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CASE REPORT

Subgroup Analysis of Topical Tranexamic Acid in Total Knee Arthroplasty

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Abstract

Evidence continues to accumulate for the efficacy of tranexamic acid (TXA) use in primary total knee arthroplasty (TKA). An essential question that remains is to determine which specific subgroups of patients undergoing TKA will benefit from TXA use and if surgeons should be more selective in its administration. We performed a retrospective cohort study involving 187 TKA patients who received intraarticular ("topical") TXA, and compared these to 168 historical controls who did not receive TXA. These patients were then subdivided into groups based on gender, age, BMI, and preoperative hemoglobin for analysis. All patients, despite their demographics, saw an improvement in primary outcome measures without a detectable increase in complications. Based on these data, there are no restrictions on the use of TXA. Obese patients, females, and those over 65 years of age undergoing total knee arthroplasty may benefit from TXA most consistently.

Introduction

Topical or intraarticular tranexamic acid (TXA) has garnered recent attention for its ability to reduce transfusion rates [1,2,3,4] reduce length of stay [5], and reduce cost [1,6,7] following total joint arthroplasty. Our institution has seen and reported similar results [8]. The essential question that remains is to determine which specific subgroups of patients undergoing total knee arthroplasty (TKA) will benefit from TXA use and if surgeons should be more selective in its administration. We performed a retrospective cohort study involving 187 TKA patients who received intraarticular ("topical") TXA, and compared these to 168 historical controls who did not receive TXA. These patients were then subdivided into groups based on gender, age, BMI, and preoperative hemoglobin for analysis.

The purpose of this study was to retrospectively identify patient characteristics that will more accurately justify the utilization of topical TXA in TKA; the ultimate goal is for a surgeon to correctly identify patients preoperatively (prospectively) who will most consistently benefit from topical TXA administration. A secondary goal was to identify patients that were unlikely to benefit from TXA and thereby limit unnecessary use and improve cost saving.

Methods

Following IRB approval, 355 primary, consecutive TKA performed by 5 orthopaedic surgeons at a single institution between March 2012 and March 2013 were retrospectively reviewed. September 1st 2012 marked the day that each of these surgeons began to administer topical TXA to all total joint patients intraoperatively. The months of August and September of 2012 were excluded from the study to prevent overlap of the experimental and control groups. The proportion of patients was similar between the two cohorts for each surgeon. Bilateral and revision knees were excluded from the study.

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Patients all underwent general anesthesia, tourniquet use, and received local 10cc of 0.5% Marcaine without epinephrine at the operative site after wound closure. All patients received preoperative antibiotics within 1 hour of surgical incision, typically cefazolin, vancomycin if MRSA history present, or clindamycin if significant cephalosporin allergy. Following release of the tourniquet, electrocautery hemostasis, and capsular closure, one gram of TXA in 10cc of normal saline was injected intraarticularly into the knee. Standard postoperative DVT prophylaxis was used including 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. 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. Hemoglobin levels were obtained each day during hospitalization and the lowest of these was used for analysis. Transfusion was triggered by a hemoglobin of less than 8 g/dL for all patients in both control and experimental groups. Each chart was reviewed via the electronic medical record and the following variables were obtained: age, gender, BMI, transfusions, preoperative hemoglobin within 30 days of operation, postoperative hemoglobin, operative time, tourniquet time, days in hospital, 30 day readmission, disposition to home or subacute nursing facility, and complications of UTI, pneumonia, MI, DVT, stroke and death within 30 days. All readmissions were recorded regardless of the reason. Not all readmission reasons qualified as complications in our analysis. 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. Independent t-tests were used for continuous variables. Statistical significance was defined as $P < 0.05$.

Results

The total 355 cases were analyzed based on gender, age, BMI and preoperative hemoglobin. Age was divided by older or younger than 65 years. BMI was divided by obesity, defined as 30 and above. A division at 12 g/dL was used for preoperative hemoglobin. The number of cases for each group is contained in Table 1.

Overall, TXA effectively reduced the transfusion rate, increased postoperative hemoglobin levels, decreased the change in hemoglobin, and increased home disposition. These effects were not evenly distributed however. The total summary without subdivision can be found in Table 2. Tourniquet time, EBL, days in hospital, surgical time, complication rate and readmission rate were similar between the groups unless otherwise stated.

GENDER

Females had a significant difference in their postoperative hemoglobin, delta hemoglobin, and disposition. The transfusion rate change was not statistically significant, a reduction from 16.5% to 7.3%, $p = 0.064$. See Table 3 for all subgroup outcome values. Women experienced one UTI, one DVT and three readmissions in the control group; the TXA group experienced 1 MI and 5 readmissions.

Males were noted to have a significant difference in their postoperative hemoglobin and transfusion rate. Male disposition and delta hemoglobin did not significantly differ. Males experienced 1 UTI and 4 readmissions in the control group; the TXA group experienced no complications and 2 readmissions.

