# Tranexamic acid and orthopedic surgery—the search for the holy grail of blood conservation

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Over the last decade an increasing amount of literature regarding the perioperative use of tranexamic acid (TXA) for bleeding control in orthopedic surgery has been published (1-6). While clinical trials found promising results regarding the reduction of blood loss and therefore a reduced rate of blood transfusions, concerns regarding prothrombotic adverse events including deep vein thrombosis, myocardial infarction, pulmonary embolism and cerebrovascular events have continued to dampen the enthusiasm and thus recommendations for wide spread use (7).

In clinical practice, this concern has thus lead to avoidance of the use of TXA in a large group of patients. Especially those with a history of coronary artery disease and stent-implantation or those having suffered a stroke are frequently considered to be potentially at increased risk for adverse events due the potential of TXA to promote clotting. These safety concerns are based on the inhibition of fibrinolysis and as a consequence the interference of TXA with the coagulation cascade. So far, there is a lack of clinical trials large enough to not only proof efficacy but also at the same time support the safety of TXA in this patient population. This dilemma is further complicated by the fact that the groups considered at risk for thromboembolic complications may be the same as those at increased risk for ischemic adversities in the setting of increased blood loss. Thus the question arises if in the setting of competing pathophysiologic mechanisms "at risk" patients could "in sum" benefit from the use of TXA, as anemia and higher blood transfusion rates are considered predictors for a worse cardiovascular outcome after surgery (8-10).

In this contentious environment, researchers have tried to address the question of safety in various ways. Given the problems faced with designing clinical trials with large enough sample sizes to identify differences in low incidence outcomes, investigators have turned to population-based administrative datasets in recent years to answer important questions such as those concerning outcomes in various clinical settings. Despite limitations including their retrospective nature, the availability of limited clinical details and the risk of cofounding, considerable benefits include the very large sample sizes providing results from "real world" practice among patient populations from hundreds of hospitals that are not subject to strict and often artificial inclusion and exclusion criteria of perspective, randomized trials.

Poeran *et al*. recently explored these advantages in the context of TXA administration in major joint arthroplasty. The group showed that the use of TXA in patients undergoing total hip or knee arthroplasty was not only effective but also potentially safe. Among 872,416 patients from 510 hospitals in the United States the authors reported reduced odds for blood transfusion by more than 60%. Patients who received TXA had lower rates of the following outcomes: allogeneic or autologous transfusion (7.7% *vs*. 20.1%, P<0.001), thromboembolic complications (0.6% *vs*. 0.8%, P=0.0057), overall complications (1.9% *vs*. 2.6%, P<0.001), need for mechanical ventilation (0.1% *vs*. 0.2%, P=0.0003), and admission to an intensive care unit (3.1% *vs*. 7.5%, P<0.001). Also, median cost of hospital stay was lower for TXA recipients, P<0.001 (3). Importantly,

while showing clear efficacy, no significantly increased risk for complications including for thromboembolic events (odds ratio 0.85 to 1.02), acute renal failure (0.70 to 1.11)—an ongoing concern with the use of antifibrinolytics since the aprotinine was taken off the market—and overall complications (0.75 to 0.98) was found (3). Overall complications included among others the event of acute myocardial infarction. This is important as the pathogenesis of a perioperative myocardial infarction is driven by insufficient myocardial oxygen supply, rupture of coronary artery plaques as well as platelet activation. If surgical bleeding is reduced by the use of TXA, tachycardia and a decrease in hemoglobin responsible for insufficient myocardial oxygen supply might be prevented (11). In this context, preliminary data using the same dataset, may suggest that no increased risk was found among those with a history of coronary artery disease, but more research is clearly needed in this arena. While providing these data, the authors also pointed out that TXA, although increasing in popularity was used in only 11.2% of all patients studied in 2012. Further, they noted, that while TXA seems to be safe on a population basis, more research into its effects among subpopulations is needed.

An additional approach to address safety issues with TXA focuses on attempts to reduce systemic levels of the drug by topical application at the surgical site. In this context, Gomez-Barrena *et al*. recently published results of a clinical trial in The Journal of Bone and Joint Surgery regarding the use of topical TXA compared to an intravenous application in patients undergoing primary total knee arthroplasty (6). The authors performed a phase III, single center, double-blind, randomized, controlled trial to proof the non-inferiority of topical TXA (3 g of TXA in 100 mL saline solution) with two intravenous doses of TXA (15 mg/kg in 100 mL saline solution), one dose before tourniquet release and another 3 hours after surgery. The primary outcome was defined as the need for postoperative blood transfusion. Secondary outcomes included blood loss through the drain at 3 and 24 hours, the postoperative hemoglobin level at 24 hours, 48 hours, and approximately 5 days after surgery, estimated blood loss (determined by the difference between the preoperative hemoglobin level and the lowest postoperative level). Moreover, complications and severe adverse events, the length of stay in the hospital, and postoperative changes in active range of motion of the knee were included in their evaluation. The sample size was calculated for a maximum expected transfusion rate of 5%, being aware of a zero transfusion rate from prior

studies in total knee arthroplasty (12-14). For the primary end point, a total of 39 patients per arm provided 99% power to demonstrate non-inferiority at a one-sided level of significance of 0.025. No significant statistical difference was found for the primary end point (blood transfusion rate was 0 for both groups), neither for the secondary efficacy outcomes (drain blood loss at 3 and 24 hours, estimated blood loss 48 hours and 5 days after surgery). In addition, decreases in hemoglobin levels at 24 hours, 48 hours, and approximately 5 days were similar in both groups (–2.3, –3.1, and –2.0 g/dL in the topical intra-articular TXA group, and –2.5, –3.4, and –2.6 g/dL in the IV TXA group, respectively).

