

2018

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M. J. Grosso

D. P. Trofa

J. R. Danoff

Zucker School of Medicine at Hofstra/Northwell

T. R. Hickernell

T. Murtaugh

See next page for additional authors

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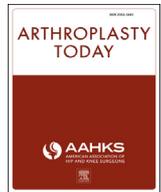
Recommended Citation

Grosso MJ, Trofa DP, Danoff JR, Hickernell TR, Murtaugh T, Lakra A, Geller JA. Tranexamic acid increases early perioperative functional outcomes after total knee arthroplasty.. . 2018 Jan 01; 4(1):Article 3703 [77 p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/3703>. Free full text article.

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Authors

M. J. Grosso, D. P. Trofa, J. R. Danoff, T. R. Hickernell, T. Murtaugh, A. Lakra, and J. A. Geller



Original research

Tranexamic acid increases early perioperative functional outcomes after total knee arthroplasty

Matthew J. Grosso, MD, David P. Trofa, MD, Jonathan R. Danoff, MD,
Thomas R. Hickernell, MD, Taylor Murtaugh, BS, Akshay Lakra, MD, Jeffrey A. Geller, MD *

New York Orthopaedic Hospital, Columbia University Medical Center, New York, NY, USA

ARTICLE INFO

Article history:

Received 8 March 2017

Received in revised form

1 May 2017

Accepted 19 May 2017

Available online 29 June 2017

Keywords:

Tranexamic acid

Total knee arthroplasty

Blood loss

Physical therapy

ABSTRACT

Background: The purpose of this study was to investigate the influence of tranexamic acid (TXA) on functional outcomes in the immediate postoperative period after total knee arthroplasty (TKA). We hypothesized that the known benefits of TXA would confer measurable clinical improvements in physical therapy (PT) performance, decrease pain, and decrease hospital length of stay (LOS).

Methods: We retrospectively analyzed 560 TKA patients, including 280 consecutive patients whose surgery was performed before the initiation of a standardized TXA protocol and the first 280 patients who received TXA after protocol initiation. Outcome measurements included postoperative changes in hemoglobin and hematocrit, LOS, pain scores, destination of discharge, and steps ambulated with PT over 5 sessions.

Results: TXA administration resulted in less overall drops in hemoglobin ($P < .001$) and hematocrit levels ($P < .001$). Moreover, patients administered TXA ambulated more than their counterparts during every PT session, which was statistically significant during the second ($P = .010$), third ($P = .011$), and fourth ($P = .024$) sessions. On average, the TXA cohort ambulated 20% more per PT session than patients who did not receive TXA ($P < .001$). TXA administration did not influence pain levels during PT, hospital LOS, or discharge destination in this investigation.

Conclusions: It is well known that TXA reduces postoperative anemia, but this study also demonstrates that it confers early perioperative functional benefits for TKA patients. Potential mechanisms for this benefit include reduced rates of postoperative anemia and reduced rates of hemarthroses.

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Introduction

Over the last decade, the perioperative use of tranexamic acid (TXA) during total knee arthroplasty (TKA) has been shown to confer significant benefits. Multiple randomized controlled trials

have clearly demonstrated clinically significant reduction in perioperative bleeding, perioperative anemia, and transfusion requirements with both intravenous (IV) and topical TXA administration [1–5]. Reduction in perioperative bleeding is reported between 110 and 690 mL, with a mean difference of 245 mL [1]. Reduction in transfusion rates across 14 studies showed a mean relative risk reduction of 2.56 ($P < .001$) [1].

Achieving faster and safer recovery in the perioperative period is of increasing importance in the arthroplasty field. Accelerated recovery can lead to decreased costs through increased patient independence, a shorter hospital stay, and decreased need for posthospital rehabilitation facilities. The considerable reductions seen in perioperative blood loss related outcomes with the use of TXA may translate to improved functional benefits in this period. Improving postoperative anemia and decreasing intra-articular

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to <http://dx.doi.org/10.1016/j.artd.2017.05.009>.

