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2023 AAHKS Award Paper

The AAHKS Clinical Research Award: Extended Postoperative Oral Tranexamic Acid in Total Knee Arthroplasty: A Randomized Controlled Pilot Study

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ABSTRACT

Background: Perioperative tranexamic acid (TXA) use with total knee arthroplasty (TKA) is widely accepted today. Recently, a few international groups have published on the safety and outcomes of extending TXA use in the postoperative period. Through a double-blinded, randomized control trial (RCT), we aimed to investigate the safety and clinical efficacy of extended postoperative oral TXA use in TKA performed in an American, free-standing ambulatory surgery center (ASC).

Methods: Based on a power analysis, 40 patients undergoing primary TKA were randomized into 2 groups: extended oral TXA versus placebo. Both groups received a standard 1g intravenous TXA dose prior to incision and at the time of closure. The extended TXA group received an additional 1.95 g oral TXA dose following ambulation the day of surgery, plus on postoperative days 1,2, and 3. Patients who had a history of venous thromboembolism (VTE) or cancer were excluded. All patients received 81 mg of aspirin twice daily for VTE prophylaxis. Patients were followed on postoperative day 3 and weeks 2 and 6. Paired *t*-tests determined statistical significance.

Results: Extended TXA patients showed significantly increased knee flexion at 6 weeks (116.05 versus 106.5, $P = .0308$), improved VAS at 2 (2.5 versus 3.85, $P = .039$) and 6 weeks (1.35 versus 2.8, $P = .011$), and superior KOOS JR at 2 (66.87 versus 60.63, $P = .03$) and 6 weeks (73.33 versus 62.47, $P = .0019$) compared to placebo patients. No significant differences were found for changes in hemoglobin levels at any time points. No significant differences were found at 12 weeks for any clinical endpoints. No adverse events were noted in either cohort.

Conclusions: When compared to placebo, the extended use of oral TXA in the postoperative period may safely result in improved motion, pain, and functional scores. Further investigation into 1-to-2-year outcomes, as well as the duration and dose of postoperative TXA use is warranted.

Clinical Trial registration number NCT05099276 (https://clinicaltrials.gov/study/NCT05099276?locStr=Tennessee&country=United%20States&state=Tennessee&distance=50&intr=Tranexamic%20Acid&rank=7).

Dr. Mihalko serves on the editorial board of the Journal of Arthroplasty.

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Intraoperative tranexamic acid (TXA), administered either intravenously or orally, has become a standard of care practice in total joint arthroplasty (TJA) [1]. The use of TXA in total knee arthroplasty (TKA) is associated with decreased blood loss and transfusion rates, decreased early swelling and ecchymosis, improved early recovery, and potentially superior long-term outcomes [2–7]. Its use has also made transitioning to outpatient TJA safer for patients [8].

Intraoperative TXA use is safe without an increased risk of venous thromboembolism (VTE), even in those patients deemed high-risk [9,10]. Tranexamic acid can be administered in an oral, topical, or IV formulation. Each route of administration has been shown to be effective in decreasing intraoperative blood loss and the need for postoperative transfusion [2,11]. Grassin-Delyle et al. studied the pharmacokinetics of IV versus oral tranexamic acid in healthy volunteers [12]. They showed that 2 g of oral TXA reached the target concentration in 66 minutes with a bioavailability of 47% compared to the IV formulation [12].

Today, with increased healthcare costs and a rise in TJA volume, there remains an emphasis on outpatient surgery, early patient safety, and patient-reported outcomes during the postoperative period [13,14]. With the intraoperative benefits of TXA clearly defined in the literature, several international centers have published on the safety and efficacy of using extended TXA regimens during the postoperative period [2,6,7,15–18]. These studies, however, demonstrated mixed clinical results and were mainly focused on blood loss rather than patient reported outcomes [19,20].

Through a pilot study, we aimed to evaluate the safety and clinical efficacy of extended oral postoperative TXA use in TKA performed in a free-standing ambulatory surgery center (ASC) in the United States. Our hypothesis was that extended oral TXA use in TKA would safely improve early patient recovery.

Materials and Methods

This study was an institutional review board (IRB)-approved, prospective, randomized, placebo-controlled trial conducted at one of 2 ASCs. Patients meeting inclusion criteria were 18 years of age and older and underwent outpatient TKA for osteoarthritis by one of four surgeons. Participating patients underwent outpatient physical therapy at a common location with a common postoperative therapy protocol beginning postoperative day (POD) 3. Patients who had a history of VTE, cancer, or TXA allergy were excluded. Patients on preoperative anticoagulants other than aspirin were also excluded. The patient, surgeon, and physical therapist were blinded. Power analysis determined that a minimum sample size of 40 patients would achieve an effect size of 95% power and alpha 5%, with a 10-point difference in Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) scores being the primary outcome.

