Topical (Intra-Articular) Tranexamic Acid Reduces Blood Loss and Transfusion Rates Following Total Knee Replacement

A Randomized Controlled Trial (TRANX-K)

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Background: Approximately one-third of patients undergoing total knee replacement require one to three units of blood postoperatively. Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that has been successfully used intravenously to stop bleeding after total knee replacement. A topical application is easy to administer, provides a maximum concentration of tranexamic acid at the bleeding site, and is associated with little or no systemic absorption of the tranexamic acid.

Methods: A double-blind, randomized controlled trial of 157 patients undergoing unilateral primary cemented total knee replacement investigated the effect of topical (intra-articular) application of tranexamic acid on blood loss. The primary outcome was the blood transfusion rate. Secondary outcomes included the drain blood loss, hemoglobin concentration drop, generic quality of life (EuroQol), Oxford Knee Score, length of stay, a cost analysis, and complications as per the protocol definitions.

Results: Tranexamic acid reduced the absolute risk of blood transfusion by 15.4% (95% confidence interval [CI], 7.5% to 25.4%; p = 0.001), from 16.7% to 1.3%, and reduced blood loss by 168 mL (95% CI, 80 to 256 mL; p = 0.0003), the length of stay by 1.2 days (95% CI, 0.05 to 2.43 days; p = 0.041), and the cost per episode by £333 (95% CI, £37 to £630; p = 0.028). (In 2008, £1 = 1.6 U.S. dollars.) Oxford Knee Scores and EuroQol EQ-5D scores were similar at three months.

Conclusions: Topically applied tranexamic acid was effective in reducing the need for blood transfusion following total knee replacement without important additional adverse effects.

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

Total knee replacement is one of the most common operations in orthopaedic practice, with 65,979 total knee replacements reported in England and Wales in 2008[1]. Approximately one-third of patients have been reported to require transfusion of one to three units of blood, although the range of reported transfusion rates was large (20% to 70%)[2-6]. Allogeneic transfusion is associated with small risks of hemolysis, infection, immunosuppression, transfusion-related acute lung injury (TRALI), and even death[7-9]. Various techniques have been utilized to reduce blood loss and/or the need for allogeneic blood transfusion, with varied success[10].

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Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that binds to the lysine binding site of plasminogen and blocks the binding of plasminogen to the fibrin surface. Thus, plasminogen activation is prevented and fibrinolysis is delayed[11]. It has been used successfully to stop bleeding after dental procedures, removal of tonsils, prostate surgery, heavy menstrual bleeding, and eye injuries, as well as in patients with hemophilia. Numerous studies have confirmed the efficacy of intravenous administration of tranexamic acid in reducing blood loss and transfusion requirements in total knee replacement[6,12-17]; however, it has rarely been adopted in orthopaedic practice and was not practiced in our center for fear of systemic side effects, particularly thromboembolic complications.

Baric et al. showed that topical use of either tranexamic acid (Cyklokapron; Pharmacia, Stockholm, Sweden) or aprotinin (Trasylol; Bayer Pharma, Ljubljana, Slovenia) efficiently reduced postoperative bleeding in cardiac surgery. Tranexamic acid seemed to be at least as potent as aprotinin but potentially safer and with a better cost-effectiveness profile[18]. De Bonis et al. showed that there was no detectable level of tranexamic acid in the bloodstream after topical application[19]. We hypothesized that intravenously administered tranexamic acid is distributed systemically, reducing its therapeutic concentration in the knee, whereas topically applied tranexamic acid is easy to administer and remains predominantly in the knee joint cavity, thus achieving a higher therapeutic concentration at the bleeding site with little or no systemic absorption and subsequent systemic side effects. We investigated the use of tranexamic acid sprayed topically into the exposed tissue around the knee joint prior to wound closure and tourniquet release.

Materials and Methods

Study Design and Patients

The TRANX-K (Tranexamic Acid in Total Knee Replacement) trial was a double-blind, placebo-controlled trial of the effect of topical (intra-articular) application of tranexamic acid on blood loss and transfusion requirements following a unilateral total knee replacement. Patients undergoing primary total knee replacement were eligible for the trial. Patients were excluded from the study if they were allergic to tranexamic acid; were receiving warfarin or heparin; had a history of hemophilia, deep venous thrombosis, pulmonary embolism, or renal impairment; or were pregnant.

