HHS Public Access

Author manuscript

Am J Orthop (Belle Mead NJ). Author manuscript; available in PMC 2018 February 19.

Published in final edited form as:

Am J Orthop (Belle Mead NJ). 2016 ; 45(7): E439–E443.

Comparing Cost, Efficacy, and Safety of Intravenous and Topical Tranexamic Acid in Total Hip and Knee Arthroplasty

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Abstract

We conducted a study to compare the cost, efficacy, and safety of intravenous (IV) tranexamic acid (TXA) and topical TXA in primary total hip arthroplasty (THA) and total knee arthroplasty (TKA). We retrospectively reviewed the cases of 291 patients who received either IV TXA or topical TXA before and after surgery.

Significant differences favored topical TXA in reducing the postoperative decrease in hemoglobin levels in THA ($P = .031$) and TKA ($P = .015$) and calculated blood loss in TKA ($P = .019$). The groups did not differ in transfusion requirements for either THA or TKA. Topical TXA cost significantly more than IV TXA ($P \leq .0001$).

The benefits of using topical TXA to reduce the perioperative decrease in hemoglobin levels come with increased cost.

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) can be associated with significant blood loss that in some cases requires transfusion. The incidence of transfusion ranges from 16% to 37% in patients who undergo THA and from 11% to 21% in patients who undergo TKA.[1–3] Allogeneic blood transfusions have been associated with several risks (transfusion-related acute lung injury, hemolytic reactions, immunologic reactions, fluid overload, renal failure, infections), increased cost, and longer hospital length of stay (LOS).[4–7] With improved patient outcomes the ultimate goal, blood-conserving strategies designed to decrease blood loss and transfusions have been adopted as a standard in successful joint replacement programs.

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Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

Tranexamic acid (TXA), an antifibrinolytic agent, has become a major component of blood conservation management after THA and TKA. TXA stabilizes clots at the surgical site by inhibiting plasminogen activation and thereby blocking fibrinolysis.[8] The literature supports intravenous (IV) TXA as effective in significantly reducing blood loss and transfusion rates in elective THA and TKA.[9,10] However, data on increased risk of thrombotic events with IV TXA in both THA and TKA are conflicting.[11,12] Topical TXA is thought to have an advantage over IV TXA in that it provides a higher concentration of drug at the surgical site and is associated with little systemic absorption.[2,13]

Recent prospective randomized studies have compared the efficacy and safety of IV and topical TXA in THA and TKA.[9,14] However, controversy remains because relatively few studies have compared these 2 routes of administration. In addition, healthcare–associated costs have come under increased scrutiny, and the cost of these treatments should be considered. More research is needed to determine which application is most efficacious and cost-conscious and poses the least risk to patients. Therefore, we conducted a study to compare the cost, efficacy, and safety of IV and topical TXA in primary THA and TKA.

Materials and Methods

Our Institutional Review Board approved this study. Patients who were age 18 years or older, underwent primary THA or TKA, and received IV or topical TXA between August 2013 and September 2014 were considered eligible for the study. For both groups, exclusion criteria were trauma service admission, TXA hypersensitivity, pregnancy, and concomitant use of IV and topical TXA.

We collected demographic data (age, sex, weight, height, body mass index), noted all transfusions of packed red blood cells, and recorded preoperative and postoperative hemoglobin (Hgb) levels and surgical drain outputs. We also recorded any complications that occurred within 90 days after surgery: deep vein thrombosis (DVT), pulmonary embolism (PE), cardiac events, cerebrovascular events, and wound drainage. Wound drainage was defined as readmission to hospital or return to operating room for wound drainage caused by infection or hematoma. Postoperative care (disposition, LOS, follow-up) was documented. Average cost of both IV and topical TXA administration was calculated using average wholesale price.

