Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied

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BACKGROUND: In total knee arthroplasty surgery, a blood conservation program is applied as a normal clinical practice to avoid allogenic transfusions. The objective of this study was to assess the effectiveness of tranexamic acid to reduce transfusions in total knee replacement even when a blood conservation program is applied.

STUDY DESIGN AND METHODS: In a double-blind prospective study the patients scheduled for total knee arthroplasty were included in a well-established blood conservation program and then randomly assigned into two groups: In tranexamic acid group, 10 mg per kg ev bolus followed by 1 mg per kg per hour perfusion was administered, while in the control group, saline was given matching the protocol.

RESULTS: Ninety-five patients were included (tranexamic acid group, 46; control group, 49). Thirty-three patients (34.7%) underwent preoperative procedures to reduce transfusions: presurgical autologous blood donation (12), recombinant erythropoietin (6), and elementary iron (15); postoperative drain for reinfusion was allocated in all the cases. Total blood loss on the fourth postoperative day was [mean (±SD)] 1744 (±804) mL in controls compared with 1301 (±621) mL in the tranexamic acid group (p < 0.05). Eleven units of blood were transfused (6 patients) in the control group versus one in the tranexamic acid group (p < 0.05). Only 2 patients (4%) in the tranexamic acid group received reinfusion of blood recovered by drains compared with 36 (73%) in the control group (p < 0.0001). No thromboembolic complications were detected.

CONCLUSION: Tranexamic acid reduces blood losses and transfusion requirements even when a blood conservation program was used and it questions the usefulness of the postoperative reinfusion drains.

ABBREVIATION: aPTT = activated partial thromboplastin time.

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major joints, producing a drug concentration in joint fluid, comparable to the serum drug concentration. Different studies have assessed the effectiveness of tranexamic acid in patients undergoing orthopedic surgery especially total hip and knee arthroplasty with variable results. A recent meta-analysis shows that the use of tranexamic acid for patients undergoing total knee arthroplasty is effective reducing the requirements of allogenic blood transfusion.6

The objective of this study was to assess the effectiveness of tranexamic acid to reduce blood loss in total knee replacement even when a blood conservation program is applied.

**MATERIALS AND METHODS**

The study was approved by the institutional review board of Hospital del Mar, Barcelona (Spain), and by the Spanish Agency of Drugs and Sanitary Products. Between March and December 2005, patients scheduled for total knee replacement surgery were included in the study. Written informed consent was obtained in all cases. We studied ASA-I to -III patients diagnosed with osteoarthritis and undergoing unilateral bicondylar cemental total knee arthroplasty. Exclusion criteria were known allergy to tranexamic acid, ASA-IV physical status or higher, severe ischemia and/or heart valve disease, history of thromboembolic episodes, known coagulopathy, and renal dysfunction (serum creatinine concentration, >1.5 mg/dL).

If a bloodless field was not achieved during surgery or another methodologic transgression was detected, the patient was also excluded (in these cases after randomization). No patient was medicated with antiplatelet drugs in the 7 days before surgery or with nonsteroidal anti-inflammatory drugs or serotonin reuptake inhibitors antidepressants in the previous 12 hours. The enrollment and consequent randomization of the patient took place the day before the surgery, after the assessment of the exclusion and inclusion criteria.

Patients scheduled for knee arthroplasty were also assessed for eligibility to be included in a blood conservation program. Patients with hemoglobin (Hb) levels of greater than 13 g per dL, reluctant to blood transfusion and without contraindications (i.e., epilepsy, poorly controlled hypertension, insulin-dependent diabetes, heart failure, ischemic heart disease, positive serology for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus infection) were offered preoperative autologous blood donation for transfusion in case of necessity were offered. Patients with Hb levels between 10 and 13 g per dL, without above-mentioned contraindications, vascular disease, or history of thrombosis received 600 IU per kg recombinant human erythropoietin (rHuEPO; Eprex, epoetinum alfa, Janssen Cilag, Madrid, Spain) subcutaneously on Days -21, -14, -7, and -1 before surgery. Patients treated with autologous blood transfusion or rHuEPO or those with contraindications for any of these two treatments received 200 mg per day elemental iron until Day -1. Patients with an Hb level of more than 13 g per dL not included in the self-transfusion group and those with a serum ferritin level of more than 40 µg per mL were not treated. Male and female patients with Hb concentrations of less than 13 and less than 12 g per dL, respectively, had workup studies to determine the cause of anemia.14 Blood recovered during the first 6 postoperative hours (minimum, 400 mL) was reinfused in patients with a postoperative Hb level of less than 13 g per dL. For thrombosis prophylaxis, 3500 IU of bemiparin was injected subcutaneously on the evening before surgery. Patients were then given 3500 IU daily for the period of hospitalization and continuing during 3 to 4 weeks after discharge from the hospital.