Participants were prescreened for eligibility and approached by trained staff in a preassessment clinic visit approximately three weeks before surgery. Those who initially responded positively were provided with an informational leaflet and a telephone number to contact for further information. Informed written consent was sought on admission for surgery.

The primary outcome was the change in the proportion of patients undergoing blood transfusion during the index procedure. Secondary outcomes measures were blood loss, the volume of blood transfused, hemoglobin and hematocrit concentration changes on the second postoperative day, length of stay, range of knee motion, generic quality-of-life measures (EuroQol EQ-5D and EQ-VAS [visual analogue scale])[20], Oxford Knee Score (OKS)[21], complications (as per the protocol definitions), and a cost analysis. EuroQol and OKS assessments were conducted at baseline and three months postoperatively to capture the postoperative consequences of tranexamic acid on knee function.

The EuroQol instrument is designed for self-completion by the participant and contains two parts, the EQ-5D and EQ-VAS. It is cognitively simple and takes only a few minutes to complete. The EQ-5D descriptive system comprises five questions in the dimensions of mobility, self care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has three possible levels: 1 = no problems, 2 = some problems, and 3 = severe problems. This descriptive system can be converted to a weighted index to facilitate statistical comparisons. The EQ-VAS records the self-rated health of the participant on a vertical VAS on which the top of the scale represents the best imaginable health state and the bottom represents the worst imaginable state. The OKS, which was developed by the Oxford Group in 1998[22], comprises twelve questions. Each question is scored from 0 to 4, with 4 representing the best or least symptomatic outcome. The scores on the individual questions are added; thus, the overall score can range from 0 to 48[21].

The study was powered to detect an absolute 20% change in the rate of transfusion relative to the mean rate of 30% at our center; 144 patients (seventy-two in each group) were expected to provide 80% power to detect such a change at a 5% level of significance (which was considered appropriate since there was only one primary outcome). The target recruitment was increased by 10% to allow for loss to follow-up.

Surgical Technique and Drug Delivery

The total knee replacement was performed with use of a spinal anesthetic except in the event of a contraindication or difficulty, in which case a general anesthetic was used. The patient was positioned supine on the operating table. A thigh tourniquet was applied and was inflated to 350 mm Hg after patient preparation and draping. A standard medial parapatellar approach was used. The patella was not routinely resurfaced. Two 40-g batches of PALACOS cement (Heraeus Medical, Newbury, United Kingdom) were used. The drain was inserted and remained clamped for thirty minutes after the tourniquet was released. Designated operating room staff prepared either the study drug, 1 g of tranexamic acid in 50 mL of saline solution, or the placebo, 50 mL of saline solution with a similar color, smell, and feel. The solution was sprayed into the wound at the end of the total knee replacement. The wound was closed in layers and a pressure dressing made from a soft roll and crepe bandage (Softpore; Richardson Healthcare, Borehamwood, United Kingdom) was applied. The tourniquet was released after the dressing was fully applied.

Blood Transfusion Protocol

A transfusion protocol was utilized to standardize the use of blood transfusions. According to the protocol (based on the recommendations of the British Orthopaedic Association[23] and the British Committee for Standards in Haematology[24]), blood transfusion was not indicated when the hemoglobin concentration was >10 g/dL; was indicated when the hemoglobin concentration was <7 g/dL; was indicated when the hemoglobin concentration was <8 g/dL in a patient who tolerated anemia poorly; and was indicated when the hemoglobin concentration was between 7 and 10 g/dL in a patient who developed fatigue, palpitation, pallor, tachycardia, and tachypnea due to anemia.

Analgesia and Thromboembolism Prophylaxis Protocol

Patients received standard patient-controlled analgesia involving morphine for the first forty-eight hours and were then transitioned to oral analgesia. Patients received mechanical thromboprophylaxis by means of a calf pump; in addition, patients with a body mass index of >30 kg/m^2 received chemical thromboprophylaxis with low-molecular-weight heparin. A weight-based prophylactic dose of tinzaparin sodium (Leo Pharmaceuticals, Buckinghamshire, United Kingdom) was used beginning on postoperative day one and continuing until discharge.