Use of IV TXA and use of topical TXA were compared in both THA and TKA. Patients in the IV TXA group received TXA in two 10-mg/kg doses with a maximum of 1 g per dose. The first IV dose was given before the incision, and the second was given 3 hours after the first. Patients in the topical TXA group underwent direct irrigation with 3 g of TXA in 100 mL of normal saline at the surgical site after closure of the deep fascia in THA and after closure of the knee arthrotomy in TKA. The drain remained occluded for 30 minutes after surgery. The wound was irrigated with topical TXA before wound closure in the THA group and before tourniquet release in the TKA group. TXA dosing was based on institutional formulary dosing restrictions and was consistent with best practices and current literature.[3,9,14,15]

Primary outcomes measured for each cohort and treatment arm were Hgb levels (difference between preoperative levels and lowest postoperative levels 24 hours after surgery), blood loss, transfusion rates, and cost. Secondary outcomes were LOS and complications that occurred within 90 days after surgery (DVT, PE, cardiac events, cerebrovascular events, wound drainage).

Calculated blood loss was determined with equations described by Konig and colleagues,[3] Good and colleagues,[16] and Nadler and colleagues.[17] Total calculated blood loss was based on the difference in Hgb levels before surgery and the lowest Hgb levels 24 hours after surgery:

$$\begin{aligned}&\text{Blood loss (mL)} = 100\,\text{mL/dL} \times \text{Hgb}_{\text{loss}}/\text{Hgb}_{\text{i}}\\&\text{Hgb}_{\text{loss}} = \text{BV} \times (\text{Hgb}_{\text{i}} - \text{Hgb}_{\text{e}}) \times 10\,\text{dL/L} + \text{Hgb}_{\text{t}}\\&= 0.3669 \times \text{Height}^3\,\text{(m)} + 0.03219 \times \text{Weight (kg)} + 0.6041\,\text{(for men)}\\&= 0.3561 \times \text{Height}^3\,\text{(m)} + 0.03308 \times \text{Weight (kg)} + 0.1833\,\text{(for women)}\end{aligned}$$

where Hgb_{i} is the Hgb concentration (g/dL) before surgery, Hgb_{e} is the lowest Hgb concentration (g/dL) 24 hours after surgery, Hgb_{t} is the total amount (g) of allogeneic Hgb transfused, and BV is the estimated total body blood volume (L).[17] As Hgb concentrations after blood transfusions were compared in this study, the Hgb_{t} variable was removed from the equation. Based on Hgb decrease data in a study that compared IV and topical TXA in TKA,[14] we determined that a sample size of least 140 patients (70 in each cohort) was needed in order to have 80% power to detect a difference in Hgb decrease of 0.36 g/dL in IV and topical TXA.

All data were reported with descriptive statistics. Frequencies and percentages were reported for categorical variables. Means and standard deviations were reported for continuous variables. The groups of continuous data were compared with unpaired Student *t* tests and 1-way analysis of variance. Comparisons among groups of categorical data were analyzed with Fisher exact tests. Statistical significance was set at $P < .05$.

Results

Data were collected on 291 patients (156 THA, 135 TKA). There was a significant ($P = .044$) sex difference in the THA group: more men in the topical TXA subgroup and more women in the IV TXA subgroup. Other patient demographics were similarly matched with respect to age, height, weight, and body mass index (Table 1). The primary outcomes (differences in cost, Hgb decrease, estimated blood loss, calculated blood loss, and transfusions) are listed in Table 2. In the THA group, mean (SD) Hgb change was significantly ($P = .031$) higher with IV TXA, 3.33 (1.02) g/dL, than with topical TXA, 2.89 (1.44) g/dL, and the cost of topical TXA ($2100) was significantly ($P \leq .0001$) higher than the cost of IV TXA ($1161). There were no differences in calculated blood loss, estimated blood loss, or transfusion rates. In the TKA group, calculated blood loss was significantly ($P = .019$) higher with IV TXA (1084.2 mL) than with topical TXA (859.6 mL), mean (SD) Hgb change was significantly ($P = .015$) higher with IV TXA, 2.35 (0.99) g/dL, than with

topical TXA, 1.93 (0.90) g/dL, and the cost of topical TXA ($2100) was significantly ($P \leq .0001$) higher than the cost of IV TXA ($1271). There were no differences in estimated blood loss or transfusion rates.

The secondary outcomes (differences in complications and LOS) are listed in Table 3. In the THA group, postoperative cardiac events occurred in 3 (6%) of the 48 patients in the topical TXA subgroup and in none of the patients in the IV TXA subgroup ($P = .007$). There were no differences in other complications (DVT, PE, cerebrovascular events, wound drainage) or LOS. In the TKA group, there were no differences in postoperative complications or LOS between the IV and topical TXA subgroups.