A correlative identification number, strictly after order of enrollment, was given to each patient when he or she gave their written consent to participate. Patients were assigned to tranexamic acid group or control group with software that provided a series of random numbers. The randomized assignment was sealed in a numbered envelope. An independent anesthetist who was not otherwise engaged in the study opened the sealed randomization envelope and was responsible for preparing the medication, a bolus of 10 mg per kg tranexamic acid (Amchafibrin, Laboratorios Fides-Ecopharma, S.A. Madrid, Spain) or a bolus of placebo (physiologic saline), which were administered by the research anesthetist 30 minutes before deflation of the tourniquet followed by an infusion of 1 mg per kg per hour starting at the end of the operation and continuing during the first 6 postoperative hours. Masking was ensured by administration of apparently identical saline drips to each patient: first a 50-mL vial followed by a 50-mL syringe for infusion pump. Neither the patient nor the anesthetist who assessed the results knew the patient’s study group: a double blind design was applied.

A complete blood cell count and coagulation tests were performed 24 hours before surgery. All patients underwent standard spinal anesthesia with 0.5 percent bupivacaine (10-15 mg according to criterion of the anesthetist). A lumbar epidural catheter was inserted at the same interspace for postoperative analgesia only. During surgery, patients received Ringer’s solution at a rate of 5 mL per kg per hour for compensation of insensible blood losses. Blood pressure was kept in the normal range (systolic blood pressure, >100 mmHg) with 5 mg of IV ephedrine as required or 5 percent hydroxyethyl starch. During the operation, all patients were given a convection-air warming blanket.

After elevation of the limb and exsanguination with an Esmarch band, a pneumatic tourniquet was inflated to 450 mmHg. The tourniquet was released at the end of
surgery when a compressive dressing was applied and the blood drainage system functioned correctly. The same design of cemented knee prosthesis (Duracon, Stryker Iberia, S.L. Madrid, Spain) was used in all patients. In each knee, one intra-articular drain was placed (Bellovac ABT, Astra Tech, S.A. L’Hospitalet de Llobregat, Barcelona, Spain).

Patients remained in the postanesthesia care unit for the first 6 hours after operation. Blood samples were analyzed for Hb concentration, hematocrit (Hct), prothrombin time, activated partial thromboplastin time (aPTT), creatinine, sodium, and potassium. After reversal from spinal anesthesia block, continuous epidural infusion of 0.2 percent ropivacaine for postoperative analgesia at a rate of 4 to 6 mL per hour was started. Patients received Ringer’s solution at a rate of 40 mL per kg per hour for the first 24 postoperative hours. Restitution of the lost volume collected in the surgical drain was made with the same colloid in a proportion of 1:1. Infusion of the study medication was withdrawn after the first 6 hours postoperatively, and blood samples were taken and analyzed for Hb, Hct, prothrombin time, aPTT, D-dimer, creatinine, sodium, and potassium. At 96 hours after operation, a blood sample was obtained and the same analyses were repeated. Further Hb levels were measured at the discretion of the attending physician. Blood transfusion (one pack of concentrated red blood cells [RBCs]) was indicated when the Hb value was less than 8 g per dL or in patients who presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnea, or syncope.

Postoperative blood loss was estimated by measurement of the volume in the suction bottles and by changes in Hct levels between the day before the operation and the day of the operation. The volume in the suction bottles and by changes in terms of age, sex, and pre- and intraoperative variables. As shown in Table 1, patients in the placebo group were comparable between the study groups regarding the use of these treatments. There were no differences in autologous blood transfusion program and in treatment with rHuEPO (n = 7), technical difficulties in the insertion of the epidural catheter (n = 7), and error in blood sampling making laboratory results inconsistent (n = 1). Therefore, the study population consisted of 95 patients, 46 of whom were randomized to the group of tranexamic acid and 49 to placebo (Fig. 1).

