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

A Randomized Controlled Trial (TRANX-H)

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Background: Approximately one-third of patients undergoing total hip replacement surgery require one to three units of blood postoperatively. Tranexamic acid is a synthetic antifibrinolytic agent that has been successfully used intravenously to control bleeding after total hip 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 161 patients undergoing unilateral primary total hip 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 Hip Score, length of stay, a cost analysis, and complications.

Results: Tranexamic acid reduced the absolute risk of blood transfusion by 19.6% (95% confidence interval [CI], 6.9% to 32.1%; $p = 0.004$), from 32.1% to 12.5%, and reduced blood loss by 129 mL (95% CI, 47 to 211 mL; $p = 0.002$), the hemoglobin concentration drop by 0.84 g/dL (95% CI, 0.41 to 1.27; $p < 0.0001$), the length of stay by 1.0 days (95% CI, −0.2 to 2.3 days; $p = 0.109$), and the cost per episode by £305 (95% CI, £0 to £610; $p = 0.05$). (In 2010, £1 = 1.5 U.S. dollars.) Oxford Hip Scores and EuroQol scores were similar at three months.

Conclusions: Topically applied tranexamic acid was effective in reducing blood loss and the need for blood transfusion following total hip replacement, avoiding the potential complications of intravenous tranexamic acid administration.

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

Blood loss and subsequent blood transfusion are common in trauma and orthopaedic surgery, and they may have a detrimental effect on the surgical outcome. Postoperative anemia may impede functional ability and delay discharge in this patient group. Although blood transfusion is relatively safe, it is not entirely free of risks (hemolysis, infection, immunosuppression, transfusion-related acute lung injury, and very rarely death). The risk of postoperative wound infection correlates with the amount of transfused allogeneic blood products, and there is a cost implication as well[1]. Thus, surgeons seek ways to minimize blood loss during surgery. Intravenous tranexamic acid is a synthetic antifibrinolytic agent that has been used successfully to stop bleeding in several surgical fields (including total hip replacement)[2-10]; however, it

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TABLE I Baseline Characteristics of the Study Population

Variable*	Placebo Group	Tranexamic Acid Group
Number	81	80
Age† *(yr)*	63 ± 11	66 ± 9
Male sex	33 (41%)	30 (38%)
BMI† *(kg/m²)*	28.5 ± 5.5	29.5 ± 4.5
Osteoarthritis	72 (95%)	78 (99%)
Ischemic heart disease	6 (7%)	6 (8%)
Hypertension	26 (35%)	32 (40%)
Hyperlipidemia	11 (14%)	18 (23%)
Diabetes mellitus	11 (14%)	9 (11%)
Chronic obstructive pulmonary disease	3 (4%)	7 (9%)
History of CVA or TIA	0 (0%)	0 (0%)
Prescribed anti-platelet agent	14 (17%)	16 (20%)
Prescribed NSAID	28 (35%)	33 (41%)
DVT prophylaxis with LMWH	53 (65%)	54 (68%)
Preop. hemoglobin† *(g/dL)*	13.19 ± 1.3	13.69 ± 1.2‡
Preop. hematocrit†	0.385 ± 0.036	0.401 ± 0.033‡
Preop. OHS†	15.6 ± 8.1	17.7 ± 8.8
Preop. EuroQol index†	0.205 ± 0.34	0.340 ± 0.32
Preop. EQ-VAS† *(%)*	53.7 ± 23.2	59.2 ± 21.1
General/spinal anesthesia	9/72	5/75
Cemented/uncemented/hybrid hip	4/60/17	4/60/16
Lateral/posterior approach	46/35	44/36

*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. ‡Significantly different.

is rarely adopted in orthopaedic practice and its use has not been practiced at our center for fear of systemic side effects, particularly thromboembolic complications. This was the case despite several systematic reviews and meta-analyses that did not indicate an increased thromboembolic risk associated with intravenous tranexamic acid[9,11-13].

