Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty

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ABSTRACT – We performed a randomized double-blind study on the effect of tranexamic acid on postoperative blood loss and blood transfusions in 39 primary THR operations. Tranexamic acid was given at the end of the operation and 3 hours later. Ultrasound examination 1 week later was performed to measure the occurrence of deep hematomas.

In contrast to previous findings in knee arthroplasty, the administration of tranexamic acid failed to give a significant reduction in the postoperative blood loss. This lack of effect was possibly related to the fact that the drug was administered too late. In 11 of the 20 patients receiving tranexamic acid, blood transfusion was not necessary, this being the case in 4/19 in the placebo group (p = 0.05). The occurrence of postoperative deep venous thromboses was similar in the tranexamic acid and placebo groups.

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In numerous reports, fibrinolytic inhibitors such as aprotinin and tranexamic acid have been found to reduce blood loss in a variety of surgical procedures, mostly in thoracic surgery (Royston 1995). Recently, aprotinin has been shown to reduce blood loss in total hip replacements (Janssens et al. 1994, Murkin et al. 1995). Tranexamic acid, a cheaper and more specific fibrinolytic inhibitor than aprotinin, reduces blood loss in knee arthroplasty (Benoni et al. 1995b, Hiippala et al. 1995, 1997, Benoni and Fredin 1996a) but has, to our knowledge, not been systematically used in hip surgery.

Previous studies in orthopedic and urologic surgery have shown that tranexamic acid reduces postoperative, but not peroperative blood loss (Hedlund 1969, Benoni et al. 1995b, Hiippala et al. 1995, 1997, Benoni and Fredin 1996a). Furthermore, Christie et al. (1995a, b), among others, have demonstrated that a shower of emboli regularly passes the heart during cementation of the femoral component. To avoid fibrinolytic inhibition during that phase of the operation and to exploit the effect of tranexamic maximally in the postoperative phase, we decided to delay the administration of tranexamic acid in the present study until the end of the operation, when the cement had cured and the arthroplasty had been repositioned.

In this study we evaluated the effect of tranexamic acid, given at the end of the operation, on postoperative blood loss and blood transfusions in elective total hip arthroplasty.

Patients and methods

We included 40 patients in a randomized, double-blind study. The number was calculated, using the results in a previous study (Benoni et al. 1995a). We compared the blood loss of the 10 patients in that study with that of 10 matched controls. Tranexamic acid reduced the postoperative blood loss by 255 mL. A power analysis showed that 36 patients were needed to confirm this difference at the 5% level with 80% power.

The Ethics Committee at Lund University approved the study. After giving informed consent, the patients (Table 1) were randomized to receive either tranexamic acid (Cyklokapron, Pharmacia & Upjohn, Sweden), 10 mg/kg body weight (20 patients) or a corresponding volume of placebo (saline) (20 patients), intravenously at the end of the operation. The administration was repeated 3 hours later. The drug was given from numbered ampoules containing either active substance or placebo and the randomization was done by a pharmacist not otherwise engaged in the study. The code was not broken until completion of the study when all clinical data had been filed in the statistics program.

The patients had osteoarthrosis or idiopathic femoral head necrosis, and no hip had been operated on previously. All operations were unilateral and performed with the patient in a supine position and a lateral approach without trochanteric osteotomy. A total hip replacement with cementation of both components was used throughout (Charnley, De Puy, Ltd., England). All patients received thromboprophylaxis with daily doses of low molecular weight heparin (Klexane, Rhone-Poulenc Rorer, France), 40 mg subcutaneously, for 10 days, starting on the evening before surgery. In most cases, continuous epidural anesthesia with mepivacain + epinephrine and bupevacain was used but in some instances spinal anaesthesia with bupevacain or general anesthesia or combinations of these methods were employed (Table 1). Crystalloid solutions were used for perioperative fluid replacement with the addition of colloids, dextran 70 (Macrodex, Medisan, Sweden) or albumin 200 mg/mL (Pharmacia & Upjohn, Sweden), when signs of hypovolemia were present (Table 1).

14 patients were given ephedrine perioperatively because of hypotension.

Flucloxacillin was routinely used as antibiotic prophylaxis, 2 grams at the beginning of the operation and 1 gram 8 and 16 hours later.

Blood loss was measured as the contents of the suction bottles plus the estimated blood lost in the swabs. One subfascial and, in most cases, one subcutaneous high-vacuum drain (Medinorm AG, Quershied, Germany) was used. Blood loss into these was recorded at 1, 4, 8, 12, 24 hours after the operation and finally in conjunction with the removal of the drains at a median of 28 hours postoperatively. The volume scaling of these drains has a mean error of + 1 mL, 95% confidence interval –4 to +6 mL (Benoni and Fredin 1997).

