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The Safety and Efficacy of Topical Tranexamic Acid Versus Intravenous Tranexamic Acid in Total Knee Arthroplasty

Erin R. Wilson
Pacific University

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The Safety and Efficacy of Topical Tranexamic Acid Versus Intravenous Tranexamic Acid in Total Knee Arthroplasty

Abstract

Background: Perioperative blood loss is of major concern for patients undergoing a total knee arthroplasty (TKA). Multiple studies have confirmed the ability of tranexamic acid (TXA), an antifibrinolytic agent, to effectively reduce blood loss and transfusion rates following TKA, without increasing the risk of thromboembolic events. However, much controversy remains about the optimal regimen of TXA in primary TKA. The purpose of this systematic review is to compare the safety and efficacy of topical TXA versus intravenous (IV) TXA in primary TKA.

Methods: An exhaustive literature search was performed using MEDLINE-Ovid, Web of Science, and Google Scholar. The following search terms were utilized: “total knee arthroplasty” OR “total knee replacement” AND “tranexamic acid.” All randomized studies comparing the effectiveness of topical versus intravenous TXA in primary, unilateral TKA were included. Analysis focused on specific outcomes including total drain blood loss, postoperative hemoglobin (Hb) drop, frequency of transfusion, and thromboembolic complications. The quality of evidence was assessed using a system known as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: Of 194 papers identified, four trials were eligible for review. Analysis showed no significant differences in total drain blood loss, postoperative Hb drop, frequency of transfusion, or thromboembolic complications when comparing topical TXA and IV TXA in primary, unilateral TKA.

Conclusion: The results of this review demonstrate that the topical administration of tranexamic has similar efficacy and safety profile to that of intravenous tranexamic acid in reducing blood loss and transfusion rates in primary TKA.

Keywords: Tranexamic acid, topical, intra-articular, intravenous, total knee arthroplasty, total knee replacement

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First Advisor
Professor Annjanette Sommers, PA-C

Keywords
tranexamic acid, topical, intra-articular, intravenous, total knee arthroplasty, total knee replacement

Subject Categories
Medicine and Health Sciences

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The Safety and Efficacy of Topical Tranexamic Acid Versus Intravenous Tranexamic Acid in Total Knee Arthroplasty

ERIN RALEY WILSON

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2016

Faculty Advisor: David Keene, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Erin Raley Wilson is a native of Colorado. She attended Montana State University in Bozeman, MT where she double majored in modern languages and photography. After completion of her undergraduate degree, she moved home to Telluride, CO where she worked as a free-lance photographer for 7 years. Inspired by her father’s work as an Emergency Physician, Erin’s career path took a different course towards medicine. Erin became an Emergency Medical Technician, which allowed her to work as an Emergency Department Technician and Medical Assistant. Erin worked full time in medicine for four years before attending Pacific University’s School of Physician Assistant Studies. Erin hopes to return to Colorado and pursue work as a PA in Emergency Medicine.
Abstract

**Background:** Perioperative blood loss is of major concern for patients undergoing a total knee arthroplasty (TKA). Multiple studies have confirmed the ability of tranexamic acid (TXA), an antifibrinolytic agent, to effectively reduce blood loss and transfusion rates following TKA, without increasing the risk of thromboembolic events. However, much controversy remains about the optimal regimen of TXA in primary TKA. The purpose of this systematic review is to compare the safety and efficacy of topical TXA versus intravenous (IV) TXA in primary TKA.

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**Results:** Of 194 papers identified, four trials were eligible for review. Analysis showed no significant differences in total drain blood loss, postoperative Hb drop, frequency of transfusion, or thromboembolic complications when comparing topical TXA and IV TXA in primary, unilateral TKA.

**Conclusion:** The results of this review demonstrate that the topical administration of tranexamic has similar efficacy and safety profile to that of intravenous tranexamic acid in reducing blood loss and transfusion rates in primary TKA.

