Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty

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We have investigated the effect of treatment with tranexamic acid, an inhibitor of fibrinolysis, on blood loss, blood transfusion requirements and blood coagulation in a randomized, double-blind, placebo-controlled study of 42 patients after total knee arthroplasty. Tranexamic acid 15 mg kg\(^{-1}\) (\(n=21\)) or an equivalent volume of normal saline (\(n=21\)) was given 30 min before surgery and subsequently every 8 h for 3 days. Coagulation and fibrinolysis values, blood loss and blood units administered were measured before administration of tranexamic acid, 8 h after the end of surgery and at 24 and 72 h after operation. Coagulation profile was examined (bleeding time, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), plasminogen, \(\beta\)-thromboglobulin and fibrinogen). Fibrinolysis was evaluated by measurement of concentrations of D-dimer and fibrinogen degradation products (FDP). Total blood loss in the tranexamic acid group was 678 (SD 352) ml compared with 1419 (607) ml in the control group (\(P<0.001\)), and occurred primarily during the first 24 h after surgery. Thirteen patients received 1–5 u. of packed red blood cells in the control group compared with two patients in the tranexamic acid group, who received 3 u. (\(P<0.001\)). Postoperative packed cell volume values were higher in the tranexamic acid group despite fewer blood transfusions. Postoperative concentrations of plasminogen were decreased significantly in the tranexamic acid group (\(P<0.001\)). Platelet count, PT, aPTT, bleeding time, \(\beta\)-thromboglobulin, fibrinogen and FDP concentrations did not differ between groups, but D-dimer concentrations were increased in the control group. Thromboembolic complications occurred in two patients in the control group compared with none in the tranexamic acid group.

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Total knee arthroplasty is associated with minimal intra-operative, but extensive postoperative, blood loss. Both surgery and application of a pneumatic tourniquet are reported to enhance coagulability and the local fibrinolytic activity in the limb.\(^1\)\(^-\)\(^5\) Increased plasma concentrations of coagulation factors, reduced concentrations of coagulation inhibitors, enhanced platelet activity, endovascular release of catecholamines and serotonin contribute to haemostasis. The fibrinolytic system is activated when tissue trauma releases tissue plasminogen activator (t-PA). Thrombin also activates fibrinolysis by triggering release of t-PA from the vascular endothelial cells.\(^6\)\(^-\)\(^7\) t-PA is the major enzyme responsible for conversion of plasminogen to plasmin. Surgical stress enhances the release of plasmin at the site of vascular damage and, in orthopaedic surgery, the use of a tourniquet increases further fibrinolytic activity.\(^8\) This may contribute to blood loss after total knee arthroplasty, although after surgery, the fibrinolytic system shuts down as a consequence of increased release of plasminogen activator inhibitor that inactivates t-PA.\(^8\)\(^-\)\(^9\)

Apart from technical operative measures, antifibrinolytic agents may improve haemostasis and reduce blood loss. Tranexamic acid, a synthetic inhibitor of fibrinolysis, competitively blocks a lysine binding site of plasminogen. Plasminogen–tranexamic acid complexes are displaced from the surface of fibrin and, as plasmin is prevented from binding to fibrinogen or fibrin monomers, lysis is delayed.\(^10\)

At higher concentrations, tranexamic acid also acts as a non-competitive inhibitor of plasmin.\(^11\)\(^-\)\(^12\)

Despite several clinical studies proving the efficacy of tranexamic acid with single or multiple boluses of different sizes with or without subsequent infusions, no consensus has been reached on the dose of tranexamic acid to be administered or duration of treatment.\(^2\)\(^-\)\(^4\)\(^13\)\(^-\)\(^15\) Previous
studies established the therapeutic plasma concentrations of tranexamic acid at 10 ng ml$^{-1}$ and the need for an 80% reduction in the activity of plasminogen activator for suppression of fibrinolysis in tissues. An i.v. dose of tranexamic acid 10 mg kg$^{-1}$ maintains such plasma concentration for only 3 h. This may be insufficient to prevent postoperative bleeding in prosthetic knee surgery and thus is an argument for using higher doses. Furthermore, there are indications that local enhancement of fibrinolysis elicited by application of a tourniquet may affect haemostasis for a considerably longer time than the surgical procedure. Thus it may be beneficial to maintain antifibrinolytic treatment for several days.

