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Topical vs Intravenous Tranexamic Acid in Primary Total Hip Arthroplasty: A Double-Blind, Randomized Controlled Trial

Wayne T. North, MD *, Nima Mehran, MD, Jason J. Davis, MD, Craig D. Silverton, DO, Robb M. Weir, MD, Michael W. Laker, MD

Division of adult reconstructive surgery, Henry Ford Hospital, Detroit, Michigan

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ABSTRACT

Background: Tranexamic acid (TXA) reduces perioperative blood loss in total hip arthroplasty (THA).
Methods: In our randomized control trial, 139 patients were enrolled and received 2 g of either topical or intravenous (IV) TXA. Preoperative and postoperative protocols were standardized.
Results: Calculated blood and Hgb loss were lower in the IV group (1195.0 ± 485.9 mL, 1442.7 ± 562.7 mL; $P = .006$), (160.3 [g] ± 63.8, 188.4 [g] ± 68.5; $P = .014$). There was a trend toward significance in transfusion reduction (11% [IV] vs 18% [topical]; $P = .3$). Both groups effectively reduced the transfusion rate. There was significant financial incentive for the use of TXA in THA with a savings of $314 per patient.
Conclusions: IV and topical TXA are effective tools to reduce blood loss and transfusion costs in THA, and we recommend the IV form for ease of use.

Perioperative blood loss and subsequent allogenic red blood cell transfusions are common in orthopedic surgery and present a potential for adverse outcome. Postoperative anemia often delays functional recovery and prolongs patient length of stay after total joint arthroplasty, subjecting patients to iatrogenic complications and hospitals to unwanted costs [1,2]. Over the last several decades, blood transfusions have demonstrated decreased risks and improved safety, especially with the introduction of leukocyte reduction and how it relates to perioperative infection in this population [3,4]. Although direct consequences of blood transfusion have decreased [5-7], we continue to transfuse to help prevent multifactorial complications such as delayed rehabilitation, falls, and cardiac manifestations to name a few. For these reasons, orthopedic surgeons seek to minimize blood loss associated with TJA. In addition to surgical and anesthetic methods, some surgeons are using pharmacologic adjuncts like tranexamic acid (TXA).

TXA has been successful at reducing blood loss and lowering transfusion rates in several surgical procedures including total hip arthroplasty (THA) [8]. Its antifibrinolytic properties arise from its chemical structure as a synthetic lysine analogue. In normal fibrinolysis, tissue plasminogen activator binds to plasminogen, and together, they engage fibrin resulting in fibrinolysis. TXA competitively binds to plasminogen at the fibrin binding site resulting in a decreased rate of fibrinolysis and a theoretical reduction in blood loss.

The number of primary THAs continues to rise annually, with a projected increase to 572,000 in the United States by the year 2030 [9]. Reduction in transfusion rate and perioperative blood loss can improve patient safety and outcomes. The use of TXA in the adult reconstructive literature is becoming more prevalent. Several studies on total knee arthroplasty have identified that topical and intravenous (IV) administration are both useful modes of administration, with IV being superior with respect to blood loss and postoperative transfusion requirement [10-13]. The THA literature has focused on IV or topical administration vs placebo without head-to-head comparison. It is our intent to address this gap with a comparative analysis of topical and IV TXA in primary unilateral uncemented THA.

Materials and Methods

We performed a prospective, double-blinded, randomized control trial recruiting patients from 2 centers within a single institution. All patients scheduled for primary, unilateral THA were

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* Reprint requests: W. T. North MD, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202.

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flagged for study inclusion. The patients were then sequentially excluded from participating if any criteria listed in Table 1 were met. Exclusion criteria were established through recommendation from a panel of clinicians, including orthopedists and anesthesiologists within the institution. A power analysis was conducted based on available data for comparison between topical and IV administration of TXA in primary THA. Using power of 0.8 and a *P* value of .05, the target enrollment was 70 patients per arm of the study. Our primary outcomes included assessment of blood and hemoglobin loss and transfusion rates within each group. Secondary outcomes included a transfusion cost analysis relative to historic controls and an assessment of thromboembolic events. Our historic transfusion rate for patients undergoing primary uncemented THA was 34% from 2009 to 2011.

The randomization algorithm was created by a blinded biostatistician, and patients were allocated in blocks of 4 by a blinded research pharmacist. The randomization was not broken until study completion; all patients underwent intent-to-treat analysis, and all data had been accounted for in a restricted access database. Surgeries were performed at 2 hospitals by 1 of 5 fellowship-trained adult reconstructive surgeons.

