Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement

A PROSPECTIVE, RANDOMISED CONTROLLED TRIAL

D. O. Molloy,
H. A. P. Archbold,
L. Ogonda,
J. McConway,
R. K. Wilson,
D. E. Beverland

*From Musgrave Park
Hospital, Belfast,
Northern Ireland*

We performed a randomised, controlled trial involving 150 patients with a pre-operative level of haemoglobin of 13.0 g/dl or less, to compare the effect of either topical fibrin spray or intravenous tranexamic acid on blood loss after total knee replacement.

A total of 50 patients in the topical fibrin spray group had 10 ml of the reconstituted product applied intra-operatively to the operation site. The 50 patients in the tranexamic acid group received 500 mg of tranexamic acid intravenously five minutes before deflation of the tourniquet and a repeat dose three hours later, and a control group of 50 patients received no pharmacological intervention.

There was a significant reduction in the total calculated blood loss for those in the topical fibrin spray group ($p = 0.016$) and tranexamic acid group ($p = 0.041$) compared with the control group, with mean losses of 1190 ml (708 to 2067), 1225 ml (580 to 2027), and 1415 ml (801 to 2319), respectively. The reduction in blood loss in the topical fibrin spray group was not significantly different from that achieved in the tranexamic acid group ($p = 0.72$).

Total knee replacement (TKR) may result in blood loss ranging from 800 ml to 1724 ml.^{1,2} Attempts to reduce this are encouraged to avoid the risks of transfusion-related complications.^{3,4} Pharmacological measures which have been proven to reduce blood loss after TKR include topically applied fibrin sprays^{5,6} and the intravenous administration of tranexamic acid.⁷⁻¹⁰

Topical fibrin sprays are biological adhesives which initiate the final stages of coagulation. They have been shown to reduce blood loss after TKR by up to 55%.⁵ Their main disadvantages are the expense and the fact that they are derived from human blood products.

Tranexamic acid is an inhibitor of fibrinolysis which acts by blocking the lysine-binding site of plasminogen to fibrin. It has been reported to reduce intra-operative and post-operative blood loss after TKR.⁷⁻⁹ It has had considerable use in TKR, since the application of a pneumatic tourniquet leads to increased activation of local fibrinolysis in the involved limb.¹¹

The aim of our study was to compare the effect of a topical fibrin spray (Quixil; Johnson & Johnson Wound Management, Somerville, New Jersey) and of tranexamic acid on blood loss after TKR. The primary end-point was the calculated total blood loss. Secondary end-points included transfusion requirements,

post-operative leg swelling, pain scores, the length of stay in hospital and the rate of complications. Particular attention was paid to the rate of proximal deep-venous thrombosis (DVT).

Patients and Methods

Between December 2004 and October 2005, 150 patients scheduled to undergo a primary TKR were enrolled into a prospective, randomised, controlled study after approval of the study protocol by the local research authority and regional ethics committee.

Inclusion criteria included a pre-operative haemoglobin (Hb) level of 13.0 g/dl or less. Pilot data showed that patients were three times more likely to receive a post-operative transfusion if they had a pre-operative Hb level < 13.0 g/dl compared with those with a pre-operative Hb level > 13.0 g/dl. Exclusion criteria included previous surgery to the knee, with the exception of meniscectomy, bleeding disorders, platelet or bone-marrow disorders, a level of creatinine > 250 $\mu\text{mol/l}$ since this is a contraindication to the administration of tranexamic acid, or a history of thromboembolism. Two patients were excluded because they had high levels of creatinine and three declined to participate after reading the patient information sheet.

■ D. O. Molloy, MRCSI, MPhil,
Orthopaedic Registrar
■ H. A. P. Archbold, MRCS,
Orthopaedic Registrar
■ L. Ogonda, MRCS, MPhil,
Orthopaedic Registrar
■ J. McConway, MRCS,
Arthroplasty Research Fellow
■ R. K. Wilson, FRCS, MPhil,
Orthopaedic Registrar
■ D. E. Beverland, MD, FRCS,
Consultant Orthopaedic
Surgeon
Orthopaedic Outcomes
Department
Musgrave Park Hospital,
Stockmans Lane, Belfast,
BT9 7JB, Northern Ireland.

Correspondence should be sent
to Mr D. O. Molloy; e-mail:
dennis.molloy@greenpark.
n-i.nhs.uk

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Table I. Mean ($\pm$ SD) pre-operative details for the three groups

Group	Hb* (g/dl)	PCV†	C-reactive protein (umol/l)	Temperature (°C)	BMI‡
Fibrin spray	11.96 $\pm$ 0.91	0.36 $\pm$ 0.02	10.69 $\pm$ 11.8	36.6 $\pm$ 3.8	29.31 $\pm$ 4.9
Tranexamic acid	12.04 $\pm$ 0.85	0.36 $\pm$ 0.03	13.34 $\pm$ 19.8	36.4 $\pm$ 2.8	29.54 $\pm$ 4.9
Control	12.04 $\pm$ 0.74	0.36 $\pm$ 0.02	10.34 $\pm$ 11.0	36.6 $\pm$ 3.6	28.03 $\pm$ 4.4

* Hb, haemoglobin

† PCV, packed cell volume

‡ BMI, body mass index

The patients were randomised using a block-design technique with permuted blocks of five, which was concealed until interventions were assigned. After obtaining informed consent, they were allocated to their group the evening before surgery with 50 enrolled in each of the treatment groups and 50 assigned to a control group which received no pharmacological intervention. All completed follow-up.

