Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement

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Background. Total knee arthroplasty (TKA) is often carried out using a tourniquet and shed blood is collected in drains. Tranexamic acid decreases the external blood loss. Some blood loss may be concealed, and the overall effect of tranexamic acid on the haemoglobin (Hb) balance is not known.

Methods. Patients with osteoarthrosis had unilateral cemented TKA using spinal anaesthesia. In a double-blind fashion, they received either placebo (n=24) or tranexamic acid 10 mg kg⁻¹ (n=27) i.v. just before tourniquet release and 3 h later. The decrease in circulating Hb on the fifth day after surgery, after correction for Hb transfused, was used to calculate the loss of Hb in grams. This value was then expressed as ml of blood loss.

Results. The groups had similar characteristics. The median volume of drainage fluid after placebo was 845 (interquartile range 523–990) ml and after tranexamic acid was 385 (331–586) ml (P<0.001). Placebo patients received 2 (0–2) units and tranexamic acid patients 0 (0–0) units of packed red cells (P<0.001). The estimated blood loss was 1426 (1135–1977) ml and 1045 (792–1292) ml, respectively (P<0.001). The hidden loss of blood (calculated as loss minus drainage volume) was 618 (330±1347) ml and 524 (330±9620) ml, respectively (P=0.41). Two patients in each group developed deep vein thrombosis.

Conclusions. Tranexamic acid decreased total blood loss by nearly 30%, drainage volume by ~50% and drastically reduced transfusion. However, concealed loss was only marginally influenced by tranexamic acid and was at least as large as the drainage volume.

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Total knee arthroplasty (TKA) is usually done with a bloodless field using a tourniquet; some of the blood loss can be measured in the drains. This drainage volume, however, does not reflect the entire loss of red cells. A hidden loss of more than 700 ml, probably from haematoma formation, also occurs.

In several studies, tranexamic acid decreased the blood loss associated with TKA. In those studies, tranexamic acid 10–15 mg kg⁻¹ was given before the release of the tourniquet and in three, further doses of tranexamic acid were given. In one, the treatment began before application of the tourniquet. In these studies the total blood loss was reported as the loss during surgery plus the drainage volume. In general, tranexamic acid reduced the blood loss by about 50%. Since there may also have been hidden blood loss, the true effect of tranexamic acid on blood loss is not clear.

We set out to assess the total blood loss during TKA and how tranexamic acid influences it. The loss was determined from haemoglobin (Hb) balance.

Patients and methods

The regional ethics committee approved the study. Informed consent was obtained from 55 patients. Patients had elective total primary unilateral tricompartmental knee arthroplasty because of osteoarthrosis, and were all classified as ASA I or II. Exclusion criteria were a history of coagulopathy, an abnormally great prothrombin or activated partial thrombin time, previous history of a thromboembolic event, treatment with aspirin or non-steroidal anti-inflammatory agents (NSAID) in the previous week, plasma creatinine greater than 115 µmol litre⁻¹ in men and 100 µmol litre⁻¹ in women, acute infection (e.g. with leucocytosis or fever), and
malignant disease. Patients with myocardial infarction in the preceding 12 months or those with unstable angina or coronary disease that would not allow haemodilution were also excluded, as were those who were given plasma or other treatment affecting coagulation during the perioperative period.

Coded ampoules containing either tranexamic acid 100 mg ml⁻¹ (Cyclokapron®, Pharmacia) or saline were prepared by Apoteksbolaget, Umeå, Sweden. The contents of the ampoules were randomized in blocks of 10 (five saline, five tranexamic acid) by computer-generated numbers. At the end of the surgical procedure, just before release of the tourniquet, tranexamic acid 10 mg kg⁻¹ or placebo was infused i.v. (maximum dose 1000 mg). The dose was repeated after 3 h. Four randomized patients were excluded from the study before the code was broken. One in the placebo group and one in the tranexamic acid group suffered a large gastrointestinal bleed and one patient in the control group was given desmopressin because of extensive blood loss from the wound. Two randomized patients in the control group were found not to fulfil the criteria for inclusion: in one the serum creatinine was too great and the other had rheumathoid arthritis. Features of the remaining 51 patients are given in Table 1.

### Perioperative management

Treatment with aspirin or NSAIDs was stopped one week before the operation. For thrombosis prophylaxis, dalteparin sodium (Fragmin®, Rhone-Poulenc Rorer) 5000 IU was injected s.c. on the evening after surgery. Patients were then given 5000 IU daily for 10 days. Oral premedication was with different combinations of diazepam, acetaminophen and codeine. In addition, ibuprofen 600 mg was given to 20 patients.