Several cardiothoracic studies have investigated the value of locally applied tranexamic acid in reducing blood loss and allogenic blood transfusion[14,15]. We hypothesized that a topical application of tranexamic acid is easy to administer, provides a maximum concentration at the bleeding site, and avoids systemic absorption. Thus, we conducted a series of seven studies[9,11,16-18] (see Appendix), generally named TRANX studies, to evaluate this novel approach in trauma and orthopaedic surgery. There are substantial similarities in the various design aspects of these studies, and other published papers are cited to avoid repetition.

In England and Wales, more than 79,000 patients underwent total hip replacement in 2009[19]. It is estimated that one-third of these patients required transfusion of one to three units of blood, although the reported range of transfusion rates is large (25% to 84%)[2,3,20-23]. Although the TRANX-K study[18] showed that topical tranexamic acid was an effective way to reduce blood loss and blood transfusion following total knee replacement, without major additional adverse effects, we were not able to confidently translate the findings to total hip replacement. In total knee arthroplasty, the operation is performed in a bloodless field due to use of a tourniquet, resulting in no or negligible intraoperative blood loss but notable postoperative blood loss—the ideal situation for using topical tranexamic acid. Moreover, more bone and less soft tissue is cut in knee replacement surgery than in hip replacement. Although underpowered, a small randomized controlled trial[21] of thirty-nine patients that compared intravenous tranexamic acid with placebo given at the end of hip replacement found no effect on blood loss. However, the proportion of patients receiving a blood transfusion (the secondary outcome) was significantly less in the tranexamic acid group (9/20 compared with 15/19, $p = 0.05$). Thus, an adequately powered trial evaluating topical tranexamic acid for hip replacement is timely.

Materials and Methods

The TRANX-H (Tranexamic Acid in Total Hip Replacement) trial was a double-blind, placebo-controlled trial of the effect of topical (intra-articular) application of tranexamic acid on blood loss following total hip replacement. Patients undergoing unilateral primary total hip replacement were

