Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty

A prospective randomized double-blind study in 40 patients

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Introduction **We performed a prospective, randomized, double-blind study on 40 patients scheduled for primary total hip arthroplasty due to arthrosis or osteonecrosis to determine the effect of tranexamic acid on per- and postoperative blood losses and on the number of blood transfusions needed.**

Patients and methods **40 patients were randomized to tranexamic acid (10 mg/kg given as a bolus intravenous injection, followed by a continuous infusion of 1 mg/kg/hour for 10 hours) or placebo (20 mL saline given intravenously) 15 minutes before the incision. We recorded the peroperative and postoperative blood losses at removal of the drain 24 hours after the operation and the number of blood transfusions.**

Results **Patients receiving tranexamic acid had a mean peroperative blood loss of 480 mL versus 622 mL in patients receiving placebo (p = 0.3), a postoperative blood loss of 334 mL versus 609 mL (p = 0.001), a total blood loss of 814 mL versus 1231 mL (p = 0.001) and a total need for 4 blood transfusions versus 25 (p = 0.04). No patient in either group had symptoms of deep venous thrombosis, pulmonary embolism or prolonged wound drainage.**

Interpretation **Transemic acid is effective in reducing the postoperative blood loss, the total blood loss and the need for blood transfusion in primary total hip arthroplasty.**

Tranexamic acid has been shown to reduce the postoperative blood loss and the need for blood transfusions in total knee arthroplasty (Hiippala et al. 1995, 1997, Benoni and Fredin 1996, Jansen et al. 1999).

Recent reports have pointed in the same direction concerning the effect of tranexamic acid on blood loss in patients receiving primary total hip arthroplasties (Duquenne et al. 1999, Ekbäck et al. 2000, Ido et al. 2000, Benoni et al. 2001). However, different doses of tranexamic acid were used, and in only one of the studies was the need for blood transfusions calculated, but no standardized criteria were used (Benoni et al. 2001).

We evaluated the effect of tranexamic acid on per- and postoperative bleeding and the number of blood transfusions needed under standardized conditions in patients who underwent a primary total hip arthroplasty.

Patients and methods

We first calculated the number of patients needed for such a study on the basis of the findings reported by Benoni et al. (2001) who, in a pilot study, had found an average reduction in blood loss of 255 mL, in patients receiving tranexamic acid. A power analysis predicted that the inclusion of 36 patients would provide 90% power at a 5% significance level. Patients scheduled for primary total hip arthroplasty due to arthrosis or osteonecrosis of the femoral head gave their informed consent to participation. The study was approved

Table 1. Patient characteristics

	Tranexamic acid group	Placebo group
Gender (female/male)	13/7	14/6
Age (mean), years	65	67
Diagnosis (osteoarthrosis/-necrosis)	17/3	18/2
Duration of surgery (mean), min.	76	76

by the local ethics committee. Exclusion criteria were: rheumatoid arthritis, malignancy, previous thrombo-embolic episodes, ischemic heart disease, previous subarachnoidal bleeding, hematuria and body weight > 100 kg. All patients had discontinued using nonsteroidal anti-inflammatory drugs and ASA 14 days before surgery.

40 patients were included and operated on in the Department of Orthopedics in Hvidovre University Hospital (Table 1). The operations were performed via the posterolateral approach, by 3 surgeons, all orthopedic specialists with experience in total hip replacement. The prostheses used were an uncemented acetabular cup and a femoral stem, which was cemented or uncemented. All patients had spinal analgesia, using bupivacaine, and were given thromboprophylaxis with low molecular weight heparin starting on the day before surgery and until discharge.

Randomization was done by a computer (Medstat, no block randomization). The drugs (tranexamic acid, 100 mg/mL, 4 ampoules of 5 mL or saline, 20 mL) were packed in numbered envelopes by a person not connected with the surgical procedure and handled by the anesthetist.

Patients randomized to receiving tranexamic acid were given a bolus intravenous injection of 10 mg/kg (maximum 1 g) during 10 minutes about 15 minutes before the incision, followed by a continuous infusion of 1 mg/kg/hour dissolved in 1 L of saline for 10 hours (maximum 1 g/10 hours). Patients randomized to receiving placebo (saline) were given a bolus intravenous injection of 20 mL about 15 minutes before the operation followed by a continuous infusion of 1 L of saline during 10 hours. The randomization code was not broken until the study was completed.