### Anaesthetic and surgical procedures

Subarachnoid spinal anaesthesia was with isobaric bupivacaine (Marcain spinal®, Astra) 17.5–20 mg. Midazolam or propofol were given i.v. for sedation if needed. Non-invasive arterial pressure and heart rate were noted every 5 min and patients were given clocaxacillin i.v. The patients underwent a standardized procedure performed by one of five surgeons, two of whom did 40 of the 51 operations. The surgeons were well balanced between groups (P=0.64, χ²-test). After partial exsanguination of the limb by elevation for 1 min, a pneumatic tourniquet was inflated to 300 mm Hg. All patients received cemented prostheses with gentamycin (Nex-gen®, Zimmer, Scandinavia) and the lumen of the femur was plugged with autologous bone. The wound was closed and a compressive bandage was applied before release of the tourniquet. The joint was drained with a single closed suction drain until less than 50 ml was collected during a 6-h period [27 (SD 6) h and 27 (8) h in the placebo and tranexamic acid groups, respectively].

### Volume substitution

Ringer’s acetate 500 ml was given i.v. before the subarachnoid injection. Volume replacement was with Ringer’s acetate and hydroxyethyl starch 200/0.5 (HAES-steril®, Fresenius) 10 mg ml⁻¹. After surgery, the venous Hb was measured when necessary in the ward using HemoCue® (HemoCue, Helsingborg, Sweden). At other times, venous Hb was determined with a modified cyano-methaemoglobin method (Celldyn 3500®, Abbott). If Hb was less than 90 g litre⁻¹, allogeneic leucodepleted red blood cell concentrate was given in 250-ml units containing about 150 ml cells and 10–20 ml plasma.

### Estimation of blood loss

Intraoperative blood loss was negligible in all patients. Blood loss after surgery was estimated by two different methods. The first was the standard clinical method where blood loss was taken as the volume recovered in drains. The second method was based on Hb balance. We assumed that blood volume (BV in ml) on the fifth day after surgery was the same as that before surgery. BV was estimated according to the method of Nadler and colleagues⁶ taking sex, body mass and height into account. The loss of Hb (in grams) was then estimated according to the formula:⁷

\[
Hb_{\text{loss}}=BV\times(Hb_t-Hb_p)\times0.001+Hb_p
\]

where Hbₜ (g) is the amount of Hb lost, Hbₚ (g litre⁻¹) the Hb concentration before surgery, Hbₜ (g litre⁻¹) is the Hb concentration on the fifth day after surgery and Hbₚ (g) is the total amount of allogeneic Hb transfused. A unit of banked blood was considered to contain 52 (SD 5.4) g Hb, according to measurements at our hospital’s blood centre using the modified cyano-methaemoglobin method (Dr J Strindberg, personal communication). The blood loss (ml) was related to the patient’s preoperative Hb value (g litre⁻¹):

\[
\text{Blood loss }=1000\times Hb_{\text{loss}}/Hb_p
\]

The blood loss minus the drainage volume gave the hidden loss.

### Table 1 Patient characteristics. Data are mean (SD) unless indicated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=24)</th>
<th>Tranexamic acid (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6/18</td>
<td>9/18</td>
</tr>
<tr>
<td>Age (yr) (range)</td>
<td>72 (50–84)</td>
<td>72 (46–83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (13)</td>
<td>79 (13)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (7)</td>
<td>165 (7)</td>
</tr>
<tr>
<td>Estimated blood volume (ml)</td>
<td>4531 (639)</td>
<td>4532 (659)</td>
</tr>
<tr>
<td>ASA class (I/II)</td>
<td>7/17</td>
<td>8/19</td>
</tr>
</tbody>
</table>
Table 2  Haemoglobin (Hb) data and blood loss. Data are median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=24)</th>
<th>Tranexamic acid (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb concentration (g litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>135 (132–146)</td>
<td>140 (128–146)</td>
<td>0.66</td>
</tr>
<tr>
<td>Day 1</td>
<td>107 (97–115)</td>
<td>112 (105–124)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Day 2</td>
<td>104 (98–110)</td>
<td>110 (103–121)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Day 5</td>
<td>104 (100–110)</td>
<td>104 (98–120)</td>
<td>0.50</td>
</tr>
<tr>
<td>Drainage (ml)</td>
<td>845 (523–990)</td>
<td>385 (331–586)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>1426 (1135–1977)</td>
<td>1045 (792–1292)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hidden blood loss (ml)</td>
<td>618 (330–1347)</td>
<td>524 (330–962)</td>
<td>0.41</td>
</tr>
<tr>
<td>Red cells transfused (units)</td>
<td>2 (0–2)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of patients transfused</td>
<td>14</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Statistical methods

The size of the study was calculated as follows. Total blood loss after TKA was 1410 (480) ml in control patients in a previous study.³ Blood loss of 400 ml was considered important. In patients with a Hb concentration of 135 g litre⁻¹, 400 ml blood would contain 54 g Hb, similar to the Hb content of one red cell unit (52 g). To obtain a power of 0.80 and an alpha value of 0.05, 23 patients would be required in each group. To allow for potential exclusions, and since we knew little about the magnitude of the hidden blood loss beforehand, 55 patients were included. Values are reported as mean (SD). However, Hb concentration, blood loss, the number of red cell units transfused and volume of fluids infused were not normally distributed and are therefore given as median (25–75% range). Groups were compared using the Mann–Whitney U-test, except for categorical data, for which Fisher’s exact test was used for 2×2 tables and the χ²-test for larger tables. Comparisons were made using StatView 4.51 on a Power Macintosh 7500 computer.

