyses related to intravenous or topical administration of TXA during THA suggest that it can be safely administered in the perioperative period with significant reductions in blood loss or hidden blood loss and rates of transfusion without increased rates of venous thromboembolism [16–18].

In this study, we evaluated a new intraoperative procedure that employs local infusion of TXA combined with DEP without drainage clamping for eligible patients undergoing THA. We compared 2 solutions, topical TXA plus DEP versus topical TXA alone, which were administered into the joint cavity immediately after the musculoaponeurotic surgical closure in THA. We hypothesized that topical TXA plus DEP would result in a maximum decline in postoperative hidden blood loss, rates of blood transfusions, and complication rates, such as thromboembolic events.

Materials and Methods

This prospective, double-blind, randomized controlled trial was conducted at a single hospital. From January 2013 to November 2014, primary unilateral uncemented THA was performed on 107 eligible patients with osteonecrosis of the femoral head. All patients were required to sign an informed consent prior to participation in the study. The written consent forms provided by the patients were stored in the hospital database and used for clinical research. Preoperative teaching and perioperative management were the same for all patients. One group of surgeons performed all surgeries. Exclusion criteria included revision surgery, bilateral joint arthroplasty, known hypersensitivity to TXA or its ingredients, active intravascular clotting disorders, and acute subarachnoid hemorrhage. Patients with a history of deep venous thrombosis (DVT) or pulmonary embolism(PE) were not excluded, as TXA has not been shown to confer an increased risk for thromboembolic events.

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Patients were randomly divided into TXA + DEP group ($n = 53$) and TXA-only group ($n = 54$). In the TXA + DEP group, patients received intra-articular injection of 50 ml normal saline mixed with 3 g TXA plus 0.25 mg DEP (1:200,000) after musculoaponeurotic surgical closure without drain insertion. In the TXA-only group, patients received intra-articular injection of 50 ml normal saline mixed with 3 g TXA alone after musculoaponeurotic surgical closure without drain insertion. Age, gender, body mass index (BMI), American Society of Anesthesiologists score (ASA), Harris Hip score, preoperative hemoglobin (Hb) concentration and hematocrit (Hct), and comorbidities were evaluated by two surgeons not involved in evaluation of the results. Preoperative demographic characteristics of the two groups are presented in Table 1.

All surgeries were performed via a posterolateral approach using cementless prostheses (Pinnacle Acetabular Cup and Porocoat Summit Stem; DePuy Orthopaedics, Inc., Warsaw, IN, USA) augmented with screw fixation, with placement of screws in the safe posterior superior quadrant. Drugs were injected to the hip joint cavity after musculoaponeurotic closure. The procedure for topical injection is shown in Fig. 1 and was as follows: With the operated hip in neutral position, the needle pierced the tip of the greater trochanter, taken out of horizontal alignment at an angle of about 15–25° (red angle in Fig. 1B) and tilted toward the rear side at an angle of about 15–25° (red angle in Fig. 1A). The needle was slowly advanced while the plunger of the syringe was gently withdrawn. When the needle point touched the hard surface of the prosthesis and there were a few positive withdrawing hematocele or bubbles in the syringe, the contents of the syringe were directly injected into the joint cavity. Prophylaxis against DVT with anticoagulant medication (rivaroxaban 10 mg orally) and anti-embolic stockings was provided. All patients underwent the same rehabilitation protocol. Once the effects of the anesthesia subsided, lower-limb isometric exercises were immediately begun. Leg and hip exercises were also gradually introduced. Patients were mobilized early postoperatively and encouraged to ambulate with an assistive device 2–3 days after the operation. Vascular Doppler ultrasonography was used to investigate any lower extremity pain or swelling.

Hidden Blood Loss

Volumes of intraoperative blood loss, postoperative blood loss, blood transfusion, and hidden blood loss were recorded. Intraoperative blood loss consisted of the increased weight of the gauze pads plus the volume in the aspirator bottle, excluding the rinse. The amounts of postoperative visible blood loss were calculated as the increased weight of the gauze pads removed after the surgery.

Hct and Hb levels were determined preoperatively and on postoperative days 1, 3, and 5. Hidden blood loss was calculated based on Hct measured on postoperative day 5 using the formula of Gross [19–21]. Blood volume was calculated from the patient's weight, height and gender according to the formula of Nadler et al [20].