Peroperative blood loss was calculated by measuring the volume in the suction apparatus and weighing the swabs. One subfascial drain (low vacuum, Ch 14) was used in all patients and the volume in the drain bag was measured after exactly 24 hours. No attempt was made to estimate postoperative hematomas.

The blood transfusions were given in a standardized way. Hemoglobin (starting level) was measured just before admission, on the recovery ward and on the second postoperative day. If a patient had a reduction in hemoglobin exceeding 25% of the starting level and had clinical symptoms, a blood transfusion(s) was given. We recorded the number of transfusions given on the recovery ward (until 6 hours after surgery) and/or on the ward. No transfusions were administered after the second postoperative day. The patients were screened clinically for postoperative thrombosis during hospitalization and at follow-up 3 months postoperatively and— if suspected—an ultrasound examination was done.

All wounds were inspected on the third postoperative day and at discharge and any signs of prolonged drainage or infection were noted.

Statistics

We used the Mann-Whitney test (two-tailed) to compare all unpaired data (per-, postoperative and total blood loss, number of blood transfusions, levels of hemoglobin). The chi-square test was used to compare the number of patients receiving blood transfusions. The analyses were made using SPSS statistical package (version 10.0). Results are presented as mean values and 95% confidence intervals.

Results (Table 2)

All patients completed the study protocol and there were no violations of it. The mean peroperative blood loss was 23% less, the postoperative blood loss 45% less and the total blood loss 34% less in the tranexamic acid group than in the placebo group; with p-values of 0.25, 0.001 and 0.001, respectively.

The total number of blood transfusions in the tranexamic acid group was 4, as opposed to 25 in the placebo group (84% less) during hospitalization, p = 0.04. 2 patients were given a blood

Table 2. Parameters evaluated in the two groups

	Tranexamic acid group	Placebo group	P-value
Peroperative blood loss, mL	480 (160–799)	622 (0–1318)	0.3
Postoperative blood loss, mL	334 (0–616)	609 (125–1093)	0.001
Total blood loss, mL	814 (222–1406)	1231 (474–1988)	0.001
Transfusions on recovery ward	0	9	0.02
Transfusions on ward	4	16	0.1
Transfusions, total	4	25	0.04
Number of patients receiving blood transfusion(s)	2	7	0.1
Hemoglobin, start, mmol/L	8.3	8.5	
Hemoglobin, postop., mmol/L	6.6	6.4	0.5

Blood losses are shown as mean values with 95% confidence intervals

transfusion in the tranexamic acid group versus 7 in the placebo group (p = 0.1). The reduction in hemoglobin values from before to after surgery was about the same in both groups.

Women had less peroperative (mean 497 mL versus 661 mL), less postoperative (mean 432 mL versus 552 mL) and thus less total blood loss than men (p = 0.04). No patient in any group had prolonged drainage, infection, clinical deep venous thrombosis or pulmonary embolism during hospitalization or at follow-up.

Discussion

Tranexamic acid has a therapeutic blood concentration of 5–10 mg/L and thus, theoretically, should reach this antifibrinolytic level during surgery, when given intravenously in doses of 10 mg/kg just before the incision, resulting in less peroperative bleeding. However, only one previous study has shown that tranexamic acid significantly reduced peroperative bleeding (Ekbäck et al. 2000). We found that it reduced the peroperative blood loss by 23%, but this was not significant (p = 0.3) (Table 2). Since we used the same bolus and infusion doses as Ekbäck et al. (2000) and others have used even higher doses without effect (Duquenne et al. 1999), other factors must play a substantial role. Factors related to patient, medication, disease, surgeon, duration of surgery and method of anesthesia may affect the peroperative blood loss.

In our study, factors known to influence the amount of blood loss were minimized or equally distributed in the two groups (the operations were performed by 3 experienced surgeons, the duration of surgery was identical in the groups, patients with rheumatoid arthritis were excluded, all of them had spinal analgesia and they had stopped using nonsteroidal anti-inflammatory drugs and ASA). In previous studies, these factors have rarely been mentiond and may cause confounding (Table 3).

We found a significant reduction of 45% in the mean postoperative blood loss, which is a rather dramatic clinical effect and in accordance with the 4 studies published so far, which all used a bolus of tranexamic acid of 10 mg/kg or more before incision (Table 4).

