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Subgroup Analysis of Topical Tranexamic Acid in Primary Total Hip Arthroplasty

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Introduction

Intraarticular or "topical" tranexamic acid (TXA) has increasingly received attention for reducing blood loss following total joint arthroplasty [1,3,6,8,14]. While our institution has seen transfusion rates drop from 17.5% to 5.5% after administration of topical TXA in total joint replacement, it is still not known which patients will benefit most from TXA administration [14]. Patients undergoing total hip arthroplasty (THA) at our institution continue to have a higher allogeneic transfusion rate compared to total knee arthroplasty (TKA). While THA patients respond to topical TXA, the question remains as to which specific subset of THA patients might benefit most from administration of topical TXA. To answer this question we performed a retrospective cohort study that involved 123 THA patients who received topical TXA, and compared them to 111 controls who did not receive TXA treatment. These patients were subdivided into groups based on gender, age, BMI, preoperative hemoglobin, and surgical approach.

Our goal in this investigation is to identify characteristics that will more accurately justify the use of topical TXA in THA; the ultimate goal is for a surgeon to correctly identify patients preoperatively (prospectively) who will most consistently benefit from topical TXA administration. Preoperative identification of patients who would most likely benefit from topical TXA administration would allow for more targeted use of the drug, ideally reducing cost and unnecessary exposure.

Methods

Following IRB approval, we retrospectively reviewed 234 primary hip arthroplasties performed by 5 orthopedic surgeons at a single institution between March 2012 and March 2013. Treatment with topical TXA in all primary hip patients was initiated intraoperatively starting September 1st, 2012. The months of August and September of 2012 were excluded from the study in order to prevent any overlap of the experimental and control group. Bilateral and revision hips were excluded from this study.

All patients received spinal or general anesthesia as well as local anesthesia; 10cc of 0.5% Marcaine without epinephrine was used at the operative site after wound closure. Patients received preoperative antibiotics within 1 hour of surgical incision. Antibiotics used included: cefazolin, vancomycin (if MRSA history was present), or Clindamycin (if significant cephalosporin allergy was observed). Standard postoperative DVT prophylaxis was used by all of the surgeons that participated in the study (e.g. TEDS, SCDs, and chemical prophylaxis). One surgeon used postoperative aspirin for chemical DVT prophylaxis, while the other four used Coumadin. No intraoperative drains were placed. One gram of TXA was injected in the pericapsular and deep tissue spaces, or intra-articularly following iliotibial band closure, depending on the surgeon's preference. Otherwise, no changes were made to each surgeon's individual surgical and postoperative protocols between the control and experimental groups. No primary, unilateral total joint patients were excluded from TXA use.

Transfusion was triggered by hemoglobin of less than 8 g/dL or symptomatic anemia for all patients in both control and experimental groups. Each chart was reviewed via the electronic medical record and the following variables were

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recorded for analysis: age, gender, BMI, transfusions, preoperative hemoglobin, postoperative hemoglobin, days in hospital, disposition, 30 day readmission, and complications (including UTI, MI, DVT, stroke, and death). No routine screening for DVT/PE was performed. Symptomatic DVT was confirmed by ultrasound.

Statistical analysis was used to confirm the significance of the results. The chi square test was used for discrete variables (e.g. transfusion rate and hospital disposition). Independent t-tests were used for continuous variables (e.g. drop in Hgb, BMI, and age). Statistical significance was defined as $P < 0.05$ (Table 2).

Table 1. Primary outcome

	Before TXA	After TXA	P-value
Readmission	5	6	0.8928
Complications	0	1	0.3411
Delta Hgb	4.8 +/- 1.1	4.0 +/- 1.0	< 0.0001
Postoperative Hgb	9.1 +/- 1.3	9.8 +/- 1.4	0.0001
Patients Transfused	24	9	0.0016
Units Transfused	39	13	0.0003
Length of Stay	3.2 +/- 1.0	3.1 +/- 1.0	0.4362

Data reported as mean +/- SD or total sum. P values calculated using either independent T-test or chi square test.