In studies related to knee surgery, tranexamic acid was administered just before release of the tourniquet. As tourniquet inflation stimulates the fibrinolytic system, we found it more logical to start administration of tranexamic acid before the tourniquet was inflated.

In this study, we have investigated, in a homogeneous healthy population undergoing total knee arthroplasty, if administration of a high dose of tranexamic acid for 3 days influences blood loss and has a blood-sparing effect. In addition, we assessed the mechanism of action of tranexamic acid on coagulation and fibrinolysis.

**Patients and methods**

The study was approved by the University Ethics Committee and written informed consent was obtained from each patient. We studied 42 ASA I–III patients, diagnosed with osteoarthrosis and undergoing unilateral bicondylar cemented total knee arthroplasty. Exclusion criteria were known allergy to tranexamic acid, preoperative hepatic or renal dysfunction, serious cardiac or respiratory disease, congenital or acquired coagulopathy or a history of, or evolving, thromboembolic disease. Non-steroidal anti-inflammatory medication was discontinued at a history of, or evolving, thromboembolic disease. Non-operative hepatic or renal dysfunction, serious cardiac or respiratory disease, congenital or acquired coagulopathy or a history of, or evolving, thromboembolic disease.

Patients were allocated randomly to receive tranexamic acid 15 mg kg$^{-1}$ (Exacyl, Bournonville Pharma, Belgium) or an equal volume of saline, in a double-blind manner, 30 min before inflation of the tourniquet and surgery, and repeated subsequently every 8 h for 3 days. Both the surgeon and anaesthetist were blinded to the treatment regimen.

General anaesthesia was induced with propofol 1–1.5 mg kg$^{-1}$, vecuronium 0.1 mg kg$^{-1}$ and fentanyl 0.1 mg, and maintained with isoflurane and a 40% mixture of oxygen and nitrous oxide, with increments of fentanyl. During surgery, patients received Ringer’s solution at a rate of 4 ml kg$^{-1}$ h$^{-1}$ for compensation of insensible fluid losses and measured blood losses were replaced with a modified fluid gelatin solution (Geloplasma) and crystalloids (Ringer’s solution) in equal volumes. Arterial pressure, end-tidal carbon dioxide concentration, oesophageal temperature and pulse oximetry were measured continuously.

To prevent intraoperative blood loss, a pneumatic tourniquet was inflated after the leg had been elevated for 5 min. An Esmarch bandage was not used for exsanguination of the limb. The tourniquet was released at the end of surgery when a compressive dressing was applied and the blood drainage system functioned correctly. Each arthroplasty was performed by the same surgeon using a standard technique. An Insall/Burstein II modular knee system, posterior stabilized series (Zimmer, Indiana, USA), was implanted in all patients using Palacos R bone cement with gentamicin (Schering-Plough SA, Belgium). In each knee, two intra-articular drains and one subcutaneous drain were placed.

Blood loss was measured by weighing swabs and operative drapes and measuring the volumes in the suction bottles after surgery, and then by checking the drain collectors on admission to the post-anaesthesia care unit (PACU) and every 8 h thereafter for 3 days until the surgical drains were removed. Patients remained in the PACU for the first 8 h after operation.

Homologous blood transfusions given during the whole hospital stay were recorded for quantity and time of administration. The indication for postoperative transfusion was set at a packed cell volume (PCV) of less than 26% in any of the postoperative measures.

Bleeding time, estimated using the Ivy method (Simplate I, Organon Teknika, Turnhout, Belgium) and concentrations of ALT, AST and creatinine were measured before operation and venous blood samples were obtained before surgery, 8 h after arrival in the PACU and at 24 and 72 h after operation. Blood samples were analysed for haemoglobin concentration, PCV, platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT), and concentrations of β-thromboglobulin, fibrinogen, plasminogen, D-dimer and fibrinogen degradation products (FDP). Plasminogen was measured in plasma using the IL Test plasminogen kit in which plasminogen is converted to a plasminogen–streptokinase complex having a plasmin-like activity. This activity is detected by a chromogenic substrate. The method is linear in the range 15–120% of plasminogen.

Standard laboratory techniques were used for all other assays. All samples were assayed in duplicate. All patients were examined daily for signs of deep venous thrombosis (DVT).

