Primary Arthroplasty

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.

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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 TXA 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
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.

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 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

Table 1

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Cemented femoral or acetabular component</td>
</tr>
<tr>
<td>Current medical management of DVT or PE</td>
</tr>
<tr>
<td>Previous embolic stroke or SAH</td>
</tr>
<tr>
<td>Active liver disease with abnormal coagulation profile</td>
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<tr>
<td>Alteration to color vision</td>
</tr>
<tr>
<td>Epilepsy</td>
</tr>
<tr>
<td>Previous surgery on the planned operative hip</td>
</tr>
<tr>
<td>Current treatment with OCP or HRT</td>
</tr>
</tbody>
</table>

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

Fig. 1. Flow chart of enrollment and randomization. IV, intravenous.
Several studies have analyzed the effect of IV TXA loss and transfusion rates in various surgical procedures including THA [12,19-21]. In one randomized controlled trial of 161 patients undergoing unilateral primary THA investigating the effect of topical application of TXA on blood loss [11], TXA reduced the absolute risk of blood transfusion by 19.6% (95% CI, 6.9%-32.1%; P = .004), from 32.1% to 12.5% [11].

IV administration of TXA in primary THA has also shown to be effective at reducing transfusion rates. A 2015 randomized trial from the Bone and Joint Journal looking at IV (2 g divided) vs placebo TXA showed a reduction in transfusion rates, P = .021 [15]. In a second randomized trial, 124 patients were given a single 15 mg/kg dose of IV TXA preoperatively and reduced their transfusion rate from 22% to 3% (P < .05) [23]. A meta-analysis of 11 published randomized control trials evaluated the effect of IV TXA in THA, concluding that TXA led to a significant reduction in the proportion of patients requiring allogeneic blood transfusion [16].

The only study comparing the efficacy of IV vs topical administration of TXA is a retrospective review of 1595 THAs, by Wind et al. They reviewed transfusion rates in patients receiving IV TXA, or topical TXA in THA. However, none have compared the 2 routes of delivery in a prospective randomized control trial. Our goal in this study was to determine differences in IV and topical TXA delivery in THA with respect to blood loss and transfusion rate.

**Blood Loss and Hemoglobin Change**

The IV group demonstrated higher postoperative hemoglobin before discharge compared to the topical group. Differences in lowest postop hemoglobin (10.4 ± 1.6 g/dL vs 9.7 ± 1.6 g/dL; P = .008), change in hemoglobin (−3.1 ± 1.2 g/dL vs −3.5 ± 1.2 g/dL; P = .014) were significantly improved in the IV group. The IV mode resulted in less calculated Hgb loss (160.3 ± 63.8 mg vs 188.4 ± 68.5; P = .014) and calculated blood loss (1195.0 ± 485.9 mL vs 1442.7 ± 562.7 mL; P = .006; Table 3).

**Transfusion Rate**

The transfusion rate was 14% (n = 20) for all patients, with the IV group having a lower rate compared with the topical group (11% vs 18%, P = .3; Table 2). The historic transfusion rate from 2009 to 2011 for primary THA was identified to be 34%. Using this data, the number needed to treat to prevent one transfusion was 5 and 7 patients for IV and topical TXA preparations, respectively.

**Cost Analysis**

**Chemoprophylaxis and Postoperative Complications**

There was no statistical difference between the groups with respect to type of postoperative chemoprophylaxis against DVT and PE (Fig. 2). There were 6 patients with a postoperative complication (2 from the IV and 4 from the topical groups, P = .441). Three patients, developed a type II non-ST elevation myocardial infarction Non-ST elevation myocardial infarction, 1 in the IV and 2 in the topical groups (P = .619). No patients experienced a DVT and 1 patient in the IV group developed a PE.

**Discussion**

There is a growing body of evidence that TXA can reduce blood loss and transfusion rates in various surgical procedures including THA [12,19-21]. Several studies have analyzed the effect of IV TXA or topical TXA in THA.

**Blood Loss and Transfusion Rates**

A retrospective comparison (CORR 2014) reviewed 346 primary un cemented THAs. The experimental group received a topical solution of TXA before fascial closure and reduced their overall transfusion rate by greater than 50%, from 35% to 17% [14]. Pei et al were also able to demonstrate a significant reduction in blood loss and transfusion rate from 22% to 6% (P < .05) in their randomized control trial using 3 g of topical TXA vs placebo in primary uncemented THA [22]. Alshryda et al performed a double-blind, randomized controlled trial of 161 patients undergoing unilateral primary THA investigating the effect of topical application of TXA on blood loss [11]. TXA reduced the absolute risk of blood transfusion by 19.6% (95% CI, 6.5%-32.1%; P = .004), from 32.1% to 12.5% [11].

