

# Topical intra-articular and intravenous tranexamic acid to reduce blood loss in total knee arthroplasty

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Submitted Jan 26, 2015. Accepted for publication Feb 06, 2015.

doi: 10.3978/j.issn.2305-5839.2015.02.25

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.02.25>

Different blood loss prevention protocols have been adopted after total knee replacement (TKR) because bleeding is a major complication of TKR and transfusions is frequently required (1). Increased bleeding has been associated with delayed recovery, increased complications, increased costs and decreased patient satisfaction.

Methods used for blood preservation are hemodilution, intraoperative and postoperative blood salvage and reinfusion, hypotensive anesthesia or epidural anesthesia, transfusion of pre-donated autologous blood, use of antifibrinolytic agents and erythropoietin. These treatments had been demonstrated to reduce postoperative blood loss in total knee arthroplasty (TKA) (2) but are associated with high costs and complications.

Obviously the most appropriate solution is to enhance hemostasis and vessels sealing at site of operation. The use of tranexamic acid (TXA) in primary TKR is today widely accepted. Several studies in the last 2 years confirm TXA efficacy for decreasing blood loss and no increased complications and costs.

Nevertheless there are concerns regarding potential risks of its use, modality and way of application, right time of infusion and above all dose of TXA applied is often different in each work.

Many RCT studies support efficacy and safety of intravenous (IV) use but there are concerns regarding IV administration of TXA in some settings, and topical application may be considered an alternative with less risk than IV use.

In a recent article published in *The Journal of Bone and Joint Surgery Am*, Gomez-Barrena and colleagues (3) compare topical intra-articular TXA with two IV doses of

TXA in preserving blood loss in patients undergoing TKA.

The objective of the present double-blind, randomized noninferiority trial was to assess the efficacy and safety of topical intra-articular application of 3 g of TXA compared with IV administration of two 15-mg/kg doses during primary unilateral TKR with cemented implants. The blood transfusion rate and drain and estimated postoperative blood loss were the efficacy end points; safety was assessed on the basis of the complications.

Authors present methods of the study satisfactorily; it is conduct in a rigorous way and statistically correct. Criteria inclusions in the study, methods of randomization and double blind analysis, surgical technique and materials are well explained. From January to October 2013, 78 patients undergoing TKR were randomized to receive either topical TXA (the experimental group, n=39) or IV TXA (the control group, n=39). No significant differences of composition features between the groups randomized were found.

No transfusion was performed in either group, confirming no inferiority for the primary efficacy end point (transfusion rate). Similarly, also for secondary efficacy end points involving blood loss there were no significant differences (in drain blood loss at 24 h or in estimated blood loss at 48 h or 5 days). Decreases in the hemoglobin level were similar in the two groups. The possibility of superiority with respect to the blood loss end points was also investigated by comparing both drain and estimated blood loss. Although non-inferiority was confirmed, no clear superiority was detected.

The mean length of stay in the hospital was similar and less than 4 days in both groups, the range of motion of the knee 48 h postoperatively and the range of motion 1 month

postoperatively was similar.

There were no differences between groups in the safety outcome, no pulmonary embolism (PE) was noted. Two patients in the experimental group and none in the control group had a clinical suspicion of deep venous thrombosis (DVT), only one present a Doppler confirmation of a superficial venous thrombosis in the femoral vein at postoperative day 30. Non inferiority of topical TXA was demonstrated for all outcomes examination at four months postoperatively. Minor adverse events were equivalent (3).

These results are similar to other in literature and are very important to manage blood loss after TKR. Verification of noninferiority in this study provides ample evidence for use of 3 g of topical intra-articular TXA in TKA with cement with predictable efficacy and safety. The results in the patients treated with topical intra-articular TXA were consistent with those in several trials (4-8) and a meta-analysis (9) in which topical TXA was compared with placebo.

Nevertheless authors underline some limitations of the study: as no transfusion was needed in either group, the analysis can not confirm superiority of either treatment with respect to blood loss, and larger studies may be necessary. Also, the estimation of blood loss at 48 h postoperatively may have been unreliable because of hemodilution, with the estimate at 5 days being more accurate. This randomized controlled trial could have had a third arm in which only placebo was administered. However, today is not possible because ethical issues regarding placebo use have been raised because of the results of prior TXA studies (10) with an increased risk of transfusion. Finally, this clinical trial had little capacity to detect differences in adverse events; large cohort studies would be required to investigate that outcome.

According to this study and recent literature some points need to be analysed and in some cases these problems remain today without a correct answer yet.

## Efficacy

TXA is widely accepted today as an effective and safe method to reduce blood loss after primary TKA. TXA use is supported by studies with a level of evidence of I that confirm its efficacy for decreasing blood loss (11-14).

