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

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Background: Abundant literature regarding the use of intravenous tranexamic acid (TXA) in primary total knee replacement is available. Randomized controlled trials have confirmed the efficacy of topical TXA compared with placebo, but the comparison between topical and intravenous TXA is unclear. The present study was designed to verify noninferior efficacy and safety of topical intra-articular TXA compared with intravenous TXA in primary total knee replacement with cemented implants.

Methods: A Phase-III, single-center, double-blind, randomized, controlled clinical trial was performed to compare topical intra-articular TXA (3 g of TXA in 100 mL of physiological saline solution) with two intravenous doses of TXA (15 mg/kg in 100 mL of physiological saline solution, one dose before tourniquet release and another three hours after surgery) in a multimodal protocol for blood loss prevention. The primary outcome was the blood transfusion rate, and the secondary outcomes included visible blood loss (as measured in the drain) at twenty-four hours postoperatively and invisible blood loss (as estimated from the Nadler formula) at forty-eight hours postoperatively. The sample size of seventy-eight patients was calculated to give a statistical power of 99% for demonstrating noninferiority. Thirty-nine patients each were allocated to receive topical intra-articular TXA (the experimental group) and intravenous TXA (the control group); there were no significant differences in demographics or preoperative laboratory values between the groups. Noninferiority was estimated by comparing the confidence intervals with a delta of 10%. Student t and Mann-Whitney tests were used to assess the significance of any differences.

Results: The transfusion rate was zero in both groups; thus, noninferiority was demonstrated for the primary efficacy end point, suggesting equivalence. Noninferiority was also demonstrated for the secondary efficacy end points. Drain blood loss at twenty-four hours was 315.6 mL (95% confidence interval [CI], 248.5 to 382.7 mL) in the experimental group and 308.1 mL (95% CI, 247.6 to 368.5 mL) in the control group ($p = 0.948$, Mann-Whitney). Also, estimated blood loss at forty-eight hours was 1259.0 mL (95% CI, 1115.6 to 1402.3 mL) in the experimental group and 1317.9 mL (95% CI, 1175.4 to 1460.4 mL) in the control group ($p = 0.837$, Mann-Whitney). No significant safety differences were seen between groups.

Conclusions: Topical administration of TXA according to the described protocol demonstrated noninferiority compared with intravenous TXA, with no safety concerns. This randomized controlled trial supports the topical intra-articular administration of TXA in primary total knee replacement with cemented implants.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

The use of tranexamic acid (TXA) in primary total knee replacement with cemented implants is supported by studies with a level of evidence of I that confirm its efficacy for decreasing blood loss[1-4], although safety concerns have not been confirmed in studies comparing TXA treatment against placebo, which showed equivalent safety[3,5-8]. Although blood loss prevention protocols have been adopted at many institutions, there are concerns regarding intravenous (IV) administration of TXA in some settings, and topical administration may be considered an appealing alternative that is potentially less risky than systemic administration.

Recent clinical trials to confirm the safety and efficacy of TXA administration in the form of a single topical intra-articular dose have been fostered by topical TXA administration in dental surgery even in patients who are receiving oral anticoagulation[9]. The results of several randomized controlled trials[10-14] and a meta-analysis[15] involving primary total knee replacement with cemented implants confirmed significantly lower transfusion rates[11] and blood loss[11] in patients treated with topical TXA compared with placebo. Retrospective and cohort studies[16-20] containing a large number of patients have also confirmed the efficacy of topical TXA.

The safety of TXA can be influenced by its biodistribution. Formal contraindications to IV TXA include a history of a thromboembolic or ischemic event such as pulmonary embolism (PE), deep venous thrombosis (DVT), ischemic cerebrovascular accident, acute myocardial infarction, or ischemic retinopathy. However, the TXA level in peripheral blood was significantly lower after topical intra-articular administration than after IV administration[13], and this may increase safety. IV administration results in rapid diffusion of TXA into the synovial fluid of the target joint, but topical intra-articular administration achieves the same result without a wide, systemic distribution, potentially reducing the thromboembolic risk[13].