Table 1. Patient characteristics

	Tranexamic acid group	Placebo group
Age, year [a]	69.5 ± 10	68 ± 10
Gender M/F	6/14	11/8
Height,cm [a]	168.5 ± 7	171 ± 11
Weight,kg [a]	76 ± 14	77 ± 11
Operation time,min [a]	107 ± 25	105 ± 17
Type of anesthesia		
Continuous epidural	10	12
Spinal	4	3
Spinal/epidural	3	3
General	3	0
General + epidural	0	1
Ephedrine during surgery		
Yes/No	7/13	7/12
Perioperative NSAID, no. of patients	4	7

[a] mean, SD

Ultrasonography

1 week after the operation, the number and size of hematomas in the operated thigh were studied by the same radiologist (PN) using real-time sonographic equipment, 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 aberrations that were visible in the wound area and were registered with regard to number, location and volume using the formula for a spheroid (length × width × depth × $\pi/6$).

Blood transfusions were given as erythrocyte concentrate units (Sagman) according to the patients' clinical need, with individual regard to age, cardiovascular status and present clinical condition and were recorded as the number of transfused units. 3 patients in the tranexamic acid group and 2 in the control group had predonated 2 units each.

Wound complications were recorded at a regular examination 3 days postoperatively or at other times when necessary.

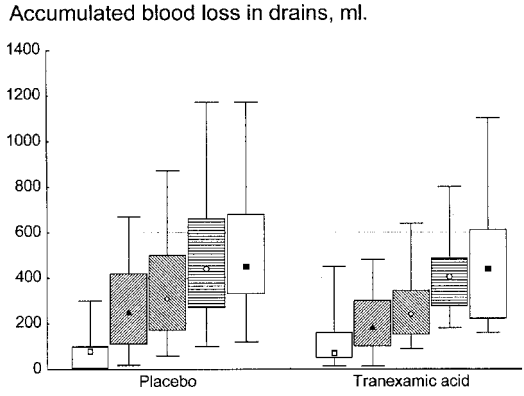

Figure 1. Postoperative blood loss at 1 (■), 4 (▲), 8 (◆), 24 (●) and finally at the time of drain removal (■), median 28 hours, after the operation. Symbols represent median values, box limits 25th and 75th percentiles, and whiskers show minimum and maximum values. There was no significant difference between the placebo and tranexamic acid groups.

We used no screening for thrombosis, but clinically detected cases during the first 6 postoperative weeks were noted.

Laboratory tests

Blood hemoglobin (Hb) concentration and hematocrit (hct) were recorded at admission (approx. 2 weeks before the operation), immediately before the operation, after the induction of anesthesia, 1 and 8 hours postoperatively and on the mornings of the 1st, 2nd, 4th and 7th postoperative days. On admission, platelet count and prothrombin time (PT) were recorded and found to be within the reference values of our laboratory. These analyses were performed according to standard methods in our Department of Clinical Chemistry.

Statistical analyses were done using the Mann-Whitney U-test for quantitative and qualitative data and Fisher's exact test for frequencies. The results are described as median values + upper and lower quartiles, unless stated otherwise. Friedman's Anova was used to test sequential variations in repeated examinations such as the laboratory examinations. Significance levels < 0.05 were considered significant. Calculations were made using the STATISTICA package, release 5.0.

Drop-out. 1 patient in the placebo group was excluded before the randomization code was broken, because of protocol violation (only 1 injection of the investigated drug).

No ultrasound examination was performed in 1 patient, but the other variables for this patient were included in the study.

Results

There were proportionally more women in the tranexamic acid than in the placebo group (Table 1). Women were shorter, weighed less and showed a tendency towards less blood loss than the men in both the tranexamic acid and placebo groups.

Peroperative blood loss was 550 (400–850) mL in the tranexamic acid group and 500 (400–700) mL in the placebo group. The accumulated blood loss into the drains was not significantly lower in patients receiving tranexamic acid (Figure 1). Blood loss into the drains at the time of removal was 440 (220–610) mL in the tranexamic acid group vs 450 (330–680) mL.

The ultrasound examination showed that most patients had multiple hematomas. These were mostly located around the joint, at the trochanter, anterior and posterior to the femur, distal to the joint and below the incision. The total hematoma volume in and around the operating field was slightly lower in the tranexamic acid group (Table 2). However, this difference was not statistically significant and we found no significant correlation with sex or use of dextran.

The sum of blood loss into the drains and the total hematoma volume, i.e., the blood loss occurring after the administration of tranexamic acid, was 660 (540–934) mL in the tranexamic acid group and 792 (607–1080) mL in the placebo group ($p = 0.2$)

The number of clinical wound complications, such as discharge from the wounds or drain sites, infections or visible hematomas, did not differ between the groups (Table 2).