**Keywords:** Tranexamic acid, topical, intra-articular, intravenous, total knee arthroplasty, total knee replacement
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To the staff and faculty at Pacific University’s School of Physician Assistant Studies: Nothing can come close to the inspirational presence of teachers like you in a student’s journey. Thank you for helping to shape brilliant futures for us all.

To my parents: Thank you for giving me the world. I’ll do my best to make it a better place. Love you to the moon and back.
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Table 1: Quality Assessment of Reviewed Studies
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List of Abbreviations

TXA………………………………………………Tranexamic Acid
TKA………………………………………………Total Knee Arthroplasty
DVT………………………………………………Deep Vein Thrombosis
PE………………………………………………Pulmonary Embolism
OA………………………………………………Osteoarthritis
ASA………………………………………………American Society of Anesthesiologists
POD………………………………………………Post Operative Day
PRBCs…………………………………………Packed Red Blood Cells
Hb………………………………………………Hemoglobin
US………………………………………………Ultrasound
CVA……………………………………………Cerebrovascular Accident
The Safety and Efficacy of Topical Tranexamic Acid Versus Intravenous Tranexamic Acid in Total Knee Arthroplasty

BACKGROUND

Total knee arthroplasty (TKA) is one of the most common surgeries in orthopedics today. According to the American Academy of Orthopedics,¹ most patients who undergo total knee replacement are age 50 to 80, with a diagnosis of osteoarthritis. There are no absolute restrictions in regards to medical history, age, or weight for TKA; however, studies² have shown that at least 85% of patients undergoing TKA have at least one comorbidity and 32.5% having three or more. Prior studies³ have also demonstrated increased surgical risk in the patient with multiple comorbidities. Added surgical risk can lead to a higher probability of complications such as increased blood loss and transfusion rates, longer hospital stays, and poor functional outcomes.

Perioperative blood loss is of major concern for patients undergoing a total knee arthroplasty (TKA) because of a large surgical incision, exposed trabecular bone, and activation of fibrinolysis.⁴ Previous studies⁵ have reported that estimated blood loss can vary between 1450 to 1790 ml. The resulting blood loss anemia in patients can cause acute complications. In order to avoid such complications, patients are transfused. Blood transfusion rates in patients undergoing TKA have been reported to be between 11 to 21%.⁶ Blood transfusions can prove beneficial; however, they come with complications of their own such as surgical site infection, hemolysis, and immunosuppression.⁷,⁸ Given that side effects and complications are common after blood loss and transfusion, it is important to maintain hemodynamic stability in order to obtain fast recovery following TKA.
In order to reduce the risks associated with blood loss and transfusion, other methods have been introduced to manage perioperative blood loss. One such method is the use of a synthetic antifibrinolytic agent called tranexamic acid (TXA). This pharmacologic agent is an analog of the amino acid lysine. TXA’s mechanism of action is to competitively inhibit plasminogen activation and plasmin binding to fibrin, resulting in a delay of fibrinolysis. TXA is not viewed as a procoagulant but more as a support for coagulation that is already in process.

Multiple studies have confirmed the ability of intravenous (IV) TXA to effectively reduce blood loss and transfusion rates following TKA, without increasing the risk of thromboembolic events. While IV TXA has been proven safe and effective, there is still concern that it could lead to thromboembolic events in a certain subset of patients, such as those with a history of recent stroke, angioplasty, or deep vein thrombosis (DVT). In consideration of these limitations, the topical use of TXA is another method that has been adopted to decrease perioperative blood loss. The effectiveness of topical TXA has also been proven to reduce peri-operative blood loss and transfusion rates without increased risk of thromboembolic events. When administered topically in the intra-articular space, TXA leads to 70% lower systemic absorption. In light of this, topical TXA may prove to be a good alternative to IV TXA; however, its safety and efficacy has only recently been compared to that of IV TXA. Can topical tranexamic acid (TXA) be as safe and effective as intravenous tranexamic acid in the reduction of blood loss in primary, unilateral total knee arthroplasty?

