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Original research

A prospective, randomized, comparative study of intravenous alone and combined intravenous and intraarticular administration of tranexamic acid in primary total knee replacement

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ABSTRACT

Background: Studies on the use of tranexamic acid (TXA) to improve clinical outcomes after joint arthroplasty have reported contrasting results between intravenous (IV) TXA alone and combined IV and intraarticular (IA) administration. We compared the effectiveness of the 2 methods in providing higher postoperative hemoglobin (Hb) levels in patients undergoing primary total knee arthroplasty (TKA).
Methods: A total of 100 TKA patients were randomly assigned to receive either IV TXA alone (group 1) or combined IV and topical IA TXA (group 2). Hb and hematocrit levels were measured before and after surgery. The amount of drained blood and transfused blood for the 2 groups was compared.
Results: The Hb level was significantly higher at postoperative day 4, together with a positive, albeit not significant, trend toward less postoperative blood loss in the group that received combined IV and IA TXA. No postoperative infections or deep venous thrombosis events occurred.
Conclusions: This study reinforces evidence that, as compared to IV TXA alone, combined IV and IA administration of TXA has a synergic effect, leading to higher postoperative Hb levels without influencing drug safety in TKA patients.

Introduction

Intra- and postoperative bleeding in total knee arthroplasty (TKA) is associated with a higher risk of developing painful intraarticular (IA) hematoma and subsequent infection, as well as increased healthcare costs due to longer hospital stay [1,2]. Currently available strategies for bleeding management include reinfusion of intra- and postoperative drainage volume, which is more expensive and less effective in controlling blood loss than the use of tranexamic acid (TXA) [3]. Fibrin sealants have also been shown to be effective in reducing intraoperative blood loss, but because of their cost, their use is not suggested in standard knee arthroplasty [4]. Postoperative blood loss can also be controlled by placing the knee in flexion for 6 hours immediately after surgery [5].

TXA, being both inexpensive and effective, has become the method of choice for controlling blood loss [6]. TXA, a synthetic antifibrinolytic that inhibits lysine from attaching to the plasminogen-binding site, blocks plasminogen from binding to the fibrin surface. In this way, plasminogen activation is inhibited and fibrinolysis is blocked [7]. Although the effectiveness of TXA in controlling blood loss has been widely demonstrated, debate continues over the potential benefit of local IA vs systemic administration. We compared the effectiveness of intravenous (IV) administration of TXA alone vs combined IV and IA administration in providing higher postoperative hemoglobin (Hb) in TKA.

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Material and methods

Between September 2015 and February 2016, a total of 100 patients underwent TKA (75 women and 25 men; age range, 48-91 years) for primary knee osteoarthritis (n = 85), post-traumatic knee osteoarthritis (n = 9), or knee osteoarthritis secondary to rheumatoid arthritis (n = 6). Inclusion criteria were primary TKA and age between 18 and 95 years. Local institutional review board approval (CdCP71498-2015) and patients' consent were obtained. Exclusion criteria were knee flexion deformity >20°; varus and valgus deformity >20°; revision unicompartmental or total knee replacement; pregnancy; known allergy to TXA, low-molecular-weight heparin, and local anesthetics; congenital or acquired coagulopathy; history of thromboembolism; use of anticoagulants or contraceptive pills 5 days before surgery; anemia; severe cardiovascular and respiratory disorders; ischemic heart disease; renal and/hepatic insufficiency; and refusal of blood transfusion for religious reasons.

Preoperative assessment included blood tests and clinical examinations to rule out severe cardiovascular and respiratory disorders. The patients were randomly assigned in a 1:1 ratio to 2 groups. Blind randomization was performed with the use of sealed envelopes opened at the time of surgery: group 1 (n = 50) received 1 g TXA IV 30 minutes before induction of anesthesia and then at 3 and 9 hours after surgery; group 2 (n = 50) received 1 g TXA IV 30 minutes before induction of anesthesia, then at 3 and 9 hours after surgery plus 3 g topical TXA, which was injected into the joint after closure of the capsule. The IA TXA was prepared intraoperatively, and 3 g of TXA was diluted in 100 mL of saline solution (0.9%) [8]. Blood loss parameters were assessed postoperatively: Hb levels and platelet count on postoperative days (POD) 1, 2, and 4; number of transfusion units; and amount of drained blood in the first 24 hours after surgery.