The efficacy of topical TXA administration compared with placebo during total knee replacement has been confirmed in trials with various dosages and routes of administration, including tissue impregnation with 1.5 g or 3 g of TXA before knee closure[13], delivery of 2 g into the wound[10], or intra-articular delivery of 2 g through the drain[12]. However, concerns regarding possible differences in efficacy according to the route of administration were fostered when 2 g of topical TXA in the joint before closure failed to achieve a significant reduction in blood transfusion in one study[21]. Therefore, it remains unclear whether the efficacy of topical TXA administration in total knee replacement is equal to or less than that of IV administration.

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 total knee replacement 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.

Materials and Methods

The present Phase-III study was registered in the European database of clinical trials (EudraCT 2011-003218-17) and the public ClinicalTrials.gov registry (NCT01881568). Approval was obtained from the hospital ethics committee. As requested by that committee and the national regulator, an insurance policy was contracted to cover any eventual complications in all participating patients, all of whom gave written informed consent.

All adult patients scheduled to undergo primary unilateral total knee replacement with cemented implants in our unit from January to October 2013 were eligible for inclusion. The exclusion criteria were absence of written informed consent, allergy to TXA, major comorbidities (severe ischemic cardiopathy, sleep apnea syndrome, severe pulmonary disease, severe renal insufficiency, or hepatic failure), coagulopathy (preoperative platelet count <150,000/mm^3, INR [international normalized ratio] >1.4, or prolonged partial thromboplastin time of >1.4 times normal), a history of arterial or venous thromboembolic disease (cerebrovascular accident, DVT, or pulmonary thromboembolism), a hematologic disorder (a hematopoietic, hemorrhagic, or thrombogenic disease), retinopathy (severe vision field limitation and/or color distortion), refusal of blood products, pregnancy, breastfeeding, and participation in another clinical trial during the last year. If an intraoperative surgical, medical, or anesthetic complication occurred before administration of the study medication, the medication was not administered and the patient was excluded. If such a complication was detected after administration, the patient was excluded from the outcome measurements and analysis but was followed for complications.

Patients with preoperative anemia (hemoglobin, <13 g/dL) were not excluded; instead, they were offered the current standard preoperative protocol at our institution (IV administration of iron and/or subcutaneous administration of 40,000 IU of erythropoietin), and surgery was postponed until the hemoglobin level was ≥13 g/dL. All patients were instructed to discontinue aspirin, anti-platelet agents, and nonselective cyclooxygenase inhibitors at least seven days prior to surgery. Two units of red cell concentrate were prepared at the time of patient admission.

Recruited patients were randomly allocated to the experimental group or the control group. The experimental group received a topical intra-articular dose of 3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols) on the basis of previous studies that confirmed the high efficacy of this dosage[13]. Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-articularly after skin closure (through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release). In addition, patients in this group received 100 mL of an IV placebo solution (physiological saline solution) fifteen to twenty minutes before tourniquet release and 100 mL three hours later. Patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery, on the basis of previous efficacy studies[22,23]. In addition, patients in this group received a topical intra-articular placebo (100 mL of physiological saline solution).

Patient assignments were prepared by a research statistician and were placed into sequentially numbered opaque sealed envelopes, which were kept by research personnel. An envelope was opened before each surgery, and the appropriate study medication and placebo were prepared under sterile conditions by uninvolved anesthesiologists under the supervision of a research pharmacist not involved in patient care. The study medication and placebo were identical in appearance. Patients, surgeons, and health-care personnel participating in treatment and evaluation were blinded to the group allocation throughout the study period.

Senior surgeons were responsible for all arthroplasties, which were performed with use of a standardized technique and a multimodal protocol for blood loss prevention. All patients received spinal anesthesia with 0.5% hyperbaric bupivacaine, fentanyl, IV midazolam, and/or continuous propofol infusion. After limb elevation and extremity exsanguination, a pneumatic tourniquet was inflated to 100 mm Hg above systolic arterial pressure. A limited anterior midline