## Safety and way of administration

Safety have been confirmed in studies comparing TXA treatment against placebo (5-8), but in many studies that showed equivalent safety, TXA is used in patients groups

that were selected to exclude complicated patients at risk of DVT, with thromboembolic or heart disease. So, there are concerns regarding IV administration of TXA in some settings, and topical administration may be considered a good alternative that is potentially less risky than systemic administration.

The results of several RCT (4-8) and a meta-analysis (9) involving primary cemented TKR confirmed significantly lower transfusion rates and blood loss (5) in patients treated with topical TXA compared with placebo. Retrospective and cohort studies (15,16), containing a large number of patients, have also confirmed the efficacy of topical TXA.

Contraindications that limit the IV use of TXA include a history of a thromboembolic or ischemic event such as PE, DVT, ischemic cerebrovascular accident, acute myocardial infarction, or ischemic retinopathy. The TXA level in peripheral blood was significantly lower after topical intra-articular administration than after IV administration (7), and this may increase safety. So at the end topical administration has the advantages of easiness of application, maximum concentration at the site of bleeding, minimising its systemic absorption and, consequently, concerns about possible side effects.

The efficacy of topical TXA administration compared with placebo during TKR has been confirmed in trials with various dosages and routes of administration, including tissue impregnation with 1.5 or 3 g of TXA before knee closure (7), delivery of 2 g into the wound (4), or intra-articular delivery of 2 g through the drain (6).

However, concerns regarding possible differences in efficacy according to the route of administration were raised because in one study application of 2 g of topical TXA in the joint before closure failed to achieve a significant reduction in blood transfusion (17).

Therefore, it remains unclear whether the efficacy of topical TXA administration in TKR is equal to or less than that of IV administration.

In conclusion for the way of administration, topical intra-articular TXA could be helpful to patients with contraindications to systemic TXA, as absorption from the joint is very low.

## Dosage

In literature there are many studies that underline efficacy of IV infusion of TXA but what is the right dosage is now unclear. Many authors use a 10-20 mg/kg dosage from 1 to 3 times during and after surgery with comparable results (18).

Levine *et al.* in a prospective randomized controlled trial

suggest that a single 1 g dose can be used with the same efficacy as a weighted 20 mg/kg dose (19). It is simple to understand as a uniform dose can be simpler for routinely use in TKA.

Also efficacy of topical TXA administration has been confirmed in trials with various dosages and routes of administration, including tissue impregnation with 1.5 or 3 g of TXA.

Jang *et al.*, in their retrospective study about intra-articular injection of TXA, find that reduction in haemoglobin levels was significantly greater in placebo group than in 1,500 mg TXA group and the 3,000 mg group, with a significant difference between the two TXA groups, so they suggest a dose dependent effect of TXA on blood loss (20).

In addition, it is simple to understand that it is easier for the surgeons to administer a single intraarticular TXA dose, rather than have a control of the one or more IV doses administered by the anesthesiologist during surgery and by other colleagues some hour after operation; so a simpler application may also facilitate wider use of topical TXA during surgery.

### Adverse events

We have already analysed possible complications related to use of TXA and what are patients with contraindication to IV administration while analysing ways of administration.

Studies involving IV or topical TXA administration revealed no increase in DVT or overall VTE rates in randomized controlled trials (7,17) or intra-articular administration, prospective cohort studies, retrospective studies, or systematic reviews and meta-analyses (9,12). Systematic use of Doppler ultrasonography (7) revealed no significant difference in the rate of thromboembolism after topical TXA administration.

It is important to underline that in all study analysed, TXA is used in patients groups that were selected to exclude patients with risk of history of DVT e PE, with thromboembolic or heart disease. So doubts are present in clinical practice yet, above all regarding IV administration of TXA for complicated patients, and topical administration may be considered a good alternative that is potentially less risky than systemic administration.

### Costs

TXA use, either IV than topical, has undoubted advantages

with significant decreases in length of stay, no pre-donated blood units preparation, blood bank costs, and total direct costs to the hospital for the TKR. Indirect cost savings would also result from the avoidance of transfusions that result in complications requiring additional treatment and an increased length of stay.

In conclusion, this randomized controlled trial indicated that a single topical intra-articular dose of 3 g of TXA was not inferior to two 15-mg/kg IV TXA doses. Both regimens were equally efficacious and safe with respect to avoiding blood transfusion, and they achieved equal control of blood loss without complications.

In recent literature some studies presents still better effectiveness of IV administration so we need further study to affirm that topical administration has the same efficacy of IV infusion. But there is no doubt that topical administration could be helpful to patients with contraindications to systemic TXA.

Further research is required to find TXA optimum dose either for IV than topical use. If IV and topical uniform doses are confirmed TXA use can be easier for routinely surgery.

### Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** Sabatini L, Atzori F. Topical intra-articular and intravenous tranexamic acid to reduce blood loss in total knee arthroplasty. *Ann Transl Med* 2015;3(S1):S18. doi: 10.3978/j.issn.2305-5839.2015.02.25