Blood conservation with tranexamic acid in total hip arthroplasty

A randomized, double-blind study in 40 primary operations

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ABSTRACT – We performed a randomized, double-blind study on the effect of tranexamic acid on blood loss and blood transfusions in 40 primary total hip arthroplasties.

Tranexamic acid, 10 mg/kg body weight, or placebo, was given intravenously just before the operation. Blood loss during the operation and postoperatively into the drains was recorded, as also were blood hemoglobin concentrations. Ultrasound examination 1 week postoperatively was done to estimate the blood loss due to remaining hematomas.

Total (operation + drain) blood loss was 0.76 (95% CI 0.63–0.89) L in the tranexamic acid group as compared to 1.0 (CI 0.81–1.2) L in the placebo group (p = 0.03). The number of blood transfusions during the day of operation was 2 vs. 10 (p = 0.07) and the total number during the hospital stay was 5 vs. 13 (p = 0.2). 1 patient in each group had a pulmonary embolism.

Various methods have been developed to reduce the need for blood transfusions in hip arthroplasty surgery, many of which are costly and/or complicated (Flordal et al. 1992, Nelson and Fontenot 1995, Bierbaum et al. 1999). The most direct way to do this is to reduce the perioperative blood loss. Tranexamic acid, a well-known fibrinolytic inhibitor, has been shown to reduce blood loss and the need for blood transfusions in urologic and thoracic surgery as well as in knee arthroplasties (Hedlund 1969, Benoni et al. 1994, Horrow 1994, Hiippala et al. 1995, 1997, Benoni and Fredin 1996, Dunn and Goa 1999).

We studied the effect of tranexamic acid (TA), given intravenously at the beginning of the operation, on blood loss as well as on need for blood transfusions in primary total hip arthroplasty.

Study, design, patients and methods

The size of the study population was decided on the basis of calculation from a pilot study of 10 patients, participating in a pharmacokinetic study on tranexamic acid in total hip replacements (Benoni et al. 1995). The blood loss in these patients was compared to that in 10 matched controls not receiving the drug. In that study, tranexamic acid reduced the postoperative blood loss by, on average, 255 mL. A power analysis indicated that a study comprising 36 patients was needed to confirm this difference having 90% power at a 5% significance level.

Thus we included 40 patients in the current study, scheduled for a unilateral, primary total hip replacement for osteoarthrosis or osteonecrosis (Table 1). The operations were performed in Malmö and Trelleborg hospitals, situated 30 km apart and both parts of the Department of Orthopedics in Malmö University hospital. The orthopedic surgeons worked in the two hospitals, but the anesthesiologists worked only in one.

All patients gave their informed consent to participation. The study was approved by the local ethics committee and by the Medical Products Agency.

The study protocol stated that the indication

Table 1. Patient characteristics

	Tranexamic acid group [a]	Placebo group
Gender, male/female	9/9	10/10
Age, mean (SD)	66 (9.5)	68 (9.4)
Weight, kg, mean (SD)	79 (16)	78 (17)
Height, cm, mean (SD)	170 (11)	174 (7)
Diagnosis, osteoarthrosis/ osteonecrosis	17/1	18/2
Location, Malmö/Trelleborg	11/7	11/9

[a] 2 patients excluded, see text.

Table 2. Anesthesia and fluid replacement

Anesthesia	Tranexamic acid group	Placebo group
Continuous epidural	6	5
Morphine spinal	7	9
General	1	2
Combined spinal/epidural	1	1
Combined general/regional	3	3
Haes-steril, mL, mean (SD)	500 (420)	600 (380)
Crystalloid solutions, mL, mean (SD)	3920 (640)	4210 (450)

for surgery was osteoarthrosis or osteonecrosis but not rheumatoid arthritis. Patients who were to undergo bone grafting or had bleeding disorders or signs of renal insufficiency were excluded, since tranexamic acid is eliminated through the kidneys. The operations were performed with the patients in a supine position, using a lateral approach without trochanteric osteotomy. All patients were operated on using the Charnley Elite total hip prosthesis (DePuy) with both components cemented.

If colloid substitution was indicated because of signs of hypovolemia perioperatively, starch solutions (Haes-steril, 60 mg/mL, Meda, Sweden) were given, but not dextran. Since we found a tendency to lower blood loss in females in a previous study (Benoni et al. 2000), the study comprised 20 patients of each sex, randomized separately.

