The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement

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Tranexamic acid is a fibrinolytic inhibitor which reduces blood loss in total knee replacement. We examined the effect on blood loss of a standardised intravenous bolus dose of 1 g of tranexamic acid, given at the induction of anaesthesia in patients undergoing total hip replacement and tested the potential prothrombotic effect by undertaking routine venography. In all, 36 patients received 1 g of tranexamic acid, and 37 no tranexamic acid. Blood loss was measured directly per-operatively and indirectly post-operatively. Tranexamic acid reduced the early post-operative blood loss and total blood loss (p = 0.03 and p = 0.008, respectively) but not the intraoperative blood loss. The tranexamic acid group required fewer transfusions (p = 0.03) and had no increased incidence of deep-vein thrombosis. The reduction in early post-operative blood loss was more marked in women (p = 0.05), in whom this effect was dose-related (r = -0.793).

Our study showed that the administration of a standardised pre-operative bolus of 1 g of tranexamic acid was cost-effective in reducing the blood loss and transfusion requirements after total hip replacement, especially in women.

Post-operative anaemia is a recognised complication of total hip replacement (THR). It can increase the length of hospital stay, delay rehabilitation and is poorly tolerated by patients with vascular disease. Homologous blood transfusion is commonly used to correct blood loss in surgical patients. However, it is associated with a risk of infection, viral transmission, fluid overload and high cost.

A variety of blood-conserving techniques have been developed to reduce the need for homologous blood transfusion (Table I). Perioperative blood salvage has not proven to be cost-effective in primary joint replacement and requires specialised equipment and trained staff. The most significant prognostic indicator for post-operative transfusion is the pre-operative level of haemoglobin (Hb). In a retrospective study of 370 hip and knee replacements Salido et al reported a rate of blood transfusion of 69% when the pre-operative Hb was less than 13 g/dl and of only 13% when it exceeded 15 g/dl. While pre-operative autologous blood donation is suitable for patients who have a healthy pre-operative level of Hb, it is this group which is the least likely to need post-operative transfusion.

Fibrinolytic inhibitors such as aprotinin and tranexamic acid have been shown to be cost-effective in reducing blood loss in surgery, particularly cardiac surgery. The use of a tourniquet during total knee replacement (TKR) activates fibrinolysis transiently by enhancing the release of tissue plasminogen activator (t-PA), and a similar mechanism occurs in THR, activated by surgical trauma. By 24 hours after surgery, the body has responded by inhibiting this fibrinolysis. Antifibrinolytics are thought to potentiate this inhibition at an earlier stage by competitively inhibiting the activation of plasminogen to plasma. Tranexamic acid is a cheaper, more specific fibrinolytic inhibitor than aprotinin, and has been shown to reduce the need for blood transfusion in TKR.

The efficacy of tranexamic acid in THR remains uncertain. Studies in THR have varied in their protocol of administration with bolus concentrations of 10, 15 and 20 mg/kg being used with or without subsequent infusion. Those using the lower dose of 10 mg/kg, at the beginning of surgery, have yielded contrasting results ranging from reduction in blood loss and transfusion requirement to no difference in perioperative bleeding and increased transfusion requirement. Those using the higher doses of 15 to 20 mg/kg have generally shown no change in intraoperative blood loss, but reduced post-operative and total blood loss with associated decreased transfusion requirements. Claey et al postulated
that there was no effect on the intraoperative blood loss because tranexamic acid delayed lysis of the fibrin clot by the proteolytic action of plasmin, rather than by influencing primary haemostasis and coagulation.

Benoni et al. showed that the administration of tranexamic acid at the end of surgery had little effect on blood loss. The biological explanation for this finding was that tranexamic acid acts on the early phase of the fibrinolytic cascade, before plasminogen is bound to the fibrin surface, and that a reduction of 80% in the activity of the proteolytic action of plasminogen activator is needed to suppress fibrinolysis. Therefore in order to be effective, tranexamic acid must be administered to give therapeutic blood concentrations at this early phase. This would span the duration of the surgery, as well as the immediate post-operative period.

Tranexamic acid has a therapeutic blood concentration of 5 mg/l to 10 mg/l. An intravenous dose of 10 mg/kg maintains this plasma concentration for three hours. Claey s et al. suggested that a dose of 10 mg/kg would not be sufficient to prevent post-operative bleeding and that higher doses would be required to be effective. However, with a larger dose of 20 mg/kg the level is maintained for eight hours, which may have the potential to cause prothrombotic complications. In addition, the calculation of dosage per kilogram is open to human error in the dose administered. For ease of use, a single standardised dose administered before surgery would provide the most attractive strategy if it could be proven to be effective.