Randomization was performed using a computer-generated random number list. Fisher’s exact test and the chi-square test were used for the FDP and D-dimer data sets and to compare qualitative variables. The temporal evolution of the biological variables was evaluated using a repeated measures analysis of variance, followed by a post hoc analysis using the Newman–Keuls test if a total time
The relative risk of blood transfusion was 2.9 times higher in the control group than in the tranexamic acid group (95% confidence interval 1.6–5.4).

The two groups were comparable in age, height, body weight, sex, preoperative concentrations of creatinine, AST and ALT, operative time and duration of tourniquet inflation (Table 1).

Total mean blood loss measured at 72 h was 678 (352) ml (range 40–1560 ml) in the tranexamic acid group and 1419 (607) ml (range 675–3020 ml) in the control group (Table 2). Blood loss on discharge from the PACU was reduced by 58% in the tranexamic acid group (P<0.001). Cumulative postoperative blood losses between 24 and 72 h were 32% lower in the tranexamic acid group than in the control group (308 (139) ml vs 443 (167) ml, respectively; P<0.01) and reflected the difference in blood loss. At 72 h, there were no differences between groups. PCV decreased to a greater extent in the control group at 24 h after operation.

There were no clinically relevant differences in aPTT or PT (Table 4). Plasminogen concentrations decreased noticeably with time in the tranexamic acid group only (P<0.001).

Peak FDP concentrations (>40 µg ml⁻¹) were found in one patient in each group on the day of surgery. The tranexamic acid group had significantly lower D-dimer concentrations on discharge from the PACU and at 24 h after operation than the control group (P<0.001). Eight patients in the control group had concentrations exceeding 200 ng ml⁻¹ while this occurred in only two patients in the tranexamic acid group. There was no relationship between D-dimer concentrations and the extent of blood loss, but there were significant correlations between blood loss during the first 24 h and fibrinogen concentrations in both groups (tranexamic acid group r=-0.349, P<0.02; control group r=-0.397, P<0.01) and with plasminogen concentrations in the tranexamic acid group only (r=0.472, P<0.002).

There were no thromboembolic complications in the tranexamic acid group. In the control group, one patient had a proven DVT 4 days after operation and another 12 days after surgery; both incidents were confirmed by phlebography.

Preoperative haemoglobin values were significantly greater in the tranexamic acid group compared with the control group (P<0.05). However, when haemoglobin concentration was compared separately for males and females between the two groups, the difference was no longer statistically significant (P=0.41 male; P=0.06 female). All other preoperative haematological, coagulation and fibrinolysis variables were comparable between groups (Tables 3, 4). Compared with respective preoperative values, mean haemoglobin concentration decreased significantly in both groups at each postoperative assessment. On the first postoperative day, haemoglobin concentration, expressed as a fraction of the preoperative value, was significantly lower in the control patients than in the tranexamic acid group (75 (8)% vs 83 (6)%, respectively; P<0.01) and reflected the difference in blood loss. At 72 h, there were no differences between groups. PCV decreased to a greater extent in the control group at 24 h after operation.

The need for blood transfusion was greater in the control group compared with the tranexamic acid group (95% confidence interval 1.6–5.4).
Tranexamic acid and blood conservation

Table 3 Perioperative haemoglobin (Hb), packed cell volume (PCV), platelet count, β-thromboglobulin and bleeding time throughout the study (mean (SD)).