Table 2. Demographic

	Before TXA (N = 111)	After TXA (N = 123)	P-value
Age	63.3 +/- 13.5	64.9 +/- 12.1	0.3349
Male	54	52	0.3282
Female	57	71	0.3282
BMI	30.3 +/- 5.2	30.7 +/- 6.4	0.6766
Preoperative Hgb	13.9 +/- 1.4	13.9 +/- 1.5	0.8502

Data reported as mean +/- SD or total sum. P values calculated using either independent T-test or chi square test.

Table 3. Subgroup Population

	Before TXA	After TXA
Age < 50	15	16
Age 50 to 65	50	46
Age > 65	46	61
BMI < 30	49	60
BMI > 30	50	63
Female	57	71
Male	54	52
Hgb < 12	6	10
Hgb > 12	92	94
Anterior-lateral	90	83
Anterior	20	35

Table 4. Primary outcomes within subgroups

	Before TXA	After TXA	P-value
Age <50			
Transfusion	2 (13.3%)	0 (0.0%)	0.13101
Delta Hgb	4.7 +/- 0.8	4.6 +/- 0.9	0.7018
Postoperative Hgb	9.4 +/- 1.2	9.9 +/- 1.7	0.3348
Age 50 to 65			
Transfusion	10 (20.0%)	3 (6.5%)	0.0538
Delta Hgb	4.8 +/- 1.3	4.2 +/- 1.0	0.0192
Postoperative Hgb	9.3 +/- 1.4	10.1 +/- 1.4	0.0105
Age > 65			
Transfusion	12 (26.1%)	6 (9.8%)	0.0261
Delta Hgb	4.8 +/- 0.9	3.7 +/- 0.9	< 0.0001
Postoperative Hgb	8.9 +/- 1.3	9.6 +/- 1.3	0.0025
BMI < 30			
Transfusion	11 (22.4%)	5 (8.3%)	0.0383
Delta Hgb	4.6 +/- 1.1	3.9 +/- 1.0	0.0051
Postoperative Hgb	9.2 +/- 1.4	9.8 +/- 1.4	0.023
BMI > 30			
Transfusion	12 (24.0%)	4 (6.3%)	0.0075
Delta Hgb	4.8 +/- 1.1	4.0 +/- 1.0	0.0004
Postoperative Hgb	9.1 +/- 1.3	9.9 +/- 1.4	0.0042
Female			
Transfusion	22 (38.6%)	8 (11.3%)	0.0003
Delta Hgb	4.8 +/- 1.2	4.1 +/- 1.0	0.0005
Postoperative Hgb	8.4 +/- 1.1	9.3 +/- 1.1	0.0001
Male			
Transfusion	2 (3.7%)	1 (1.9%)	0.5805
Delta Hgb	4.7 +/- 1.1	3.9 +/- 1.0	0.0002
Postoperative Hgb	9.9 +/- 1.1	10.6 +/- 1.4	0.0034
Hgb < 12			
Transfusion	6 (100%)	3 (30%)	0.0063
Delta Hgb	3.4 +/- 1.2	3.0 +/- 0.7	0.4451
Postoperative Hgb	7.6 +/- 0.3	7.8 +/- 0.5	0.3126
Hgb > 12			
Transfusion	16 (17.4%)	4 (4.3%)	0.0038
Delta Hgb	4.9 +/- 1.1	4.1 +/- 1.0	0.0001
Postoperative Hgb	9.2 +/- 1.3	10.1 +/- 1.3	0.0001
Anterior-Lateral			
Transfusion	19 (21.1%)	5 (6.0%)	0.00413
Delta Hgb	4.4 +/- 1.9	3.9 +/- 1.0	0.0442
Postoperative Hgb	9.2 +/- 1.4	9.9 +/- 1.5	0.0015
Anterior			
Transfusion	5 (25.0%)	2 (5.7%)	0.039
Delta Hgb	5.5 +/- 1.1	4.1 +/- 1.0	0.0001
Postoperative Hgb	8.7 +/- 1.1	9.7 +/- 1.2	0.0098

Data reported as mean +/- SD or total sum. P values calculated using either independent T-test or chi square test.