METHODS

An exhaustive literature search was performed using MEDLINE-Ovid, Web of Science, and Google Scholar. The following search terms were utilized: “total knee arthroplasty” OR
“total knee replacement” AND “tranexamic acid.” The bibliographies of identified articles were searched for potential eligible reports. Inclusion and exclusion criteria were then applied.

Inclusion criteria consisted of randomized studies, patients who underwent primary, unilateral total knee arthroplasty, intravenous tranexamic acid compared to topical or intra-articular tranexamic acid, and reported outcomes including total blood loss, blood transfusion rates, and thromboembolic event rates. Additional inclusion criteria required studies in English, published within the last five years, and involving humans only. Studies were excluded if they if they addressed TXA therapy in additional orthopedic surgeries (such as total hip arthroplasty), or addressed other TXA methods of administration, beyond topical or IV. The quality of evidence was assessed using a system known as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). GRADE is a method used to assess the quality of evidence and decide whether to recommend an intervention. GRADE differs from other appraisal tools because it separates quality of evidence and strength of recommendation, the quality of evidence is assessed for each outcome, and studies can be ‘upgraded’ or ‘downgraded’ if they meet or fail to meet certain criteria.

RESULTS

In the initial search, there were 194 articles for review. After eliminating duplicates and screening for relevant articles using inclusion and exclusion criteria, there were a total of four relevant studies. Of the included studies, all were randomized, controlled studies in English and all were published after 2012.

All participants in the study were adults, with mean ages ranging from 64.8 to 71.8. All patients were diagnosed with osteoarthritis (OA) and underwent primary, unilateral TKA (Table 2). Doses of topical TXA ranged from 1.5 g to 3 g, all in 100 mL of normal saline (NS). Topical
TXA was administered either topically as a TXA wash before closure of the surgical incision, or through a non-clamped drain during or immediately after closure. Doses of IV TXA ranged from 1.5 g to 15 g, and were given in single-dose to triple-dose pre-op, intra-op, and post-op (Table 3).

Gomez-Barrena et al

This was a single-center, double-blind, randomized, controlled clinical trial\(^\text{16}\) that compared topical intra-articular TXA with two IV doses of TXA. The authors were looking at blood transfusion rate as their primary outcome. Secondary outcomes included but were not limited to blood loss (measured through a drain), change in hemoglobin (Hb) levels (pre-op to post-op), and thromboembolic events.\(^\text{16}\)

The authors started with all adult patients diagnosed with osteoarthritis who were scheduled to undergo primary, unilateral total knee replacement with cemented implants from January to October 2013 at La Paz Hospital in Cantoblanco, Madrid, Spain. Excluded from the study were patients who did not have written informed consent, allergy to TXA, major comorbidities, coagulopathy, history of arterial or venous thromboembolic disease, hematologic disorders, retinopathy, refusal of blood products, pregnancy, breastfeeding, or participation in another clinical trial during the last year.\(^\text{16}\) After meeting criteria, 78 patients were randomly allocated, 39 to an experimental group and 39 to a control group. A research statistician who used sequentially numbered opaque sealed envelopes, which were kept by research personnel until the day of surgery, organized group assignments. Envelopes were opened just prior to each surgery, and an uninvolved research anesthesiologist and pharmacist prepared the assigned study medication and placebo. Patients, surgeons, and health-care personnel involved in patient treatment and evaluation were blinded to group allocation throughout the entire study.\(^\text{16}\)
The average age of patients in the experimental group was 70.1, and 71.8 in the control group (Table 2). There were 26 female patients and 13 males in the experimental group. The control group consisted of 25 females and 14 males. There were no significant differences between the groups with respect to weight, height, body mass index, ASA (American Society of Anesthesiologists) status, preoperative lab results, or surgical characteristics.12

