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AAHKS Award Paper

The James A. Rand Young Investigator's Award: A Randomized Controlled Trial of Oral and Intravenous Tranexamic Acid in Total Knee Arthroplasty: The Same Efficacy at Lower Cost?

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ABSTRACT

Background: Tranexamic acid (TXA) is a synthetic antifibrinolytic agent successfully used intravenously (IV) to reduce blood loss after total knee arthroplasty (TKA). An oral formulation of the medication is available, at a fraction of the cost of the IV preparation. The purpose of this randomized controlled trial is to determine if oral TXA is equivalent to IV TXA in reducing blood loss in TKA.
Methods: In this double-blinded, placebo-controlled trial, patients undergoing primary TKA were randomized to receive 1.95g of TXA orally 2 hours preoperatively or 1g IV bolus before wound closure. The primary outcome was reduction of hemoglobin. Power analysis determined that 30 patients were required in each group. Equivalence analysis was performed with pooled and Satterthwaite *t* tests with a *P*-value of <.05 suggesting equivalence between treatments.
Results: Thirty-four patients received oral TXA and 37 patients received IV TXA. There was no difference in the mean reduction of hemoglobin between oral and IV groups (3.45g/dL vs 3.31g/dL, respectively; $P = .001$, equivalence), and total blood loss was equivalent at 1281 mL vs 1231 mL, respectively ($P = .02$, equivalence). One patient in each group was transfused.
Conclusion: Oral TXA provides equivalent reductions in blood loss, at a cost of $14 compared with $47-$108 depending on the IV formulation selected. As approximately 700,000 primary TKA are performed in the United States annually, a switch to oral TXA could yield total cost savings of between $23 million and $67 million dollars per year for our health care system.

Minimizing the risk of transfusion has long been a goal of surgeons performing total knee arthroplasty (TKA), as perioperative anemia has been associated with increased morbidity and cost [1-9]. Tranexamic acid (TXA) is an antifibrinolytic agent that has been identified as an effective tool for reducing the risk of transfusion after TKA [3,10-16]. TXA is a synthetic amino acid derivative of lysine whereby the drug binds to the lysine site of plasminogen to promote clot stabilization [17].

TXA can be administered intravenously (IV), topically (intra-articular), and orally. When IV and topical TXA have been compared, the outcomes have shown no statistical difference and non-inferiority between the routes of administration. Investigation of TKA and oral TXA used in isolation has been limited to just 4 studies [18-21]. To our knowledge, no prospective examination for equivalence between oral and either IV or topical TXA has been reported. One major advantage of oral administration is decreased costs, with an appropriate oral dose costing approximately $14 compared with $47-$108 depending on the IV formulation selected.

We performed a prospective, double-blinded, randomized, placebo-controlled study to investigate the efficacy between oral and IV routes of TXA. Based on serum and pharmacokinetic studies, a single 2-gram dose of oral TXA allows for serum concentrations to reach the therapeutic threshold after approximately 2 hours while maintaining adequate concentrations for 6 hours after administration [18,22]. When the pharmacokinetic profile is compared to a single gram of IV TXA, the therapeutic concentration is achieved more rapidly but falls below the threshold after approximately

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5 hours [18,22]. As a result, we hypothesized proper timing of oral TXA would allow for equivalent results to IV TXA.

Materials and Methods

Study Design and Patients

This study was a single-center, prospective, double-blinded, randomized, placebo-controlled trial designed to test equivalence between oral and IV TXA in the setting of a primary total knee replacement. Our institutional review board approved the present study, and it was registered with the public ClinicalTrials.gov registry (NCT02233101). All patients scheduled to undergo unilateral primary TKA were eligible for inclusion. Patients were excluded if they had a known allergy to TXA, history of renal failure or kidney transplant, a history of arterial thromboembolic event (eg, myocardial infarction, stroke) within the past year, placement of an arterial stent within the past year, a history of thromboembolic event, or refusal to receive blood products.

Enrolled patients were randomly allocated between the 2 treatment groups of oral and IV TXA using a random number algorithm to provide a binary output to assign the patient's treatment. The oral TXA group was administered 1950 mg TXA (3 tablets of 650 mg) approximately 2 hours before incision and given a placebo of 10-mL normal saline immediately before wound closure. The IV TXA group received the standard dosing for our institution of 1 g TXA (diluted in 10-mL normal saline) given as an IV bolus immediately before wound closure and received 750 mg of ascorbic acid (3 tablets of 250 mg) as a placebo approximately 2 hours before the incision.