Surgical technique

Spinal anesthesia was used in all patients (Chirocaine 10-20 mL) together with intraoperative sedation with IV propofol if needed; all patients received antibiotic prophylaxis with 2 g of IV cefazolin 30 minutes before surgery, followed with 1 g every 8 hours after surgery. Patients with a known allergy to cephalosporins received an alternative antibiotics for prophylaxis. A midline skin incision with a medial parapatellar approach was used; the tourniquet was insufflated before skin incision and deflated to obtain accurate hemostasis after the cuts were completed. Local anesthetic (150 mL of ropivacaine [0.2%]) was injected around the soft tissues (Hoffa's body, capsule, subcutaneous fat tissue), and the femoral canal was closed with a press-fit bone plug obtained from the patient's bone cuts. The tourniquet was then again insufflated before cementing and implanting the definitive components and released for hemostasis before closing the capsule. An IA drain was placed and kept clamped for the first 3 postoperative hours. Postoperative blood transfusion was given to patients with anemia (Hb <8 g/dL) or ischemic heart disease (Hb 10 g/dL).

Outcome assessment

The main outcome measure was the Hb value at POD 4. According to previously published studies, and in line with our clinical experience, the Hb level is usually lowest on POD 4 [9]. Secondary outcome measures were amount of drained blood (mL) in the first 24 hours after surgery, number of blood transfusion units, and total postoperative blood loss. Patients were monitored for deep vein thrombosis (DVT) events or other postoperative complications; patients with clinically suspected DVT would be further investigated by ultrasound examination.

Postoperative program

Low-molecular-weight heparin was given according to patient's weight the day before surgery and then repeated every 24 hours. All patients were mobilized with the assistance of a physiotherapist and 2 crutches on the evening of the operative day.

Sample size

Sample size was calculated based on previous studies. As reported by Nielsen et al. [8] in a study comparing combined IV and IA administration of TXA with IV-only administration of TXA in TKA, the combined administration of IV and IA TXA resulted in a clinically relevant reduction in Hb compared with IV TXA alone. Mean values and standard deviations (SD) in the 2 groups at day 2 are as follows: 12.2 ± 1.1 g/dL and 11.1 ± 1.3 g/dL in IV+IA TXA vs IV TXA alone, respectively. On the other hand, Chen et al. [9] observed that Hb reaches its nadir at fourth POD. Our hypothesis was that Hb difference between groups (IV+IA TXA vs IV TXA alone) turns to be significant at the fourth POD. The achievements from the study by Nielsen et al. [8] were used to test the sample size required to obtain a significant difference between groups. Thus, 43 patients per group achieved a 80.530% power to reject the null hypothesis of equal means when the population mean difference is $\mu 1 - \mu 2 = 12.6 - 11.8 = 0.8$ with a SD for both groups of 1.3 and with a significance level (alpha) set at 0.050 using a 2-sided 2-sample equal-variance *t*-test.

Statistical analysis

Descriptive statistical analysis (number, mean ± SD) was applied to continuous variables. Hb levels (g/dL) before and after surgery and the amount of drained blood were defined as continuous variables and analyzed using descriptive statistics. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Statistical analysis was performed using a heteroskedastic 2-tailed Student *t*-test for unpaired data. The statistical power of the study was analyzed and a *P* value of .5 was set to determine statistical significance with a confidence interval of 95%. Analyses were performed using the Number Cruncher Statistical System (NCSS version 2007) and Power Analysis and Sample Size Software (PASS version 2008), (NCSS LLC, Kaysville, UT).

Results

There were no significant differences in age ($P > .05$), height ($P > .05$), weight ($P > .05$), and preoperative Hb levels ($P > .05$) between the 2 groups The Hb levels were comparable between the groups at POD 1 and 2; at POD 4, significantly higher Hb levels were noted in group 2 ($P = .0075$), with a trend, albeit not statistically significant, for a lower amount of drained blood in the first 24 hours and total blood loss in this group ($P > .05$). Two patients in group 1 received a blood transfusion (Table 1). No postoperative infections or thromboembolic events occurred. All patients were discharged on POD 5.

Discussion

We compared the effectiveness and safety of combined systemic and topical administration (IV and IA) of TXA vs topical (IA) TXA alone. The main findings were a significantly higher Hb level at POD 4 and a positive, albeit not statistically significant, trend toward less