Results

All 234 THA were analyzed based on gender, age, BMI, preoperative hemoglobin, and surgical approach. Age was divided into: younger than 50 years, between 50 and 65 years, and older than 65 years, BMI was divided by obesity (defined as > 30 by the World Health Organization). Preoperative hemoglobin (Hgb) status was delineated by 12 g/dL, and surgical approach was divided into direct anterior and anterolateral approach. There was no statistically significant difference in demographics between the pre and post TXA groups (Table 3). The total number of cases for each group is located in Table 1.

Topical TXA consistently reduced transfusion rate, increased postoperative Hgb, and decreased the change in Hgb (Table 2). However, further analysis of the subgroups revealed that these effects were not evenly distributed (Table 4).

GENDER

Both males and females had a significant difference in their postoperative Hgb and delta Hgb. However, after administration of TXA, only females experienced a significant reduction in transfusion rate. The transfusion rate in females went from 38.6% to 11.3% after administration of TXA, p = 0.0003. Males experienced a transfusion rate reduction from 3.7% to 1.9% after TXA administration, which was not significant (p = 0.5805). One possible explanation for the difference in transfusion rates between men and women could be the increased risk for transfusion normally seen in women who undergo THA [2]. As seen in the control group of this study, women generally have a lower average Hgb than men (13.2 g/dL compared to 14.6 g/dL), which results in women having lower postoperative Hgb (8.4 g/dL compared to 9.9 g/dL). The female control group had 2 readmissions and no complications, while the TXA group had 3 readmissions and one UTI complication. The male control group had 3 readmissions and no complications, while the TXA group also had 3 readmissions and no complications.

BODY MASS INDEX

All patients, regardless of their BMI, experienced significant differences in their delta Hgb, post-operative Hgb, and transfusion rate. In patients with a BMI of > 30, the control group had 3 readmissions and no complications, while the TXA group had 1 readmission and no complications. In patients with a BMI < 30, the control group showed 1 readmission and no complications, while the TXA group had 5 readmissions and 1 UTI complication.

AGE CATEGORY

Patients younger than 50 years experienced no significant changes in delta Hgb, postoperative Hgb, and transfusion. In patients over 65 years and patients between 50 and 65 years, both groups had a significant difference in delta Hgb and postoperative Hgb. Patients over 65 years experienced a significant reduction in transfusion rate (26.1% to 9.8% after administration of TXA, p = 0.0261). Patients between 50 and 65 years experienced a transfusion reduction rate from 20% to 6.5% after administration of TXA, p = 0.0538. In patients over 65 years, the control group had 2 readmissions and no complications, while the TXA group had 3 readmissions and 1 UTI complication. The control group of patients between 50 and 65 years contained 1 readmission and no complications, while the TXA group had 3 readmissions and no complications. The control group of patients less than 50 years contained no readmissions or complications, and the TXA group also had no readmissions or complications.

PREOPERATIVE HEMOGLOBIN

After TXA administration, patients with preoperative Hgb < 12 g/dL saw significant reductions in the rate of transfusion (100% to 30%, p = 0.0063). Also, after TXA administration, patients with a preoperative Hgb of > 12 g/dL experienced both a significant reduction in the rate of transfusion (17.4% to 4.3%, p =0.0038), and a significant change in delta Hgb (4.9 +/- 1.1 to 4.1 +/- 1.0, p = 0.0001). The control group in patients with a preoperative Hgb of < 12 g/dL had 1 readmission and no complications, and the TXA group also had 1 readmission and no complications. Additionally, in patients with a preoperative Hgb > 12 g/dL, the control group had 4 readmissions and no complications, while the TXA group had 3 readmissions and no complications.

Surgical Approach to the Hip

After administration with TXA, patients who underwent either the direct anterior approach (DAA) or anterior-lateral approach (AL) both experienced significant differences in their postoperative Hgb, delta Hgb, and transfusion rates. The control group in patients who underwent DAA had 3 readmissions and no complications, while the TXA group had 2 readmissions and no complications. Furthermore, in patients who underwent AL, the control group had 3 readmissions and no complications, while the TXA group had 2 readmissions and no complications.

