Reduction of Blood Loss with Tranexamic Acid in Primary Total Hip Replacement Surgery

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Key words. Tranexamic acid ; blood loss ; deep venous thrombosis ; total hip replacement.

Abstract. Background : In this prospective, placebo-controlled, double-blind, randomized clinical trial, we investigated the effect of a single preoperative bolus dose of tranexamic acid (15 mg/kg) on perioperative blood losses and packed cell transfusion requirements in patients scheduled for primary unilateral total hip replacement surgery for degenerative osteoarthritis.

Patients and methods : 40 patients were randomized to receive either 15 mg/kg tranexamic acid (TA group) or an equal volume of saline (placebo group) given as a single slow intravenous bolus injection 15 minutes before incision. We recorded per- and postoperative blood losses and transfusion requirements up to 24 hours postoperatively. The patients were screened for deep venous thrombosis with bilateral compression ultrasonography using colour Doppler imaging on the tenth postoperative day.

Results : Poperative blood loss was not significantly different between the two treatment groups (TA group : 423 ml, placebo group 516 ml ; p = 0.093). Postoperative blood loss up to 24 hrs, and total blood loss were significantly less in the TA group : 352 vs 524 ml (p = 0.013), and 801 vs 1038 ml (p = 0.013), respectively. Packed red blood cell transfusion requirements were significantly lower in the TA group (6/20 patients, total 2 units) compared to the placebo group (12/20 patients, total 13 units). Compression ultrasonography on the 10th postoperative day was positive for deep venous thrombosis in 3 patients in the TA group (17 patients screened) and negative in all patients of the placebo group (18 patients screened).

Conclusion : Tranexamic acid 15 mg/kg given as a single preoperative bolus dose reduces postoperative and total blood loss, and packed cell transfusion requirements in primary total hip replacement surgery.

Introduction

Different techniques can be used to reduce the risk of perioperative allogenic blood transfusion in total hip replacement surgery such as preoperative autologous blood donation, intra- and postoperative red blood cell salvage, controlled hypotension, normovolemic haemodilution, or lowering the transfusion trigger. These techniques have several disadvantages: they are time consuming, expensive devices are needed, or the risk of poor blood quality increases, especially if using postoperatively salvaged but untreated blood (1).

Currently, there is sufficient literature evidence concerning the efficacy of natural (aprotinin) or synthetic (tranexamic acid) antifibrinolytic agents in reducing blood loss and transfusion requirements in orthopaedic surgery (2-4). Aprotinin comes from bovine lymphatic tissue, is very expensive, and is known to induce allergic reactions. For tranexamic acid (TA), questions remain with regard to its effects according to the type of surgery, dosage, and timing of administration. Although significant reductions in blood loss and transfusion requirements are very consistent in TA trials for total knee replacement, the results observed in trials for total hip replacement show a much greater discrepancy (5-11). These discrepant results in total hip replacement might be related to differences in TA administration, with TA trials having administered the drug only as a bolus of 10 mg/kg, and other trials having used a 10 mg/kg bolus with a constant infusion of 1 mg/kg per hour to a variable length of time.

In a randomized clinical trial, conducted in our department during the late 1990s among patients having total knee replacement, we found that TA decreased blood loss by 48%, significantly reduced transfusion requirements, and did not increase the risk of thrombogenesis (2). We used a TA dose of 15 mg/kg, given the knowledge that an 80% reduction in the activity of plasminogen activator is needed for suppression of fibrinolysis, and that an intravenous dose of TA of 10 mg/kg maintains such a plasma concentration for only 3 hours (2). These data suggest that a dose of 10 mg/kg may not be sufficient to prevent postoperative bleeding and support the rationale for using higher doses. In
addition, *BENONI et al.* (6) found no significant reduction in postoperative blood loss in total hip replacement patients when TA was given towards the end of surgery and 3 hours later.

For the current, placebo-controlled randomized clinical trial, we have chosen to look at the effects of tranexamic acid in a single preoperative dose of 15 mg/kg. We hypothesized that this single dose is both necessary and sufficient for optimal efficacy in terms of reduction of blood loss. More specifically, we evaluated the effect of a single preoperative bolus of 15 mg/kg tranexamic acid on perioperative blood losses, packed cell transfusion requirements, and postoperative incidence of deep venous thrombosis in primary total hip replacement surgery.

**Material and methods**

Following institutional approval and written informed consent, 40 patients, ASA I-II, scheduled for unilateral elective total hip replacement, were included.