Thirty-three patients (34.7%) underwent preoperative procedures to reduce transfusion needs, including autologous blood transfusion in 12, treatment with rHuEPO in 6, and administration of elemental iron in 15 (patients in autologous blood transfusion program and in treatment with rHuEPO also received elementary iron: a total number of 33 patients). There were no differences between the study groups regarding the use of these treatments. As shown in Table 1, patients in the tranexamic group and patients in the placebo group were comparable in terms of age, sex, and pre- and intraoperative variables. Patients in the tranexamic group showed a significantly higher mean aPTT, although levels were within normal limits.

Postoperative data regarding drained blood, volumes of crystalloid and colloid solutions infused, and transfusion requirements are shown in Table 2. There was a significantly smaller blood loss measured at 6 hours in the tranexamic acid group than in controls (mean [SD], 159 [110] mL vs. 534 [351] mL, p < 0.001), with a difference of lost volume collected in the surgical drain of 70.3 percent. Patients in the control group received a significantly higher volume of colloid solutions (364 [438] mL vs. 77 [183] mL, p < 0.001). Total blood loss recovered in the surgical drain was also significantly higher in controls than in patients given tranexamic acid (551 [352] mL vs. 170 [109] mL, p < 0.001). Hb values were significantly lower in controls than in patients given tranexamic acid either at 6 hours after surgery (10.9 [1.5] g/dL vs. 11.5 [1.2] g/dL, p < 0.05) or at the fourth postoperative day (9.9 [1.07] g/dL vs. 10.4 [1.29] g/dL, p < 0.05; Fig. 2). Total blood loss at the fourth postoperative day was 1744 (804) mL in controls compared with 1301 (621) mL in the tranexamic acid group (p = 0.002), representing a
25.4 percent reduction of total blood loss due to the use of tranexamic acid.

Six patients in the control group received blood transfusions (two patients received 1 unit, three received 2 units, and one received 3 units), whereas in the tranexamic acid group, one patient received 1 unit ($p = 0.036$). In contrast, only two patients (4%) in the tranexamic acid group received reinfusion of blood recovered by surgical drains compared with 36 patients (73%) in the control group ($p < 0.0001$). Patients in the control group showed a sixfold increased relative risk for blood transfusion than patients treated with tranexamic acid. The number of patients needed to be treated with tranexamic acid to save 1 blood unit (homologous or autologous) was 9.2.

There were no thromboembolic complications in the tranexamic acid group or the control group. Other complications, such as impairment of renal function, nausea, or gastrointestinal complaints occasionally associated with the use of tranexamic acid were not observed.

**DISCUSSION**

The present results show that the use of tranexamic acid reduces blood loss and transfusion requirements in total knee arthroplasty. In the group of patients treated with tranexamic acid there was a significant reduction of blood loss recovered in the surgical drain, a lower decrease of Hb concentration postoperatively, and total blood loss at the fourth postoperative day. These findings are consistent with data previously reported by others,\(^5,10\) Reduction of blood loss due to the administration of tranexamic acid was associated with a decrease in the number of blood units transfused during the postoperative period, which is also consistent with results of other studies.\(^8-10,17,20\)

In contrast, tranexamic acid was also effective when other blood transfusion–sparing strategies were used. In this study all patients were included in a blood conservation program based on the administration of rHuEPO, autologous blood transfusion, elementary iron preoperatively, and reinfusion of blood recovered by the surgical drains. As far as we are aware, no previous study has assessed the effect of tranexamic acid in association with blood transfusion sparing multimodal protocol.

The percentage of patients requiring homologous blood transfusion in our hospital before the use of the blood conservation program was 44 percent,\(^14\) which was reduced to 14.5 percent after the implementation of the blood transfusion–sparing protocol. In the control group, six patients received blood transfusion (12.2%) probably due to the use of cell salvage drain added to the previous protocol. In contrast, in the group of patients treated with tranexamic acid only one patient required blood transfusion. In fact, whereas the implementation of a blood transfusion–sparing program (expensive and complex) achieved a 32 percent reduction of the number of patients requiring transfusion, the use of tranexamic acid was able to decrease by 10.1 percent the percentage of patients transfused.