* Corresponding author. Chief Division of Hip & Knee Reconstruction, New York-Presbyterian at Columbia University, 622 West 168th Street, PH 1147, New York, NY 10032, USA. Tel.: +1 212 305 1120.

E-mail address: JGeller@columbia.edu

<http://dx.doi.org/10.1016/j.artd.2017.05.009>

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hematoma formation may lead to decrease pain and measurable clinical improvement in functional outcomes in the acute postoperative period.

The primary purpose of this study was to investigate the influence of TXA on functional improvement in the immediate postoperative period after TKA. We hypothesized that TXA would confer measurable clinical improvement in physical therapy (PT) performance by improving postoperative anemia and decreasing pain associated with intra-articular hematomas, which would result in short hospital length of stay (LOS) and a decreased rate of patient discharges to a rehabilitation facility.

Material and methods

Experimental protocol

After institutional review board's approval, we retrospectively analyzed patients receiving a TKA by the senior surgeon at one institution between October 1, 2010 and November 1, 2014. Our institution began implementing the use of TXA protocol for TKA patients in May 2013. Patients undergoing bilateral TKA, or who had an operative diagnosis that included infection or trauma, and patients who suffered from blood-related disorders that may have affected their need for transfusion were excluded.

In this case-control study, the patients were divided into 2 groups. The control group consisted of 280 consecutive patients who underwent surgery between October 2010 and May 2013, and did not receive TXA, whereas the TXA cohort comprised the subsequent 280 patients, who underwent TKA between May 2013 and November 2014 after initiation of the TXA protocol. These patients received 1 gram of IV TXA immediately before incision and an additional 1 gram of IV TXA before wound closure. There were 22 patients who did not have complete records and were eliminated from the analysis leaving 264 patients in the TXA cohort and 274 patients in the control cohort.

Data collected included demographics, preoperative functional status based on American Society of Anesthesiologists (ASA) physical status classification system, preoperative hemoglobin (HGB) and hematocrit (HCT) levels. Outcome measures collected included postoperative changes in HGB and HCT levels, transfusion events, LOS, visual analogue scale (VAS) pain scores, distance ambulated with PT over 5 sessions or until discharge, and destination of discharge (home or rehabilitation center).

Statistical analysis

Demographics, preoperative functional status, and preoperative HGB and HCT levels were compared between the 2 groups to identify any baseline differences between the 2 cohorts. Preoperative differences and postoperative outcome measures between the

2 groups were compared using chi-square analysis or Fischer exact test for categorical variables, and Student *t* test for continuous variables. Multivariate analysis using multiple logistic regression comparing outcome measures for each group were performed while controlling for gender, BMI, age, preoperative HCT and HGB levels, and preoperative functional status. A *P* value <.05 was considered significant for all analyses.

Results

Patient demographics and preoperative characteristics

The patient cohorts had similar demographics and preoperative variables including age, ASA grade, body mass index (BMI), and preoperative HGB and HCT levels (Table 1). However, there were a significantly higher proportion of female patients in the TXA cohort (76.1%) compared with the control cohort (66.1%) (*P* = .01).

Outcomes for TXA vs control cohort

TXA administration resulted in reduced postoperative decreases in HGB (1.9 vs 2.6) and HCT (5.8 vs 7.8) (*P* < .001) (Table 2). There was also a trend toward decreased transfusion rates in TKA patients receiving TXA, although this was not significant (1.1% vs 3.7%, *P* = .089).

Patients administered TXA ambulated more than their counterparts during every PT session (Fig. 1, Table 3), which was statistically significant during the second (*P* = .010), third (*P* = .011), and fourth (*P* = .024) sessions. On average, the TXA cohort ambulated 20% more per PT session than patients who did not receive TXA, 65.8 feet vs 54.9 feet (*P* < .001). TXA did not significantly influence VAS pain scores taken before and after PT sessions, or mean VAS score through hospital stay (Table 3). There was no significant difference in knee range of motion (ROM) between the 2 cohorts at 3 months (control 115.0°, TXA 114.1°, *P* = .54) and 1 year follow-up (control 117.1, TXA 118.6, *P* = .36).