The fibrinolytic inhibition which occurs at 24 hours is due to an increased release of plasminogen activator inhibitor (t-PAI) which inactivates t-PA. Studies have shown that this response is not augmented by subsequent bolus doses or continuous infusion of tranexamic acid.

The half-life of 1 g of intravenously administered tranexamic acid has been found to be 1.9 hours and plasma concentrations remain above the minimum therapeutic level for up to four hours. Three previous studies have investigated the use of a single pre-operative dose of 1 g of tranexamic acid, and while they have shown a reduction in post-operative blood loss, the numbers were small, the reduction in blood transfusion and cost-benefit were not investigated, and there was no routine investigation for thromboembolism.

We have therefore studied the effect of the administration before THR of a standardised dose of 1 g of intravenous tranexamic acid. The intraoperative blood loss, the post-operative reduction in haematocrit and level of Hb, and the blood-transfusion requirements were analysed. The potential prothrombotic effect of the antifibrinolytic was studied using venography to exclude deep-vein thrombosis.

Patients and Methods

Our data-set has been derived from a randomised, double-blind thromboprophylaxis study with approval of the ethics committee. In the unrelated thromboprophylaxis study patients were randomly assigned to receive oral rivaroxaban 10 mg once daily for 31 to 39 days (with placebo injection for 10 to 14 days) or enoxaparin 40 mg once daily subcutaneously for 10 to 14 days (with placebo tablet for 31 to 39 days). It was noted that some patients had received tranexamic acid according to the surgeon’s preference. There were 73 patients in the study, 36 (13 men, 23 women) in the group which received tranexamic acid and 37 (13 men, 24 women) in the control group which did not. The mean age of both groups was 67.5 years (SD 10.3). The level of Hb and the haematocrit were measured pre-operatively and at one, six and 13 days post-operatively. The intra-operative blood loss, height, weight, type of anaesthesia, cementing and surgical time were documented.

An estimated blood volume was calculated for each patient using the formula:

\[ \text{Blood volume (BV)} = 70 \times \text{weight (kg)} \]

All the operations involved the use of a conventional stemmed unilateral THR. Cemented, uncemented and hybrid THRs were used. The method of anaesthesia was either spinal epidural with or without an indwelling catheter or spinal or epidural only, according to the anaesthetist’s preference. In the tranexamic acid group a single dose of 1 g was administered intravenously before the skin incision. In the control group, none was given. The intra-operative blood loss was calculated from the volume of fluid within suction drains and the swabs used during surgery. Post-operatively, when a drain had been used, the volume was recorded at 24 hours when it was removed.

The early reduction in Hb level and the fall in the haematocrit were defined as the difference in Hb or haematocrit between the pre-operative and post-operative sample taken on the evening of the day of surgery. The late reduction was defined as the difference between the post-operative level taken on the evening of surgery and that taken on day six. The early and late changes were also expressed as a percentage of the pre-
operative Hb or haematocrit. The maximum reduction in Hb and haematocrit was calculated for each patient by subtracting the lowest post-operative Hb or haematocrit from the pre-operative value.

Actual blood loss (ABL) was calculated using the formula of Gross\cite{36} as follows:

\[\text{Estimated ABL} = \text{estimated blood volume} \times \left(\frac{\text{haematocrit reduction}}{\text{mean haematocrit}}\right)\]

where the reduction in haematocrit was the difference between the pre-operative and the lowest post-operative haematocrit.

Significant complications were recorded. The decision to transfuse a patient was made by the duty physician after the clinical assessment of anaemia. No set transfusion level was implemented. At a mean of 36 days (SD 4) post-operatively a venogram was performed to assess the presence of DVT.

**Statistical analysis.** Student \(t\)-test, the chi-squared test and Pearson’s correlation coefficient were used to analyse the data. A \(p\)-value \(\leq 0.05\) was considered to be statistically significant.

**Results**

Table II gives the details of the patients. Patient demographics, clinical details and the pre-operative level of Hb and haematocrit in the study group and control groups were similar (Table II). A dose of 1 g of tranexamic acid equated to a mean dose of 15.0 mg/kg (SD 3.5) in women and to 12.9 mg/kg (SD 1.7) in men (\(p = 0.05\)).