Patient's blood volume (PBV) was calculated [19–21] as follows:

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

where $k1 = 0.3669$, $k2 = 0.03219$, and $k3 = 0.6041$ for men; and $k1 = 0.3561$, $k2 = 0.03308$, and $k3 = 0.1833$ for women.

$$\text{Total blood loss} = \mathrm{PBV} \times (\text{preoperative Hct} - \text{postoperative Hct})$$
$$\text{Hidden blood loss} = \text{Total blood loss} - \text{Dominant blood loss} + \mathrm{ABT}$$

Hidden blood loss can be determined by subtracting visible blood loss from calculated blood loss. The results were converted to whole blood volume for each patient using their average Hct [21]. Patients received blood transfusions according to the following protocol [22]: (1) patients with Hb levels less than 70 g/l received a homologous blood transfusion until the level reached or exceeded 80 g/l; (2) patients with Hb levels between 70 and 100 g/l received a transfusion determined by each patient's specific circumstance. Data on the number of patients requiring blood transfusions and the amount of blood transfused were documented for both groups. The staff evaluating the results was blinded to patient allocation.

Clinical data on anesthesia method, skin incision, surgical duration, rehabilitative activity, length of hospital stay, and postoperative complications were also collected. Two staff members who judged the results were blinded to group assignments. Incidences of symptomatic DVT and pulmonary embolism were assessed until postoperative day 90. Clinical symptoms including pain and swelling of the limb, calf tenderness, superficial venous engorgement, and Homan's sign were evaluated daily during the postoperative period until the patient was discharged. Dyspnea and/or chest pain, which can be indicative of PE, was also evaluated. Patients were followed up on postoperative days 30 and 90 and were instructed to report any signs of DVT.

Statistical Analysis

Quantitative variables were reported as mean and standard deviation (SD) and compared using 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 concentration, Hct, volume of blood loss, and volume of allogenic transfusion were compared using independent exponent t tests. All data analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). Significance was set at $P < 0.05$.

Table 1
Demographic Characteristics and Perioperative Details for Patients.

Variables	TXA + DEP group ($n = 53$)	TXA-only group ($n = 54$)	P value
Gender (male:female)	41:12	39:15	0.541
Age (years)	58.6 ± 9.3	61.7 ± 7.9	0.604
Height (cm)	167.5 ± 14.2	169.2 ± 13.1	0.352
Weight (kg)	75.4 ± 10.8	76.7 ± 9.9	0.807
BMI (kg/m^2)	25.8 ± 5.3	24.7 ± 6.2	0.771
Operated side (right%)	28 (52.8%)	32 (59.3%)	0.503
Preoperative comorbidities			
Hypertension	5	7	0.563
Diabetes mellitus (type 2)	2	5	0.437
Coronary heart disease	1	5	0.205
Cerebrovascular disease	0	0	1.000
Preoperative Hb (g/dl)	137.8 ± 14.0	129.9 ± 12.3	0.139
Preoperative Hct (%)	39.2 ± 6.9	37.6 ± 7.4	0.486
Preoperative Harris score	40.9 ± 12.7	39.7 ± 11.2	0.529
ASA grade 0–I/II–III	49/4	53/1	0.205
Anesthesia(ESA/GA)	51/2	47/7	0.161
Surgical duration (min)	76.3 ± 10.4	78.1 ± 11.5	0.732
Skin incision (cm)	15.2 ± 3.1	13.5 ± 2.7	0.813
Length of stay (days)	8.4 ± 2.4	8.9 ± 3.3	0.617

BMI, body mass index; Hb, hemoglobin; Hct, hematocrit; ASA, American Society of Anesthesiologists score; ESA, epidural spinal anesthesia; GA, general anesthesia. Data reported as mean ± SD or total sum.

Results

From January 2013 to November 2014, 136 patients scheduled for primary THA were screened and assessed for eligibility. Thirty-one patients were eliminated by exclusion criteria, and 26 patients declined enrolment. One hundred ten patients were randomized using a block-randomization technique to receive the study drug. After randomization, three patients withdrew consent prior to surgery. Therefore, 107 patients (53 patients in the TXA + DEP group and 54 patients in the TXA-only group) were included in our trial (Fig. 2).

There were no significant between-group differences in the baseline demographic and clinical characteristics, including baseline age, gender, weight, height, BMI, Harris Hip Score, ASA status, Hb concentration, Hct, and predetermined preoperative comorbidities (Table 1). No between-