TABLE I Baseline Patient Characteristics

Variable	Topical Intra-Articular TXA Group, N = 39*	IV TXA Group, N = 39*	P Value
General characteristics			
Age *(yr)*	70.1 ± 9.1	71.8 ± 10.3	0.205†
Female sex	26 (67%)	25 (64%)	0.500‡
Weight *(kg)*	78.4 ± 12.8	75.3 ± 12.2	0.228†
Height *(m)*	1.6 ± 0.1	1.6 ± 0.1	0.137†
Body mass index *(kg/m^2)*	30.4 ± 4.1	30.2 ± 4.2	0.760†
ASA class	2.0 ± 0.4	2.2 ± 0.5	0.052§
I	3 (8%)	1 (3%)	0.198‡
II	32 (82%)	28 (72%)	
III	4 (10%)	10 (26%)	
Preop. laboratory values			
Hemoglobin *(g/dL)*	14.5 ± 1.1	14.5 ± 1.0	0.781§
Hematocrit *(%)*	43.9 ± 3.9	47.1 ± 12.5	0.250†
Iron *(μg/dL)*	95.6 ± 40.9	95.1 ± 25.1	0.951†
Transferrin *(mg/dL)*	256.2 ± 59.1	244.4 ± 55.2	0.447†
Transferrin saturation index *(%)*	30.5 ± 13.8	39.1 ± 47.5	0.573†
Ferritin *(ng/mL)*	207.7 ± 249.1	181.1 ± 121.6	0.559†
Platelet count *($x10^3/\mu L$)*	216.7 ± 47.8	230.1 ± 50.9	0.233§
Recruitment characteristics			
Preop. iron treatment	5 (13%)	7 (18%)	0.859‡
Preop. erythropoietin treatment	1 (3%)	1 (3%)	0.888‡
Preop. halt of medications#	5 (13%)	1 (3%)	0.115‡
Surgery characteristics			
Prosthesis type			0.158‡
Modular tibial component	33 (85%)	28 (72%)	
All-polyethylene tibial component	6 (15%)	11 (28%)	
Left side	20 (51%)	21 (54%)	0.500‡
Tourniquet time *(min)*	79.9 ± 15.2	80.5 ± 14.4	0.855§
Operative time *(min)*	76.4 ± 15.5	75.1 ± 14.1	0.698§

*Values are given as the mean and the standard deviation or as the number of patients with the percentage in parentheses. †Mann-Whitney test. ‡Fisher exact test. §T test. #Two patients halted antiplatelet medications, two halted cyclooxygenase inhibitors, and two halted aspirin.

incision followed by a parapatellar medial approach without patellar eversion and minimally invasive surgical instrumentation were utilized in all patients. A cemented posterior-stabilized NexGen prosthesis (Zimmer) was implanted. Sixty-one patients received an LPS (lateral posterior stabilizing) design with a modular tibial component, and the remaining seventeen received an LPS design with an all-polyethylene tibial component; patellar replacement was performed in all patients. The cement was Palacos R+G (Heraeus Medical). Autologous bone was used to fill the femoral medullary canal before implant cementation. After all components were cemented, the joint was thoroughly irrigated and aspirated. Half of the volume of the topical study medication or of the topical placebo was applied to the open joint surfaces with a syringe and was left in contact with the tissue for five minutes. Excess solution was removed by placing the suction tip on the components. After wound closure, the remaining half of the study medication or placebo was introduced into the joint via the 12-mm drain placed below the lateral aspect of the quadriceps.

All knees received multimodal analgesia consisting of intra-articular and periarticular injection of 80 mL of physiological saline solution containing 0.3 mg adrenalin, 10 mg morphine chloride, 100 mg tobramycin, 6 mg betamethasone sodium phosphate, 6 mg betamethasone acetate, and 200 mg ropivacaine (a total of 30 mL in the posterior capsule, collateral ligaments, and medial wall before cementing; a total of 50 mL in the synovium, arthrotomy, and subcutaneous tissues after implantation). Patients also received standard analgesia (paracetamol, metamizole, and ketorolac administered for twenty-four hours through an IV pump). A single intra-articular drainage tube (Drenofast CH-12/4,0; Iberhospitex) was first used to administer half of the study medication, then closed and opened (at atmospheric pressure without vacuum) after two hours and removed after twenty-four hours. The tourniquet was released after wound closure and knee bandaging. Prophylaxis against thromboembolism in all patients consisted of daily subcutaneous injection of 40 mg of enoxaparin (Clexane; Sanofi-Aventis) for two weeks, starting six hours after wound closure. Antibiotic prophylaxis included 2 g of cephalosporin one hour before surgery and 1 g every eight hours for twenty-four hours. Patients with a cephalosporin allergy received a slow infusion of 1 g of vancomycin before surgery and 500 mg every twelve hours for twenty-four hours.