Randomization and Masking

Randomization was web-based and provided by a commercial entity (Sealed Envelope). The site was accessed by designated, named operating room staff only, each of whom had been assigned a user name, password, and PIN (personal identification number). When a patient who had provided consent arrived at the operating room, the designated staff accessed the randomization web site. Anonymous basic details regarding the patient and surgeon were entered (to allow stratification and subsequent identification), and the staff confirmed this

TABLE I Baseline Characteristics of the Study Population

Variable*	Placebo Group	Tranexamic Acid Group
No.	78	79
Age† *(yr)*	67.1 ± 10.2	65.5 ± 9.6
Male sex‡	44 (56%)	30 (38%)
BMI† *(kg/m²)*	31.05 ± 5.03	32.24 ± 5.93
Osteoarthritis/rheumatoid arthritis§	65/3	72/4
Ischemic heart disease	14 (18%)	12 (15%)
Hypertension	43 (55%)	39 (49%)
History of CVA or TIA	4 (5%)	1 (1%)
Diabetes mellitus	5 (6%)	6 (8%)
Prescribed anti-platelet agent	27 (35%)	25 (32%)
Prescribed NSAID	21 (27%)	25 (32%)
Preop. hemoglobin† *(g/dL)*	13.6 ± 1.3	13.2 ± 1.3
Preop. hematocrit†	0.397 ± 0.036	0.39 ± 0.038
Preop. range of motion† *(deg)*	93.6 ± 28.14	96.4 ± 18.38
Preop. OKS†	19.4 ± 7.7	19.3 ± 7.7
Preop. EuroQol index†	0.431 ± 0.33	0.377 ± 0.31
Preop. EQ-VAS, max. 100†	59.4 ± 18.3	61.5 ± 21.8
DVT prophylaxis with LMWH	32 (41%)	38 (48%)
Tourniquet time† *(min)*	72 ± 10.2	74 ± 10.2
General/spinal anesthesia#	7/65	3/66

*BMI = body mass index, CVA = cerebrovascular accident, TIA = transient ischemic attack, NSAID = nonsteroidal anti-inflammatory drug, DVT = deep venous thrombosis, and LMWH = low-molecular-weight heparin. †The values are given as the mean and the standard deviation. ‡The percentages were significantly different. §A few patients with other diagnoses are not listed. #A few patients who received combined anesthesia are not listed.

information before randomization. A unique identification number and the allocation group were subsequently assigned. The staff prepared the study medicine and provided it to the surgeons. The surgeons, their team members, and the patient remained blinded to the allocation. The outcomes measures consisted of objective data (blood transfusion, hemoglobin level, hematocrit level, and length of stay) and patient self-reported questionnaires.

Regulatory Framework, Registration, and Interim Analysis

The study was registered with EudraCT (the European Union Drug Regulating Authorities Clinical Trials) (number 2007-007813-35), the ISRCTN register (number 68578366), and the National Research and Ethics Service (number 08/H0906/57). It was approved by the National Research and Ethics Service in June 2008 and by the Medicine and Healthcare products Regulatory Authority (MHRA) in July 2008. Recruitment was started in August 2008 and finished in June 2009.

An independent data monitoring committee reviewed the data to assess the safety profile when seventy-five patients had been recruited. The criteria for premature termination of the study were a significant excess of complications such as deep venous thrombosis or fatal pulmonary embolism in the tranexamic acid group compared with the placebo group.

Analysis

Analysis was on the basis of intention to treat. The primary outcome was the proportion of patients who received blood transfusions. Categorical outcomes (e.g., the blood transfusion rate and complications) were analyzed with use of the Fisher exact test. Continuous outcomes (e.g., blood loss, the volume transfused, and hemoglobin and hematocrit concentration decreases) were analyzed with use of the independent-samples t test. Since some continuous data distributions were highly skewed, bootstrapped estimation (10,000 bootstrap samples) was also performed and was reported when the result differed qualitatively from the parametric findings. The number of units of blood transfused was analyzed with use of the Mann-Whitney U test. A p value of 0.05 was considered significant.