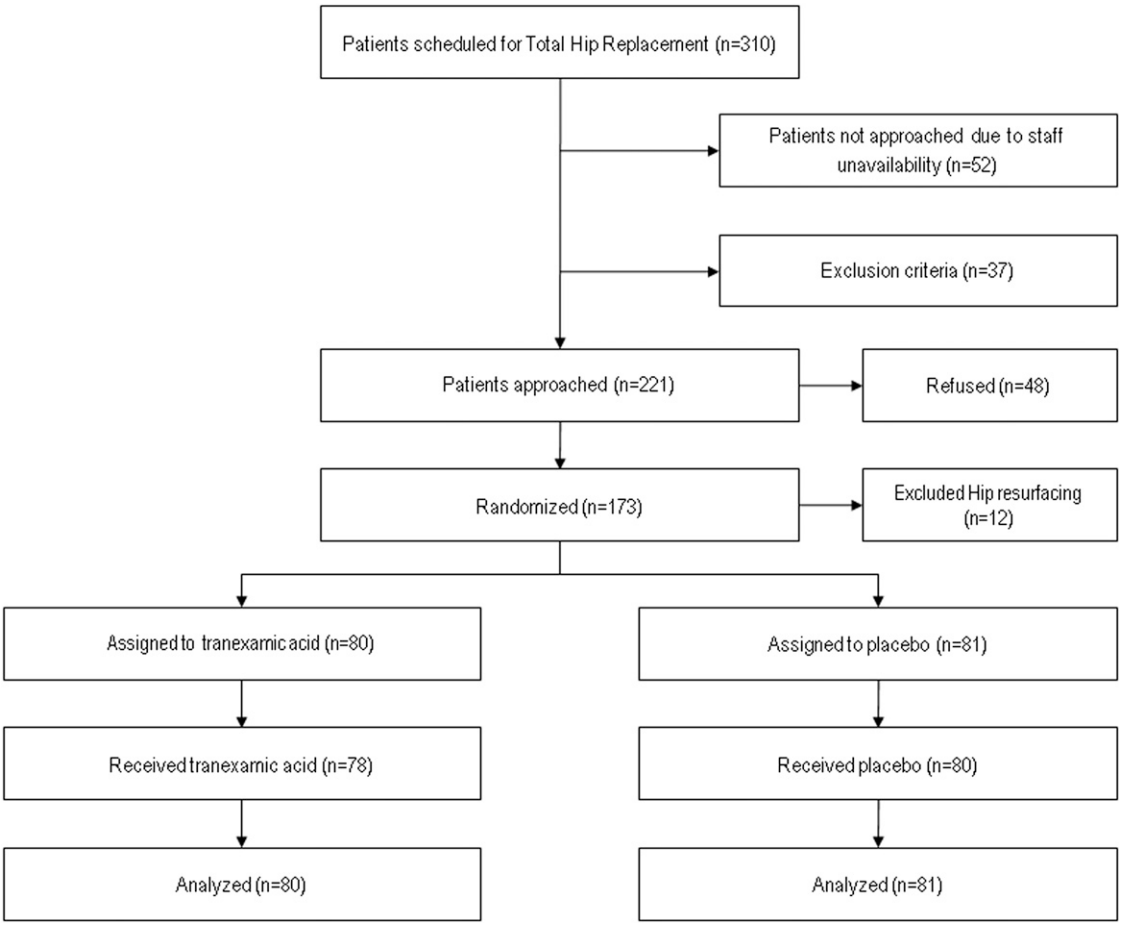

Fig. 1

Flow diagram of patients involved in the trial.

eligible for the trial. The exclusion criteria, randomization, masking, drug delivery, power and statistical analyses, blood transfusion protocol, primary outcome (transfusions), and secondary outcomes are similar to those used in the sister trial, TRANX-K, with the exception that the Oxford Hip Score (OHS) was used instead of the Oxford Knee Score. The OHS was developed by the Oxford Group in 1996[24]. It comprises twelve questions, each 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[25].

Although the thromboembolism prophylaxis protocol was initially the same as that in the TRANX-K trial, this was changed during the course of the study. Initially, all patients received mechanical thromboprophylaxis by means of a leg pump; patients with a body mass index (BMI) of >30 kg/m^2 additionally received chemical thromboprophylaxis with low-molecular-weight heparin. In January 2010, the National Institute for Health and Care Excellence (NICE) introduced a recommendation to use low-molecular-weight heparin in joint replacement; hence, ninety-five patients who underwent total hip replacement received low-molecular-weight heparin after this date. A weight-based prophylactic dose of tinzaparin sodium (Leo Pharmaceuticals, Buckinghamshire, United Kingdom) was used from postoperative day one until discharge in these patients.

The study was registered with EudraCT (the European Union Drug Regulating Authorities Clinical Trials) (number 2009-012141-34), the ISRCTN register (number 59245192), and the National Research and Ethics Service (number 09/H0906/62). It was approved by the National Research and Ethics Service in June 2009 and by the Medicine and Healthcare products Regulatory Authority (MHRA) in June 2009. Recruitment was started in August 2009 and finished in October 2010.

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 2009 to September 2010, 310 patients were scheduled to have a total hip replacement in the University Hospitals of North Tees and Hartlepool. Fifty-two patients were not approached because of the unavailability of research staff, forty-eight declined participation, thirty-seven were ineligible, and twelve were excluded after randomization because they underwent hip resurfacing. The remaining 161 eligible participants were recruited and formed the study cohort; eighty-one were randomized to the placebo group and eighty, to the tranexamic acid group (Fig. 1). Three patients deviated from the protocol; one patient randomized to each group did not receive either tranexamic acid or placebo, and one patient randomized to the tranexamic acid group was given intravenous tranexamic acid by the anesthetist. These deviations from the protocol did not influence the final outcome when