TABLE II Postoperative Blood Loss

Variable	Time Point	Topical Intra-Articular TXA Group *(mL)*		IV TXA Group *(mL)*		P Value*
		Mean and Std. Dev.	95% CI	Mean and Std. Dev.	95% CI	
Drain blood loss	3 hr	160.3 ± 123.6	120.2 to 200.3	157.1 ± 103.2	123.6 to 190.5	0.916
	24 hr	315.6 ± 207.1	248.5 to 382.7	308.1 ± 186.5	247.6 to 368.5	0.948
Estimated blood loss	48 hr	1259.0 ± 442.2	1115.6 to 1402.3	1317.9 ± 439.6	1175.4 to 1460.4	0.837
	Approx. 5 d†	811.9 ± 511.5	613.6 to 1010.2	992.5 ± 504.5	793.0 to 1192.1	0.225
Total blood loss	48 hr	1574.5 ± 542.9	1398.5 to 1750.5	1626.0 ± 519.2	1457.6 to 1794.3	0.656
	Approx. 5 d†	1087.2 ± 530.6	881.4 to 1293.0	1309.2 ± 587.4	1076.8 to 1541.6	0.194

*Mann-Whitney test. †The laboratory testing was performed at 6.18 ± 2.5 days postoperatively.

Outcome Measures

Postoperative blood transfusion was the primary outcome. Blood loss through the drain was measured at three and twenty-four hours and served as one of the secondary outcomes. The postoperative hemoglobin level was measured at twenty-four hours, forty-eight hours, and approximately five days. The estimated blood loss was determined by the difference between the preoperative hemoglobin level and the lowest postoperative level. The estimated blood loss was calculated with use of the Nadler formula[24] at forty-eight hours and approximately five days after surgery. Other secondary outcomes included complications and severe adverse events, the length of stay in the hospital, and postoperative changes in active range of motion of the knee (which was measured with a standard clinical goniometer before and thirty days after the operation with the patient in a supine position). Active physiotherapy was started on the same day as the surgery.

Patients were examined daily while hospitalized for clinical symptoms of DVT. A diagnostic Doppler ultrasonography examination was performed when there was a clinical suspicion of a DVT. The patient was instructed to return if limb swelling or calf pain appeared after discharge. All patients remained in the hospital for a minimum of three days.

Blood transfusion was planned for patients with a hemoglobin level of <8.0 g/dL who were asymptomatic and appeared healthy. Transfusion was planned for patients with a level of <10.0 g/dL if they had (1) symptoms that were not well tolerated (including any organ dysfunction), were related to anemia, and were not attributable to another cause (myocardial ischemia or hypoxemia), or (2) ongoing blood loss.

Sample Size and Statistical Methods

Prior reports involving total knee arthroplasty[13,25,26] have indicated a zero transfusion rate with IV or topical TXA treatment, so we planned for a maximum expected transfusion rate of 5%. Conservatively, the noninferiority threshold was defined as the one-sided upper bound of the 97.5% confidence interval (CI) for a treatment difference (delta value) of 10%. We chose this noninferiority threshold on the assumption that the experimental treatment would be noninferior if the results obtained were at least similar to those of either a lower 10-mg/kg IV dose of TXA or a single 15-mg/kg IV dose[27,28]. For this primary end point, we calculated that a total of thirty-nine patients per arm provided 99% power to demonstrate noninferiority at a one-sided level of significance of 0.025.

An intention-to-treat analysis was performed. Distributions of demographic data, baseline data, surgical characteristics, and primary and secondary outcomes were assessed with measures of central tendency (mean, standard deviation, and 95% CI) for quantitative variables and with percentages for qualitative variables. The Student t or Mann-Whitney test was used to compare continuous variables, and the Fisher exact test was used for categorical variables.

We also performed noninferiority analyses of the secondary outcomes with two possible delta thresholds, 10% and 5%. The resulting noninferiority thresholds were thus 5% and 10% greater than the upper bound of the CI for the outcome in the control group. We considered that topical TXA would not demonstrate clinically relevant inferiority to IV TXA if the upper limit of the outcome in the experimental group was below the noninferiority threshold. We reserved the option of testing superiority after establishing noninferiority.