Source of Funding

The study was funded jointly by the Department of Trauma and Orthopaedics and the Department of Research and Development, University Hospitals of North Tees and Hartlepool, Stockton-on-Tees, United Kingdom. No external funding was received.

Results

During the recruitment period from August 2008 to June 2009, 380 patients were scheduled to have a total knee replacement in the University Hospitals of North Tees and Hartlepool. One hundred and sixty patients were not approached because of the unavailability of research staff, thirty-five declined participation, twenty-seven were ineligible, and one was excluded after randomization because he underwent a unicompartmental knee replacement. The remaining 157 eligible participants were recruited and formed the study cohort; seventy-eight were randomized to the placebo group and seventy-nine, to the tranexamic acid group (Fig. 1). One patient who was

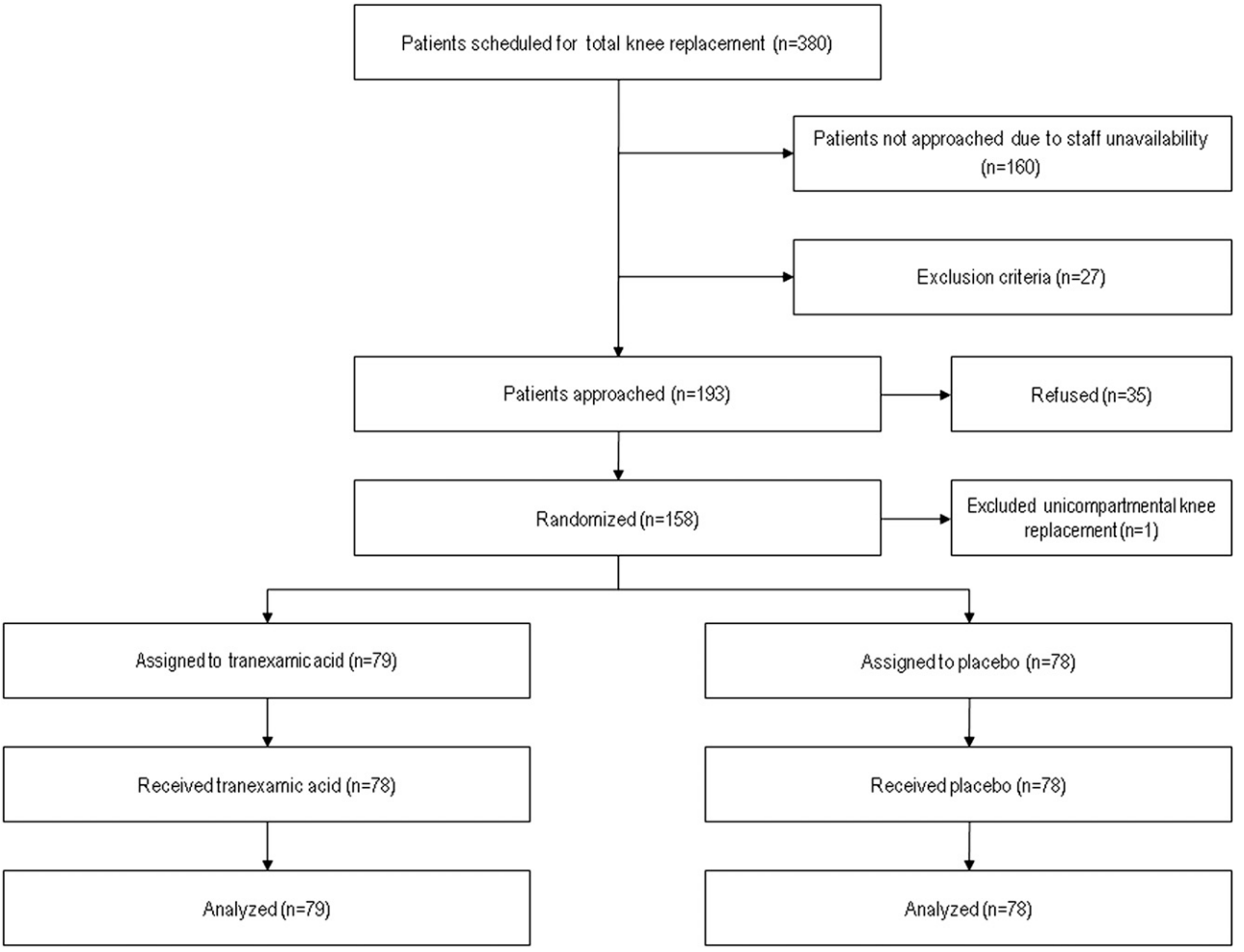

Fig. 1
Flow of patients through the study.

randomized to receive tranexamic acid but did not receive it was analyzed in the tranexamic acid group on the basis of the intention-to-treat principle.

The two groups were similar at baseline (Table I) with the exception of a chance imbalance in sex (56% male in the placebo group compared with 38% in the tranexamic acid group; $p = 0.025$). The eight surgeons who participated in the trial treated two to fifty-six patients each, but stratification ensured that each surgeon performed similar numbers of procedures in which tranexamic acid and placebo were administered.

Blood Transfusion

Thirteen participants (16.7%) in the placebo group and one (1.3%) in the tranexamic acid group required blood transfusions; the absolute risk reduction of 15.4% was significant ($p = 0.001$) (Table II).

Table I reveals that the only baseline characteristic that differed significantly between the two groups was sex. There was no prior rationale for believing that sex would interact with treatment in the study. A sensitivity analysis to investigate the effect of sex on the trial findings revealed no significant differences between male and female participants with respect to the blood transfusion rate ($p = 0.54$), drain blood loss ($p = 0.72$), decrease in hemoglobin concentration ($p = 0.58$), and length of stay ($p = 0.57$). Moreover, when sex was added to a logistic regression model with transfusion as the dependent variable and treatment as the extant explanatory variable, the model fit did not improve (difference in -2 log likelihood = 0.029; $p = 0.86$, chi-square test with one degree of freedom).