Perioperative Protocols

Once informed consent was obtained, the patient was randomized to receive 2.0 g of either topical or IV TXA in 100 ml of 0.9% normal saline solution. Two solutions labeled “IV” and “Topical” accompanied the patient to the operating room (one solution contained the 2.0 g of TXA and the other contained saline placebo). Pragmatic dosing was decided on for ease of administration and demonstrated effectiveness from previous studies [10,14-16]. The IV solution was administered by anesthesia in two 50-ml doses, each over 20 minutes using a pump to ensure the correct volume was administered. One administration was started 10 minutes before incision, and the second during the fascial closure. The topical solution was applied to the wound by the surgical team after component placement and allowed to sit undisturbed for 5 minutes at which point it was removed by suction. No drains were used on study patients. The timing and duration of topical administration emulates several studies in the literature [10,14-16]. By study design, each patient received a topical and an IV administration of study solution, only one of which included TXA.

Postoperative venous thromboembolic chemoprophylaxis was not standardized in an attempt to improve generalizability, but abided by the American Academy of Orthopaedic Surgeons clinical practice guidelines [17]. Patients received either Lovenox (enoxaparin) 40 mg daily for 21 days, rivaroxaban 10 mg daily for 35 days, or aspirin 325 mg bid for 21 days. All chemoprophylaxis was initiated on the morning of postoperative day one. All patients received mechanical thromboprophylaxis with early mobilization and pneumatic leg compression devices. Patients had a standardized preoperative and postoperative employment of a pain management ladder.

Hemoglobin levels were obtained preoperatively and daily thereafter until postoperative day 3. All patients stayed 3 or more days. A standardized postoperative transfusion protocol was used. Patients were transfused at Hgb <7 g/dL in all cases and in cases of symptomatic anemia when Hgb <8 g/dL. We chose the parameters to align with current practice within the institution to avoid confusion and variability in the after care of study participants. Calculated values of hemoglobin and blood loss were resulted according to a previously validated formula described by Nadler et al [18].

There was no routine screening for thromboembolic events. However, all clinically suspicious scenarios were investigated by either duplex ultrasound or CT angiography for suspected deep vein thrombosis (DVT) or pulmonary embolism (PE), respectively.

Table 1
Exclusion Criteria.

Cemented femoral or acetabular component
Current medical management of DVT or PE
Previous embolic stroke or SAH
Active liver disease with abnormal coagulation profile
Alteration to color vision
Epilepsy
Previous surgery on the planned operative hip
Current treatment with OCP or HRT

DVT, deep vein thrombosis; HRT, hormone replacement therapy; OCP, oral contraceptive pill; PE, pulmonary embolism; SAH, subarachnoid hemorrhage.

Trial Registration and Data Analysis

The trial was approved by our institutional review board and registered with clinicaltrials.gov (National Institutes of Health Registry, NCT01683955). All patients provided preoperative informed consent to participate in the study.

The 2 groups were compared using chi-square and Fisher’s exact tests for the binary and categorical variables. Continuous variables were reported as mean ± standard deviation, median and range. Normally distributed continuous variables were compared using 2-sided 2-sample *t*-tests, and non-normally distributed continuous variables, such as length of stay, were compared using 2-sided Wilcoxon rank-sum tests.

Results

Patient Recruitment and Characteristics

From January 1, 2013, to October 31, 2013, 232 primary THAs were scheduled and completed. One hundred eighty-four of these were deemed eligible for the study, 48 met exclusion criteria and 45 declined enrollment. One hundred thirty-nine went on to consent for study participation; 70 received the IV preparation; and 69 received the local preparation (Fig. 1). All 139 consented patients underwent an intention-to-treat analysis. The 2 groups demonstrated similar characteristics at baseline indicating a successful randomization process (Table 2). There was an uneven distribution

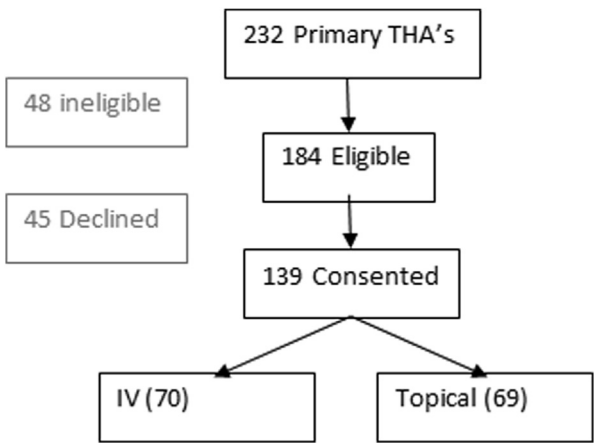

Fig. 1. Flow chart of enrollment and randomization. IV, intravenous.