BMI

Patients with a BMI of less than 30 showed a significant difference in their postoperative hemoglobin, delta hemoglobin, and transfusion rate. Their disposition did not dif-

Table 1. The total number of patients in each subgroup is presented before and after TXA.

Subgroup	Before TXA	After TXA
Age <65	75	86
Age >65	93	101
BMI <30	69	82
BMI >30	85	105
Female	109	109
Male	59	78
Hgb <12	17	15
Hgb >12	128	154

Table 2. Outcome measurements for TXA intervention in all TKA patients before division into subgroups.

Outcome	Before TXA	After TXA	P Value
Disposition home	95 (56.5%)	132 (70.6%)	**0.0059**
Disposition SNF	73 (43.5%)	55 (29.4%)	**0.0059**
Readmission	7	7	0.8379
Complications	3	1	0.2622
Delta Hgb	4.4+/-1.1	3.7+/-1.6	**0.0001**
Postoperative Hgb	9.2+/-1.2	10.2+/-1.8	**0.0001**
Patients Transfused	25 (14.9%)	8 (4.3%)	**0.0018**
Units Transfused	41	20	**0.0041**
Length of stay	3.2	3.2	0.7606

Table 3. Subgroups divided by age, gender, BMI, and preoperative hemoglobin (Hgb), before and after TXA use.

Subgroup	Before TXA	After TXA	P Value
Age <65			
-Transfusion	7 (9.3%)	2 (2.3%)	0.0864
-Delta Hgb	4.31+/-1.13	3.76+/-1.06	**0.0034**
-Postoperative Hgb	9.48+/-1.25	10.2+/-1.33	**0.0005**
-Disposition home	50 (66.7%)	58 (67.4%)	0.4297
Age >65			
-Transfusion	18 (19.4%)	6 (5.9%)	**0.0132**
-Delta Hgb	4.30+/-1.2	3.74+/-0.95	**0.0013**
-Postoperative Hgb	9.01+/-1.18	10.28+/-2.20	**0.0001**
-Disposition home	45 (48.4%)	70 (69.3%)	**0.0024**
BMI <30			
-Transfusion	14 (20.3%)	5 (6.1%)	**0.0214**
-Delta Hgb	4.56+/-1.23	3.99+/-0.99	**0.0015**
-Postoperative Hgb	8.95+/-1.30	10.15+/-1.23	**0.0001**
-Disposition home	41 (59.4%)	58 (70.7%)	0.1451
BMI >30			
-Transfusion	9 (10.6%)	3 (2.9%)	**0.0415**
-Delta Hgb	4.12+/-1.07	3.65+/-0.97	**0.0032**
-Postoperative Hgb	9.43+/-1.14	10.26+/-2.23	**0.0021**
-Disposition home	42 (49.4%)	74 (70.5%)	**0.0031**
Female			
-Transfusion	18 (16.5%)	8 (7.3%)	0.0636
-Delta Hgb	4.19+/-1.18	3.51+/-1.67	**0.0016**
-Postoperative Hgb	8.84+/-1.01	9.60+/-1.17	**0.0001**
-Disposition home	53 (48.6%)	71 (65.1%)	**0.0138**
Male			
-Transfusion	7 (11.9%)	0 (0%)	**0.0028**
-Delta Hgb	4.49+/-1.09	4.08+/-1.47	0.0863
-Postoperative Hgb	9.85+/-1.26	11.08+/-2.23	**0.0002**
-Disposition home	42 (71.2%)	62 (79.5%)	0.3966
Hgb <12			
-Transfusion	8 (47.1%)	5 (33.3%)	0.6067
-Delta Hgb	3.17+/-1.25	2.98+/-1.03	0.6447
-Postoperative Hgb	7.84+/-0.80	8.27+/-1.01	0.1997
-Disposition home	4 (23.5%)	6 (40.0%)	0.3158
Hgb >12			
-Transfusion	14 (10.9%)	1 (0.6%)	**0.0003**
-Delta Hgb	4.47+/-0.99	3.86+/-0.94	**0.0001**
-Postoperative Hgb	9.43+/-1.14	10.46+/-1.86	**0.0001**
-Disposition home	78 (60.9%)	109 (70.8%)	0.0566

fer significantly. The control group had 3 readmissions and 1 UTI complication. The TXA group required 5 readmissions, 1 MI complication.

Patients with a BMI greater than 30 had a significant difference in their delta hemoglobin, disposition, postoperative hemoglobin and their transfusion rate. The control group had 3 readmissions, 1 symptomatic DVT and 1 UTI. The TXA group suffered no complications, but two readmissions.

AGE

Those patients over 65 years had a significant difference in delta hemoglobin, postoperative hemoglobin, transfusion rate, and disposition. In the control group 3 patients were readmitted and 3 had postoperative complications: 2 UTIs, and 1 symptomatic DVT. In the TXA group there were 5 readmissions and 1 MI.