Discussion

TXA, an analog of the amino acid lysine, is an antifibrinolytic agent that has been used for many years to inhibit fibrin degradation.[3,18] TXA works by competitively inhibiting tissue plasminogen activation, which is elevated by the trauma of surgery, and blocking plasmin binding to fibrin.[3,19] The mechanism of action is not procoagulant, as TXA prevents fibrin breakdown and supports coagulation that is underway rather than increasing clot formation. These characteristics make the drug attractive for orthopedic joint surgery—TXA reduces postoperative blood loss in patients who need fibrinolysis suppressed in order to maintain homeostasis without increasing the risk of venous thromboembolism. IV TXA has been well studied, which supports its efficacy profile for reducing blood loss and transfusions; there are no reports of increased risk of thromboembolic events.[20–22] Despite these studies, the risk of adverse events is still a major concern, especially in patients with medical conditions that predispose them to venothrombotic events. Topical TXA has become a viable option, especially in high-risk patients, as studies have shown 70% lower systemic absorption relative to IV TXA plasma concentration.[23] Still, too few studies have compared the efficacy, safety, and cost of IV and topical TXA in both THA and TKA.

Topical TXA costs an average of $2100 per case, primarily because standard dosing is 3 g per case. Despite repeat dosing for IV TXA (first dose at incision, second dose 3 hours after first), IV TXA costs were much lower on average: $939 less for THA and $829 less for TKA. As numerous studies have outlined results similar to ours, cost-effectiveness should be considered in decisions about treatment options.

Patel and colleagues[14] reported that the efficacy of topical TXA was similar to that of IV TXA and that there were no significant differences in Hgb decrease, wound drainage, or need for transfusions after TKA. Their report conflicts with our finding significant differences favoring topical TXA for Hgb change ($P = .015$) and reduced calculated blood loss ($P = .019$) in TKA. A potential reason for these differing results is that the topical TXA doses were different (2 g in the study by Patel and colleagues,[14] 3 g in our study). Martin and colleagues[24] compared the effects of topical TXA and placebo and found a nonsignificant difference in reduced blood loss and postoperative transfusions when the drug was dosed at 2 g. Konig and colleagues[3] found that topical TXA dosed at 3 g (vs placebo) could reduce blood loss and transfusions after THA and TKA. These studies support our 3-g dose protocol for topical TXA rather than the 2-g protocol used in the study by Patel and

colleagues.[14] Our results are congruent with those of Seo and colleagues,[25] who found topical TXA superior in decreasing blood loss in TKA. Furthermore, our study is unique in that it compared costs and found topical TXA to be more expensive by almost $1000 on average.

Wei and Wei[9] concluded that IV TXA 3 g and topical TXA 3 g were equally effective in reducing total blood loss, change in hematocrit, and need for transfusion after THA. In contrast, we found a significant ($P = .031$) difference favoring topical TXA for Hgb change. The 2 studies differed in their dosing protocols: Wei and Wei[9] infused a 3-g dose, whereas we gave a maximum of two 1-g IV doses. The higher IV dose used by Wei and Wei[9] could explain why they found no difference between IV and topical TXA, whereas we did find a difference. Our study was unique in that it measured Hgb change, blood loss, and cost.

Our study included an in-depth analysis of blood loss: estimated blood loss, drain outputs, calculated blood loss, and Hgb change. The equation we used for calculated blood loss is well established and has been used in multiple studies.[3,16,17] To thoroughly assess the safety of TXA, we reviewed and documented complications that occurred within 90 days after surgery and that could be attributed to TXA. This study was adequately powered and exceeded the required sample size to detect a difference in one primary outcome measure, perioperative Hgb change, as calculated by the prestudy statistical power analysis.