In this study, blood loss in the control group is consistent with results of other clinical series,\(^16,19,20\) but reduction of transfusion requirements associated with the use of tranexamic acid is lower than that reported in other studies, ranging between 30 and 50 percent\(^8-10,18,20,21\) (compared with 25% in our study). This may be explained by the total dose of tranexamic acid administered to patients (16 mg/kg), which was at least 20 percent lower due to the continuous infusion of the drug during the first 6 postoperative hours instead of repeating the administration of
the intraoperative bolus as performed in other studies.\textsuperscript{16,18,20} The dosage of tranexamic acid in total knee replacement surgery is poorly defined.\textsuperscript{6} All authors agree that administration of the drug should be always prophylactic, in the majority of studies before deflation of the tourniquet, although in some studies patients received tranexamic acid before inflation of the tourniquet without apparent complications.\textsuperscript{16} In contrast, a single postoperative bolus between 3 and 4 hours after the previous one was administered in most of the studies, although in other studies up to nine bolus over the first 3 postoperative days have been used.\textsuperscript{9} In this study, the purpose of continuous infusion of tranexamic acid postoperatively was to maintain an effective dose, decreasing the total dose of the drug during the period of the highest risk of bleeding (within 6 hr after operation) and hypothetically minimizing the occurrence of adverse events. This schedule could be effective in reducing the rate of adverse events but its effectiveness in reducing blood loss was less favorable than in other studies. The analyses of some studies in a meta-analysis concludes that the efficacy versus placebo was greater with a dose regimen of more than 30 mg per kg tranexamic acid\textsuperscript{22} and it supports our hypothesis. It is

<table>
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<th>TABLE 1. Preoperative and intraoperative data of the study population*</th>
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<td>Data</td>
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<td>Age, years, mean (SD)</td>
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<tr>
<td>Sex (male/female), number</td>
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<tr>
<td>Body mass index, kg/m\textsuperscript{2}, mean (SD)</td>
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<td>ASA Class I/II/III, number</td>
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<td>Hct, %, mean (SD)</td>
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<td>Predonation + Fe, number</td>
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<td>Preoperative rhEPO, number</td>
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<td>Duration of ischemia, sec, mean (SD)</td>
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<tr>
<td>Crystalloid volume, mL, median (IQR)</td>
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<td>Colloids volume, mL, median (IQR)</td>
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* Data are reported as mean and SD for continuous variables. Crystalloid volume and colloids volume are reported as median and interquartile range.
† Statistical significance (p < 0.05).

<table>
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<th>TABLE 2. Postoperative data in the study groups*</th>
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<td>Crystalloids volume, mL, mean (SD)</td>
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<td>Colloids volume, mL, mean (SD)</td>
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<td>Drained blood, mL, mean (SD)</td>
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<td>From cell saver, number (%)</td>
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<td>Autologous blood, units</td>
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* Data are reported as mean and SD for continuous variable and number (%) or units for transfusion data.

Fig. 2. Reduction of Hb levels between preoperative and fourth postoperative day. Significant difference of Hb levels between groups 6 hours after surgery and at the fourth postoperative day (p < 0.05). (●) Control group; (■) tranexamic acid.
likely that postoperative continuous infusion of tranexamic acid should be maintained for some more hours. It would be interesting to identify the length of time of persistence of postoperative fibrinolysis to optimize antifibrinolytic therapy, however, particularly regarding reduction of hidden blood loss.