The experimental group received a topical intra-articular dose of 3 g TXA in 100 ml saline (Table 3). Half of the volume was used to irrigate the surgical wound before closure, and the remaining half was administered intra-articularly through a drain tube after closure. The experimental group also received 100 ml of IV placebo saline solution 15 to 20 minutes before tourniquet release and 100 ml 3 hours later. Patients in the control group received an IV infusion of 100 ml of saline containing 15 mg/kg of TXA in the same aforementioned IV schedule. Additionally, the control group also received a topical intra-articular placebo.16

Blood loss was measured through a drain at 3 and 24 hours. Postoperative hemoglobin level was measured at 24 hours, 48 hours, and approximately 5 days. While in the hospital, patients were examined daily for clinical suspicion of DVT, and a Doppler ultrasound was performed when there was clinical suspicion of DVT. Blood transfusion thresholds were set for patients with a hemoglobin level <8.0 g/dl who were asymptomatic, or <10.0 g/dl with symptoms.16

No patients were lost or excluded during follow-up in this study. No transfusion was performed in either group (Table 4). Total drain blood loss in the experimental group and control group was 475.9 mL and 465.2 mL, respectively. Maximum post-operative hemoglobin drop was -3.4 in the experimental group, and -3.1 in the control group. No pulmonary embolism (PE) was noted in either group. Two patients in the experimental group had a clinical suspicion of DVT.
One had a negative Doppler, and the other had Doppler confirmation of a superficial venous thrombosis, which was successfully treated with enoxaparin.16

The authors of this study concluded that topical administration of TXA was not inferior to IV administration of TXA for patients undergoing primary TKA. They further assert that both regimens were equally safe and effective with respect to decreasing blood loss, blood transfusion rates, and thromboembolic events. The authors do recognize that their study lacked a placebo group, however; they note that the use of placebo would pose ethical issues regarding patient health and surgical success.16

Patel et al

This was a single center, single surgeon, prospective, randomized study17 that compared efficacy and safety profiles of IV versus topical TXA in patients undergoing primary, unilateral total knee arthroplasty within a nine month period. For a primary outcome, authors were most interested in the maximum difference between preoperative and postoperative hemoglobin. Secondary outcomes included but were not limited to: total drain output, frequency of transfusion, and rate of DVT or PE.17

A total of 145 patients with a diagnosis of osteoarthritis underwent primary TKAs at the Jewish Hospital/Kentucky One Health, Louisville, KY. Of those patients, 100 consented to the study. Exclusion criteria for all patients included TKA for secondary osteoarthritis (eg, rheumatoid arthritis, gouty arthritis), simultaneous bilateral TKA, cardiovascular conditions, thromboembolic conditions, clotting disorders, religious objection to blood transfusion, preoperative hemoglobin >15.0 g/dl, allergy to TXA, and pregnancy.13 A total of 89 patients remained after criteria was applied, with 47 patients randomized to the topical group and 42 patients to the IV group. Patients were randomized to their respective groups using Excel’s
randomization generator. The surgeon and anesthesiologist were not blinded to the treatment groups due to the different routes of administration. However, postoperative nursing staff was blinded to group allocation.\(^{17}\)

The average age of patients in the topical group was 64.8, and 64.9 in the IV group (Table 2). The number of males and females in the topical group was 13 and 34, respectively. The IV group included 10 males and 32 females. There were no statistically significant differences between the two groups with regard to BMI, tourniquet time, or ASA status.\(^{17}\)

The IV TXA group received one IV 10 mg/kg dose of TXA 10 minutes prior to tourniquet release (Table 2). The topical group received 2.0 g TXA in 100 mL of normal saline, which was bathed in the surgical site and allowed to sit undisturbed for 2 minutes prior to tourniquet deflation. All patients received one deep and one superficial drain, and total drain outputs were measured on post-operative day (POD) 2. Postoperative hemoglobin was measured in morning of POD #1, 2, and 3, which were then compared to preoperative Hb. Guidelines for blood transfusion were patients with Hb <8 g/dl with symptoms. Patients were monitored daily for clinical suspicion of DVT/PE and received radiological studies if warranted.\(^{17}\)