Clinical pathways between the 2 cohorts remained the same, with regards to similar multimodal pain management protocols (including a preoperative femoral nerve block), anesthesia protocols, rehabilitation protocols, and mobilization protocols. The average hospital LOS for controls (3.8 days) and TXA patients (3.6 days) was not significantly different (Table 2). There was no difference in the distribution of patients going home vs rehabilitation at the time of discharge, with about 36% of patients able to go home after TKA regardless of TXA administration.

Multivariate analysis

When taking into account age, BMI, gender, preoperative functional ASA status, and preoperative HCT and HGB levels,

Table 1
Patient demographics and preoperative characteristics.

Variable	Total (n = 538)	Control cohort (n = 274)	TXA cohort (n = 264)	<i>P</i> value
Age, y	69.1 (19-94, 10.4)	69.5 (35-92, 10.0)	68.7 (19-94, 10.9)	.202
Gender				
Male	155 (29)	92 (34)	63 (24)	.010 ^a
Female	383 (71)	182 (66)	201 (76)	
BMI, kg/m ²	31.0 (18.1-92.2, 6.7)	31.1 (18.1-58.2, 6.0)	31.0 (18.2-54.6, 7.5)	.368
Preoperative HGB, g/dL	13.1 (7.6-17.3, 1.4)	13.1 (7.6-17.3, 1.4)	13.1 (9-16.9, 1.4)	.837
Preoperative HCT, %	39.9 (23.4-51.7, 3.7)	39.7 (23.4-51.7, 3.7)	40.1 (28.5-49.9, 3.7)	.530
ASA status	2.3 (1-4, 0.5)	2.4 (1-4, 0.5)	2.3 (1-4, 0.5)	.283
PNB, %	528 (94)	260 (93)	268 (96)	.152

PNB, peripheral nerve block.

For continuous variables mean (range, standard deviation); for categorical variables N (%).

^a Significant for *P* value <.05.

Table 2
Outcomes for TXA vs control cohort with univariate analysis.

Variable	Control cohort (n = 274)	TXA cohort (n = 264)	P value
Postoperative HGB, g/dL	12.0 (7.5-17, 1.4)	12.2 (7.1-15.4, 1.4)	.066
POD1 HGB, g/dL	10.5 (6.2-15.4, 1.3)	11.2 (8.5-14.8, 1.3)	<.001 ^a
Change in HGB, g/dL	-2.6 (-7.1 to 0.1, 0.98)	-1.9 (-1 to 4.5, 1.0)	<.001 ^a
Postoperative HCT	36.7 (23.9-50.7, 3.9)	37.3 (7.1-15.4, 1.4)	.047 ^a
POD1 HCT	32.0 (18.6-46.6, 3.9)	34.2 (20.1-47.3, 3.7)	<.001 ^a
Change in HCT	-7.8 (-21.8 to 1.1, 3.1)	-5.8 (-14.9 to 2.8, 2.9)	<.001 ^a
Postoperative transfusion	10 (3.7)	3 (1.1)	.089
Length of stay, d	3.8 (2.1-33, 2.3)	3.6 (1.3-8.4, 1.1)	.231
Discharge location			
Home	100 (36)	95 (36)	.569
Rehabilitation facility	174 (64)	169 (64)	

POD, postoperative day.
For continuous variables mean (range, standard deviation); for categorical variables N (%); ^aSignificant for P value <.05.

multivariate logistic regression analysis confirmed an association between TXA use and significantly increased ambulation with PT during the second, third, and fourth PT sessions (Table 4). In addition, increased total PT ambulation was significantly associated with TXA use.