Our study had several limitations. First, it was a retrospective chart review; documentation could have been incomplete or missing. Second, the study was not randomized and thus subject to drug selection bias. Third, patients were selected for topical TXA on the basis of perceived risk factors, such as prior or family history of DVT, PE, cardiac events, or cerebrovascular events. It was thought that, given the decrease in systemic absorption with topical TXA, these high-risk patients would be less likely to have a thromboembolic event. Their complex past medical histories may explain why the topical TXA group had more cardiac events. Furthermore, 1 orthopedic surgeon used topical TXA exclusively, and the other 3 used it selectively, according to risk factors. In addition, unlike TKA patients, not all THA patients received drains. This study was powered to measure a difference in perioperative Hgb change but may not have been powered to detect the statistically significant difference favoring topical TXA for calculated blood loss in TKA. In the THA group, a statistically significant difference was found for reduced Hgb decrease but not for estimated or calculated blood loss. This finding reinforces some of the disparities in measurements of the effects of blood conservation strategies. The study also lacked a placebo or control group. However, several other studies have found that both IV TXA and topical TXA are superior to placebo in decreasing blood loss, Hgb change, and transfusion requirements.[10,12,20,22] In addition, the effects of TXA are based on estimates of blood conservation and are not without their disparities.

Conclusion

The present study found that both IV TXA and topical TXA were effective in decreasing blood loss, Hgb levels, and need for transfusion after THA and TKA. Topical TXA appears to be more effective than IV TXA in preventing Hgb decrease during THA and TKA and

calculated blood loss during TKA. This increased efficacy comes with a higher cost. Thromboembolic complications were similar between groups. More studies are needed to compare the efficacy and safety profiles of topical TXA against the routine standard of IV TXA, especially in patients with perceived contraindications to IV TXA.

References

1. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999; 81(1): 2–10. [PubMed: 9973048]
2. Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty. 2014; 29(12):2452–2456. [PubMed: 24793893]
3. Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty. 2013; 28(9):1473–1476. [PubMed: 23886406]
4. Stokes ME, Ye X, Shah M, et al. Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res. 2011; 11:135. [PubMed: 21627788]
5. Lemos MJ, Healy WL. Blood transfusion in orthopaedic operations. J Bone Joint Surg Am. 1996; 78(8):1260–1270. [PubMed: 8753721]
6. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood. 2009; 113(15):3406–3417. [PubMed: 19188662]
7. Kumar A. Perioperative management of anemia: limits of blood transfusion and alternatives to it. Cleve Clin J Med. 2009; 76(suppl 4):S112–S118. [PubMed: 19880828]
8. Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. Biochim Biophys Acta. 1981; 673(1):75–85. [PubMed: 7193484]
9. Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty. 2014; 29(11):2113–2116. [PubMed: 25155138]
10. Zhang H, Chen J, Chen F, Que W. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2012; 20(9):1742–1752. [PubMed: 22065294]
11. Ido K, Neo M, Asada Y, et al. Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg. 2000; 120(9):518–520. [PubMed: 11011672]
12. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am. 2012; 94(13):1153–1159. [PubMed: 22623147]
13. Alshryda S, Mason J, Sarda P, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX-H). J Bone Joint Surg Am. 2013; 95(21):1969–1974. [PubMed: 24196467]
14. Patel JN, Spanyer JM, Smith LS, Huang J, Yakkanti MR, Malkani AL. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. J Arthroplasty. 2014; 29(8):1528–1531. [PubMed: 24768543]
15. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011; 93(12):1577–1585. [PubMed: 22161917]
16. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth. 2003; 90(5):596–599. [PubMed: 12697586]
17. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962; 51(2):224–232. [PubMed: 21936146]
18. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg. 2010; 18(3): 132–138. [PubMed: 20190103]

19. Mannucci PM. Homostatic drugs. N Engl J Med. 1998; 339(4):245–253. [PubMed: 9673304]
20. Wind TC, Barfield WR, Moskal JT. The effect of tranexamic acid on transfusion rate in primary total hip arthroplasty. J Arthroplasty. 2014; 29(2):387–389. [PubMed: 23790499]
21. Dahuja A, Dahuja G, Jaswal V, Sandhu K. A prospective study on role of tranexamic acid in reducing postoperative blood loss in total knee arthroplasty and its effect on coagulation profile. J Arthroplasty. 2014; 29(4):733–735. [PubMed: 24184325]
22. Tan J, Chen H, Liu Q, Chen C, Huang W. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res. 2013; 184(2):880–887. [PubMed: 23643299]
23. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 2010; 92(15):2503–2513. [PubMed: 21048170]
24. Martin JG, Cassatt KB, Kincaid-Cinnamon KA, Westendorf DS, Garton AS, Lemke JH. Topical administration of tranexamic acid in primary total hip and total knee arthroplasty. J Arthroplasty. 2014; 29(5):889–894. [PubMed: 24238825]
25. Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013; 21(8):1869–1874. [PubMed: 22729012]