No patients were lost or excluded during follow-up in this study. One patient in the topical group required blood transfusion (Table 3). The patient received preoperative clearance but was anemic prior to surgery with hemoglobin of 10.8. She was given 2 units of PRBCs on POD 3, after which time she experienced no further symptoms or complications. The total drain blood loss in the topical group was 630.2 mL and 558.7 mL in the IV group. Maximum Hb drop in the topical and IV group was -3.42 mg/dl and -3.06 mg/dl, respectively. There were no patients with DVT or PE, however; four patients in the IV group and two patients in the topical group received ultrasound (US) studies for DVT, which all showed negative results.\(^{17}\)
The authors of this study concluded that topical administration of TXA has similar efficacy and safety profile to IV TXA in reducing blood loss following primary, unilateral TKA. The authors do recognize that their study failed to address functional outcomes of the two methods of administration. They also admitted that a longer follow-up period, beyond an average of 18.3 weeks, might be required to adequately compare the two groups.\textsuperscript{17}

**Soni et al**

This was a single surgeon, randomized study\textsuperscript{18} that compared the results of intravenous versus intra-articular, topical administration of TXA in perioperative blood loss in TKA surgery. The authors looked at total drain blood loss, maximum Hb drop from preoperative and postoperative lab values, frequency of transfusion, and incidence of DVT or PE.

A total of 80 patients with a diagnosis of osteoarthritis were scheduled to undergo primary TKA at a hospital in India. All 80 patients met eligibility criteria for the study. Exclusion criteria was as follows: known allergy to TXA, preoperative use of anticoagulants within 7 days, history or arterial or venous thromboembolic disease, fibrinolytic disorder, and renal or hepatic dysfunction. Patients were randomly divided into two groups. Group 1 contained 40 patients who received IV TXA and group 2 contained 40 patients who received intra-articular TXA. Patients were randomly divided into these groups using computer derived random charts. There was no mention of blinding patients or staff in this study.\textsuperscript{18}

The average age of patients was 69.05 in IV group and 69.45 in topical group (Table 2). The number of males and females in IV group was 19 and 21, respectively. There were 17 males and 23 females in topical group. There was no significant difference in preoperative Hb between the two groups.\textsuperscript{18}
The intravenous group received three 10 mg/kg doses of TXA. The first dose was given 20 minutes before tourniquet was applied. The second dose was administered intraoperatively and 15 min before deflation of the tourniquet, and the final dose was given 3 hours after the intra-operative dose (Table 3). For the topical group, 3 g of TXA diluted in 100 ml of normal saline was applied in the intra-articular space, after cementing of the implants and before tourniquet release. At least 5 minutes of contact was allowed. Postoperative protocol was the same for all patients. Total drain output was recorded at 48 hours; Hb was recorded after 48 hours of surgery. Blood transfusion protocol was Hb <8 mg/dl. The authors state that patients were monitored for thromboembolic complications for 6 weeks postoperatively.18

There were no reports of patients lost to follow-up. Three patients in the IV group and four patients in the topical group received blood transfusions of 1 unit each. There were no adverse thromboembolic events reported in the study. Total drain blood loss in the IV group was 409.50 ml and 386.50 ml in the topical group (Table 4). Maximum Hb fall in the IV group was -2.42 mg/dl and -2.21 mg/dl in the topical group.18

The authors reported that there was no significant difference in Hb fall, blood drain output, transfusion rates, or safety profiles between the two groups. They concluded that intra-articular TXA is as effective as three doses of IV TXA in preventing blood loss during TKA. The authors admit that they did not screen for thromboembolic events in their study but state that clinically they did not observe any symptoms among their patient groups. They also believe that their sample size is small and that a larger study is indicated to yield more thorough and applicable results.18
This was a prospective, randomized, placebo controlled study\textsuperscript{19} designed to determine if topical or IV administration of TXA is more effective in controlling hemodynamic stability after TKA. Outcome measures included but were not limited to blood loss during surgery, difference between preoperative and postoperative hemoglobin levels, frequency of transfusion, and complications of DVT or PE.