Discussion

Summary of findings

Similar to numerous previously published level 1 studies, we found that TXA is efficacious in reducing postoperative anemia. In this study, we also found that the administration of IV TXA conferred additional functional benefits for the TKA patient as patients who received IV TXA were more active than the non-TXA patients, with statistically improved ambulation within the days immediately after surgery. No influence was found for decreased pain scores, earlier hospital discharge, or discharge location. Nevertheless, as improved mobility in the postoperative period may help to minimize complications [6-9], this study further supports TXA as a useful adjunct for lower extremity arthroplasty.

Comparison to the literature

The role of TXA in improving patient function has not been well studied. In a similarly designed retrospective study, Serrano Mateo et al. [10] examined 388 TKAs, for which roughly half received

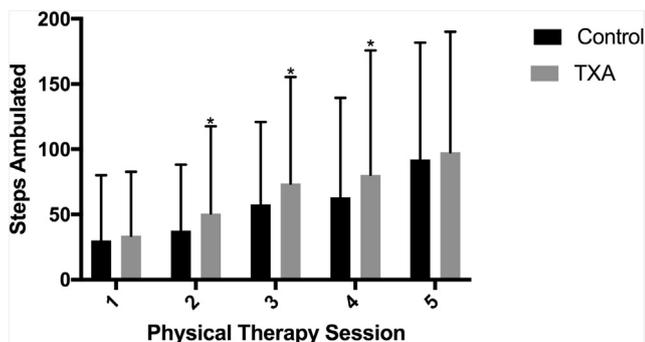


Figure 1. Comparison of number of steps ambulated during the first 5 physical therapy sessions between patients who received TXA and who did not receive TXA. *P < .05.

Table 3
Outcomes for TXA vs control cohort for PT ambulation and VAS pain scores.

Variable	Control cohort (n = 274)	TXA cohort (n = 264)	P value
PT ambulation (steps)			
First session	30 (0-600, 50)	33.8 (0-600, 49)	.38
Second session	38 (0-400, 51)	51 (0-400, 67)	.010 ^a
Third session	58 (0-400, 63)	74 (0-600, 82)	.011 ^a
Fourth session	76 (0-550, 76)	80 (0-600, 96)	.024 ^a
Fifth session	92 (0-600, 90)	98 (0-600, 93)	.532
Total PT ambulation	262 (2-1760, 247)	310 (4-2210, 299)	.041 ^a
VAS pain scores pre-PT			
First session	3.0 (0-10, 2.8)	3.4 (0-10, 2.9)	.07
Second session	3.0 (0-10, 2.8)	3.3 (0-10, 2.9)	.19
Third session	3.4 (0-10, 2.8)	3.3 (0-10, 2.7)	.92
Fourth session	3.1 (0-10, 2.9)	2.7 (0-10, 2.6)	.13
Fifth session	2.6 (0-10, 2.6)	2.3 (0-10, 2.4)	.28
VAS pain scores post-PT			
First session	3.4 (0-10, 2.9)	3.4 (0-10, 2.9)	.93
Second session	3.3 (0-10, 2.9)	3.3 (0-10, 3.0)	.92
Third session	3.8 (0-10, 2.8)	3.3 (0-10, 2.8)	.070
Fourth session	3.3 (0-10, 2.9)	2.8 (0-10, 2.7)	.070
Fifth session	3.1 (0-10, 2.7)	2.6 (0-10, 2.5)	.067

Mean (range, standard deviation); ^aSignificant for P value <.05.

topical TXA, and examined differences in functional Knee Society Score and knee-specific Knee Society score (KKSS) between the 2 groups at 6 weeks and 4 months. They reported significantly greater functional Knee Society Score for the TXA group at 6 weeks, although this difference disappeared at 4 months. In addition, two other studies reported patient reported outcomes at 3 months follow-up, but they reported no difference between TXA and control groups [2,4]. Lastly, Wang et al. and Georgiadis et al. [11,12] examined ROM at 3 weeks or 6 weeks, and only Wang et al. found significantly greater ROM in the TXA group at 6 weeks.