*P<0.05, **P<0.001 vs control group; ††P<0.01 vs preoperative values

<table>
<thead>
<tr>
<th></th>
<th>Hb (g dl⁻¹)</th>
<th>PCV (%)</th>
<th>Platelets (10⁹ mm⁻³)</th>
<th>β-thromboglobulin (iu ml⁻¹)</th>
<th>Bleeding time (s)</th>
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<tr>
<td>Tranexamic acid group</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Preoperative</td>
<td>13.6 (1.1)*</td>
<td>40.8 (3.1)</td>
<td>240 (72)</td>
<td>105.1 (67.5)</td>
<td>125 (58)</td>
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<tr>
<td>Day 0</td>
<td>13.4 (1.0) (males)</td>
<td>13.4 (1.0) (females)</td>
<td>12.4 (1.3)††</td>
<td>37.3 (3.2)††</td>
<td>225 (66)</td>
</tr>
<tr>
<td>Day 1</td>
<td>12.1 (1.2)††</td>
<td>33.6 (3.5)††</td>
<td>207 (56)</td>
<td>70.9 (51.6) (n=17)</td>
<td>95 (42)</td>
</tr>
<tr>
<td>Day 3</td>
<td>10.7 (1.2)††</td>
<td>32.0 (3.3)††</td>
<td>207 (57)</td>
<td>86.3 (51.4) (n=17)</td>
<td>82 (41)§</td>
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<td>Control group</td>
<td></td>
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<td>Preoperative</td>
<td>12.8 (1.0)</td>
<td>38.7 (3.3)</td>
<td>243 (54)</td>
<td>119.6 (57.3)</td>
<td>105 (49)</td>
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<tr>
<td>Day 0</td>
<td>12.7 (1.0) (males)</td>
<td>12.7 (1.0) (females)</td>
<td>12.1 (1.1)††</td>
<td>36.6 (3.6)††</td>
<td>240 (62)</td>
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<td>Day 1</td>
<td>9.5 (1.1)††</td>
<td>28.3 (3.0)††</td>
<td>218 (59)</td>
<td>71.8 (51.0)†† (n=17)</td>
<td>109 (57)</td>
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<tr>
<td>Day 3</td>
<td>10.1 (1.7)††</td>
<td>30.4 (5.4)††</td>
<td>204 (67)</td>
<td>88.1 (53.3) (n=17)</td>
<td>95 (53)</td>
</tr>
</tbody>
</table>

Table 4 Perioperative prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, plasminogen and fibrinogen values throughout the study (mean (SD)).

**P<0.01, ***P<0.001 vs control group; ††P<0.01 vs preoperative values

<table>
<thead>
<tr>
<th></th>
<th>PT (s)</th>
<th>aPTT (s)</th>
<th>Fibrinogen (mg dl⁻¹)</th>
<th>Plasminogen (%)</th>
</tr>
</thead>
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<td>Tranexamic acid group</td>
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<tr>
<td>Preoperative</td>
<td>12.6 (0.8)</td>
<td>30.1 (3.7)</td>
<td>385 (105)</td>
<td>89.5 (16.2)</td>
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<td>13.2 (0.9)</td>
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<td>75.8 (14.9)††</td>
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<td>Day 1</td>
<td>14.0 (1.2)†† (n=20)</td>
<td>34.6 (10.5) (n=20)</td>
<td>442 (120) (n=20)</td>
<td>46.4 (9.7)††* (n=20)</td>
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<td>Day 3</td>
<td>13.7 (2.1)††* (n=20)</td>
<td>32.9 (4.0)</td>
<td>623 (143)††</td>
<td>47.6 (9.6)††*</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>12.5 (1.0)</td>
<td>30.8 (3.6)</td>
<td>367 (87)</td>
<td>81.1 (10.1)</td>
</tr>
<tr>
<td>Day 0</td>
<td>12.9 (1.0)</td>
<td>31.1 (4.4)</td>
<td>337 (96)</td>
<td>73.4 (12.0)</td>
</tr>
<tr>
<td>Day 1</td>
<td>13.9 (0.9)††</td>
<td>34.7 (5.0)</td>
<td>420 (107)</td>
<td>71.9 (11.6)</td>
</tr>
<tr>
<td>Day 3</td>
<td>12.7 (0.9)</td>
<td>32.1 (4.0)</td>
<td>577 (131)††</td>
<td>80.1 (13.0)</td>
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</table>

blood-sparing effect of tranexamic acid was most evident during the first 24 h after operation when blood loss was significantly reduced compared with the control group. Despite the larger amounts of blood transfused, PCV remained lower in the control group 24 h after operation. The degree of blood loss during the first 24 h correlated significantly with both fibrinogen and plasminogen concentrations in the tranexamic acid group but with only fibrinogen in the control group.

