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# Tranexamic acid reduces blood loss in cemented hip arthroplasty

## A randomized, double-blind study of 39 patients with osteoarthritis

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**Background** Tranexamic acid has been found to reduce blood loss and the need for blood transfusions in knee arthroplasty. In hip arthroplasty, the benefit of tranexamic acid is not as clear.

**Patients and methods** In a randomized, double-blind study, 39 patients with primary cemented hip arthroplasty for osteoarthritis were divided into two groups; one receiving tranexamic acid and the other not receiving it. Tranexamic acid was given in a dose of 10 mg/kg before the operation and twice thereafter, at 8-hour intervals.

**Results and interpretation** Total blood loss was smaller in the tranexamic acid group than in the control group. No thromboembolic complications were noticed. Tranexamic acid appears to be an effective and economic drug for reduction of blood loss in cemented primary hip arthroplasty for osteoarthritis.

Tranexamic acid, a fibrinolytic inhibitor, has been found to reduce blood loss and the need for blood transfusions in knee arthroplasty (Benoni and Fredin 1996, Hiiippala et al. 1997). In hip arthroplasty, the benefit of tranexamic acid is not as clear due to the small number of studies published. According to earlier studies, tranexamic acid given before hip arthroplasty reduces perioperative blood loss and drainage (Ekbäck et al. 2000) or drainage alone (Duquenne et al. 1999, Ido et al. 2000, Benoni et al. 2001, Husted et al. 2003), but has no effect when given afterwards (Benoni et al. 2000).

We examined whether tranexamic acid given before and after hip arthroplasty reduces perioperative, postoperative and total blood loss, and secondly, whether the need for blood transfusions is reduced.

### Patients and methods

The patients came from Päijät-Häme hospital district (210,000 inhabitants). Consecutive patients who were scheduled for a cemented hip arthroplasty for osteoarthritis were candidates for the study. Upon entering the orthopedics department, the patients were told about the study by the nursing personal. 40 volunteer patients were enrolled in the study—which took place during the year 2003—after written consent. The study was approved both by the Ethics Committee of the hospital (29.11.2002, Q27), and by the Finnish National Agency for Medicines.

A cemented Elite Plus or C-Stem prosthesis (DePuy, Leeds, UK) was used in all patients. Spinal anesthesia followed by epidural analgesia until the next morning was used in 39 patients, and 1 patient had general anesthesia. A posterior approach was used. The posterior capsule was closed and a 10-ch closed suction drain was placed under the gluteal muscle. The same anti-thrombotic prophylaxis during hospitalization, low-molecular-weight heparin (dalteparin) and elastic leg dressing were used for all patients.

Antibiotic prophylaxis was discontinued on the day after surgery.

Patients with rheumatoid arthritis and osteonecrosis, and with known coagulation disturbances including thromboembolic events, were not considered eligible for the study. Patients using warfarin-related preparations, or with allergy to tranexamic acid, or with signs of renal insufficiency were also excluded. The use of acetylsalicylic acid was discontinued a week before the operation. All other pain-relieving drugs were allowed according to how the patients usually took them.

The patients were randomized into two groups by an envelope method in a double-blind manner (Table 1). The randomization and preparation of the drug were done in the absence of other personnel by 2 anesthesia nurses not engaged in the study. The code was broken after the last patient had been treated. Half of the patients received 3 doses of tranexamic acid (100 mg/mL, Cyklokapron, Pharmacia, later Pfizer) 10 mg/kg of body weight mixed in 100 mL saline. Half of the patients received a corresponding dose of saline. The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses of tranexamic acid or placebo were given 8 h and 16 h after the first injection.

One patient in the tranexamic group was excluded from the study. Postoperatively, she had a fit of coughing with a short period of unconsciousness. She recovered promptly, but the doctor on duty discontinued her medication. Thus, 39 patients were included in the final (on-treatment) analysis. The basic characteristics of the patients did not differ between the groups (Table 1).

The primary outcome variables were blood loss during the operation and the amount of drainage after the operation. Secondary variables were the amount of transfused units of red cells, wound leakage postoperatively, swelling and ecchymoses of the thigh, hematocrit, and possible complications. Intraoperative blood loss was estimated from the swabs and sucker bottle content minus irrigation fluid, with accuracy within 50 mL. Even though we had an indicative 0.28–0.30 level of hematocrit for blood transfusions, it was the clinical situation that determined the need for blood transfusions. Hematocrit was measured on the first and third postoperative days, and additional measurements were per-

Table 1. Patients' basic characteristics, mean (SD)

	Tranexamic acid group (n = 19)	Placebo group (n = 20)
Male/female	6 / 13	7 / 13
Age, years	66 (9.1)	65 (8.2)
Weight, kg	80 (19)	82 (14)
Height, cm	164 (8.6)	169 (7.4)
Operation time, min	93 (12)	96 (12)

formed when required clinically. The lowest value was used for the comparison. The drainage was measured using the intervals at which the injections were delivered, i.e. after 8 h and 16 h. The last measurement was done after 24 h, when the drain was removed. Swelling was measured at the level of 1 cm by comparing the circumference of the thigh 15 cm from the upper pole of the patella before the operation, and on the fifth postoperative day. Ecchymoses were noted.

Ultrasound was performed for detection of deep thrombosis, but only if thrombosis was suspected clinically.