To our knowledge, our study is the first to examine functional outcomes in the immediate postoperative period. Increased early activity after TKA is associated with reduced complications, which may be an additional potential benefit of TXA [6-9]. Although we did not report significant differences in ROM at 1 month follow-up, other studies did see functional improvements during this period. Serrano Mateo et al. and Wang et al. studies [10,11] report improved ROM and functional scores during the first 1-2 postoperative months. Regarding functional outcomes, postoperative anemia can take weeks to months to correct, and therefore, the functional benefit can possibly extend for this period. Although ROM was not significantly different between groups, this study limited its measurement of other long-term functional outcome measures. Diminished local bleeding (hidden blood loss) and swelling in the postoperative period can lead to improved comfort and knee function. In a study by Ishida et al. [13], they observed a significantly decreased thigh, suprapatellar, and calf girth in the TXA group compared with the control group at 1 week. Karaaslan et al. [14] observed decreased rates of intra-articular hemarthrosis in knee surgery after the administration of TXA. Reduced rates of hemarthroses in the knee

Table 4
Results of multivariate logistic regression analysis for physical therapy ambulation.

Physical therapy ambulation	Odds ratio	95% confidence interval	P value
First session	1.002	0.998-1.006	.381
Second session	1.004	1.001-1.008	.007 ^a
Third session	1.003	1.001-1.006	.009 ^a
Fourth session	1.003	1.000-1.005	.024 ^a
Fifth session	1.001	0.999-1.003	.377
Total PT	1.001	1.000-1.001	.034 ^a

^a Significant for P value <.05.

after the administration of TXA may be the potential mechanism for improved perioperative functional outcomes.

In this study, no significant differences were observed for pain scores, time to hospital discharge, and rates of discharge to a rehabilitation facility or home between the 2 groups. One possibility for similar VAS scores was efficacy of the multimodal pain regimen. For example, most patients received peripheral nerve blocks, which likely controlled knee pain in the first 24–48 hours, limiting the pain effect of an increased hemarthrosis, while still potentially effecting willingness to ambulate. The current literature varies on whether TXA administration reduces LOS, with both randomized control trials and retrospective studies showing both outcomes [2,3,12,15–18]. Like disposition status, this outcome is multifactorial in nature, and can vary based on personal and institutional preferences. Of note, none of the studies that report decreased LOS were performed in the United States [2,16–18]. Longer average LOSs in countries outside of the United States may account for this difference. Furthermore, patient disposition is not always dependent on functional status, and it is often affected by patient's preference.

Study limitations

The primary limitation of this study is that it is a retrospective study of prospectively collected data. We attempted to identify potential selection bias between the 2 cohorts that may affect functional outcomes (Table 1). There were no differences for any of the variables, except for percentage female. Of note, gender did not influence functional outcomes in our subanalysis, and the effect of TXA on ambulation remained after a logistic regression analysis which included gender as a variable. There were no major changes regarding drain usage, pain management, or implants used during this period. However, there could be changes in surgical management, as well as hospital policy, that the authors did not identify that may affect these findings, and this is a limitation of this study. Secondly, at our institution, we used IV TXA for our TKA patients. The optimal administration of TXA is controversial, with some studies showing no difference between topical and IV administration [19,20], some favoring topical [21], and some favoring IV [22]. Many studies examining functional outcomes used topical TXA, and the difference, if any, between IV and topical on functional outcomes is yet to be determined.

Furthermore, we did not specifically subanalyze groups based on their mode of venous thromboprophylaxis, as those patients using a stronger agent may have affected the groupings. We evaluated the cohort across all modalities of prophylaxis to evaluate the effect irrespective of blood thinner. The main agents were aspirin (325 mg bid), rivaroxaban (10 mg qd), and warfarin (international normalized ratio [INR] goal 2.0–2.5).

Conclusions

In summary, TXA is efficacious in reducing postoperative anemia, which conferred functional benefits for arthroplasty patients in being able to perform better with PT in the immediate postoperative period after TKA. Improved mobility in the perioperative

period, which can help minimize complications, is one more indication for the use of TXA in TKA.

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