The fourteen transfused participants received two to six units of blood each. Thirty-two units were transfused into thirteen participants in the placebo group compared with only two units into one participant in the tranexamic acid group ($p = 0.001$, Mann-Whitney U test).

Blood Loss

The mean drain blood loss was 465 mL in the placebo group and 297 mL in the tranexamic acid group (mean difference, -168 mL; $p = 0.0003$). Total blood loss was estimated with use of the formula developed by Gross[25,26]. The mean total blood loss was 1725 mL in the placebo group and 919 mL in the tranexamic acid (mean difference, -806 mL; $p < 0.0001$). The blood loss

TABLE II Primary and Secondary Outcomes

	Placebo Group	Tranexamic Acid Group	Difference (95% CI)	P Value
Primary end point				
Transfusion	13/78 (16.7%)	1/79 (1.3%)	−15.4% (−25.4% to −7.5%)	0.001
Secondary end points*				
Drain blood loss *(mL)*	465 ± 298, n = 65	297 ± 196, n = 64	−168 (−256 to −80)	0.0003
Total blood loss *(mL)*	1725 ± 823, n = 61	919 ± 487, n = 64	−806 (−565 to −1048)	<0.0001
Postop. hemoglobin *(g/dL)*	10.69 ± 1.35, n = 78	11.52 ± 1.33, n = 79	0.83 (0.41 to 1.26)	<0.0001
Postop. hematocrit	0.31 ± 0.04, n = 78	0.34 ± 0.04, n = 79	0.027 (0.015 to 0.039)	<0.0001
OKS	35.9 ± 8.6, n = 45	34.8 ± 9.4, n = 53	−1.1 (−4.7 to 2.6)	0.557
EuroQol index	0.780 ± 0.24, n = 46	0.705 ± 0.31, n = 52	−0.075 (−0.188 to 0.037)	0.187
EQ-VAS	75.6 ± 16.8, n = 47	75.2 ± 19.2, n = 52	−0.4 (−7.6 to 6.9)	0.917
Length of stay *(d)*	6.1 ± 4.6, n = 72	4.8 ± 2.3, n = 77	−1.24 (−2.43 to −0.05)	0.041
Cost† *(£)*	1450 ± 1157, n = 72	1117 ± 538, n = 77	−333 (−630 to −37)	0.028

*The values in the two groups are given as the mean and the standard deviation, followed by the number of patients with available data. †Includes the hospital stay, blood transfusions, and tranexamic acid (in British Pound Sterling). In 2008, £1 = 1.6 United States dollars.

and the transfusion rate did not differ significantly between the patients who received low-molecular-weight heparin and those who received mechanical thromboprophylaxis only.