Patients were randomized at a 1:1 ratio into two groups by using computer randomization software. All patients and the senior author were blinded to randomization assignments. The control group received a placebo, and the experimental group received extended oral TXA postoperatively. All participants received a standard 1 g intravenous TXA dose prior to incision and another IV dose at the time of closure. The extended TXA group received an additional 1.95 g oral TXA dose following ambulation on the day of surgery and self-administered another 1.95 g oral TXA dose on POD 1, 2, and 3. The control group received a placebo pill with the same postoperative frequency as the intervention group.

All TKAs were performed under a mepivacaine spinal anesthetic. A preoperative adductor canal block was utilized along with an intraoperative periarticular cocktail of ropivacaine, ketorolac, duramorph, and epinephrine [21]. Patients met discharge criteria after they were able to ambulate with physical therapy or a trained nurse, after voiding, and after achieving adequate pain control. All patients were discharged on an oral multimodal pain medication regimen including scheduled doses of celecoxib (or meloxicam if sulfa allergy), acetaminophen, tramadol, and oxycodone for breakthrough pain. Patients were examined, and patient-recorded outcome measures (PROMs) data were collected prospectively on POD 0 while in recovery, at the first physical therapy visit on POD 3, and again at 2 and 6 weeks, and 3 months postoperatively.

Baseline demographic information was recorded, including age, sex, body mass index (BMI), and operative laterality (Table 1). Baseline characteristics, including preoperative hemoglobin (g/dL), knee range of motion (ROM), knee circumference, visual analog score (VAS), and KOOS JR, were collected. Postoperative hemoglobin and VAS pain scores were collected by a recovery room nurse prior to discharge. Hemoglobin, VAS, KOOS JR, knee circumference, and knee ROM were collected at the first physical therapy visit on POD 3, and except for hemoglobin, all data were collected again at 2, 6, and 12 weeks postoperatively. Time to independent ambulation was recorded, as were reoperations, 90-day complications, and readmissions. Paired *t*-tests were performed to compare groups for all normally distributed data, and $P < .05$ was utilized for statistical significance.

Out of 453 patients who were scheduled for primary TKA between December 7, 2021 and March 15, 2023, 46 patients met inclusion criteria and provided informed consent (Figure 1). Patients were randomized into an extended TXA group (n = 24) and a placebo group (n = 22). There were 4 patients in the extended TXA group who did not meet the inclusion criteria, and 2 patients in the placebo group who withdrew consent and, therefore, were withdrawn from the study. There were no significant differences in demographics or preoperative knee function between groups (Table 1).

Results

The addition of an extended oral TXA regimen improved short-term patient-reported outcomes at 2 and 6 weeks following TKA (Table 2). Patients who received oral TXA scored 1.35 lower on mean VAS ($P = .039$) and 6.24 higher on mean KOOS JR ($P = .03$) at 2 weeks postoperatively when compared with those who received placebo. At 6 weeks postoperatively, those who received oral TXA scored 1.45 lower on mean VAS ($P = .011$) and 12.4 higher on mean KOOS JR ($P = .0019$).

Patients in the extended TXA group demonstrated improved knee function at 6 weeks postoperatively. They showed a 9.0 degree increase in mean knee flexion ($P = .03$) at 6 weeks postoperatively,

Table 1
Demographics and Preoperative Knee Function.

Outcome	Extended TXA	Control	*P*-Value
Demographics			
Age (years), mean	64	64	.845
Women, N (%)	10 (50)	8 (40)	.537
BMI	32.2	33.8	.42
Preoperative knee function			
Flexion ROM (degrees), mean	108.20	103.85	.50
Extension ROM (degrees), mean	3.90	4.20	.81
Knee Circumferences, mean	39.31	41.71	.21
VAS, mean	4.50	4.98	.58
KOOS JR, mean	54.88	51.04	.46

BMI, body mass index; KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; ROM, range of motion; TXA, tranexamic acid; VAS, visual analog score.