The median number of blood transfusions was 0 (0–4) in patients receiving tranexamic acid vs 2 (0–3) among the controls ($p = 0.3$) (Table 3).

The decrease in blood hemoglobin concentration from the level on admission to the 7th postoperative day was not significantly different, 28 ± 10 g/L in the placebo group vs 27 ± 8 in the tranexamic acid group (Figure 2).

Table 2. Hematomas and wound complications

	Tranexamic acid group	Placebo group	P-value
No. of hematomas detected by ultrasound, median, quartiles	6 (4–9)	6 (5–9)	
Total ultrasound volume, mL	270 (176–351)	319 (170–482)	0.20
Clinical wound hematoma	1	2	
Redness or secretion from wound	6	9	
Secretion from drain sites	4	3	
Clinical infection	0	0	

Table 3. Blood and fluid replacement

	Tranexamic acid group	Placebo group	P-value
Total no. of Sagman units	21	26	0.2
No. of patients avoiding any blood transfusion	11	4	0.05
Crystalloid solution, mL, mean, SD	4600 ± 502	4336 ± 672	0.2
Dextran, mL, mean, SD	375 ± 222	342 ± 239	0.7
No. of patients receiving dextran	15	13	
Total no. of patients receiving albumin, 100–200 mL	3	3	

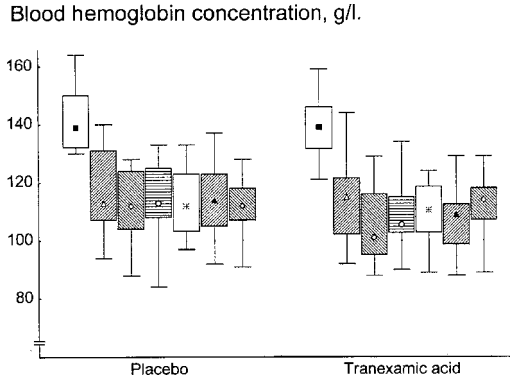

Figure 2. Blood hemoglobin concentrations before and after the operation in the placebo and tranexamic acid groups. Symbols represent median values, box limits 25th and 75th percentiles, and whiskers show minimum and maximum values. Admission (■): approx. 2 weeks before the operation, 1 (▲) and 8 (◆) hours postoperatively, the mornings of the 1st (●), 2nd (✳), 4th (▲) and 7th (◆) postoperative days. The difference between the two groups is not significant.

Phlebography was performed in 6 patients in the tranexamic acid group and 6 in the control group due to clinical suspicion of deep venous thrombosis. Thrombosis was confirmed in 3 patients in each group, 3 women and 3 men. 1 patient in the control group underwent pulmonary scintigraphy because of malaise, chest discomfort and fever 4 weeks postoperatively. This showed a low probability of pulmonary embolism. A chest radiograph was normal and the patient recovered spontaneously.

Discussion

In this study, tranexamic acid did not significantly reduce the blood loss in primary hip arthroplasty. More patients in the tranexamic acid than in the placebo group did not require a blood transfusion but the difference in the total number of blood transfusions (26 vs 21) was not statistically significant.

When measuring the surgical blood loss, the amount of bleeding into the tissues around the wound is difficult to estimate. It is generally believed that this volume may be substantial in hip surgery (Flordal 1997). We tried to include the volume of this hidden blood loss into our estimate.

This was done by using ultrasonography to measure the number and volume of hematomas that had collected in and around the wound area.

A previous experimental study on rabbits has shown that ultrasound examination accurately measures the volume of the contused muscle, better than MRI (Thorsson et al. 1993), a method that was unsuitable in our study due to the magnetic properties of the Charnley prosthesis. Thorsson and co-workers made their measurements about 1 hour after the injury. We made the ultrasound measurements 1 week after the operation and the hematoma volumes may have already diminished through absorption.

Our study was not dimensioned to evaluate the frequency of postoperative thromboembolic complications. However, considering the prolonged period of thrombogenesis after hip arthroplasty (Bergqvist et. al. 1996, Planes et. al. 1996), it is unlikely that tranexamic acid, given only during and shortly after the operation, should substantially increase the risk of postoperative deep venous thrombosis (Benoni and Fredin 1996b, Howes et al. 1996).

In contrast to the effect in knee arthroplasty, the administration of tranexamic acid at the end of hip arthroplasty operations did not reduce the postoperative blood loss. Whether this lack of effect was due to an inadequate timing of the drug administration remains to be investigated. The effect of tranexamic acid, given as prophylaxis before the start of the operation, merits further studies.

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