The clinical details, the body mass index (BMI), and the American Society of Anaesthesiologists (ASA) grading¹² were recorded pre-operatively (Table I). The pre-operative level of Hb and C-reactive protein (CRP) and the haematocrit and activated prothrombin time were also recorded. The post-operative haematocrit measured at eight hours determined if a transfusion was indicated from a protocol with a threshold of 0.25. The Hb level on the first, second and third post-operative days was also recorded. The CRP level was recorded on the second post-operative day to determine if there was any difference in the inflammatory response between the groups. Any blood transfusion during the period of hospitalisation was recorded.

All patients received spinal anaesthesia of intrathecal 0.5% bupivacaine with intravenous midazolam or propofol for intra-operative sedation. Thigh and calf circumferences were measured pre-operatively. One surgeon (DEB) experienced in TKR performed or supervised all the operations. A standardised technique was used under a tourniquet which was deflated after the application of dressings. A midline incision and modified Insall approach¹³ were used in all cases. All the patients received a Low Contact Stress uncemented rotating platform prosthesis (Depuy, Leeds, United Kingdom) without patellar resurfacing. The hole created for the intramedullary guide rod was occluded with bone before implantation of the femoral component.

Those patients randomised to the topical fibrin group received 10 ml of the reconstituted product intra-operatively, with 6 ml sprayed on to the posterior capsule and surrounding soft tissues before the prosthesis was inserted, and the remaining 4 ml sprayed on to the bone which was exposed after placement of the prosthesis and on the soft tissues after closure of the capsule. Those randomised to the tranexamic group received 500 mg of tranexamic acid intravenously five minutes before deflation of the tourniquet and a repeat dose three hours later. The control group had no pharmacological intervention. All the patients and staff, except those directly administering the topical fibrin spray or tranexamic acid, were blinded to the

treatment, including those assessing and collecting the post-operative measurements, investigations and outcomes.

All the knees were placed in 90° of flexion for six hours post-operatively as is the senior surgeon's (DEB) policy. Thigh and calf circumferences were measured at levels 12 cm above and below the patella. Total increase in diameter (cm) of both the thigh and calf were recorded on the first, second and third days post-operatively as well as the body temperature using a tympanic thermometer. Pain scores were recorded every two hours post-operatively for the first 24 hours using a 100 mm visual analogue scale (VAS) in which 0 represented no pain and 100 the most severe pain.¹⁴ All patients received 150 mg of aspirin as a single dose the evening before surgery and daily for six weeks post-operatively as prophylaxis against DVT.

Calculation of total blood loss. The patient's blood volume (PBV) was calculated using the formula of Nadler, Hidalgo and Bloch¹⁵ as follows:

$$PBV = (k1 \times height^3 (m)) + (k2 \times weight (kg)) + k3,$$

where $k1 = 0.3669$, $k2 = 0.03219$ and $k3 = 0.6041$ for men and $k1 = 0.3561$, $k2 = 0.03308$ and $k3 = 0.1833$ for women.

Multiplying the PBV by the haematocrit (Hct), gives the red blood cell (RBC) volume. Thus a change in the RBC volume can be calculated from a change in the Hct level¹⁶ as follows:

$$\text{Total RBC volume loss} = PBV \times (\text{Hct pre-op} - \text{Hct post-op}).$$

Transfusions (mean volume per unit, 285 ml) were taken into account by calculating the total blood loss as follows:

$$\text{Total blood loss (litres)} = \text{Total RBC volume loss} + (\text{Number of units transfused} \times 0.285) \div ((\text{Hct pre-op} + \text{Hct post-op}) \div 2).$$

The number of units of blood transfused during the hospital stay was recorded, along with any complications attributed to the surgery or occurring within 90 days of the operation.

Statistical analysis. A power calculation based on pilot data showed that 50 patients in each group would be required to show a difference of 0.5 g/dl in the post-operative decrease in Hb with an α value = 0.05, a β level = 0.10, and

Table II. Mean ($\pm$ SD) post-operative details for the three groups

Group	Hb* (g/dl)	Total blood loss (ml)	Leg swelling† (cm)	VAS‡ scores (6 hours post-operatively)	Transfusion rate (units/ patient)
Fibrin spray	2.68 $\pm$ 1.02	1190 $\pm$ 490	7.35 $\pm$ 3.0	17.6 $\pm$ 15.9	0.22 $\pm$ 0.62
Tranexamic acid	2.75 $\pm$ 1.03	1225 $\pm$ 499	8.26 $\pm$ 4.0	19.4 $\pm$ 17.9	0.16 $\pm$ 0.51
Control	3.20 $\pm$ 1.12	1415 $\pm$ 416	8.72 $\pm$ 4.3	20.03 $\pm$ 20.4	0.34 $\pm$ 0.69

* Hb, haemoglobin

† calf and thigh measured

‡ VAS, visual analogue scale

a power of 90%. Independent samples *t*-tests and one-way analysis of variance (ANOVA) were used in the analysis of the results using SPSS version 11.0 (SPSS Inc., Chicago, Illinois). All 150 randomised patients were included in the data analysis with a level of significance set at $p \leq 0.05$.