Postoperative Hemoglobin and Hematocrit

Hemoglobin and hematocrit levels were tested on postoperative day two unless there was an earlier clinical need. The postoperative hemoglobin level was significantly higher (difference, 0.83 g/dL; $p < 0.0001$) in the tranexamic acid group compared with the placebo group. Similarly, the postoperative hematocrit level was significantly higher (difference, 0.027, $p < 0.0001$) in the tranexamic acid group compared with the placebo group.

Hospital Stay, OKS, and EuroQol

Patients who received the placebo had a mean hospital stay of 6.1 days compared with 4.8 days for patients who received tranexamic acid (mean difference, −1.2 days; $p = 0.041$).

Knee function at the three-month follow-up visit was similar in the two groups, with a mean OKS of 35.9 in the placebo group compared with 34.8 in the tranexamic group (difference, −1.1; $p = 0.557$).

Quality of life at the three-month follow-up visit was similar in the two groups, with a mean EQ index of 0.780 in the placebo group compared with 0.705 in the tranexamic acid group (difference, −0.075; $p = 0.187$) and a mean EQ-VAS of 75.6 in the placebo group compared with 75.2 in the tranexamic acid group (difference, −0.4; $p = 0.917$).

Preliminary Cost Analysis

The major cost item, the index arthroplasty, was similar in the two arms of the trial. However, cost differences resulted from differences in the blood transfusion rate, length of hospital stay, and management of complications as well as from the cost of the tranexamic acid itself. Costs were calculated in British Pound Sterling; in 2008, £1 = 1.6 United States dollars. The unit price for blood was £133, the hospital per diem cost was £230, and the cost of the tranexamic acid was £2.20. It was not possible to calculate the costs of the complications. Conservatively, taking the costs associated with the tranexamic acid, transfusions, and length of stay into account, use of tranexamic acid was associated with a net cost saving of £333 (95% confidence interval [CI], £37 to £630) per patient ($p = 0.028$). The cost data were highly skewed; however, bootstrapped estimation yielded a similar net cost saving of £333 (95% CI, £62 to £641; $p = 0.044$).

Adverse Events

There were three complications in the tranexamic acid group (two deep venous thromboses and one superficial infection) and five in the placebo group (one transient ischemic attack, one chest infection, one periprosthetic fracture, one superficial infection, and one deep infection) (Table III). The diagnoses

TABLE III Complications During the Trial

Complication	Placebo Group	Tranexamic Acid Group	P Value
Deep venous thrombosis	0	2	0.497
Pulmonary embolism	0	0	—
CVA/TIA*	1	0	0.241
Chest infection	1	0	0.427
Periprosthetic fracture	1	0	0.427
Superficial infection	1	1	0.736
Deep infection	1	0	0.427

*CVA = cerebrovascular accident, and TIA = transient ischemic attack.

of deep venous thrombosis were confirmed by Doppler ultrasonography and were treated with low-molecular-weight heparin and warfarin. The heparin was discontinued when the international normalized ratio (INR) reached the therapeutic range (INR = 2 to 3). Warfarin was stopped after three months. The frequencies of these complications did not differ significantly between the two arms of the study. However, this should be interpreted with caution as the study was not designed to detect a difference in these complications. The low incidence rate of their occurrence would necessitate a very large number of participants to detect a difference precisely.

Discussion

Topical tranexamic acid appears to represent an effective way to reduce blood loss and blood transfusion following total knee replacement without substantial additional adverse effects. Only one participant in the tranexamic acid group received a blood transfusion compared with thirteen in the placebo group. Thus, topically applied tranexamic acid reduced the risk of transfusion thirteenfold. The NNT value (number needed to treat; in this case, the number of patients who would need to be treated with tranexamic acid to prevent transfusion of one unit of blood) was seven.