Reduction of blood loss associated with the use of tranexamic acid mostly occurs at the expense of external bleeding, whereas differences in hidden blood losses between the study groups were not significant as already described by Good and coworkers. The administration of tranexamic acid resulted in a 70 percent reduction of total blood loss collected in the surgical drain (50% in the study of Good and coworkers), although reduction of total blood loss is lower (25.4%). There were no differences in the amount of hidden blood loss between the study groups. The reason for this selective effect of tranexamic acid is unclear, although it has been suggested that hidden blood in the hematoma corresponds to bleeding in the initial phase when the role played by fibrinolysis is not important and therefore it is not influenced by drugs interfering with fibrinolysis. Data in the literature, however, indicate that the period immediately after release of ischemia is the phase with the highest fibrinolysis. In our opinion, initial bleeding is the most important surpassing the capacity of compliance of soft tissue and occurring more rapidly and, consequently, there is a visible reduction of blood loss by the surgical drains in relation to the effect of tranexamic acid. Then, after some hours, there is a better adaptation of soft tissue to a lower bleeding flow, fibrinolysis being less important in this phase, so that hidden blood loss is not affected by the action of tranexamic acid. We observed that differences in external blood loss were limited to the first 6 postoperative hours, the period in which tranexamic acid was administered. Moreover, this was also reflected by the significant difference in Hct levels between the two study groups at the end of this period. Probably due to the short elimination half-life of the drug (80 min), tranexamic acid may have had no effect on bleeding beyond this period. In contrast, this phase is that of the highest fibrinolytic activity in which the administration of tranexamic acid is particularly useful.

It should be noted that reduction of external blood loss as a result of tranexamic acid makes the use of a cell salvage drain as a blood-sparing strategy unnecessary. In this study, only 2 patients (4%) in the tranexamic acid group received reinfusion of blood recovered by surgical drains compared with 36 patients (73%) in the control group. If tranexamic acid mostly reduces external blood loss, it may be expected that the use of cell salvage drain may compensate this effect in the control group, but our study shows that despite a higher reinfusion rate, homologous blood transfusion was not avoided. Accordingly, the use of cell saver in the postoperative management of patients treated with tranexamic acid should not be recommended because it is an unnecessary expense.

In contrast, results of this study also question the use of presurgical donation of autologous blood in patients undergoing total knee arthroplasty in our institution because of 11 patients in which this procedure was used, only 3 received blood transfusion. Therefore, the use of presurgically donated units is far from the 70 percent recommended for an adequate cost-effectiveness ratio.

In our study, like others, no thromboembolic complications were documented among patients treated with tranexamic acid. Nevertheless, one of the limitations of the study is the assessment of these complications. The rate of clinical thromboembolic complications in knee replacement is very low to be determined in this study. Moreover the clinical exploration in the knee arthroplasty surgery could be deceptive for the detection of deep venous thrombosis. Maybe the big question today in the prophylactic use of tranexamic acid continues being its safety. Only big clinical trials with systematic use of ultrasonography and angiography in the postoperative period could resolve this question. Another limitation of our study is that some of the patients were excluded after randomization; this could jeopardize the benefits of randomization and internal validity of the study (intention of treat analysis).

We conclude that the use of tranexamic acid in total knee arthroplasty administered before deflation of the tourniquet followed by continuous infusion during the first 6 hours postoperatively reduced blood losses and transfusion requirements even when a blood conservation program, including presurgical autologous donation, EPO, iron, and postoperative cell salvage, was used. If tranexamic acid is used, postoperative cell salvage is unnecessary. Further studies are warranted to define the effective dose of tranexamic acid with the lowest adverse events and the postoperative period of time in which the administration of the drug should be maintained.

ACKNOWLEDGMENT

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REFERENCES

TRANEXAMIC ACID REDUCES BLOOD TRANSFUSION IN KNEE ARTHROPLASTY


APPENDIX 1

Total RBC loss (mL) = [Uncompensated RBC loss (mL)] + [Compensated RBC loss (mL)]

Uncompensated RBC loss (mL) = [Initial RBC (mL)] - [Final RBC (mL)]

Compensated RBC loss (mL) = [Sum of RBCs received from the various sources of transfusion]*

Initial RBC = [Estimated blood volume (mL)] × [Initial Hct level (%)] on Day 0.

Final RBC = [Estimated blood volume (mL)] × [Final Hct level (%)] on Day + 4.

Estimated blood volume (mL) = Women: [Body surface area (m²)] × 2430. Men: [Body surface area (m²)] × 2530.

Body surface area (m²) = 0.0235 × [Height (cm)]^{0.42246} × [Weight (kg)]^{0.551456}

*Estimated blood volume of different sources of transfusion:

Allogenic blood unit = 180 mL of red cells (this is obtained from our blood bank data analysis)

Autologous blood unit = [Volume reinfused (mL)] × [Initial Hct level (%)] on Day 0.

Drained reinfusion blood = [Volume reinfused (mL)] × 30 percent.