The results of the haematological investigations are given in Table III. There was no statistically significant difference in intra-operative blood loss between the groups measured by actual volume or in percentage terms (\(p = 0.7\) and \(p = 0.57\), respectively). The mean percentage early fall in the haematocrit in the tranexamic acid group was 21% less than that in the control group (\(p = 0.03\)). There was no statistically significant difference in the mean late percentage reduction in Hb or haematocrit in the groups (\(p = 0.48\) and \(p = 0.99\), respectively). The mean maximum decrease in Hb was 16.6% lower in the tranexamic acid group than in the control group (\(p = 0.004\)) (Fig. 1). The mean maximum percentage decrease in haematocrit was 16.7% lower in the tranexamic acid group than in the control group (\(p = 0.008\); Fig. 2). The estimated total mean actual blood loss was significantly less (18.5%) in the tranexamic acid group than in the control group (\(p = 0.03\)).

Gender comparison results are shown in Table IV. The mean actual blood loss was greater in men (1896 SD 861) than in women (1567 SD 593) in the control group although the difference was not statistically significant (\(p = 0.18\)). Also in the control group the mean percentage late reduction in haematocrit was significantly more in men (12.3 SD 10.6) than in women (4.4 SD 10.0) (\(p = 0.03\)) (Fig. 3). This difference was not seen in the tranexamic acid group, in which the mean percentage late reductions were similar in men and women. There was no significant difference in the mean percentage early reduction in Hb and haematocrit in men (16.9 SD 8.7, 16.9 SD 8.6, respectively) and women (19.7 SD 7.7, 2.04 SD 9.5, respectively) in the control group.

The mean percentage early fall in the haematocrit was significantly lower in women in the tranexamic acid group (15.8 SD 6.0) compared with those in the control group (20.4 SD 9.5) (\(p = 0.05\)). A similar difference was not seen in

**Table II. Details of the patients in both groups**

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>67.5 (11.0)</td>
<td>67.7 (9.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Mean body mass index in kg/m² (SD)</td>
<td>26.5 (5.8)</td>
<td>25.9 (5.1)</td>
</tr>
<tr>
<td>Mean pre-operative Hb g/dl (SD)</td>
<td>13.0 (1.3)</td>
<td>13.4 (1.3)</td>
</tr>
<tr>
<td>Mean pre-operative haematocrit (SD)</td>
<td>0.38 (0.04)</td>
<td>0.39 (0.04)</td>
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<td>26/5/6</td>
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<td>Osteoarthritis</td>
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<td>36</td>
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<td>1</td>
</tr>
<tr>
<td>Anaesthesia</td>
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<td></td>
</tr>
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<td>14</td>
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<tr>
<td>Spinal + epidural without indwelling catheter</td>
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<td>4</td>
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<td>9</td>
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<td>2</td>
</tr>
<tr>
<td>Mean (SD) operating time in mins</td>
<td>79.3 (25.4)</td>
<td>69.1 (23.7)</td>
</tr>
</tbody>
</table>
the men. In addition, women in the tranexamic acid group had significantly lower mean percentage maximum reductions in Hb and haematocrit (24.1 SD 5.4, 23.6 SD 5.1 respectively) than women in the control group (27.6 SD 5.5, 27.2 SD 6.9, respectively) (p = 0.03 and p = 0.05, respectively). In men, although these values were lower in the tranexamic acid group, they were not statistically significant (p = 0.06 and p = 0.07 respectively). Men in the tranexamic acid group had a lower mean percentage late reduction in Hb and mean actual blood loss (6.1 SD 9.3, 1420 SD 281, respectively) than in the control group (12.7 SD 10.2, 1896 SD 861, respectively), but this was not statistically significant (p = 0.10 and p = 0.07 respectively).

In women there was a negative correlation between the dose per kilogram of tranexamic acid and the total blood loss (r = -0.793; Fig. 4). In men no correlation was seen (r = 0.075; Fig. 4).

In the tranexamic acid group, two patients had an episode of low oxygen saturation, 13 had an episode of hypotension and six low urine output. In the control group, one patient experienced low oxygen saturation, 17 hypotension and four low urine output.

No episode of pulmonary embolism occurred in either group. Venography confirmed one case of DVT in the tranexamic acid group and two in the control group. In total, six patients (three in each group) did not have a venogram. Venepuncture was unsuccessful in two patients, one patient had diarrhoea, one had shingles and two failed to attend for follow-up. None of these patients had any clinical signs or symptoms of DVT.

Three patients in the tranexamic acid group required a blood transfusion, compared with ten in the control group (p = 0.04, chi-squared test). A total of six units of blood was transfused in the tranexamic acid group, compared with 21 units in the control group (p = 0.07). The variance was statistically significant (p < 0.001, F-test).