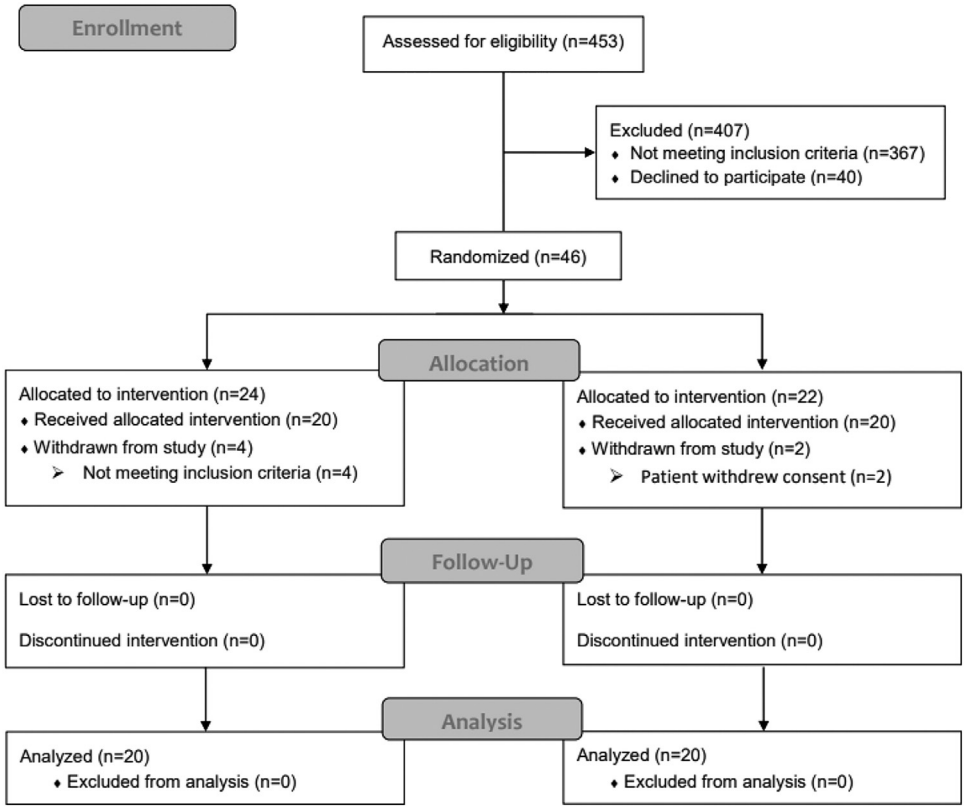

Fig. 1. Consolidated Standards of Reporting Trials.

compared to the placebo group. There were 90% of patients in the extended TXA group who were ambulating independently, and 10% were using canes to ambulate at 6 weeks postoperatively in comparison to 60% ambulating independently and 40% using canes to ambulate in the placebo group ($P = .03$). No significant differences were noted in knee circumference at any time point.

Relative changes in hemoglobin were comparable between the extended TXA and placebo groups in the postanesthesia care unit (PACU) and at POD 3. No differences in any measured outcome were observed at the PACU, at POD3, or at 12-week timepoints. No adverse events, including DVT, cardiac complications, infections, wound dehiscence, seizures, severe headaches, or death, were noted in either group. No patients required hospital readmission.

Discussion

Intraoperative administration of TXA in TJA, regardless of timing and route, has been proven effective in decreasing blood loss and complications. Multiple studies have proven its intraoperative use to be safe, even in patients deemed high-risk [9]. The extended use of TXA in the postoperative period, however, is not widely accepted, and no American centers, to our knowledge, have published on its safety and efficacy. Our prospective randomized trial suggests that the use of extended oral TXA may improve early recovery in the first 6 weeks after TKA with respect to KOOS JR score, VAS, flexion, and time to independent ambulation.

Several studies have looked at extended postoperative use of TXA with blood loss as a primary outcome measure. Yuenyongviwat et al. [19] compared 48 hours of additional postoperative intravenous (IV) TXA with placebo in TKA patients (with both groups receiving intraoperative TXA) and found no difference in hemoglobin reduction or closed suction drainage outputs up to

Table 2
Patient-Reported and Clinical Outcomes After Surgery.

Outcome	Extended TXA	Control	*P*-Value
VAS, mean			
PACU	0.80	2.20	.104
POD3	4.25	4.38	.89
2 wk	2.50	3.85	.04
6 wk	1.35	2.80	.01
12 wk	1.35	1.65	.50
KOOS JR, mean			
POD3	54.7571	53.72495	.3798
2 wk	66.87375	60.63273684	.0325
6 wk	73.33355	60.97395	.0012
12 wk	74.1302	70.5156	.16
Knee Circumference (cm), mean			
OD3	43.78	44.74	.59
2 wk	42.00	43.00	.58
6 wk	40.75	42.42	.28
12 wk	39.39	42.51	.06
Flexion ROM (degrees), mean			
POD3	81.8	81.1	.906
2 wk	107	102	.307
6 wk	116	107	.031
12 wk	119.1	112.6	.090
Extension ROM (degrees), mean			
POD3	4.8	6.8	.199
2 wk	3.5	3.7	.874
6 wk	2.3	2.85	.578
12 wk	2.1	2.2	.920
Hemoglobin (g/dL), difference			
PACU	−1.335	−0.82	.394
POD3	−2.33	−1.95	.523
2 wk	−1.535	−1.43	.885

KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; PACU, postoperative care unit; POD, postoperative day; ROM, range of motion; VAS, visual analog score.