Exclusion criteria were: allergy to tranexamic acid, preoperative renal or hepatic dysfunction, known bleeding disorders or preoperative coagulation anomalies, anticoagulant or aspirin-like medication and long acting NSAID medication. Short acting NSAIDs were discontinued at least 24 hrs before surgery.

Thromboprophylaxis with subcutaneous LMWH (Fraxiparine, Sanofi-Winthrop) was given routinely in every patient the evening before surgery and was continued postoperatively for 10 days. The patients were randomly allocated into two groups in a double-blind fashion and received either tranexamic acid (15 mg/kg) or an equal volume of saline in a slow infusion 15 minutes before surgery.

All patients received a spinal anaesthesia with plain bupivacaine 0.5% and were operated in a lateral position using a lateral approach. An uncemented acetabular cup and a cemented femoral stem were used. After lavage of the femoral shaft with saline under pulsatile pressure a polyethylene plug was inserted in the bottom of the drilled cavity of the femur. Vacuum-mixed cement was injected with a syringe and the femoral prosthesis was inserted during the viscous phase of the cement. Three low vacuum drains were used for postoperative wound drainage (intra-articular, subfacial and subcutaneous).

Perioperative blood loss was measured by carefully weighting the swabs and measuring the volumes in the suction bottles during surgery. Postoperative blood loss in the vacuum collectors was noted upon arrival at the PACU and 2, 4, 5, 8 and 24 hrs postoperatively.

Cristalloids (Plasmalyte®) and colloids (Voluven 6%®) were used to replace intraoperative blood loss. Hb and Hct values were recorded preoperatively, upon admission at the PACU, 6 hrs and 24 hrs postoperatively.

The indication for blood transfusion of packed cells was set at Hb < 8.5 g/dl or Hct < 27%. The number of units of packed cells and the time of transfusion was recorded. All patients were examined daily for clinical signs of DVT. On the tenth postoperative day a compression ultrasonography with colour Doppler imaging of the proximal and distal venous system of both legs was performed to evaluate the presence of deep venous thrombosis.

The person responsible for quantifying blood loss, for making the decision to administer transfusions, and for daily examining patients for clinical signs of DVT, was unaware of the group to which the patient was assigned.

Results for continuous variables are represented as mean values ± SD. Statistical analysis of continuous variables included unpaired (2 tailed) t-tests for independent samples. Chi-square test was used to compare the number of patients receiving packed cell transfusion. A p value of < 0.05 was considered statistically significant.

**Results**

All patients were comparable for age, gender, weight, preoperative platelet count, PTT, aPTT and duration of surgery (Table I).

Perioperative blood loss is shown in Table II.

Perioperatively, there was no statistical significant difference in blood loss between the two groups (TA group 423 ml ± 174 ml, placebo group 516 ml ± 167 ml; p = 0.093).

Postoperative blood loss however was significantly lower in the TA group, mainly until 8 hrs postoperatively, and remained significant lower until 24 hrs postoperatively (TA group 352 ml ± 152 ml/placebo group 524 ml ± 255 ml; p = 0.013). Total blood loss at 24 hrs was significantly lower in the TA group (801 ml ± 370 ml/placebo group 905 ml ± 406 ml; p = 0.004). The number of patients receiving packed cell transfusion was 10/20 in the TA group and 19/20 in the placebo group (p = 0.39).

**Table I**

<table>
<thead>
<tr>
<th>Patient characteristics and surgical data</th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>73 ± 8</td>
<td>68 ± 11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 8</td>
<td>164 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 15</td>
<td>72 ± 16</td>
</tr>
<tr>
<td>Sex (M/F, number of patients)</td>
<td>5/15</td>
<td>7/13</td>
</tr>
<tr>
<td>PTT (%)</td>
<td>93 ± 10</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>30 ± 2</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>261 ± 65</td>
<td>301 ± 60</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>98 ± 18</td>
<td>94 ± 15</td>
</tr>
</tbody>
</table>

Results for continuous variables are represented as mean values ± SD.
Reduction of Blood Loss with Tranexamic Acid

Compression ultrasonography on the 10th postoperative day was positive in 3 patients in the TA group (17 patients investigated) and negative in all patients in the placebo group (18 patients investigated). Postoperative doppler examination was not carried out in 5 of the 40 patients (12.5%), because these 5 patients refused the scheduled compression ultrasonography of their lower extremities.

Discussion

Peroperative blood loss

We found a reduction of 18% in peroperative blood loss in the TA group, but this was not statistically significant. The same result was observed by other investigators (5, 8-9). Only one study (11) showed a significant reduction in peroperative blood loss with TA administered preoperatively in total hip replacement surgery.