A total of 150 patients between the ages of 55 and 80 years old with diagnoses of osteoarthritis underwent TKAs at hospitals in South Korea. All 150 patients met eligibility criteria for the study. Exclusion criteria was patients with any cardiovascular problems, cerebrovascular accident (CVA) conditions, thromboembolic disorders, or those showing a deteriorating disorder.\textsuperscript{19} Fifty patients were randomly allocated to the IV group, 50 patients to the intra-articular group, and 50 patients to the placebo group. Patients were allocated to each group using a random number list. There is no mention of blinding patients or staff in this study.\textsuperscript{19}

The average age of patients in the IV group was 66.8 and 67.5 in the intra-articular group (Table 2). The number of males and females in the topical group was 5 and 45 respectively. There were 6 males and 44 females in the IV group. There was no significant difference in BMI, preoperative flexion/contraction, skin incision, or operation time between the two groups.\textsuperscript{19}

Patients in the IV group received 1.5 g of TXA in 100 ml of saline, which was administered immediately following closure of surgical site. The intra-articular group received 1.5 g TXA in 100 ml of saline injected directly into the joint cavity while suturing (Table 3). All patients received two intra-articular drains, which were removed at 24 hours after the drainage amount was recorded. Hb levels were recorded preoperatively and postoperatively, and the
greatest Hb was calculated. Blood transfusion protocol was set at <8 g/dl or <10 g/dl with symptoms.²⁹

There were no reports of patients lost to follow-up. Ten patients in the topical group and 17 in the IV group required postoperative transfusions (Table 4). The average amount of transfused PRBCs in the topical and intravenous group was 129.6 ml and 273.6 ml, respectively. There were three reported cases of DVT in the topical group and none in the IV group. All patients with DVT were treated and experienced no further complications. Total drain blood loss was not recorded in this study. Maximum Hb fall in the topical group was -1.8 and -1.6 in the IV group.²⁹

Of note are study results for the placebo group, who received an equal volume of 100 ml normal saline intravenously, as well as a 100 ml of saline directly into the knee joint cavity while suturing. Results for the placebo group included a maximum Hb fall of 2.0 mg/dl. Forty-seven placebo patients received blood transfusions; averaging 920.8 ml of PRBCs. Mean blood loss for the placebo group during surgery was 833 ml, compared to 528 ml and 426 ml in the intravenous and intra-articular groups respectively.

The authors of this study concluded that the intra-articular injection of TXA seemed to be more effective than IV injection in reducing blood loss and transfusion frequency in patients undergoing TKA. The authors admit that their study, while large, still lacked enough patients to prove statistical significance. They further admit that all patients in their study underwent TKA using extramedullary alignment technique by a single surgeon thus, it would be impossible to compare the findings in this study with those who used a more conventional TKA approach. The authors also recognize that there was no formal observation or recording of patient symptoms or recovery beyond the observational time frame of this study.
DISCUSSION

Tranexamic acid, an antifibrinolytic drug, has been routinely used to prevent perioperative bleeding in patients undergoing TKA. The effectiveness of IV TXA in orthopedic surgery has been well researched. However, there remains concern regarding the systemic absorption and sequelae of IV TXA. Intra-articular application of TXA is considered to be a safer method of administration because it works directly at the surgical site and systemic absorption is not as significant. Thus, the question addressed in this review is if topical TXA is as safe and effective as IV TXA in controlling blood loss in patients undergoing TKA.