Source of Funding

The study was performed with funding from our orthopaedic department supplemented with an institutional research grant from SERHOSA, a local distributor for Zimmer, Inc., which did not play any role in the investigation.

Results

From January to October 2013, ninety-three patients scheduled for primary unilateral total knee replacement at our hospital were assessed for participation in this trial (Fig. 1). Fifteen

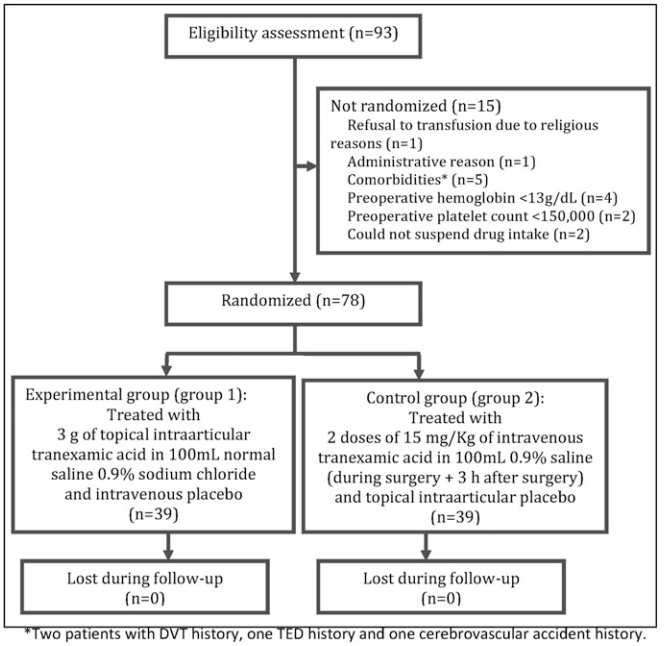

Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) diagram for the study. TED = thromboembolic disease.

TABLE III Postoperative Hemoglobin (Hb) Level

	IV Tranexamic Acid Group		Topical Tranexamic Acid Group		
	Mean and Std. Dev.	95% CI	Mean and Std. Dev.	95% CI	P Value*
Postop. Hb *(mg/dL)*					
24 hr	12.0 ± 1.2	11.6 to 12.4	12.2 ± 1.2	11.8 to 12.5	0.645†
48 hr	11.2 ± 1.1	10.8 to 11.5	11.4 ± 1.1	11.0 to 11.7	0.377†
Approx. 5 d‡	12.1 ± 1.3	11.5 to 12.6	12.5 ± 1.2	12.0 to 12.9	0.206§
Change from preop. Hb					
24 hr	−2.5 ± 0.8	−2.8 to −2.2	−2.3 ± 0.8	−2.6 to −2.0	0.305†
48 hr	−3.4 ± 0.9	−3.7 to −3.1	−3.1 ± 1.0	−3.4 to −2.8	0.167†
Approx. 5 d‡	−2.6 ± 1.2	−3.1 to −2.1	−2.0 ± 1.2	−2.5 to −1.6	0.083†

*The mean Hb level did not differ significantly between the groups at any time point. †T test. ‡The laboratory testing was performed at 6.18 ± 2.5 days postoperatively. §Mann-Whitney test.

patients were excluded; four had a preoperative hemoglobin level of <13 g/dL, two had a preoperative platelet count of <150,000/mm^3, two used medications that should have been discontinued before surgery, and seven did not meet other inclusion criteria. The remaining seventy-eight patients were randomized to receive either topical TXA (the experimental group, n = 39) or IV TXA (the control group, n = 39). No patient was lost or excluded during follow-up. No significant differences between the groups were found with respect to age, weight, height, body mass index, ASA (American Society of Anesthesiologists) status[29], preoperative laboratory values (hemoglobin, hematocrit, iron, transferrin, transferrin saturation index, ferritin, platelet count), or surgical characteristics (site, prosthesis type, surgical time, tourniquet time) ($p > 0.05$ for all; Table I). Two patients (one in each group) received preoperative erythropoietin, and twelve patients (five in the experimental group) received preoperative iron treatment.