**Discussion**

In our study, post-operative blood loss was measured indirectly as a fall in Hb or haematocrit levels. This may be a more accurate method than directly measuring drainage fluid since hidden blood losses can occur, particularly in post-operative haematomas.\(^7\) Such loss can be difficult to measure, and ultrasonographic examination of these haematomas have suggested that it is often underestimated.\(^17\) An intermediate measurement at day three may also have been a useful parameter since it has been shown that the Hb level plateaus by this time.\(^15\) The intra-operative blood loss in our study was calculated by
measurement of fluid within suction chambers and the estimation of blood in swabs which may vary between observers.

Since the study was not blinded, there may be concerns regarding selection bias, but other than when there were specific contraindications, the surgeons’ preference was routinely followed for all patients.

Our study showed that the intraoperative blood loss was not influenced by the administration of 1 g of tranexamic acid, which is consistent with the results of other studies using this dose.28-30 We found that early blood loss and total blood loss were significantly reduced in the tranexamic acid group while the late blood loss was not. Again, this was consistent with the findings of previous studies and supported the hypothesis that tranexamic acid induces inhibition of early fibrinolysis before the body’s usual response after 24 hours.28-30

Within the control group in our study the actual total blood loss was greater in men than in women, although the difference was not statistically significant (p = 0.18). Other studies report similar gender-specific findings in hip and knee replacement.39-41 By comparison, in the tranexamic acid group the mean actual total blood loss in men and women was similar, suggesting that the administration of 1 g of tranexamic acid reduces blood loss to a similar level in both genders.

Our study showed that when tranexamic acid was not used, the blood lost in the late post-operative period was significantly greater in men than in women. This is a new finding. Another study has noted that post-operative drainage was significantly higher in men than in women after THR.42

We have shown that the reduction in total blood loss and early post-operative blood loss after a single dose of intravenous tranexamic acid of 1 g was more pronounced in women than in men. This has not been previously reported, possibly due to small numbers in previous reports.28-30 Our study also showed that in women a dose-related response was seen in the reduction in blood loss with a correlation of r = -0.793 whereas in men this was not seen (r = 0.075). This may account for the more marked reduction in blood loss seen with tranexamic acid in women. This itself may be a function of the effective dose per kilogram which for women produced a mean dose of 15 mg/kg (SD 3.5) and for men 12.9 mg/kg (SD 1.7).

The relatively greater proportion of blood lost in the early post-operative period in women compared with men may also account for the increased effect of tranexamic acid in women since this is the period in which it is most effective. In men the strength of the effect of tranexamic acid was also correspondingly smaller since a smaller proportion of blood was lost in this period. Interestingly, in the tranexamic acid group the early and late post-operative blood losses in men and women were similar, suggesting that it reduced post-operative losses to a similar level regardless of gender.

Previous studies investigating a standardised dose of 1 g of tranexamic acid have not examined its effect on the need for transfusion or the number of transfusions.
required. Our study found that the number of patients requiring blood transfusion was statistically significantly lower in the tranexamic acid group \((p = 0.03)\) and although the total number of units of blood transfused was lower, this did not reach statistical significance \((p = 0.07)\). At our institution, the cost of a standard unit of packed red blood cells is £140 but this can rise to £380 for specially typed or irradiated units. The cost of 1 g of intravenous tranexamic acid is £2.62 (2 × 5 ml ampoules of 100 mg/ml). In the control group the total cost of the transfused blood was £2940. In the tranexamic acid group the combined cost
of this and blood transfusions was £934.32, representing a saving of £2005.68. In 2008, 49 867 hip procedures were carried out in the National Health Service (NHS) in England and Wales according to the National Joint Registry (NJR). The use of tranexamic acid in all these patients would have provided a potential saving of £2.8 million to the NHS.43

The major concern with antifibrinolytic agents is that their use may increase the risk of thrombosis. Most previous studies have only investigated patients if clinically indicated. In our study venography was undertaken post-operatively to detect DVT. No increase in the incidence of thromboembolic events was seen after the administration of tranexamic acid. This agent is thought to stabilise a clot which has already formed and does not promote clot formation. However, since the incidence of post-operative DVT is less than 5%, a large study population would be required to detect an increase of 25%.

However, we recognised that as our patient groups were identified from a study investigating the influence of two forms of anticoagulation, this is a strong confounding factor to our investigation of the relationship of tranexamic acid to the formation of DVT.

In conclusion, our study has shown that tranexamic acid as a standardised intravenous bolus of 1 g administered before surgery is a cost-effective way of reducing blood loss and transfusion requirements after primary THR especially in women. It has also highlighted the need for further work into bleeding characteristics after THR in men and women. Further large-scale randomised trials are required to ascertain the most effective dose of tranexamic acid which can be administered safely to men and women.

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References


