Intra-articular versus intravenous tranexamic acid in primary total knee replacement

Jerry Yongqiang Chen, Shi-Lu Chia, Ngai Nung Lo, Seng Jin Yeo

Department of Orthopaedic Surgery, Singapore General Hospital, Singapore

Correspondence to: Jerry Yongqiang Chen, MBBS, MRCS (Edin), MMed (Ortho). Department of Orthopaedic Surgery, Singapore General Hospital, Outram Road, Academia Building Level 4, Singapore 119228, Singapore. Email: yqjchen@gmail.com.

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We commend Gomez-Barrena *et al*. on their recent study entitled "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". The study was well-designed and appropriate statistical analysis was performed. They compared 39 patients who received 3 grams of intra-articular tranexamic acid (TXA) with another 39 patients who had two doses of 15 milligrams/kilogram of intravenous TXA (one dose before tourniquet release and another three hours after surgery). There was zero incidence of blood transfusion. The visible blood loss as measured in the drain output at 24 hours postoperatively and the invisible blood loss estimated using the Nadler formula at 48 hours postoperatively were comparable in both groups of patients. They conclude that intra-articular TXA according to their described protocol demonstrated noninferiority when compared with intravenous TXA (1).

Total knee replacement (TKR) is a cost-effective and efficacious treatment modality for severe osteoarthritic knees. Growth in the proportion of obese population, combined with the increase in demand from an ageing population, will inevitably lead to a rise in the number of patients requiring TKR. This number is expected to increase five-fold by 2030.

However, TKR can be associated with significant blood loss with 10-38% of patients requiring allogenic blood transfusion perioperatively. Serious complications associated with blood transfusion include viral infections, transfusion-related reactions and fluid overload. Furthermore, transfusions significantly increase the length of hospital stay and hospital cost. The risks and costs of blood transfusion, together with challenges in obtaining sufficient labile blood products, have generated interest in blood-conserving strategies. These include hypotensive anaesthesia, intra-operative blood salvage as well as the use of erythropoietin and anti-fibrinolytic agents.

TXA is a synthetic anti-fibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, procoagulant factors V and VIII. At higher concentration, TXA also acts directly to inhibit plasmin activity. Consequently, there is a decrease in proteolytic action on the fibrin monomers and fibrinogen, which results in clot stabilization. The trauma of surgery activates fibrinolysis by promoting the release of tissue plasminogen activator. Although the body naturally inhibits fibrinolysis by 24 hours after surgery, anti-fibrinolytic agents such as TXA can block the activation of plasminogen to plasmin earlier and thereby decreasing the perioperative blood loss.

The use of intravenous TXA in TKR has been a common practice. It can be given as a: (I) preoperative dose before tourniquet inflation; (II) intraoperative dose before deflation of the tourniquet; (III) postoperative dose three hours after surgery; or (IV) various permutations combining these three doses. TXA, when given intravenously, has a wide distribution throughout the extracellular and intracellular compartments. It diffuses rapidly into the synovial fluid until the concentration of TXA in the synovial fluid equals that of its concentration in the serum. Its biological half-life is 3 hours in the joint fluid and 90% of it is eliminated within 24 hours by glomerular filtration. Meta-analyses have shown that intravenous TXA effectively reduces the perioperative blood loss and incidence of blood transfusion after TKR, without increasing the risk of thromboembolic

events (TEE) (2-6). However, many common medical conditions including renal impairment, cardiovascular diseases, cerebrovascular conditions and the concurrent presence of hormonal treatment may preclude the use of intravenous TXA at the time of surgery (7).

Giving intra-articular TXA during TKR has only started to gain popularity in recent years. It can be given as a topical wash or into the knee joint after wound closure via the drain. Compared to intravenous administration, advocates of intra-articular TXA believe the benefits include ease of administration, ability to achieve maximum concentration at the bleeding site and minimal systemic absorption. Furthermore, the use of tourniquet in TKR results in negligible intraoperative blood loss but notable postoperative blood loss, which is the ideal scenario for using intra-articular haemostatic agents intraoperatively. A recent meta-analysis by Alshryda *et al*. which included nine randomised controlled trials in TKR found that intra-articular TXA significantly reduced the rate of blood transfusion, without an increase in the incidence of TEE (8).

Despite several studies proving the efficacy of both intra-articular and intravenous TXA in reducing blood loss after TKR, the ideal route of administering TXA will remain a topic for ongoing debate and controversy in the upcoming years.

Four other recent studies also concluded that the two routes of administration are comparable for blood transfusion incidences after TKR (9-12). Their findings support the postulation that the therapeutic effect of TXA becomes apparent when proteolysis of plasmin prematurely dissolves the fibrin clot. As TXA works at active bleeding site of the wound rather than within the blood vessels, its presence within the clot is considered effective irrespective of the route of administration. However, there are two recent studies that favoured intra-articular TXA to intravenous administration (13,14), while another study reported significantly lower blood transfusion incidence with intravenous TXA (15).

Huang *et al*. compared 92 patients who received 3 grams of intravenous TXA during TKR with another 92 patients who had 1.5 grams of intra-articular TXA combined with 1.5 grams of intravenous TXA. Interestingly, while both groups had similar effectiveness in reducing blood transfusion rate, patients in the intra-articular-intravenous combined group had significantly lesser drainage volume, lesser postoperative knee pain, lesser knee swelling, shorter length of hospital stay and higher short-term satisfaction (16).

The conflicting findings across these studies are possibly contributed by: (I) the variation in surgical techniques using conventional intra- and extramedullary jigs or computer-assisted surgery; (II) the variation in dosing regimen for intravenous TXA, with some studies giving one dose while others giving three doses; (III) the variation in indications for blood transfusion across hospitals.

Wang *et al*. promptly performed a meta-analysis of six prospective randomized controlled trials and cohort studies comprising 679 patients (739 knees) to evaluate the efficacy of intra-articular versus intravenous TXA in primary TKR. They found no significant difference between the two routes of administration in terms of blood loss, blood transfusion requirements and TEE (17).

From the hospital administrators' point of view, the cost savings associated with the use of TXA in TKR is of paramount importance. The cost of intra-articular TXA is as little as $6 in some countries but it has proven to shorten hospital stay by a mean of 1.2 days (18,19). While the pharmacy cost is higher with the routine use of TXA, the blood bank cost and total direct hospital cost were lower. A recent study by Moskal *et al*. found that the total direct hospital cost (the combined cost of TXA and blood transfusion) was $39.14/TKR, $82.59/TKR and $84.90/TKR for intra-articular, intravenous and without TXA respectively. Similarly, the man-hour cost (the time required to successfully deliver a unit of blood and to address transfusion complications) was zero in the intra-articular group as none of the patients required blood transfusion, as well as 0.007 man-hour/TKR and 0.13 man-hour/TKR for the intravenous and without TXA groups respectively. They concluded that intra-articular TXA has the potential to achieve larger cost saving and decrease hospital man-hour/TKA (20).

While we acknowledge the authors of these studies for their contribution to our current knowledge, there remains no consensus regarding the ideal route of administrating TXA. To yield greater insight into the debate of intra-articular versus intravenous TXA in primary TKR, the need for a multi-centered randomized controlled trial with standardize operative and transfusion protocols or a meta-analysis with significantly larger sample size comprising only randomized controlled trials is clearly evident.

Nonetheless, the current evidence appears to suggest that the efficacy of intra-articular TXA in reducing perioperative blood transfusion incidence is not inferior to intravenous TXA, with no additional safety concerns. We recommend intra-articular TXA as an alternative to surgeons caring for TKR patients in whom intravenous TXA is cautioned.

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