No transfusion was performed in either group, confirming noninferiority for the primary efficacy end point (transfusion rate) and suggesting equivalence (95% CI according to the Wilson test, −9% to 9%). Similarly, when secondary efficacy end points involving blood loss were analyzed, there were no significant differences in drain blood loss at twenty-four hours or in estimated blood loss at forty-eight hours or five days (Table II).

Decreases in the hemoglobin level were similar in the two groups (Fig. 2, Table III). The decreases at twenty-four hours, forty-eight hours, and approximately five days were −2.3, −3.1, and −2.0 g/dL, respectively, in the topical intra-articular TXA group and −2.5, −3.4, and −2.6 g/dL in the IV TXA group, with no significant differences between the groups.

The possibility of superiority with respect to the blood loss end points was also investigated by comparing both drain and estimated blood loss with use of the appropriate CIs (Fig. 3). Although noninferiority was confirmed, no clear superiority was detected. For example, the upper bound of the CI was below both the 10% and 5% delta noninferiority thresholds for drain blood loss at three hours ($p = 0.562$) and twenty-four hours ($p = 0.588$) postoperatively and for estimated blood loss at forty-eight hours postoperatively ($p = 0.205$). The other variables were also inconclusive with respect to superiority; for example, estimated blood loss at five days likewise failed to confirm superiority for topical TXA ($p = 0.036$ for noninferiority; $p = 0.963$ for superiority).

The mean length of stay in the hospital was similar and less than four days in both groups ($p = 0.316$), with a global mean (and standard deviation) of less than four days (3.5 ± 0.9 days [95% CI, 3.2 to 3.8 days] in the experimental group and 3.9 ± 1.6 days [95% CI, 3.4 to 4.5 days] in the control group). The range of motion of the knee forty-eight hours postoperatively was 91° ± 10.5° (95% CI, 88.4° to 95.0°) in the experimental group and 88° ± 6.7° (95% CI, 86.4° to 90.7°) in the control group ($p = 0.241$). The range of motion one month postoperatively was 104° ± 10° (95% CI, 101° to 108°) in the experimental group and 105° ± 11° (95% CI, 101° to 109°) in the control group ($p = 0.612$).

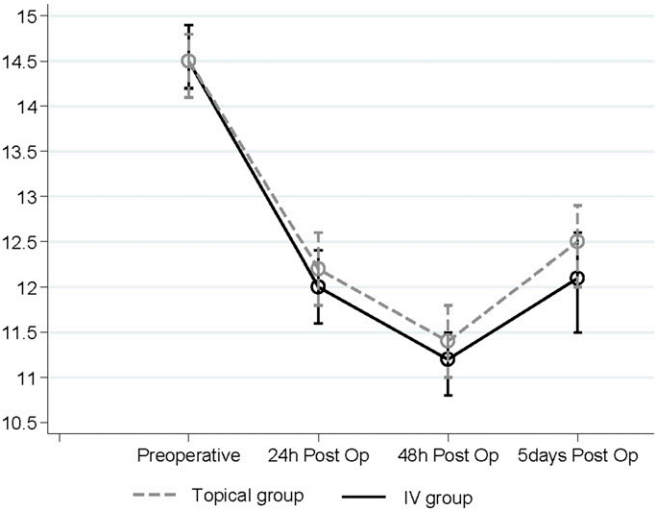

Fig. 2

Hemoglobin concentration in g/dL (and 95% CI) according to time in each treatment group.