Table 1

Patient Demographics for Primary Total Hip and Knee Arthroplasty

THA	**IV TXA (n = 108)**	**Topical TXA (n = 48)**	***P***
Sex, M/F[a]	42/66	27/21	.044
Mean (SD)			
Age, y	59 (12.9)	63 (14.4)	.086
Height, m	1.67 (0.092)	1.70 (0.107)	.068
Weight, kg	87.4 (23.1)	88.3 (24.8)	.823
BMI, kg/m^2	31.2 (7.2)	30.4 (7.5)	.534
TKA	**IV TXA (n = 83)**	**Topical TXA (n = 52)**	***P***
Sex, M/F	32/51	23/29	.577
Mean (SD)			
Age, y	62 (10.6)	63 (9. 35)	.418
Height, m	1.67 (0.114)	1.69 (0.121)	.370
Weight, kg	98 (20.9)	100 (27.1)	.621
BMI, kg/m^2	35.3 (7.46)	34.8 (7.78)	.736

Abbreviations: BMI, body mass index; IV, intravenous; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid.

[a]Significant difference.

Table 2

Primary Outcomes for Primary Total Hip and Knee Arthroplasty

THA	**IV TXA (n = 108)**	**Topical TXA (n = 48)**	***P***
Mean (SD)			
Preoperative Hgb, g/dL	13.8 (1.31)	13.7 (1.40)	.625
Postoperative Hgb, g/dL	10.5 (1.63)	10.8 (1.65)	.134
Hgb decrease, g/dL[a]	3.33 (1.02)	2.89 (1.44)	.031
Estimated blood loss, mL	509.3 (25.8)	557.3 (38.6)	.303
Calculated blood loss, mL	1287.3 (41.5)	1226 (62.2)	.418
Transfusions, n (%)	8 (7%)	5 (10%)	.538
Cost, $[a]	1161	2100	≤.0001
TKA	**IV TXA (n = 83)**	**Topical TXA (n = 52)**	***P***
Mean (SD)			
Preoperative Hgb, g/dL	13.8 (1.27)	13.8 (1.23)	.861
Postoperative Hgb, g/dL	11.5 (1.43)	11.8 (1.13)	.107
Hgb decrease, g/dL[a]	2.35 (0.988)	1.93 (0.900)	.015
Estimated blood loss, mL	101.1 (89.4)	102.6 (105.1)	.93
Calculated blood loss, mL[a]	1084.2 (605.4)	859.6 (386.6)	.019
Transfusions, n (%)	2 (2%)	1 (2%)	.26
Cost, $[a]	1271	2100	≤.0001

Abbreviations: Hgb, hemoglobin; IV, intravenous; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid.

[a]Significant difference.

Table 3

Secondary Outcomes for Primary Total Hip and Knee Arthroplasty

THA	**IV TXA (n = 108)**	**Topical TXA (n = 48)**	***P***
Complication, n (%)			
Wound drainage	8 (7%)	1 (2%)	.151
Deep vein thrombosis	0	1 (2%)	.124
Pulmonary embolism	0	0	—
Cardiac event[a]	0	3 (6%)	.007
Cerebrovascular event	0	1 (2%)	.124
Mean (SD) length of stay, d	2.7 (1.59)	2.6 (1.67)	.889
TKA	**IV TXA (n = 83)**	**Topical TXA (n = 52)**	***P***
Complication, n (%)			
Wound drainage	7 (8%)	2 (4%)	.281
Deep vein thrombosis	3 (4%)	0	.085
Pulmonary embolism	0	1 (2%)	.166
Cardiac event	0	1 (2%)	.166
Cerebrovascular event	1 (2%)	0	.322
Mean (SD) length of stay, d	2.3 (1.23)	3.2 (6.42)	.248

Abbreviations: IV, intravenous; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid.

[a]Significant difference.