72 hours postoperatively. Magill et al. [2] evaluated the difference in indirect calculated blood loss between a group of TKA patients who received 1 g of IV TXA intraoperatively compared with a group of patients who received intraoperative TXA plus an additional 4 doses of 1 g oral TXA over 24 hours. They found a significant decrease in indirect blood loss without any increased risk of complications with the extended use of TXA [2]. Wang et al. [7] evaluated the outcomes of TKA patients receiving an additional 14 days of oral TXA postoperatively compared to placebo. They reported a significant decrease in mean total blood loss, ecchymosis, and knee circumference at 14 days for those patients receiving extended TXA. No significant differences were found in knee function or pain scores, and no difference in complications was noted between the groups [7].

Our study suggests that patients who were administered extended oral TXA in the postoperative setting may demonstrate improved early recovery for up to 6 weeks when compared with a placebo. At 2 and 6 weeks, extended oral TXA patients demonstrated significantly better mean VAS and KOOS JR. Range of motion was also significantly better at 6 weeks for extended TXA patients. A greater percentage of patients in the extended TXA group were also independently ambulating compared to the placebo group at 6 weeks. We could not detect any significant difference in hemoglobin change between the groups. There were no statistical differences noted between the TXA and placebo groups at 12 weeks.

Intraoperative TXA administration in TKA has been shown to have an anti-inflammatory effect. In another international study, Wang et al. [22] were able to show significant reductions in inflammatory markers (IL-6, ESR, and CRP) for up to 32 hours postoperatively with an extended oral TXA regimen. The anti-inflammatory effects of TXA have also been examined in the cardiovascular surgery literature. Jimenez et al. performed a randomized control trial (RCT) showing that multiple doses of IV TXA intraoperatively attenuated the inflammatory response compared to both placebo and a single-dose regimen in cardiopulmonary bypass patients [23,24]. We hypothesize that our extended TXA cohort clinically benefitted at 2 and 6 weeks postoperatively, primarily due to the anti-inflammatory effect of TXA as opposed to decreased early blood loss, as we were not able to demonstrate a significant change in hemoglobin between the TXA and placebo groups.

Use of tranexamic acid has been shown to be cost-effective in multiple studies when used in primary total joint arthroplasty [25–27]. The oral formulation is less expensive than the standard dosing of IV tranexamic acid ($14 versus $47 to $108) and is similarly priced to a 6-week supply of 81 mg aspirin commonly prescribed postoperatively for VTE prophylaxis [28]. Oral tranexamic acid is FDA-approved for treatment of menorrhagia and is commonly used and carried by pharmacies for this indication [29].

All patients in our study were discharged the same day of surgery from the ASC. No patients reported major complications (including VTE), and no patients required hospital admission postoperatively. No patients reported severe headaches or seizures at any time. No patients reported intolerance to large pill sizes.

Our study did have potential limitations. Our cohorts are relatively small (although powered for a 10-point difference in KOOS JR at 6 weeks), and the patients were only followed for a total of 12 weeks. The majority of excluded patients in our study could not participate because of inability to participate in therapy locally at our main facility's location. Variables such as anesthetic administration, intra-articular injection, multimodal pain regimen, and rehabilitation protocol were standardized. However, multiple surgeons participated with potentially varying techniques and different implant choices. The authors also cannot independently confirm compliance with the prescribed treatment regimen as the oral TXA and placebo were administered on an outpatient basis postoperatively. Although we found statistical differences in VAS, KOOSJR, and knee ROM at several short-term time intervals, these were equivalent at 12 weeks. A larger prospective study is required to fully elucidate the clinical significance of our findings. We also excluded patients at higher risk for VTE from our study and, thus, were unable to assess the safety of extended TXA use in higher-risk patients. Selection bias may also exist granted all surgeries were performed on patients healthy enough to undergo surgery at an ASC.

Conclusions

The authors present, to our knowledge, the first U.S.-based randomized controlled pilot study investigating extended postoperative TXA use for TKA patients. When compared with placebo, the extended use of oral TXA in the postoperative period may safely result in improved motion, pain, and functional scores for TKA patients. Larger, prospective clinical trials are required to determine the true clinical significance of extended postoperative TXA use.

CRediT authorship contribution statement

Mateo J. Kirwan: Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Zachary R. Diltz:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Derek T. Dixon:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Carlos A. Rivera-Peraza:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Christal J. Gammage:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Willliam M. Mihalko:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **James W. Harkess:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **James L. Guyton:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **John R. Crockarell:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcus C. Ford:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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