The patients received tranexamic acid 100 mg/mL (Cyklokapron, Pharmacia & Upjohn, Sweden), 10 mg/kg body weight (maximum 1 g), in a slow (5–10 minutes) intravenous injection or a similar volume of placebo (saline) immediately before the operation started, contained in specially-prepared ampoules with 10 mL of the substance, identified by their numbers only. The hospital's chief pharmacist, who was not otherwise involved in the study, kept the code, which was broken only after the study.

As thromboprophylaxis, all patients received low molecular weight heparin (Klexane, Rhone-Poulenc Rorer), 40 mg subcutaneously, starting the day before surgery and continuing for 7–10 days. 1 patient in the placebo group, with previous deep venous thrombosis (DVT), continued her medication for 1 month according to the routines in our department.

Cloxacillin or clindamycin was routinely given as antibiotic prophylaxis before surgery and on two more occasions on the day of surgery.

Analgesia was usually obtained with continuous epidural anesthesia with mepivacaine/epinephrine and bupivacaine or spinal block using bupivacaine and morphine. General anesthesia was given to 3 patients (Table 2).

We determined the blood loss during the operation by measuring the volumes in the suction apparatus and estimating the swab contents. One subfascial, and in obese patients one subcutaneous, low vacuum drain (Ch 14) (Bellovac, Astra Tech, Sweden) was routinely used and the volumes drained were recorded at 1, 3, 8 hours and finally on drain removal 24–33 hours after surgery.

We did not prescribe blood transfusions for patients with a certain level of blood hemoglobin concentration. Transfusions were given on a case-by-case basis with regard to age, cardiovascular status, hemoglobin concentration and blood loss (Spence 1995). Most patients who had blood transfusions received these at a hemoglobin concentration between 80 and 100 g/L.

The transfusions were recorded as the number of transfused red cell concentrates (Sagman) units. One Sagman unit is processed from about 450 mL of donor blood and contains approximately 270–330 mL of red cell concentrate at a hematocrit of about 60%.

We noted transfusions given on the day of surgery until the morning of the first postoperative day separately from those given during the rest of the period of hospitalization.

The hemoglobin concentration in blood was recorded on admission (usually about 10 days

before the operation), 1 and 8 hours postoperatively and in the mornings of the 1st, 2nd, 4th and 7th postoperative days.

Capillary transcutaneous oxygen saturation was regularly monitored with a pulse oxymeter (Eagle, Marquette Corp., USA) during the operation and in the postoperative ward.

1 week after the operation, the number and size of hematomas in the operated thigh were estimated by ultrasound examination using a Hitachi EUB with 3.5 and 5 MHz transducers. The patients were examined in the supine and lateral oblique positions. Hematomas were defined as the volume of echogenic changes that were visible in the wound area and were recorded with regard to their number, location and volume, using the formula for a spheroid (length × width × depth × π/6). The same investigator performed all ultrasound examinations.

We did not screen for postoperative thrombosis, but all clinical events up to a minimum of 6 weeks after the operation were recorded.

Protocol violations

1 patient in the tranexamic acid group was operated on in a lateral recumbent position, using a posterior incision. Another patient in this group received 500 mL of dextran 70 as colloid substitution instead of Haes-steril. Both patients were excluded from the study.

1 patient in the placebo group was given 15 mg of desmopressin i.v. (Octostim, Ferring, Sweden) 5 hours postoperatively. The ultrasound examination was not done on 1 patient in each group, 1 because of urosepsis on the day of examination and 1 because of consent withdrawal. These 3 patients remained in the study.

Statistics

Continuous data were compared, using the Student's t-test. For discontinuous data, such as the number of blood transfusions, the Mann-Whitney U-test adjusted for ties was used. Repeated comparisons of the same variable (e.g., hemoglobin concentrations and oxygen saturation at different times) were compared with ANOVA, repeated design. Fisher's exact test was used to compare frequencies. Results and data are shown as mean values and one standard deviation (SD) or 95% confidence interval (CI). All analyses were made using STATISTICA (StatSoft, USA) version 5.0.

Results

During the operation, the blood loss was similar in the TA and placebo groups (561 (CI 428–694) mL vs. 608 (CI 482–734) mL; p = 0.6).

The postoperative blood loss was significantly lower in the TA group (Figure 1). On removal of the drains, the mean blood loss was 199 (CI 142–256) mL in the TA group and 388 (CI 281–495) mL in the placebo group (p = 0.003).