Our findings are underpinned by a strong biological rationale. TA has no major influence on primary haemostasis and coagulation per se. The therapeutic effect of TA is apparent when the haemostatic system has produced a fibrin clot which is normally dissolved by the proteolytic action of plasmin. TA delays this clot lysis by blocking the lysine binding sites on the plasminogen molecule and thereby prevents the binding of the activated plasmin to the fibrin surface.

During surgery the acetabulum is reamed and the femoral shaft is broached and washed with NaCl under pulsatile pressure. During this period there is no time for clot formation. This may explain why most authors find no significant reduction in peroperative blood loss.

Postoperative blood loss

While most studies show a reduced postoperative blood loss with TA in total knee replacement surgery, the results in studies for total hip replacement surgery show a greater discrepancy. In studies for total hip replacement surgery, the dose regimens for TA administration are quite different, ranging from a single 10 to 15 mg/kg bolus preoperatively (5, 10), a preoperative bolus repeat-

244 ml) compared to the placebo group (1038 ml ± 289 ml; p = 0.013).

Perioperative Hb and Hct results (Table III) showed no significant differences between the two groups. Packed cell transfusion requirements (Table IV) were greater in the placebo group (6/20 patients, total 13 units) compared to the TA group (1/20 patients – 2 units).

No clinical signs of deep venous thrombosis were observed in any of the two groups during hospital stay.

Table II

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroperatively</td>
<td>423 ± 174</td>
<td>516 ± 167</td>
<td>N.S</td>
</tr>
<tr>
<td>Drain 2 h</td>
<td>95 ± 60</td>
<td>195 ± 129</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Drain 4 h</td>
<td>162 ± 77</td>
<td>286 ± 174</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Drain 6 h</td>
<td>196 ± 85</td>
<td>327 ± 188</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Drain 8 h</td>
<td>262 ± 84</td>
<td>397 ± 204</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Drain 24 h</td>
<td>352 ± 152</td>
<td>524 ± 244</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Total blood loss 24 h</td>
<td>801 ± 244</td>
<td>1038 ± 289</td>
<td>&lt; 0.05</td>
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</tbody>
</table>

Results for blood loss are represented as mean values ± SD.

Table III

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n = 20)</th>
<th>Placebo (n = 20)</th>
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</thead>
<tbody>
<tr>
<td>Mean Hb (± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>preoperative</td>
<td>13.9 ± 1.3</td>
<td>14.1 ± 0.9</td>
</tr>
<tr>
<td>postoperative</td>
<td>11.5 ± 1.4</td>
<td>11.3 ± 0.8</td>
</tr>
<tr>
<td>6 h</td>
<td>11.8 ± 1.4</td>
<td>11.2 ± 1.0</td>
</tr>
<tr>
<td>24 h</td>
<td>11.1 ± 1.4</td>
<td>10.5 ± 1.0</td>
</tr>
<tr>
<td>Lowest Hb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>preoperative</td>
<td>12.0</td>
<td>12.6</td>
</tr>
<tr>
<td>postoperative</td>
<td>9.0</td>
<td>10.0</td>
</tr>
<tr>
<td>6 h</td>
<td>10.1</td>
<td>9.0</td>
</tr>
<tr>
<td>24 h</td>
<td>9.1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

There are no significant differences between the groups (p > 0.05).

Table IV

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n = 20)</th>
<th>Placebo (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total units packed cells transfused</td>
<td>2 units</td>
<td>13 units</td>
</tr>
<tr>
<td>Packed cells transfused ≤ 8 h postoperatively</td>
<td>2 units / 1 patient</td>
<td>4 units / 2 patients</td>
</tr>
<tr>
<td>Packed cells transfused &gt; 8 h postoperatively</td>
<td>0</td>
<td>9 units / 4 patients</td>
</tr>
</tbody>
</table>

The differences between the groups are significant (p < 0.05).
ed after 3 hrs (7, 11), a single preoperative bolus dose followed by a continuous infusion (8-9), or TA given towards the end of surgery and 3 hrs later (6).

Surgery and venous stases enhance the release of tissue plasminogen activator (t-PA), activating the fibrinolytic system. This t-PA is the major enzyme responsible for the conversion of plasminogen into active plasmin.