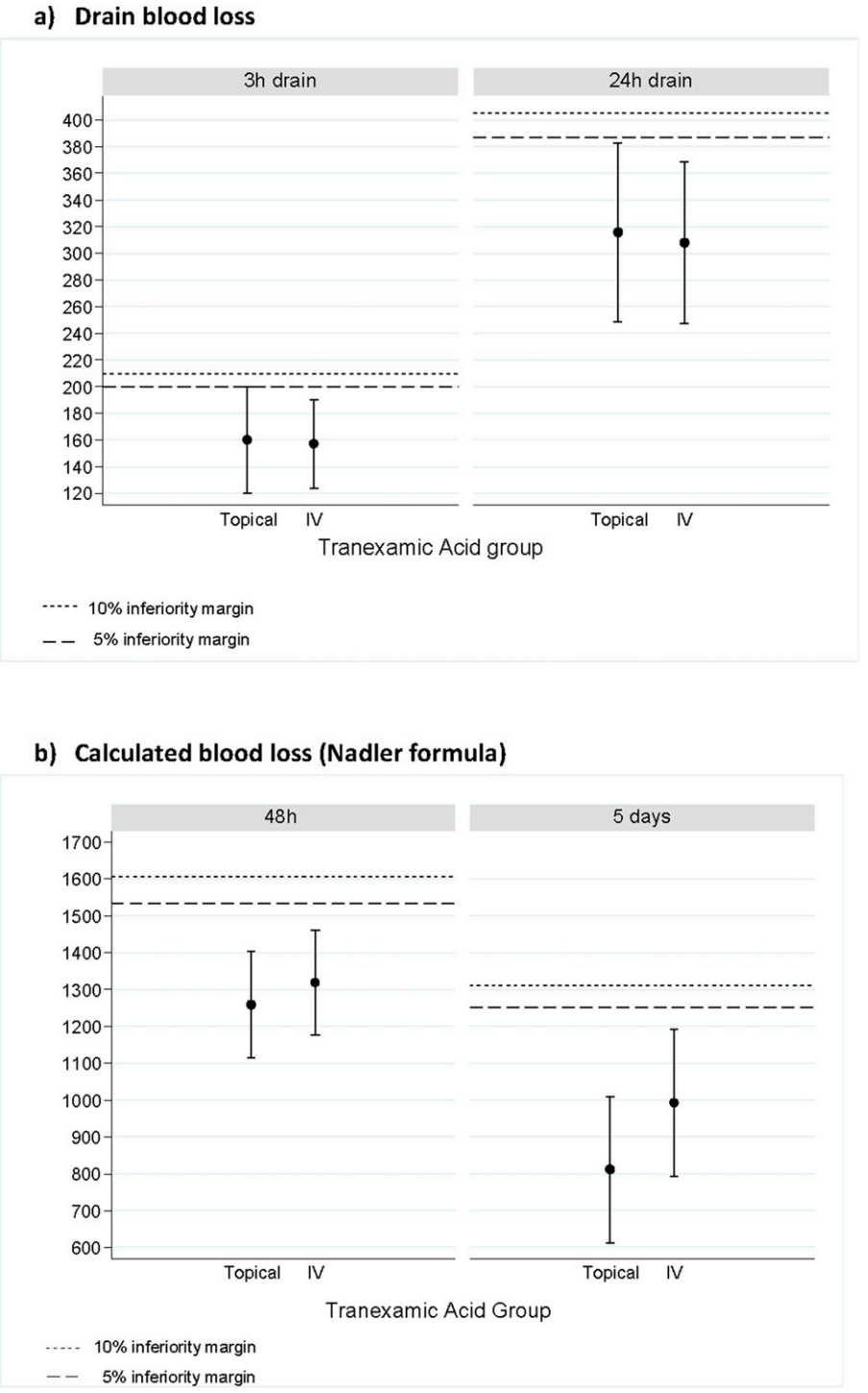

Fig. 3

Blood loss (with 95% CI) in each treatment group. The horizontal lines correspond to blood loss 5% and 10% greater than the upper bound of the 95% CI for the control (IV) group. Noninferiority of topical TXA was demonstrated for all outcomes.

There were no differences between groups in the safety outcome ($p = 0.722$). No PE was noted. Two patients in the experimental group and none in the control group had a clinical suspicion of DVT. One of the former patients (a seventy-year-old woman with a history of hypertension) had a negative Doppler evaluation; the other patient (a seventy-two-year-old woman) had Doppler confirmation of a superficial venous thrombosis in the femoral vein at postoperative day 30, which was treated with a therapeutic enoxaparin does of 100mg/24 hr for three months and was no longer visible on a repeat Doppler

examination at four months postoperatively. Two patients in the experimental group had delayed wound closure that resolved under nursing care with use of wet to dry dressings. Adverse events were equivalent; two patients in the experimental group and three in the control group developed postoperative vomiting, and seven in the control group developed other adverse events (nausea in two, dizziness in one, hypertension in two, and constipation in two). All adverse events were occasional and resolved without sequelae or death.