For patients younger than 65 years the delta hemoglobin, postoperative hemoglobin were both significant. The transfusion reduction and disposition were not significantly changed. There were no readmissions in the control group, two in the TXA group. There were no complications in this group.

PREOPERATIVE HEMOGLOBIN

Patients that preoperatively had a hemoglobin of 12 g/dL or greater showed a significant difference in delta hemoglobin, postop hemoglobin and transfusion rate. Disposition did not differ significantly. The control group contained 3 readmissions and 1 UTI. The TXA group had 4 readmissions and no complications.

Patients with a preoperative hemoglobin less than 12 showed no significant difference in their delta hemoglobin, postoperative hemoglobin, transfusion rate or disposition. The control group had 4 readmissions, 1 UTI and 1 symptomatic DVT. The TXA group had 3 readmissions and 1 MI. Refer to Table 3 for a subgroup summary of outcomes.

Discussion

Topical administration of tranexamic acid is becoming more widely used, however the method used to apply it and discerning which specific patients will benefit most from its use has not been clearly established in the literature. The goal of this study was to present an effective method of topical tranexamic acid administration and rigourously examine the subgroups of patients within the study population to determine which patients TXA is most likely to benefit.

There are several weaknesses of this study, including

its retrospective design. Patients were followed for 30 days postoperatively in the electronic database. Any complication that presented either after this time period or to a different healthcare facility was not recorded. The study includes five different surgeons with their own slightly different TKA surgical protocols; however, the method of TXA administration was standardized. Importantly, some of the subgroups may be underpowered to detect significant differences, particularly the preoperative hemoglobin <12 group which contained a notably lower case volume in the series.

The data is consistent with the current literature [9,10,11,12,13] revealing significant differences with topical TXA use: a transfusion rate reduction of 10.6%, delta hemoglobin decrease by 0.7g/dL, increased postoperative hemoglobin by 1g/dL, and increased disposition to home by 14.1%. See Table 2 for primary outcomes of all patients.

Ritter et al found no difference in outcomes based on gender following total knee arthroplasty [14]. The gender cohorts in our study responded to TXA differently. Females saw a significant difference in postoperative hemoglobin, delta hemoglobin, and disposition. Their transfusion rate reduction of 9.2% approached significance (P = 0.064). Males dropped to a transfusion rate of zero following TXA implementation; however this did not significantly affect their delta hgb or their disposition. Only 49% of females compared to 71% of males in the control group went home. Following TXA implementation, 65% of females were able to go home, compared to 80% of males. A large percentage of males went home postoperatively despite transfusion requirements or postoperative hemoglobin. This discrepancy may be due to gender differences in postoperative care expectations or may relate to overall postoperative hemoglobin level, which was higher in males. TXA had a significant impact on female disposition and increased male disposition home but not significantly.

Suleiman et al concluded that there was no difference in postoperative complications in total knee arthroplasty when comparing cohorts based on BMI [15]. The BMI cohorts in our study mirrored their results showing no difference in complications. Both groups significantly benefited from TXA implementation. Patients who were not obese did not see a significant increase in home disposition. At baseline without TXA, non-obese patients were 10% more likely to be discharged home (59% compared to 49% in obese individuals). With TXA use, both obese and non-obese patients went home at the same rate, 70% and 71%, respectively.

Kennedy et al found that complications were higher in the elderly following TKA [16]. The patients over 65 years old in our study were more likely to suffer complications following TKA than those under 65 regardless of TXA administration. Those over 65 benefitted significantly from TXA in all outcome measurements: lower transfusion rates, lower delta hemoglobin, higher postoperative hemoglobin and higher home disposition. Patients under 65 had a significantly higher postoperative hemoglobin and lower delta hemoglobin, however this did not significantly affect their transfusion or disposition rate, likely due to their ability to compensate for relative anemia.

Friedman et al found a direct correlation between preoperative hemoglobin and transfusion requirement following total knee arthroplasty [17]. Our data confirms this finding, showing that patients with a preoperative hemoglobin of less than 12g/dL had a 47% transfusion rate. This rate dropped to 33% after TXA implementation; however this was not statistically significant. This particular cohort may have too few patients to detect a difference, as no outcome measures were significantly affected. Patients with a preoperative hemoglobin over 12g/dL went from a 10.9% transfusion rate to 0.6%, (P = 0.0003) following the use of TXA. Home disposition approached significance in this group (P = 0.0566), an increase from 60.9% to 70.8%.

Overall, patients who are obese or over the age of 65 are most likely to benefit from TXA use. Females had a relatively greater clinical response to TXA use than their male counterparts. Patients with preoperative anemia (Hgb <12) would theoretically seem to benefit from TXA but our study was underpowered to assess this accurately, warranting further study in anemic patients undergoing TKA. All patients, despite their demographics, saw an improvement in primary outcome measures without a detectable increase in complications. Based on these data, there are no restrictions on the use of TXA. Obese patients, females, and those over 65 years of age undergoing total knee arthroplasty may benefit from TXA most consistently.

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