The study was powered to detect an absolute 20% change in the rate of transfusion relative to the mean rate of 30% at our center. There was a significant and clinically important 15.4% reduction in the absolute blood transfusion rate, consistent with findings from trials featuring intravenous tranexamic acid administration. However, the transfusion rate in the control group was much lower than predicted (16.7%), which precluded achieving the planned 20% absolute reduction. Although this should be interpreted with caution, a post hoc power calculation based on these findings suggests that the study retained 90% power to detect the observed difference.

Although a chance imbalance in sex occurred in the treatment allocation process, this did not influence the study findings. The simple nature of the study and intervention encouraged protocol adherence with very few deviations in treatment, although there was some variation in the completeness of outcome recording.

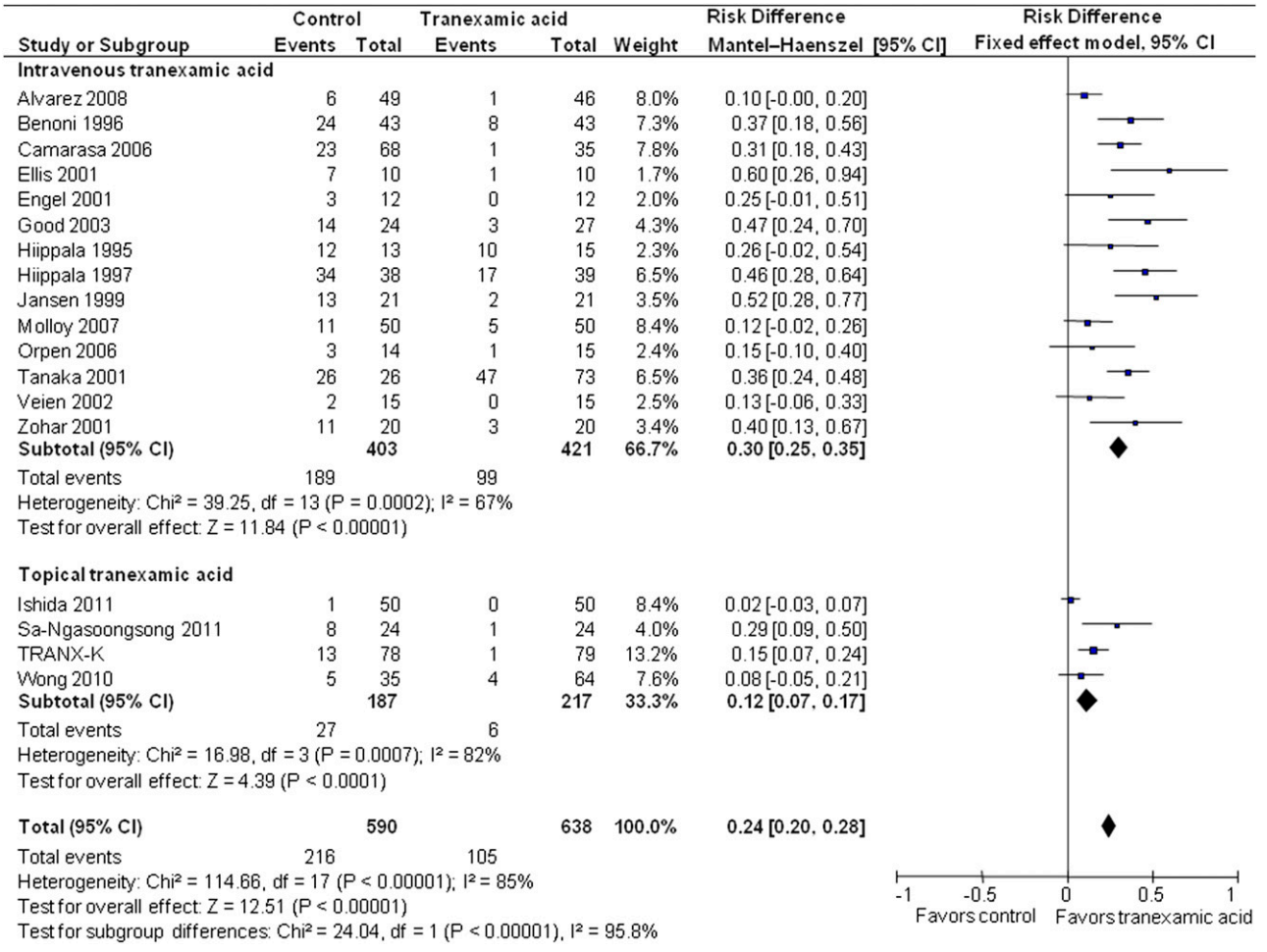

Fig. 2

Forest plot comparing published studies of intravenous and topical tranexamic acid. The studies that used intravenous tranexamic acid are listed in Benoni et al.[13]. df = degrees of freedom.

The study intervention was not expected to adversely affect either functional outcome or quality of life following total knee replacement. This was formally tested with use of the OKS and EuroQol measures, which participants were asked to complete preoperatively and at three months postoperatively. There were no significant differences between the two groups.

We identified three[27-29] previously published placebo-controlled trials addressing topical use of tranexamic acid. Wong et al.[27] investigated the use of topical tranexamic acid in ninety-nine patients undergoing knee replacement surgery. This was a three-arm trial comparing 3 g, 1.5 g, and placebo doses. The patients receiving 3 g and 1.5 g of tranexamic acid had mean postoperative hemoglobin levels that were 17% and 16% higher, respectively, than those in the placebo group. Transfusion rates were 0%, 13%, and 14% in the 3-g, 1.5-g, and placebo arms, respectively. Although these transfusion rates appear inconsistent with the reported changes in the hemoglobin concentration, they derive from a very small number of events and may be a chance finding. Ishida et al.[29] performed a trial that included 100 patients (fifty in each arm) and reported that one patient in the control group and none in the tranexamic acid group required blood transfusion. This may be a chance finding, but it is uncommon to find a case series on knee replacement without blood transfusion. Sa-Ngasoongsong et al.