### Statistics

Basic patient data are given as mean (SD). Results for continuous data are expressed as average and 95% confidence interval (CI). To compare the means, we used the non-parametric Mann-Whitney U-test. Regarding blood transfusions, patients were divided into two groups: no transfusion given and transfusion given, and Fisher's exact test was used. For power analysis, we used earlier studies of Benoni (Benoni et al. 2000, 2001). These indicated that 36 patients should be included in order to have 90% power at a 5% significance level, to measure difference in postoperative blood loss. To exclude unexpected protocol violations, 40 patients were enrolled in this study.

### Results

The total measurable blood loss was less in the tranexamic acid group ( $p = 0.03$ ). Most bleeding occurred during the first 6 postoperative hours (Table 2).

The circumference of the thigh increased on average 2.9 cm in the tranexamic acid group and

Table 2. Bleeding and drainage in mL (CI)

	Tranexamic acid group	Placebo group	P-value
Peroperative bleeding	626 (492–761)	790 (599–981)	0.2
8 h	83 (54–112)	192 (142–242)	0.001
16 h	57 (40–74)	85 (57–112)	0.1
24 h	26 (15–37)	35 (21–49)	0.5
Total drainage	166 (122–220)	312 (231–393)	0.005
Bleeding + drainage	792 (624–971)	1102 (885–1319)	0.03

4.2 cm in the placebo group ( $p = 0.09$ ). Ecchymosis was noted in 10 thighs of the tranexamic acid group (data missing for 1 patient), and in 12 thighs of the placebo group.

Allogeneic blood transfusion was given to 8 patients in the placebo group and to 5 patients in the tranexamic acid group ( $p = 0.3$ ). The amounts of red cells were 18 and 10 units, respectively. The hematocrit decreased in the tranexamic acid group from 0.42 to 0.31, and from 0.43 to 0.30 in the placebo group.

The patients were discharged 7–8 days postoperatively, without any differences between the groups.

3 complications occurred in the tranexamic acid group: 1 superficial wound infection, 1 transient dyspnea on the third postoperative day, and 1 pyelonephritis 1 month later. In the placebo group, 1 male patient had voiding difficulties, which were managed with a suprapubic catheter. 1 patient suffered from acute gluteal eczema. No untoward reactions to tranexamic acid were noticed.

## Discussion

In this study, patients receiving tranexamic acid had slightly less bleeding and patients in both groups recovered similarly. The only exception was the patient who was excluded from the final on-treatment analysis because of coughing—an unlikely consequence of the use of the tranexamic acid.

Previous studies in hip arthroplasty have used different dosages, single injections or even continuous infusion after the first injection. The biological half-time of tranexamic acid is about 3.5 h in the serum and about 3 h in the joint fluid (Ahlberg et al. 1976). Benoni et al. (1995) have also noticed

that the therapeutical level of the tranexamic acid is maintained only for 3 hours, but with a larger dose (20 mg/kg) the level is maintained for 8 h. In spite of this, we used the dosage (10 mg/kg) and interval (8 h) recommended by the manufacturer.

The use of tranexamic acid in hip arthroplasty does not appear to increase thrombosis. We had no

thromboembolic complications, but on the other hand, we did not examine our patients routinely with ultrasound. However, our policy is justified by the results of earlier randomized studies which have reported equal amounts of deep vein thrombosis (5%) (Ekbäck et al. 2000), or pulmonary embolism (5%) (Benoni et al. 2001), in both groups. Others have reported no thromboembolic complications (Ido et al. 2000, Husted et al. 2003). A clinically relevant increase in deep venous thrombosis after arthroplasty would demand a total study population of thousands of patients (Ekbäck et al. 2000).

Reducing allogeneic blood transfusions brings straight economic benefits and minimizes the risk of virus transmission. One other consideration which is given less attention is the fact that allogeneic blood transfusion itself may elevate the risk of serious infections and fluid overload through an immunomodulating effect (Bierbaum et al. 1999, Carson et al. 1999). This study was not intended to be an economic one, but some calculations can be done. One unit of red cells costs EUR 90, and 6 ampoules of tranexamic acid used for one patient cost EUR 13. Thus, the total cost per patient amounts to EUR 58 in the tranexamic acid group and EUR 81 in the placebo group. If we use only 2 ampoules of tranexamic acid preoperatively and drain only in the placebo group, the costs would amount to EUR 50 and EUR 100. According to the Finnish arthroplasty registry, about 2500 hip operations per year in Finland might be suitable for this kind of policy (Nevalainen et al. 2003). It means a saving of about EUR 32,500–125,000. If we take uncemented and revision cases into account, the saving will increase many fold.

According to a meta-analysis that appeared after we began our study, tranexamic acid appears to

be safe and effective in reducing blood transfusion in arthroplasty surgery (Ho and Ismail 2003). Although earlier studies have shown similar results, they have included patients with different diagnoses and the dosage and timing of medication have been different. There has been only one study on uncemented hip arthroplasty with similar results (Yamasaki et al 2004).

Our findings are valid only for primary cemented hip arthroplasty for osteoarthritis. Before our results can be generalized—and to find the clinical importance of reduction of blood transfusion—further research on larger patient groups is needed in order to find out the proper dosage and patient groups. Uncemented and revision cases should be examined separately in greater detail.

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