Discussion

While the perioperative administration of TXA is being used more widely in total joint replacement surgery, both the method / route of TXA application and the exact patient population who stands to benefit the most from TXA utilization in THA have yet to be established in the literature. The goal of this study was to retrospectively determine which patients undergoing THA had a significant response to topical TXA.

The greatest weakness of this study was its retrospective design. Patients were followed for 30 days postoperatively in the electronic database, and therefore long-term complications or complications managed at a different healthcare facility were not recorded in this study. Some subgroups may be under powered to determine a significant difference in our outcome variables. For example, no significant differences were found in the <50 age group; this may be a false negative, or younger patients may truly not benefit from topical TXA in THA.

This study is consistent with the current literature by revealing significant differences in transfusion rate reduction, delta Hgb, and postoperative Hgb with topical TXA [7,12,13,15].

In concordance with Judge et al.'s paper, our study concludes that BMI has no bearing in primary hip replacement surgery despite TXA treatment [5]. The two BMI subgroups in our study showed no significant change in complication rates, and both subgroups experienced significant differences in their delta Hgb, postoperative Hgb, and transfusion rate after administration with TXA.

Surgical approach had no effect on the outcomes in THA despite TXA use. In both the direct anterior approach group and anterolateral approach group there was no significant change in complication rates. Also, both subgroups experienced significant differences in their delta Hgb, postoperative Hgb, and transfusion rate after administration with TXA.

Patients who are normally at risk for transfusions in THA appear to benefit the most with TXA treatment: women experienced a significant reduction in transfusion rate after TXA treatment. One explanation could be the increased risk for transfusion normally seen in women who undergo THA. According to Morrison et al.'s findings, the clinical significance of TXA is strongest in patients who have the highest anticipated blood loss [10]. Danninger et al. and Saleh et al. concluded that women are at an increased risk for transfusion in THA, our data is consistent with these findings showing a higher transfusion rate in women (38.6% compared to 3.7%) [2,11]. Also, women had a relatively greater clinical response to TXA (with transfusion rate reduction from 38.6% to 11.3% in women compared to transfusion rate reduction from 3.7% to 1.9% in men).

According to Saleh et al., a risk factor for transfusion after THA is increased age [11].Our study has shown that the rate of transfusion was highest in patients over 65 years old (26% compared to 20% in patients between 50 and 65 years old, and 13.3% in patients less than 50 years old). While the subgroup may be underpowered, patients less than 50 years of age do not appear to benefit from TXA use. This may be due to their ability to compensate for relative anemia compared to the older cohorts. Patients over the age of 65 consistently benefit from TXA use (Table 4).

Our study is consistent with the conclusion that low preoperative Hgb is associated with an increased risk of transfusion during admission for THA [4, 11]. 100% of patients with Hgb < 12.0 g/dL received transfusion prior to TXA administration, while 17.4% of patients with Hgb >12.0 g/dL received transfusion prior to TXA administration. Only patients with Hgb > 12.0 g/dL experienced a significant change in delta and postoperative Hgb after TXA administration. There are two likely possibilities for this difference. The first is that patients with a low preoperative Hgb are more likely to receive an intraoperative transfusion which would alter both delta Hgb and postoperative Hgb. Second, the number of patients in the < 12 Hgb group may be too low to detect these differences. TXA appears to be effective despite preoperative Hgb status.

According to Mayr et al., when compared to the traditional AL approach, patients who undergo DAA experience a faster return to normal function [9]. Our results do not indicate a significant difference between the two approaches for THA regarding short term outcomes, and demonstrated similar blood product utilization in both groups. Patients undergoing either approach stand to benefit from TXA administration (Table 4).

Conclusion

According to this study, there are no restrictions on the use of topical TXA in THA, however not all patients should be expected to benefit equally. A preoperative Hgb >12 is protective against perioperative transfusions especially in combination with TXA, however TXA significantly reduces transfusion rates regardless of preoperative Hgb status. Female patients and those over 65 years of age appear to have the most reliable and consistent response to topical TXA use in THA.

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