Analysis of four randomized clinical trials showed no significant differences in total drain blood loss, postoperative Hb drop, frequency of transfusion, or thromboembolic complications when comparing topical TXA and IV TXA in primary, unilateral TKA (Table 4). In regards to total drain blood loss, there were three of four studies that reported on this outcome. In two of the studies the IV groups showed slightly less volume loss, ranging between 71.5 and 10.7 ml when compared to topical groups. Maximum postoperative Hb drop in three of the studies favored the IV groups, but only by a difference of 0.2 to 0.36 mg/dl. Interestingly, when comparing all four studies, there were four more patients in the IV groups who received blood transfusions when compared to topical groups. Lastly, while DVT and PE were uncommon across all studies, there were three reported DVTs among patients in the topical group of Seo et al. However, it should be mentioned that there was uncertainty surrounding DVT and PE screening in all four studies. All four studies evaluated patients with clinical symptoms of DVT and PE, and provided no screening for asymptomatic patients. Therefore, it is difficult to draw an accurate conclusion in regards to the thromboembolic events.
It seems that the observed outcomes discussed above do not reach the level of major clinical importance. As such, topical TXA could be a good option for patients at higher risk for thromboembolic events, or patients where IV TXA use is cautioned or contraindicated.

There were limitations of the studies reviewed. Firstly, the quality of each study differs. Soni et al\textsuperscript{18} and Seo et al\textsuperscript{19} were lower quality randomized trials, due to lack of information on blinding of participants and personnel. The remaining two studies\textsuperscript{16,17} were moderate-to-high quality. Secondly, not all reporting was standardized across the four trials,\textsuperscript{16,17,18,19} making it difficult to accurately compare data points. As a result, this review was limited to four common outcomes, when there were in fact many other outcomes of interest. Third, further studies should include functional outcomes data. While follow-up was substantial for the outcomes of interest, there was a lack of relevant data in regards to quality of life post TKA. Finally, all four trials\textsuperscript{16,17,18,19} excluded high-risk patients, such as those with cardiac history or history of thromboembolic events. Given the fact that the average age of TKA patients is 50 to 80 years old with comorbidities, the results and conclusions listed here should be used taken with caution in clinical practice. Medical providers should continue to evaluate each patient individually for contraindications to the use of TXA.

Worth noting are the role of placebo groups in these four clinical trials. Seo et al\textsuperscript{19} implemented a placebo group in their study design, and the results compared to both the IV and TXA groups are significant. Forty-seven of the 50 patients in the placebo group received blood transfusions, compared to 10 patients in the topical group and 17 in the IV group. Furthermore, mean blood loss during surgery was approximately 300 ml more than either the topical or IV groups. Gomez-Barrena et al\textsuperscript{16} chose not to add a placebo group to their study based on ethical
issues that have been raised as a result of prior TXA studies. These studies illustrated the likelihood of increased risk of transfusion among patients in the placebo arm.

It is advised that future studies not include a placebo group due to the unethical nature of placing patients at risk of increased blood loss and transfusion rates. Secondly, future studies should include patients with significant comorbidities, or those who are considered high risk so that the safety profile of TXA can be more accurately defined. Thirdly, functional outcomes and quality of life should be measured. By incorporating a longer follow-up period, the lasting effects of TXA administration, both IV and topical, could be delineated. Future studies also need a more consistent and reliable method to screen patients for DVT or PE, beyond the use of clinical suspicion. Finally, a shared drawback in regards to fully assessing safety of topical TXA of all four of the studies discussed above was their small sample size. Studies with more patients and improved methods are needed to conclusively define the optimal regimen of TXA in primary TKA.

CONCLUSION

In conclusion, the results of this review demonstrate that the topical administration of tranexamic has similar efficacy and safety profile to that of intravenous tranexamic acid in reducing blood loss during total knee arthroplasty. With respect to avoiding blood transfusions, both regimens were equally efficacious and safe. Additionally, both regimens equally controlled blood loss, without complications. Considering topical TXA works directly at the surgical site and has markedly decreased systemic absorption, topical application could be a more rational choice. Medical providers may want to choose the topical route of administration for patients who are poor candidates for intravenous TXA, such as those with renal insufficiency, history of previous DVT, and cerebrovascular and cardiac disease.