The total blood loss (peroperative + drains) was 759 (CI 630–889) mL in the treated group and 996 (CI 818–1174) mL in the placebo group (p = 0.03). The hematoma volumes, as measured with ultrasound 7 days after the operation, were 270 (CI 209–331) mL in the TA group and 376 (CI 257–494) mL in the controls (p = 0.1).

The sum of operative blood loss + drain loss + hematoma volumes was 1028 (CI 863–1192) mL in the prophylactic group and 1382 (CI 1169–1595) mL in the placebo group (p = 0.01). Of 18 patients in the TA group, 4 received a total of 5 blood transfusions during the entire hospitalization period, compared to 8/20 patients in the placebo group who received a total of 13 blood transfusions (p = 0.2). Corresponding numbers for the day of operation alone was 2 and 10 units transfused (p = 0.07).

The 2 patients who were excluded had a total blood loss below the mean of the other patients. If their results are included in the calculations, the total blood loss was 745 (CI 627–863) mL in the TA group and 996 (CI 818–1174) mL in the placebo group (p = 0.02). Neither of these patients received a blood transfusion. The p-value for the difference between the TA and placebo groups concerning the number of blood transfusions during the day of operation was then 0.05.

The women were shorter than the men, 165 (SD 7) cm vs. 178 (SD 8) cm and weighed less, 71.5 (SD 14.7) kg vs. 86 (SD 14.5) kg. They sustained a slightly lower blood loss during the operation and into the drains, 809 (CI 652–966) mL vs. 959 (CI 787–1132) mL for the men (p = 0.18).

There was no significant difference in blood hemoglobin concentrations during the study

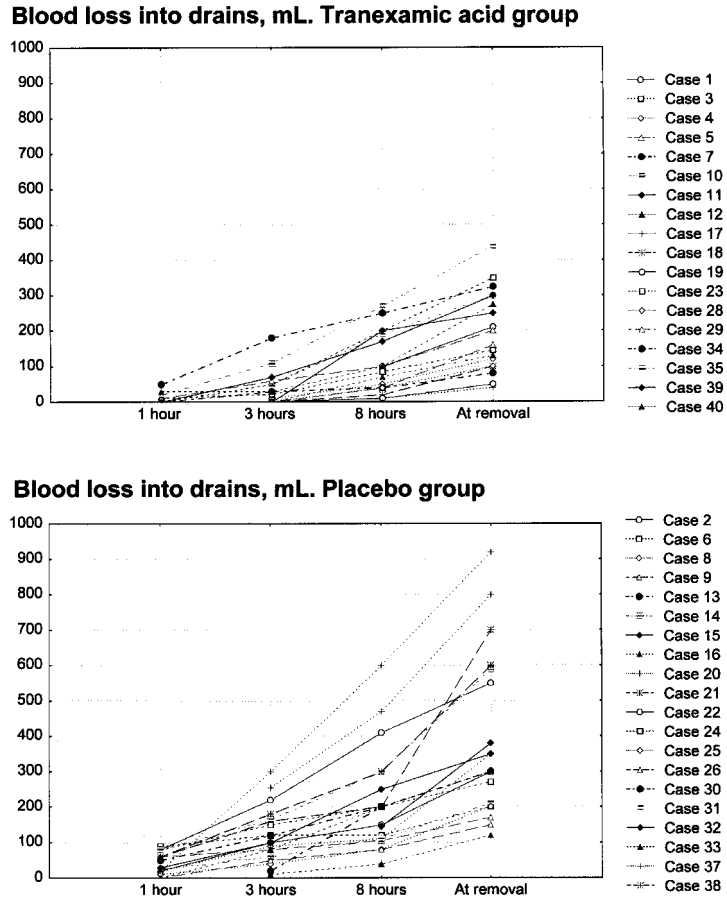

Figure 1. Line drawings of individual accumulated blood loss into the drains 1, 3, and 8 hours after the operation and at the time of drain removal in the tranexamic acid (upper) and placebo (lower) groups. P-value for the different blood losses on drain removal in the tranexamic acid and placebo groups = 0.003.

between the two groups (Figure 2). We found no significant change in percutaneous oxygen saturation during the operation, or any difference between the TA and placebo groups.