Results

The groups had similar characteristics before surgery (Table 1). The extent of synovectomy did not differ between groups (controls: none 6, partial 12, total 6; tranexamic acid group: none 5, partial 18, total 4; P=0.47). The control group received more hydroxy ethyl starch solution than the tranexamic acid group [500 (500–750) ml vs 500 (0–500) ml; P<0.001] but similar amounts of crystalloid solutions [2000 (2000–3000) ml and 3000 (2000–3000) ml, respectively; P=0.51]. The drainage and total blood loss were greater in the control group (Table 2). The total loss was greater than the measured volume of drainage fluid [by 618 (330–1347) ml in the control group and 524 (330–962) ml in the tranexamic acid group; P=0.41].

The Hb values did not differ between the groups before surgery or on day 5, but were different on days 1 and 2. Patients in the control group were given more red cells (Table 2). Altogether, the control group was given 35 units, compared with 7 units in the tranexamic acid group. Eleven control patients received 2 units, two received 4 units and one received 5 units. In the tranexamic acid group, one patient received 1 unit, one received 2 units and one received 4 units.

Eight patients in the control group and 12 in the tranexamic acid group were given ibuprofen. The data in these patients did not differ in any respect from those of the others.

Two patients in the control group and two in the tranexamic acid group had clinical symptoms of deep vein thrombosis, which was verified by ultrasound. One patient in the tranexamic acid group developed a wound infection.

Discussion

In TKA, the external blood loss is routinely taken as the volume in suction bottles and drains, together with a visual estimate of the blood content in swabs and dressings.³,⁸ In some studies,²,⁴,⁵ blood loss was estimated by weighing; however, evaporation and variations in the Hb concentration of the wound blood are potential sources of error. Assay of recovered Hb in swabs, dressings and in drainage fluid⁹ is the ‘gold standard’ to determine external loss, but in orthopaedic surgery there can be hidden loss of blood. Following total hip replacement, thigh haematomas averaging 400 ml have been shown with ultrasound.¹⁰ After TKA, blood collects in the joint and thigh¹¹ and the circumference of the latter increases.³ For these reasons, we assessed the total blood loss from the Hb balance. This loss would include red cells lost in haematoma and by haemolysis. However, the method does not take into account erythropoiesis during the observation period. Thus, if anything, the total blood loss (and hence hidden loss) could be even larger than indicated by our data.

In our control patients, the hidden loss of blood was of similar magnitude to that in the drains, supporting findings by Sehat and colleagues.¹ In that study, as in ours, virtually all external blood loss was postoperative and minor bleeding from the ischaemic limb during the surgery was disregarded. In some studies,²,³,⁴ but not in others,¹,⁵ the tourniquet was released before the wound was closed to allow for haemostasis, a strategy that would increase the blood loss during surgery. We expressed the drainage loss in ml, whereas the total blood loss was estimated as ml of the
preoperative venous Hb concentration. The Hb concentration in the drainage fluid must have been less than the preoperative venous value, however, as the blood loss took place after some haemodilution was caused by the fluid given before and during the operation and later to compensate for the loss of blood volume. Also, Hb in the drainage fluid can be less than in simultaneous samples of venous blood.12 This strongly suggests that the hidden loss of Hb during TKA exceeds that in the drains. Therefore, it must be highly questionable to use the volume of drainage fluid as a measure of blood loss in TKA.

Plasmin binds to fibrinogen or fibrin structures and promotes fibrinolysis. Tranexamic acid competitively blocks a lysine-binding site of plasminogen and thereby inhibits its conversion to the active enzyme plasmin. Tranexamic acid is also a weak non-competitive inhibitor of the active enzyme. Tranexamic acid reduced drainage volume by about 50%, supporting previous findings.2±5 In TKA under regional anaesthesia, mental stress before the surgery activates both coagulation and fibrinolysis and this is enhanced during surgery.8 This activation is more pronounced in blood from the wound just after tourniquet release than in simultaneous venous samples. There is increased release of the tissue plasmin activator from the endothelium in the limb, by tissue trauma, thrombin13 and ischaemia,14 accelerating fibrinolysis. In TKA, tranexamic acid exerts its effects mainly in the wound.8 Tranexamic acid does not influence fibrinolytic activity in vein walls,15 which may explain why previous studies2±5 and the present study have not shown a higher incidence of deep vein thrombosis in patients treated with tranexamic acid.

Tranexamic acid reduced the estimated loss of blood by a third, which is less than the effect on drainage volume. The drug did not significantly reduce the hidden blood loss. The reasons for this are not clear. One explanation may be that the hidden loss, to a large extent, represents extravasation of red cells just after tourniquet release. At this time, the haemostasis may be by vascular and primary haemostatic mechanisms, before fibrinolysis has any effects. Haematoma in the joint and thigh could be limited by mechanisms, before fibrinolysis has any effects. We conclude that after TKA the hidden loss of blood is as large or larger than that in the drains. Tranexamic acid reduced the total loss of blood, but not as much as it decreased drainage volume.

Acknowledgements

The study was supported by grants from the County Council of Östergötland.

References