TABLE II Primary and Secondary Outcomes

	Placebo Group	Tranexamic Acid Group	Difference (95% CI)	P Value
Primary end point				
Transfusion	26/81 (32.1%)	10/80 (12.5%)	−19.6% (−32.1% to −6.9%)	0.004
Secondary end points*				
Drain blood loss *(mL)*	389 ± 187, n = 41	260 ± 188, n = 42	−129 (−211 to −47)	0.002
Total blood loss *(mL)*	1981 ± 1007, n = 38	1617 ± 188, n = 56	−364 (−742 to 15)	0.059
Postop. hemoglobin *(g/dL)*	9.78 ± 1.45, n = 81	10.62 ± 1.34, n = 80	0.84 (0.41 to 1.27)	<0.0001
Postop. hematocrit	0.29 ± 0.04, n = 79	0.31 ± 0.04, n = 78	0.024 (0.011 to 0.037)	<0.0001
OHS	35.2 ± 9.8, n = 44	32.4 ± 10.7, n = 46	−2.8 (−7.1 to 1.5)	0.198
EuroQol index	0.686 ± 0.33, n = 47	0.715 ± 0.30, n = 45	0.029 (−0.102 to 0.161)	0.658
EQ-VAS	71.5 ± 18.0, n = 47	78.7 ± 17.5, n = 44	7.1 (−0.26 to 14.5)	0.058
Length of stay *(d)*	6.2 ± 4.4, n = 80	5.2 ± 3.6, n = 79	−1.0 (−2.3 to 0.2)	0.109
Cost† *(£)*	1526 ± 1087, n = 80	1221 ± 842, n = 79	−305 (−610 to 0)	0.05

*The values in the two groups are given as the mean and the standard deviation, followed by the number of patients with available data. †In British Pounds Sterling. In 2010, £1 = 1.5 United States dollars.

analyses according to an intention-to-treat or a per-protocol basis were compared.

The two groups were similar at baseline (Table I) with the exception of a chance imbalance in the preoperative hemoglobin and hematocrit levels (hemoglobin, 13.19 g/dL in the placebo group compared with 13.69 g/dL in the tranexamic acid group; p = 0.011). The seven surgeons who participated in the trial treated fourteen to thirty-four patients each, but stratification ensured that each surgeon performed similar numbers of procedures in which tranexamic acid and placebo were administered.

Blood Transfusion

Twenty-six participants (32.1%) in the placebo group and ten (12.5%) in the tranexamic acid group required blood transfusions; the absolute risk reduction of 19.6% was significant (p = 0.004) (Table II).

The effect of the chance imbalance in the preoperative hemoglobin level on the findings was explored in a sensitivity analysis. It was anticipated that the preoperative level would be correlated with the postoperative level and the subsequent need for transfusion. A higher preoperative hemoglobin level in the tranexamic acid group might therefore overestimate the value of tranexamic acid in reducing the transfusion rate. In logistic regression with transfusion as the dependent variable and treatment as the extant explanatory variable, addition of the preoperative hemoglobin level significantly improved the model fit (difference in −2 log likelihood = 23.2; p < 0.001, chi-square test with one degree of freedom). The odds ratio for transfusion (placebo relative to tranexamic acid) was reduced from 3.3 (95% confidence interval [CI], 1.5 to 7.4; p = 0.032) to 2.6 (95% CI, 1.6 to 6.6; p = 0.032).

The thirty-six transfused participants received two to five units of blood each (eighty-four units in total). Sixty-four units were transfused into participants in the placebo group compared with twenty units in the tranexamic acid group (p = 0.003, Mann-Whitney U test).

Blood Loss

The mean drain blood loss was 389 mL in the placebo group and 260 mL in the tranexamic acid group (mean difference, 129 mL; p = 0.002). Total blood loss was estimated with use of the formula developed by Gross[26,27]. The mean total blood loss was 1981 mL in the placebo group and 1617 mL in the tranexamic acid group (mean difference, 364 mL; p = 0.059).

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, 0.84 g/dL; p < 0.0001) in the tranexamic acid group compared with the placebo group. Similarly, the postoperative hematocrit level was significantly higher (difference, 0.024; p < 0.0001) in the tranexamic acid group compared with the placebo group.

Hospital Stay, OHS, and EuroQol

Patients who received the placebo had a mean hospital stay of 6.2 days compared with 5.2 days for patients who received tranexamic acid (mean difference, 1.0 days; p = 0.109).

Hip function at the three-month follow-up visit was similar in the two groups, with a mean OHS of 35.2 in the placebo group compared with 32.4 in the tranexamic acid group (difference, −2.8; p = 0.198).