Complications

1 patient in the TA group developed chest pain 24 hours after the operation. She had ECG signs of myocardial ischemia, but examinations of Troponin I were not suggestive of a myocardial infarction. Another patient in this group, with hypertension, developed slight hemiparesis 58 days postoperatively, but the CT of her brain was normal. A CT 3 months later, after another episode, showed signs of older infarctions in the right hemisphere. We do not attribute these complications to treatment with tranexamic acid.

1 patient in each group sustained a pulmonary embolism, confirmed on a spiral CT examination, 32 and 43 days after the operation. The patient in the TA group was the one who had postoperative chest pain, mentioned above. There were no other clinical venous thromboembolic events. 2 patients in the placebo and 1 in the tranexamic acid group underwent phlebography postoperatively, but the findings were normal.

On the third postoperative day, the numbers of patients with clinically observed wound-hematomas and secretions from the wounds were similar in both groups (Table 3). 1 patient in the TA group had continuous secretions from his wound and was re-operated on for hematoma evacuation 14 days after the arthroplasty. Cultures showed growth of Staphylococcus epidermidis. He underwent reoperation because of a deep infection 5 months later. This patient withdrew his consent to ultrasound examination. 1 patient in the placebo group developed nausea when the drug

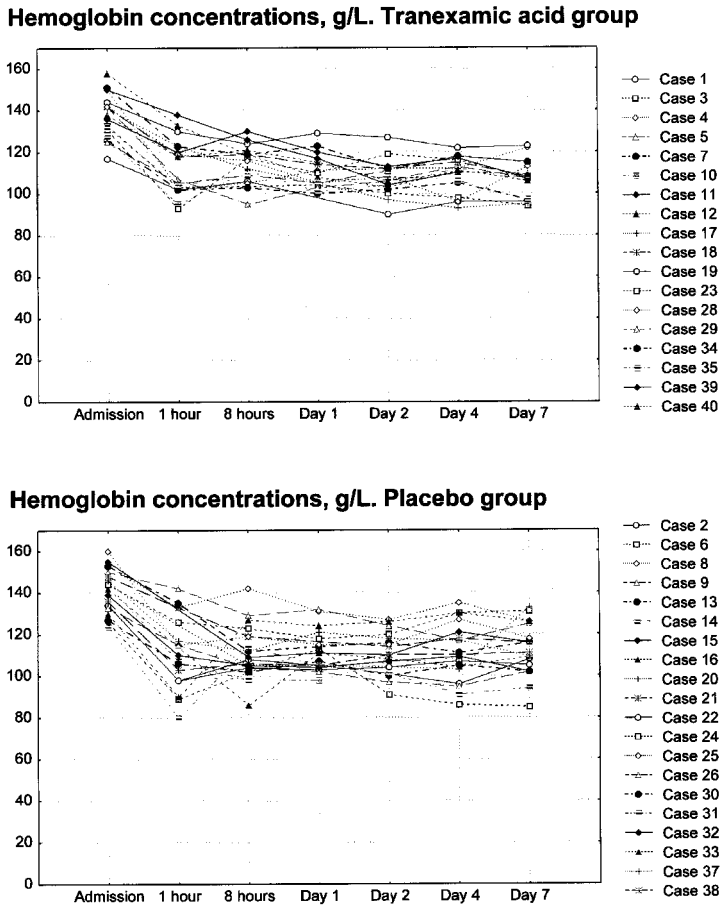

Figure 2. Line drawings of individual blood hemoglobin concentrations on admission, 1 and 8 hours after the end of the operation and in the mornings of the 1st, 2nd, 4th and 7th postoperative days. No significant difference was found between the tranexamic acid (upper) and placebo (lower) groups, p = 0.85, ANOVA with repeated design.

Table 3. Wound complications

	Tranexamic acid group	Placebo group
Hematoma	6	7
Secretion from drainsite	3	5
wound	2	6

was injected. We found no untoward reactions to tranexamic acid.

Cost

The price of one ampoule of tranexamic acid (1 gram) in Sweden is 5 Euro. In our department, 1 unit of leukocyte-filtrated erythrocyte concentrate costs 77 Euro. The total cost of tranexamic acid and blood transfusions in the TA group was 475 Euro versus 1100 Euro in the placebo group.