[28] reported on a small trial of only forty-eight patients (twenty-four in each arm). Topical tranexamic acid reduced the blood transfusion rate from 33% (eight of twenty-four) to 4% (one of twenty-four). Our present study was adequately powered to estimate changes in the transfusion rate and found a clear benefit for a 1-g dose.

Existing data on the effectiveness of topical and intravenous tranexamic acid administration on blood transfusion are summarized in the meta-analysis in Figure 2. Although topical tranexamic acid was effective in reducing the blood transfusion rate compared with placebo (risk difference, 12%; $p < 0.0001$), it does not appears to have been as effective as intravenously administered tranexamic acid (risk difference, 30%; $p < 0.0001$). However, there was significant heterogeneity in the findings ($I^2 = 85\%$, $p < 0.00001$), making the indirect comparison of doubtful value.

The short (three-month) duration of follow-up in the present study might have concealed a different long-term safety profile for the use of tranexamic acid. However, tranexamic acid has been available since 1964 and is believed to have a good safety profile. It has a biological half-life of 1.9 to 2.7 hours, with approximately 90% of an intravenously administered dose being excreted, largely unchanged, in the urine within twenty-four hours. Thus, the three-month follow-up period was adequate to observe attributable side effects or adverse reactions. A biomechanical study (named BioTRANX) was conducted to explore the longer-term effect of tranexamic acid on the mechanical performance of the replacement joint and will be reported separately. Approval will be sought to review the safety profile of tranexamic acid in the study participants at five and ten years postoperatively. This will include a review of medical notes and an invitation for patients to complete OKS and EuroQol questionnaires; if significant differences are apparent between the groups, the patients will be invited to return for clinical evaluation and radiographic assessment.

On the basis of our study findings, the routine use of topical (intra-articular) tranexamic acid following total knee replacement reduces bleeding and the need for blood transfusion, preventing many patients from undergoing unnecessary and potentially hazardous blood transfusions as well as reducing health-care costs. ■

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