Results

The mean calculated blood loss for the topical fibrin spray, tranexamic acid and control groups was 1190 ml (708 to 2067), 1225 ml (580 to 2027) and 1415 ml (801 to 2319), respectively (Table II). Both the topical fibrin spray and tranexamic acid groups differed significantly from the control group ($p = 0.016$ and $p = 0.041$, respectively), but there was no significant difference between the topical fibrin spray and the tranexamic acid groups ($p = 0.72$).

There were no significant differences between the clinical characteristics, pre-operative blood parameters or peri-operative temperatures between the groups. Swelling of the leg on the first, second and third post-operative days was least in the topical fibrin group and greatest in the control group (Table II). Pain scores were analysed and compared between the groups. They showed no statistical difference between the groups but followed the trend of leg swelling.

Transfusion rates were also analysed. Seven patients (14%) in the topical fibrin group, five (10%) in the tranexamic acid group and 11 (22%) in the control group received a transfusion post-operatively. There was no significant difference in the number of patients transfused or in the mean number of units transfused between the fibrin spray ($p = 0.72$) or tranexamic acid group ($p = 0.79$). (Table II).

The CRP level increased significantly in all groups ($p = 0.12$) with no significant differences in increase between the groups (topical fibrin $p = 0.71$, tranexamic acid $p = 0.62$).

The topical fibrin group had the mean shortest length of stay of 4.82 days (3 to 11) in hospital, followed by the tranexamic acid group with a mean of 5.10 days (2 to 25) and the control group with a mean of 5.86 days (2 to 33).

Complications. Two patients, both from the control group, developed a superficial wound infection, which responded to short courses of oral antibiotics. No deep infections occurred. One patient in the tranexamic acid group received intravenous antibiotics for a chest infection from the second day post-operatively.

One patient from the topical fibrin group developed a femoral DVT and was given warfarin therapy 25 days after surgery and another from the same group suffered a pulmonary embolism, confirmed by spiral CT, and was given warfarin 20 days after surgery. Patients who did not show clinical evidence of DVT were not systematically investigated. There were no fatalities during the study.

Discussion

The administration of systemic tranexamic acid has been shown to reduce blood loss by up to 45% when used in TKR.⁸ Its efficacy and safety at TKR have been proven in other studies.⁷⁻¹⁰ We compared its use with that of a topical fibrin spray, the safety and efficacy of which, in producing a reduction in blood loss of up to 55% after TKR, have also been reported.⁵ In similar groups of patients undergoing TKR with a standardised operating technique, post-operative care, and rehabilitation programme, we found a significant reduction in blood loss of 15.9% between the control group and the topical fibrin spray group ($p = 0.016$) and of 13.4% between the control group and the tranexamic acid group ($p = 0.041$). The difference in the reduction of blood loss was not significant between the patients in the topical fibrin and tranexamic acid groups ($p = 0.72$).

When we examined the transfusion rates we found that those in the tranexamic acid group received fewer allogenic blood transfusions than those in the topical fibrin group although those in the tranexamic acid group had a higher mean blood loss. This was because some patients received blood transfusions in breach of the transfusion protocol since they were deemed to be necessary medically as a result of hypotension or tachycardia. However, both topical fibrin and tranexamic acid reduced allogenic transfusion rates by 35% and 52.9%, respectively.

As a measure of the inflammatory response the lack of difference in the CRP level between all the groups did not indicate that the therapeutic interventions disturbed the inflammatory process.

The reduction in blood loss produced by the topical fibrin spray was not as marked as that reported in other studies.^{5,6} Possibly this was because we did not spray the prepared bone surfaces before placement of the cementless components as we felt there was a possibility that topical fibrin spray might interfere with bony ingrowth into the porous-backed prosthesis. Trends identified in our study, such as the length of stay in hospital, may have reached

statistical significance if a larger number of patients had been involved.

At the time of our study, the cost of the pharmaceutical intervention involved in the topical fibrin group was £380 per patient whereas in the tranexamic acid group it was less than £4.

Our study supports the routine use of intravenous tranexamic acid at the time of primary TKR, and that the increased blood-sparing effect of the topical fibrin spray did not justify its additional cost.

Although none of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, benefits have been or will be received but will be directed solely to a research fund, foundation, educational institution, or other nonprofit organisation with which one or more of the authors are associated.

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