Discussion

Recently, Duquenne et al. (1999), Ekback et al. (2000) and Ido et al. (2000) have reported results similar to ours. The prophylactic administration of tranexamic acid significantly reduced the postoperative (Ido et al. 2000) and total blood losses (Ekback et al. 2000). This has also been shown in total knee arthroplasties (Benoni et al. 1994, Hiippala et al. 1995, 1997, Benoni and Fredin 1996, Jansen et al. 1999). In knee arthroplasties, tranexamic acid also reduced the number of blood transfusions. Likewise, in our present study, we found a 60% reduction in the number of blood transfusions in patients receiving tranexamic acid, but the difference between the groups was not statistically significant.

In previous studies, apart from that by Ekback et al. (2000), tranexamic acid has only reduced the postoperative, but not the peroperative, blood loss (Hedlund 1969, Hiippala et al. 1995, 1997, Benoni and Fredin 1996). In view of this, we did a previous study on patients underging hip arthroplasty in which tranexamic acid was given towards the end of the operation, but found no effect on postoperative blood loss (Benoni et al. 2000).

The reason for this difference between our present and our previous studies may be a biochemically more accurate timing for the administration of tranexamic acid in the present study. Tranexamic acid inhibits fibrinolysis mainly by blocking the lysine binding sites of plasminogen (Nilsson 1980), the same sites which plasminogen uses for its binding to fibrin. On the fibrin surface, plasminogen is activated to plasmin and starts to degrade the fibrin molecules. To be effective, tranexamic acid probably has to interact with the plasminogen binding site before binding to fibrin occurs. In hip arthroplasty, fibrin plug formation occurs during the operation while blood vessels are severed, leaving ample time for plasminogen binding if tranexamic acid is not present initially. If tranexamic acid is given later, the drug is probably much less likely to affect the fibrinolytic process, since the plasminogen is already bound to fibrin. In an in vitro study, Krishnamurti et al. (1994) found that tranexamic acid inhibited clot lysis more efficiently when it was added before clot formation than after it.

The estimate of blood lost during surgery and measurement of the volume lost in the drains do not account for the total amount of blood lost from the circulation (Flordal 1997). Some blood is extravasated as postoperative hematomas, which are difficult to detect and measure. Theoretical methods to estimate this hidden blood loss have been suggested (Lisander et al. 1996, Flordal 1997), but ultrasound is the method that most accurately measures the size of posttraumatic hematomas (Thorsson et al. 1993).

Concern is often expressed that the perioperative use of tranexamic acid may increase the risk of postoperative deep venous thrombosis (DVT) (Howes et al. 1996). This has no support in the literature (Dunn and Goa 1999). Studies have failed to show any statistically significant increase in the risk of DVT after various types of surgery or in pregnancy, even after prolonged use of the drug. We have traced 4 randomized studies on tranexamic acid and knee arthroplasty (Hiippala et al. 1995, 1997, Benoni and Fredin 1996, Jansen et al. 1999) comprising a total of 232 patients. These studies report a total of 6 clinical thromboembolic complications among patients receiving tranexamic acid and 11 among patients receiving placebo. In 3 randomized studies on hip replacements (119 patients), the numbers of DVT were the same (Benoni et al. 2000, Ekback et al. 2000, present study). Several studies indicate that thrombogenesis after hip arthroplasty is a prolonged process, where a substantial proportion of the thrombi occur a week or more after the operation (Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997). We have previously shown that the concentration of tranexamic acid in the plasma remains at or above the minimum therapeutic level for only about 3 hours after one intravenous dose of 10 mg/kg body weight (Benoni et al. 1995). Considering the fact that TA in orthopedic surgery is given in one or a few perioperative doses during a period of increased fibrinolytic activity (Risberg 1990, Eriksson et al. 1991, Benoni et al. 1995), the theoretical reasons for a thrombogenic effect of TA in orthopedic surgery seem weak.

In our study, tranexamic acid, given intravenously at the beginning of the operation, was an efficient and cost-effective way to reduce blood loss in total hip replacement. Whether tranexamic acid also significantly reduces the need for allogeneic blood transfusions should be discussed in future studies.

Pharmacia & Upjohn supported the production of the tranexamic acid and placebo ampoules produced by Apoteksbolaget, Umeå, Sweden. They were randomized by Pål Stenberg, chief pharmacist in our hospital. Astra Tech, Mölndal, Sweden, supplied the drains used in the study. Jan Åke Nilsson, B.Sc., gave statistical advice. Financial support was obtained from Malmö University Hospital funds.

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