Fibrinolytic activation is a cascade process that is most easily inhibited in its early phase. TA inhibits clot lysis more efficiently when administered before clot formation than after the fibrine clot is formed. Once plasminogen is bound to the fibrine surface, TA is no longer effective (12). This may explain why TA has little effect when administered at the end of surgery. BENONI et al. (6) found no significant reduction in postoperative blood loss in total hip arthroplasty when TA was given. In cardiac surgery (13) a postoperative 12 h continuous infusion of TA did not reduce the postoperative blood loss compared to no postoperative TA administration.

Fibrinolytic response after surgery, however, is biphasic (14) with an increased fibrinolytic activity during the first hours, followed by a fibrinolytic shutdown that peaks at about 24 hrs. The fibrinolytic shutdown is a consequence of an increased release of plasminogen activator-inhibitor (t-PAI) that inactivates t-PA (15); t-PAI-1 is an acute phase reactant and t-PA inhibition shows a rapidly changing pattern in response to trauma (16). During total hip replacement surgery and within 1 hour postoperatively, ERIKSSON et al. (17) found a significant increase in t-PA antigen and PAI-1 activity in the operated limb compared to preoperative values and compared to the non-operated limb. Compared to preoperative values, KASSIS et al. (18) found a 225% increase in t-PAI-1 antigen and a 190% increase of t-PAI activity 18 hours after total hip replacement surgery. So, while early administration of the first dose of TA seems to be important, a second bolus dosis after 3 hrs or starting a continuous infusion seems not to augment the effect. The rationale for the use of multiple doses or continuous infusion regimens of TA during a period of fibrinolytic shutdown may therefore be questioned.

Transfusion requirements
In total hip replacement surgery some authors found a significant reduction of red blood cell transfusion requirements in TA treated patients (6, 8-9), while others found no reduction (5, 11) or even an increased transfusion requirement (10). Moreover, there are discrepancies between the reduction in blood loss and the transfusions given.

Different criteria for transfusion limits makes it difficult to compare the results of packed cell transfusion requirements: lower limits set as in our study (9, 11), case by case basis (5, 9), 25% decrease compared to preoperative values (8), perioperative autotransfusion (9, 11).

Measurement of postoperative blood loss can also differ depending to the number of drains used postoperatively. In order to decrease the risk of infection, surgical drains are now removed more rapidly, or a smaller number of drains are placed. The hidden blood loss in haematomas could also add to the discrepancy between the lack of difference in postoperative blood loss and the reduction of patients requiring red blood cell transfusion in TA treated patients, although studies have shown that the hidden blood loss in total hip replacement surgery is small (19-20).

We set the transfusion limits at Hb $\leq 8.5$ g/dl and/or Hct $\leq 27\%$. We observed a significant reduction in the number of patients needing transfusion (1/20 in the TA group vs 6/20 in the placebo group; $p = 0.038$). The total amount of units of packed cells transfused was decreased by 85% in the TA group (total : 2 units) compared to the placebo group (total : 13 units; $p = 0.044$). The reduction in the risk associated with the transfusion of allogenic blood, as well as the cost-effectiveness are obvious (3 amp TA $\equiv 5, 1$ unit of packed cells $\equiv 67$; total cost TA group : $\euro 100$ vs placebo group : $\euro 871$).

Risk of deep venous thrombosis
Thromboembolic complications are a major concern especially in orthopaedic surgery.

In our study the compression ultrasonography with colour Doppler imaging on the 10th postoperative day was positive for DVT in 3 patients in the TA group (17/20 studied) and negative in the placebo group (18/20 studied). With an overall reported incidence of postoperative DVT of 5% however, a detection of a 25% increase of incidence would demand a much larger population study (7200 patients). A more sophisticated screening approach, such as bilateral ascending contrast phlebography, would possibly have allowed a better definition of the risk of DVT, but at the expense of a 3% risk of postphlebography DVT (10, 21, 22). Instead, we relied on a less invasive screening tool (21-22).

In line with our results, other clinical trials have also failed to show an increased incidence of DVT in TA treated patients. Even a meta-analysis (23) found no increase of thromboembolic complications with the use of TA in total hip and knee replacement surgery. BENONI et al. (24) suggest that TA is not associated with an increase in venous thromboembolic events because the effect of TA is more pronounced in operative wounds than in the peripheral venous blood.
Conclusion

A single bolus dose of 15 mg/kg TA given 15 minutes before surgery reduces the postoperative and total blood loss and the need for transfusions in primary total hip replacement surgery. This dose seems to be an adequate compromise between fibrinolytic inhibition by TA in the early hyperfibrinolytic stage and the postoperative period of fibrinolytic shutdown.

References