The approach using topical TXA may provide an elegant way to overcome the problem of potentially increased systemic clotting risk, especially in the patient population of concern discussed above. However, while the hypothesis that systemic TXA levels could be reduced compared to the scenario where TXA is administered intravenously, thus leading to a reduction in systemic clotting risk warrants further investigation, both because (I) it remains unknown which levels can be considered safe and (II) pharmacodynamic data derived from large patient samples are rare. Interestingly, some evidence suggests that topically administered TXA in doses of 1.5 and 3 g can reach mean plasma levels of 4.5 and 8.5 mg/L (12). Plasma concentrations one hour after intravenous administration of 10 mg/kg TXA have produced mean values of 18 mg/L (15). While topically administered TXA seems therefore to result in lower plasma concentrations, one must consider that levels between 5-10 mg/L are considered to be therapeutically active (16), thus making it at least in theory possible that even the topical approach has systemic effects and potentially side effects. In addition, the possibility that a higher local concentration of TXA when administered topically could lead to increased local complications at the operative site should also be considered and investigated. Several clinical trials and meta-analysis have shown the benefit of intravenous TXA compared with placebo in orthopedic surgery. More recently, a meta-analysis by Zhao-Yu *et al*. showed no significant differences for intra-articular use of TXA in patients undergoing total knee arthroplasty compared to placebo in regard of deep vein thrombosis or pulmonary embolism (17). However, Gomez-Barrena *et al*. could show the non-inferiority of topically administered TXA (3 g TXA in 100 mL saline) compared to a regime using two times 15 mg/kg of TXA intravenously in patients undergoing total knee arthroplasty. This leads the

latter author to state that continuing to use a placebo group is raising ethical questions with regards to the published literature.

One other important aspect seems to be the economical advantage of TXA in the orthopedic patient population. Its ability to reduce the overall hospital costs associated with total hip or knee arthroplasty seems promising. In addition to the drugs low cost (approximately $6 per vial), Poeran *et al.* could show a significant reduction in median hospital costs in patients receiving TXA (3). With regards to the increase in total joint arthroplasties in the United States and elsewhere over the next decades, an economically efficient approach to joint arthroplasty procedures is indispensible (18,19).

In conclusion, the overwhelming evidence to date suggests that TXA is effective in reducing blood loss and the need for blood transfusions in the setting of joint arthroplasty surgery. Data on perioperative safety are emerging and look promising, however questions remain regarding populations at risk for thromboembolic complications and thus more research is needed. In the meantime, approaches should be sought to identify the lowest possible dose and safest route of administration. Topical administration of TXA may offer benefits over the intravenous approach in terms of reducing systemic plasma levels while not affecting its effectiveness, but nevertheless adequately powered studies are needed to draw firm conclusions regarding safety. In the meantime, the use of TXA is likely to increase in popularity due to its clinical and cost benefits, however risks and benefits need to be assessed continuously as new information emerges, especially among those at risk for adverse events. A critical and frequent reassessment of available data is imperative in order to assure an evidence-based approach to the appropriate use of TXA.

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## References

1. Kagoma YK, Crowther MA, Douketis J, et al. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb Res 2009;123:687-96.
2. Gandhi R, Evans HM, Mahomed SR, et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes 2013;6:184.
3. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ 2014;349:g4829.
4. Huang F, Wu D, Ma G, et al. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. J Surg Res 2014;186:318-27.
5. Zhou XD, Tao LJ, Li J, et al. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. Arch Orthop Trauma Surg 2013;133:1017-27.
6. Gomez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, et al. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. J Bone Joint Surg Am 2014;96:1937-44.
7. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology 2006;105:1034-46.
8. Möhnle P, Snyder-Ramos SA, Miao Y, et al. Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. Intensive Care Med 2011;37:97-109.
9. Hopewell S, Omar O, Hyde C, et al. A systematic review of the effect of red blood cell transfusion on mortality: evidence from large-scale observational studies published between 2006 and 2010. BMJ Open 2013;3.
10. Koch CG, Khandwala F, Li L, et al. Persistent effect of red cell transfusion on health-related quality of life after cardiac surgery. Ann Thorac Surg 2006;82:13-20.
11. Roberts I. Scientific letter: could tranexamic acid use in surgery reduce perioperative myocardial infarction? Heart 2013;99:1785.
12. 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;92:2503-13.
13. Moráis S, Ortega-Andreu M, Rodríguez-Merchán EC, et al. Blood transfusion after primary total knee arthroplasty can be significantly minimised through a multimodal blood-loss prevention approach. Int Orthop 2014;38:347-54.
14. Ortega-Andreu M, Pérez-Chrzanowska H, Figueredo R, et al. Blood loss control with two doses of tranexamic Acid in a multimodal protocol for total knee arthroplasty. Open

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Orthop J 2011;5:44-8.

15. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol) 1980;14:41-7.

16. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005-32.

17. Zhao-Yu C, Yan G, Wei C, et al. Reduced blood loss after intra-articular tranexamic acid injection during total knee arthroplasty: a meta-analysis of the literature. Knee Surg Sports Traumatol Arthrosc 2014;22:3181-90.

18. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.

19. Kurtz SM, Ong KL, Lau E, et al. Impact of the economic downturn on total joint replacement demand in the United States: updated projections to 2021. J Bone Joint Surg Am 2014;96:624-30.