Tranexamic acid (trans-4-aminomethyl cyclohexane carboxylic acid) inhibits the conversion of inactive plasminogen to the active proteolytic enzyme plasmin by competitive blocking of a high affinity lysine binding site of plasminogen. This prevents plasmin from binding to fibrinogen and fibrin structures after clot formation. The drug is a weak non-competitive inhibitor of plasmin.11 Fibrinolytic activation is a cascade process that is most easily inhibited in its earlier phase, which may explain why tranexamic acid has little effect when given after heavy blood loss.19 20

Despite the efficacy of tranexamic acid for reducing bleeding, no direct correlation was found between blood loss and variables of fibrinolysis (D-dimer, FDP). As tranexamic acid inhibits the transformation of plasminogen into active plasmin, a higher plasma concentration of plasminogen could be expected in this treatment group. However, as in the study of Benoni, Lethagen and Fredin,21 plasminogen concentrations were significantly lower after surgery in the tranexamic acid group than in the placebo group (P<0.001). It is known that tranexamic acid interferes with assay of plasminogen and decreases measured plasminogen concentrations by 16%.21 But the reduction in plasminogen concentrations observed in our patients was much larger (range 17–66% vs preoperative values). Reduced plasminogen concentrations may represent contributory evidence of enhanced fibrinolysis. However, we considered this unlikely. If decreased plasminogen indicates enhanced conversion to plasm and exaggerated fibrin degradation with consumption of fibrin and to a lesser extent fibrinogen, an attendant increase in serum concentrations of FDP and decreased concentrations of fibrinogen would be expected. In contrast, tranexamic acid-treated patients showed no bleeding tendency, increased fibrinogen concentrations and no increase in FDP concentrations.

We also found significantly fewer patients with increased D-dimer concentrations in the tranexamic acid group. Increased concentrations of D-dimer in the control group during the first 24 h after operation indirectly support the antifibrinolytic effect of tranexamic acid. D-dimer con-
centrations reflect degradation of fibrin when plasmin acts on cross-linked fibrin and are not a direct indicator of plasmin activity. A decrease in D-dimer and FDP concentrations in plasma was also reported after tranexamic acid treatment in cardiac surgery where more intense fibrinolytic activation occurs.

Our data confirmed that tranexamic acid did not induce platelet activation. Indeed, platelet count and β thromboglobulin, a marker of platelet activation, were similar in both groups and decreased at 24 h after operation, while bleeding time was unaffected. A platelet-sparing effect of tranexamic acid was not found. The amount of modified fluid gelatin used never exceeded 300 ml in 24 h and should therefore have no significant effect on platelet function. Extrinsic coagulation (PT) and the intrinsic pathway of coagulation (aPTT) were unaffected by tranexamic acid and varied within their reference limits, indicating that the observed blood loss was not caused by any major deficit in coagulation factors.

Is the timing of the initial dose of tranexamic acid crucial? In our study, tranexamic acid was given before inflation of the tourniquet. Application of a pneumatic tourniquet enhances fibrinolysis as a result of plasminogen activator released from the vascular endothelium, triggered by hypoxia or venous stasis. Nevertheless, the reported incidence of DVT after total knee replacement varies from 40 to 84%. Thrombi develop during tourniquet inflation. Concentrations of fibrinopeptide A and thrombin–antithrombin III complexes (TAT), which are circulating indices of thrombin generation, are increased markedly immediately after deflation of the tourniquet while t-PA activity increases during tourniquet inflation and is already decreased 1 h after surgery. Starting an antifibrinolytic treatment before inflation of the tourniquet could interfere with the natural defence mechanisms of the body against thrombosis formation. Previous research on tranexamic acid and thrombosis failed to show any thrombogenic effect, but thrombotic complications were reported with therapy exceeding 24 h. Investigation of clot stability by thrombelastography may have demonstrated evidence of increased fibrinolysis after use of the tourniquet in the control group and its absence in the tranexamic acid group. In our study, there were no thromboembolic complications in the tranexamic acid group, but two patients in the control group had a DVT. It has been reported that increased plasma concentrations of TAT and D-dimer correlate with thrombotic tendency. Although we have no data on TAT, decreased D-dimer concentrations could be an indication of reduced risk of DVT in the tranexamic acid group, but our study was not designed with sufficient power to detect differences in the incidence of DVT. Treatment with tranexamic acid before inflation of the tourniquet did not seem to augment the risk of DVT, but this could be attributable to the additional protection offered by low-molecular weight heparin given for thrombosis prophylaxis in all patients.

In summary, tranexamic acid, given over 72 h after operation, was effective in reducing blood loss and transfusion needs after prosthetic knee surgery. Inflation of the tourniquet after administration of a bolus dose of tranexamic acid did not augment the risk of thrombogenesis. A dose regimen of 15 mg kg⁻¹ every 8 h for 24 h would seem appropriate as longer administration of tranexamic acid was not accompanied by further reductions in blood loss.

Acknowledgement
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