Quality of life at the three-month visit was similar in the two groups, with a mean EuroQol (EQ) index of 0.686 in the placebo group compared with 0.715 in the tranexamic acid group (difference, 0.029; p = 0.658) and a mean EQ-VAS (visual analog scale) of 71.5 in the placebo group compared with 78.7 in the tranexamic acid group (difference, 7.1; p = 0.058).

TABLE III Complications During the Trial

Complication	Placebo Group	Tranexamic Acid Group	P Value
Deep venous thrombosis	2	2	1.000
Pulmonary embolism	0	0	—
Superficial infection	1	2	0.529
Deep infection	0	0	—
Metal allergy	0	1	0.476
Dislocation	1	2	0.570
Total	4	7	0.413

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 Pounds Sterling; in 2010, £1 = 1.5 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 £305 (95% CI, £0 to £610) per patient ($p = 0.050$). The cost data were highly skewed; however, bootstrapped estimation yielded a similar net cost saving of £304 (95% CI, £15 to £613; $p = 0.046$).

Adverse Events

There were seven complications in the tranexamic acid group (two deep venous thromboses, two superficial infections, one metal allergy, and two dislocations) and four in the placebo group (two deep venous thromboses, one superficial infection, and one dislocation) (Table III). The diagnoses 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. There was no sciatic nerve irritation from the diluted dose of tranexamic acid used in the study. However, the study was not adequately powered to detect differences in rare complications. The low incidence rate of their occurrence would necessitate a very large number of participants to detect a small difference precisely.

Discussion

As in the TRANX-K study, this trial showed that topical tranexamic acid was effective in substantially reducing blood loss and blood transfusion following total hip replacement, without important additional adverse effects or impairment of functional outcomes. 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 secondary outcome recording.

A chance imbalance in the preoperative hemoglobin level occurred in the treatment allocation process. A post hoc exploration of its effect suggests that the reduction in transfusion risk may have been inflated as a result, but qualitatively the result was unchanged.

Visible drain blood loss was significantly lower in the tranexamic acid group, although it is understood that some blood loss is not clinically visible. Eipe and Ponniah[26] showed that surgical blood loss was underestimated by 64% when clinical methods were used to assess blood-soaked sponges and blood lost to suction bottles and the vacuum drain. They therefore recommended using a biochemical method based on the hematocrit level. In our study, the total blood loss was estimated with use of the Gross formula[26,27].

In a recent systematic review and meta-analysis[9] of eleven randomized controlled trials, intravenous tranexamic acid reduced blood loss and transfusion needs significantly. However, only one of the included trials had more than fifty participants. Only five studies described a transfusion trigger, which is essential to standardize blood transfusion as an outcome measure. No study used a generic quality-of-life measure or a disease-specific outcome measure. Overall, intravenous tranexamic acid reduced blood transfusion rates by 20% (range, −8% to 34%), comparable with topical tranexamic acid. A similar trend was seen in drain blood loss.

Our study was carefully designed to minimize error (minimizing bias through use of a randomized design and sampling error through adequate study power). The study design, protocol, and patient information sheets were reviewed by expert research bodies, and both the health professionals delivering care and the patients receiving care were blinded to the treatment allocation. Treatment and placebo solutions had the same color, smell, and feel, maintaining blinding throughout the surgery. The trial was developed to fulfill the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) group[28].

Some potential weaknesses became apparent during the study. The three-month follow-up period was thought to be adequate to identify known adverse events, but it might be inadequate to detect longer-term safety issues, such as accelerated wear of the joint due to exposure to tranexamic acid. 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.

In conclusion, the use of topical (intra-articular) tranexamic acid was an effective, safe, and cost-effective modality that reduced bleeding following total hip replacement. Intravenous tranexamic acid is distributed throughout the body fluids, reducing its therapeutic concentration in the hip joint. In contrast, topically applied tranexamic acid is distributed predominantly within the hip joint, thus achieving a higher therapeutic concentration at the bleeding site, effectively limiting blood loss with little or no systemic absorption and subsequent opportunity for systemic side effects. Long-term surveillance studies are appropriate to address remaining uncertainties about safety.

Appendix

eA A table summarizing the TRANX series of studies is available with the online version of this article as a data supplement at jbjs.org. ■

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