Assignments of the study participants were prepared by a research assistant and were kept blinded from the study participants and clinical staff involved with decisions regarding study outcomes (ie, ordering transfusion of blood). Preparation of the study medications and placebos were prepared by research pharmacists not involved in patient care to ensure identical appearance and blinding between the medications and placebos. All study participants, surgeons, and clinical staff participating in treatment were blinded to the study group allocation throughout the study period.

Patient demographic and preoperative characteristics were documented for comparison between the treatment groups. The recorded characteristics included the following: age, sex, American Society of Anesthesiologists' physical status classification, weight, height, body mass index, and pertinent preoperative laboratory values (prothrombin time/international normalized ratio [PT/INR], platelet count, hematocrit, and hemoglobin).

Surgical Technique and Postoperative Care

The operative procedures were performed by 2 adult reconstruction fellowship-trained attending surgeons. Anesthesia was performed with a combined spinal-epidural or an adductor canal block combined with either a spinal or general anesthetic. Intravenous prophylactic antibiotic was administered within 60 minutes before incision and dosing continued for 24 hours after surgery. A pneumatic tourniquet was applied to the upper thigh and inflated before incision. A medial parapatellar approach to the knee was performed followed by implantation of cemented posterior cruciate retaining designed implants with patellar resurfacing. All patients had an intraarticular drain inserted, which was placed to bulb suction 2 hours after closure of the incision. All drains were removed from the patients during morning rounds on postoperative day 1. Thromboembolic prophylaxis was initiated on postoperative day 0 using warfarin with a therapeutic INR goal of 1.8-2.2 on the international normalized ratio.

The transfusion protocol for the study participants was planned for a hemoglobin level of less than 7.0 g/dL. If a transfusion was to be given at a hemoglobin level higher than 7.0 g/dL, it would only be performed secondary to a specific patient history (ie, cardiac disease) under the request of an internal medicine physician.

Outcome Measures

The primary outcome measure of the study was postoperative drop in hemoglobin, which was measured as the preoperative hemoglobin minus the patient's lowest postoperative hemoglobin. Secondary outcomes were postoperative blood loss, postoperative hemoglobin loss, drain output, number of blood units transfused, length of hospital stay, and thromboembolic events. Postoperative blood and hemoglobin loss were calculated as a function of patient characteristics including sex, weight, and height as well as preoperative and postoperative hemoglobin balance [13,23,24]. All outcome measures were recorded after the patient had been discharged from the hospital by a research assistant, who was not involved in the clinical management of the study participants.

Sample Size and Statistical Analysis

Sample size requirements were determined for the primary outcome of change hemoglobin based on previously gathered data on the same measures. The standard deviation from our previous data on hemoglobin change was 1.25 g/dL and was used for the current power analysis. Using a clinically relevant difference of 1.0 g/dL, we chose our equivalence margin as ±1.0 g/d with alpha at 5% and 80% power. Testing equivalence of hemoglobin change between groups it was determined that a sample size of 29 subjects per group or 58 total subjects were needed. The primary outcome was tested for equivalence using a two one-sided tests procedure. Secondary outcomes and covariates were compared using traditional *t* tests. Complications and other categorical measures were tested using chi-square or Fisher's exact tests. Ordinal scale outcome variables were tested using nonparametric methods such as Mantel-Haenszel chi-square, sign-test, or Mann-Whitney *U* test. Significance was set at 5% ($P < .05$) and correction for error inflation due to multiple testing, for analysis subsets, was accomplished through use of step-down Bonferroni method. All analyses were performed using SAS version 9.2 (SAS inc, Cary, NC).

Results

During the period of study enrollment from August 2014 and February 2015, 116 patients were scheduled for a primary total knee replacement. Thirty-eight patients were ineligible due to the exclusion criteria. Among the seventy-eight enrolled study participants who underwent randomization, seventy-one patients (37 IV subjects, 34 oral subjects) were included in the per-protocol analysis. Seven study participants were excluded; three patients received the wrong study drug, three withdrew prior to surgery, and one received an incomplete dose of the study drug (Fig. 1). No patient was lost or excluded during the follow-up period.

The average age of an enrolled patient was 63 years old (standard deviation [SD], 10 years) with 47 females and 24 males. There were no statistical differences in the patient characteristics and preoperative measurements pertaining to age, sex, weight, height, body mass index, American Society of Anesthesiologists physical status classification, predicted blood volume, and pertinent preoperative laboratory values including PT/INR, platelet count, hematocrit, and hemoglobin (Table 1). Similarly, operative