### Table 1: Quality Assessment of Four Reviewed Studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
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<td></td>
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<td>Limitations</td>
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<td>Total Drain Output</td>
<td>3</td>
<td>RCT, cohort</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Max Hemoglobin Drop</td>
<td>4</td>
<td>RCT, cohort</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Blood Units Transfused</td>
<td>4</td>
<td>RCT, cohort</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Thromboembolic Events</td>
<td>4</td>
<td>RCT, cohort</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

\(^a\)Lack of blinding  
\(^b\)Small sample size

### Table 2: General Characteristics of Four Reviewed Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year of Publication</th>
<th>Number of Patients</th>
<th>Country</th>
<th>Patient Age</th>
<th>Unilat primary TKA</th>
<th>Gender</th>
<th>FU</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Barrena, E</td>
<td>2014</td>
<td>39</td>
<td>Spain</td>
<td>70.1</td>
<td>All</td>
<td>M: 13</td>
<td>4</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39</td>
<td></td>
<td>71.8</td>
<td></td>
<td>M: 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel JN</td>
<td>2014</td>
<td>47</td>
<td>USA</td>
<td>64.8</td>
<td>All</td>
<td>M: 13</td>
<td>4.6 mos</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td></td>
<td>64.9</td>
<td></td>
<td>M: 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soni A</td>
<td>2014</td>
<td>40</td>
<td>India</td>
<td>69.45</td>
<td>All</td>
<td>M: 17</td>
<td>1.5 mos</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td>69.05</td>
<td></td>
<td>M: 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seo JG</td>
<td>2013</td>
<td>50</td>
<td>South Korea</td>
<td>67.5</td>
<td>All</td>
<td>M: 5</td>
<td>2 mos</td>
<td>RCT</td>
</tr>
<tr>
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<td></td>
<td>50</td>
<td></td>
<td>66.8</td>
<td></td>
<td>M: 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>Intervention</td>
<td>Technique</td>
<td>Pneumatic Tourniquet</td>
<td>Transfusion Protocol</td>
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<tr>
<td>-------------------</td>
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<td>----------------------</td>
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</tr>
</tbody>
</table>
| Gomez-Barrena, E  | 3 g/100mL NS | Two doses of 15 mg/kg | Half topical before closure, half admin through drain during closure | Yes | Hb<8.0 g/dL OR Hb<10 g/dL + sx 
| Patel             | 2 g TXA/100mL NS | One dose of 10mg/kg | 2 min topical before tourniquet release, with drain | One dose intra-op | Yes | Hb<8.0 g/dL + sx 
| Soni A            | 3 g TXA/100mL NS | 3doses of 10mg/kg | 1.5g TXA; IA injected through drain after closure | One dose PO, IO, PO | Yes | Hb<8.0 g/dL 
| Seo JG            | 1.5g TXA/100mL NS | 1.5 g TXA/100mL NS | IA while suturing w/non-clamp drain | One dose post-op | Yes | Hb<8.0 g/dL OR Hb<10 g/dL + sx |
### Table 4: Summary of Findings

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number of pts</th>
<th>Total Drain Blood Loss (ml)</th>
<th>Max Postop Hb Drop (mg/dl)</th>
<th>Number of patients who received post-op blood transfusion</th>
<th>DVT</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Barrena, E</td>
<td>39</td>
<td>475.9</td>
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<td>Patel</td>
<td>47</td>
<td>630.2</td>
<td>-3.42</td>
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<td>0</td>
</tr>
<tr>
<td>Soni A</td>
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<td>386.50</td>
<td>-2.21</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seo JG</td>
<td>50</td>
<td>-</td>
<td>-1.8</td>
<td>10</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>