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**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combined (N = 139)</th>
<th>IV TXA (N = 70)</th>
<th>Topical TXA (N = 69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.9 ± 11.3</td>
<td>64.1 ± 12.0</td>
<td>65.7 ± 10.6</td>
<td>.396</td>
</tr>
<tr>
<td>Male gender</td>
<td>77 (55%)</td>
<td>38 (54%)</td>
<td>39 (57%)</td>
<td>.791</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.1 ± 5.9</td>
<td>31.1 ± 5.4</td>
<td>31.1 ± 6.4</td>
<td>.991</td>
</tr>
<tr>
<td>Anesthesia type (g/s)</td>
<td>59 (43%)/79 (57%)</td>
<td>26 (37%)/44 (63%)</td>
<td>33 (49%)/35 (51%)</td>
<td>.176</td>
</tr>
<tr>
<td>ASA score 1/2/3/4</td>
<td>1 (1%)/36 (26%)/89 (72%)/1 (1%)</td>
<td>0 (0%)/16 (23%)/52 (75%)/0 (0%)</td>
<td>1 (1%)/20 (29%)/47 (68%)/1 (1%)</td>
<td>.449</td>
</tr>
<tr>
<td>Preoperative INR</td>
<td>1.02 ± 0.06</td>
<td>1.03 ± 0.06</td>
<td>1.1 ± 0.07</td>
<td>.123</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>30.2 ± 5.5</td>
<td>30.9 ± 4.9</td>
<td>29.5 ± 6.1</td>
<td>.173</td>
</tr>
<tr>
<td>Platelet count preop</td>
<td>234.0 ± 60.4</td>
<td>231.5 ± 67.4</td>
<td>236.6 ± 52.9</td>
<td>.623</td>
</tr>
<tr>
<td>Preop Hgb (g/dL)</td>
<td>13.3 ± 1.4</td>
<td>13.4 ± 1.3</td>
<td>13.2 ± 1.4</td>
<td>.323</td>
</tr>
</tbody>
</table>

ASA, aminosalicylic acid; BMI, body mass index; INR, international normalized ratio; IV, intravenous; preop, preoperative; TXA, tranexamic acid.

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV (N = 70)</th>
<th>Topical (N = 69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest postop Hgb (g/dL)</td>
<td>10.4 ± 1.6</td>
<td>9.7 ± 1.6</td>
<td>.008</td>
</tr>
<tr>
<td>Change in Hgb (g/dL)</td>
<td>−3.1 ± 1.2</td>
<td>−3.5 ± 1.2</td>
<td>.014</td>
</tr>
<tr>
<td>Hgb loss (mg)</td>
<td>160.3 ± 63.8</td>
<td>188.4 ± 68.5</td>
<td>.014</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>1195.0 ± 485.9</td>
<td>1442.7 ± 562.7</td>
<td>.006</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>8 (11%)</td>
<td>12 (18%)</td>
<td>.300*</td>
</tr>
</tbody>
</table>

* The values are given as the mean and standard deviation.

**Fig. 2.** Perioperative chemoprophylaxis in topical and IV groups.
topical TXA, and no treatment. The transfusion rates were 4.33% (P \leq 0.0001), 12.86% (P = .15), and 19.86%, respectively [24].

This trial demonstrates a significant difference in postoperative Hgb, change in Hgb, calculated Hgb loss, and calculated blood loss, all favoring the IV TXA group. There was no statistically significant difference between the 2 groups when comparing transfusion rate, similar to that in Wind et al. Many studies demonstrate a statistically significant decrease in transfusion rates in both IV and topical groups when compared with placebo [11, 12,14-16, 19, 20,22-25]. Given the effectiveness of the topical solution, our trial was unable to detect a statistically significant difference between IV and topical TXA with respect to transfusion rates. However, we do believe a reduction in transfusion rates from 34% (our historical control) to 11% and 18% in the IV and topical groups, respectively, is clinically significant. Our institution currently advocates for IV administration of TXA, mainly for its ease of use and seamless integration into surgical workflow in addition to its superior efficacy.

Financial Implications

Several studies have demonstrated a cost reduction per THA if TXA is applied broadly to reduce transfusion requirements. Transfusion rates in primary THA vary widely across the United States with a range from 5% to 80% and a mean of 18% [26]. Using our historic transfusion rate, before the use of TXA, of 34% in primary cementless THA, cost analysis using IV TXA demonstrated a savings of $314 USD per patient. Our cost analysis does not take into account the savings with TXA based on resultant shorter hospital stay by avoiding transfusion or the increased cost of acute transfusion reactions or infection.

This value is similar to other studies in the orthopedic literature [11,27-29]. Alshryda et al identified a net cost savings of £305 per patient (equivalent to ~500 USD), while taking into account the requisite increase in hospital stay [11]. As medicine continues to respond to pressures of fiscal responsibility and moves toward bundled payment for orthopedic care, IV TXA could save larger centers hundreds of thousands of dollars annually.

Strengths and Limitations

A strength of our study lies within the study design; to our knowledge, there are no other prospective, double-blind, randomized control trials with greater than 100 subjects reported from a single institution comparing IV and topical TXA in primary un cemented THA. The patients were randomized by an independent (of the institution) research pharmacist and a biostatistician reviewed the results to maintain blinding of the patients and all staff involved in patient care. Both treatment and placebo solutions had the same physical characteristics to ensure that the health care professionals could not differentiate between the 2 groups.

There were several potential limitations in our study. First, the variance in follow-up (3–11 months) could create inconsistencies in reports of adverse outcomes if late-appearing. Also, our cost analysis is based on a historical control group. Our cost analysis was based on a historical transfusion figure, before the use of TXA. Although our historical control group had similar patient characteristics there are minor biases for which we could not control. In addition, our venous thromboembolic prophylaxis was surgeon dependent, which may improve the generalizability of the results, as it provides a realistic comparison to the heterogeneous community protocols based on American Academy of Orthopaedic Surgeons/American Academy of Chest Physicians (AACP)-approved guidelines. However, the uncontrolled nature of an independent variable inherently introduces the chance of error within the study.

In conclusion, IV and topical TXA are safe and cost-effective adjuncts which decrease blood loss after primary un cemented THA and compared with placebo have been shown to reduce transfusion requirements. Although no significant difference between modes of administration was identified, the IV route of administration may be preferred, in most patients, given the ease of integration into current care models.

References