Discussion

In this randomized clinical trial, topical administration of 3 g of TXA was not inferior to the standard protocol involving IV administration of two 15-mg/kg doses. Verification of non-inferiority in this study provides ample evidence for use of 3 g of topical intra-articular TXA in total knee arthroplasty with cement as part of a multimodal protocol for blood loss prevention, with predictable efficacy and safety. The results in the patients treated with topical intra-articular TXA were consistent with those in several trials[10-14] and a meta-analysis[15] in which topical TXA was compared with placebo. A high transfusion rate of 20% was reported in patients who received topical TXA in another previous trial, but the transfusion rate in that trial was also 34% after IV TXA and 94% after placebo; all three rates were above the typical rate with use of blood loss prevention techniques[30].

Our study has limitations. As no transfusion was needed in either group, the analysis was likely underpowered for confirming superiority of either treatment with respect to blood loss, and larger studies may be warranted. Also, the estimation of blood loss at forty-eight hours postoperatively may have been unreliable because of hemodilution, with the estimate at five days being more accurate. This randomized controlled trial could have had a third arm in which only placebo was administered. However, ethical issues regarding placebo use have been raised because of the results of prior TXA studies[25]; including a placebo arm for comparison with TXA administered by any route would result in an increased risk of transfusion. Finally, this small clinical trial had little capacity to detect differences in adverse events; large cohort studies would be required to investigate that outcome.

Topical intra-articular TXA could be helpful to patients with contraindications to systemic TXA, as absorption from the joint is clinically negligible[13]. The ability of the surgeon to administer a single TXA dose, rather than the two IV doses often administered by the anesthesiologist, may also facilitate wider use of topical TXA during surgery.

Blood loss prevention has a major influence on total knee replacement costs[31] through decreases in morbidity and mortality, complications, and length of stay in the hospital. Blood transfusion is the most important predictor of increased length of stay after total knee replacement; in a previous study in which the mean length of stay following "fast-track" knee replacement was only 3.8 days, the length of stay for the 12% of patients who required a transfusion was threefold greater than the mean[32]. Waiting for blood transfusion was also associated with an increased length of stay after total knee replacement in another study[33]. Retrospective clinical and economical evaluations have indicated an estimated $1500 savings per primary total knee replacement performed with use of topical TXA[16], with significant decreases in length of stay, blood bank costs, and total direct costs to the hospital for the total knee replacement. We confirmed that the length of stay was short and blood bank costs were reduced to a minimum when TXA was used in the present study. Indirect cost savings would also result from the avoidance of transfusions that result in complications requiring additional treatment and an increased length of stay.

The risk of DVT or overall risk of a venous thromboembolic event (VTE) following TXA use in total knee arthroplasty has been thoroughly addressed. Data on thousands of patients have not revealed an increase in DVT or overall VTE rates[2,3,5]. Although heterogeneity in the thromboprophylactic regimens may confound comparisons, low DVT and PE rates have been confirmed even with less aggressive thromboprophylaxis protocols[8] such as the one in the present study (which utilized enoxaparin). Studies involving topical TXA administration revealed no increase in DVT or overall VTE rates in randomized controlled trials (involving wound impregnation with 1.5 to 3 g before closure[13,21] or intra-articular administration of 1 g[11]), prospective cohort studies[30], retrospective studies (involving wound impregnation before closure[20]), or systematic reviews and meta-analyses[2,15]. Systematic use of Doppler ultrasonography[13] revealed no significant difference in the rate of thromboembolism after topical TXA administration. In the present study, a single DVT was detected, in the group treated with intra-articular TXA, and it resolved uneventfully after three months. The difference in DVT rate between the groups was neither significant nor clinically relevant, and the DVT rate in the experimental group falls within the currently reported range after total knee replacement[34].

In summary, this randomized controlled trial indicated that a single topical intra-articular dose of 3 g of TXA, administered as part of the described multimodal protocol for blood loss prevention, 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. ■

NOTE: The authors thank the staff surgeons, anesthesiologists, nurses, and paramedical personnel of La Paz Hospital in Cantoblanco for their support and collaboration.

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