We made no attempt to evaluate postoperative hematomas, since one of the previous studies had noted no significant difference in the amounts of the hematomas between patients treated with tranexamic acid or placebo (Benoni et al. 2001). The significant reduction of 34% in total blood loss in our study also accords with the 2 studies, which investigated this matter (Ekbäck et al. 2000, Benoni et al. 2001).

The duration of surgery and pre- and postoperative hemoglobin values were about the same in both groups, the former indicating identical surgical conditions, the latter identical standardized indications for blood transfusions.

Using standardized criteria for blood transfusions, our study permitted comparison of the need

Table 3. Data in 5 studies on tranexemic acid and total hip arthroplasty

	A	B	C	D	E	F	G	H	I	J	K	L
Duquenne et al. 1999	Yes	70	NR	NR	NR	No	Bolus 15 mg/kg	G	NR	NR	Yes/NR	NR
Ekbäck et al. 2000	Yes	40	20/20	NR	No	No	Bolus×2 10 mg/kg Infusion 1 mg/kg/h	S-E	NR	Yes	Yes/US×2	No
Ido et al. 2000	NR	40	NR	A,RA,ON	Yes	No	Bolus×2 1000 mg	NR	NR	No	Yes/NR	No
Benoni et al. 2001	Yes	38	19/19	A,ON	Yes	No	Bolus 10 mg/kg	V	NR	No	Yes	Yes
Husted et al. 2003	Yes	40	27/13	A,ON	Yes	Yes	Bolus 10 mg/kg Infusion 1 mg/kg/h	S	Yes	Yes	Yes/C	Yes

NR not reported
A Randomized, prospective double-blinded study
B No. of patients
C Women/men
D Preoperative diagnosis: A arthrosis, ON osteonecrosis, RA rheumatic arthritis
E Exclusion criteria
F Discontinued use of NSAID and ASA
G Doses of tranexamic acid
H Anesthesia: E epidural, G general, S spinal, V various
I Duration of surgery
J Standardized transfusion criteria
K Screening for thrombo-embolic episodes/method: C clinical, US Ultrasonic
L Screening for wound problems

Table 4. Data in 5 studies on tranexamic acid and total hip arthroplasty

	A	B	C	B	D	B	E	B
Duquenne et al. 1999	NR/NR	0.43 (NR)	NR/NR	0.048 (NR)	NR/NR	NR	NR/NR	NR
Ekbäck et al. 2000	605/850	0.001 (S)	525/925	0.001 (S)	1130/1770	NR	1/2	NR
Ido et al. 2000	NR/NR	NR	581/867	0.002 (S)	NR/NR	NR	NR/NR	NR
Benoni et al. 2001	561/608	0.6 (S)	199/388	0.003 (S)	759/996	0.03 (S)	5/13	0.2 (MW)
Husted et al. 2003	480/622	0.25 (MW)	334/609	0.001 (MW)	814/1231	0.001 (MW)	4/25	0.04 (MW)

NR not reported
A Peroperative blood loss, tranexamic acid group/placebo group (mL)
B P-value and (test): S Student, MW Mann Whitney
C Postoperative blood loss, tranexamic acid group/placebo group (mL)
D Total blood loss, tranexamic acid group/placebo group (mL)
E Number of blood transfusions, tranexamic acid group/placebo group

for blood transfusions in the two groups. Unlike in previous studies, we found a significant reduction in the number of blood transfusions given on the recovery ward (within 6 hours) and in total during hospitalization in the tranexamic group (Ekbäck et al. 2000, Benoni et al. 2000).

Tranexamic acid has a T1/2 of 1–2 hours and a fall in its blood concentration (below the level of efficacy) as the bolus injection wears off (despite the continuous infusion of 1 mg/kg/hour) could explain the failure to find a significant difference in our study on transfusions between the 2 groups given on the regular ward. Benoni et al. (2001) found a trend towards the same, but which did not reach significance, without using standardized criteria for blood transfusions. In the tranexamic acid group, 2 patients had blood transfusions, as opposed to 7 in the placebo group ($p = 0.1$). 4 transfusions were given in the tranexamic group versus 25 transfusions in the placebo group, a reduction of 84% ($p = 0.04$).There are obvious medical as well as financial advantages in reducing transfusions to a minimum (Mercuriali and Inghilleri 1999, Hadjianastassiou et al. 2002).

1 blood transfusion costs 93 Euro; 4 ampoules (2 grams) of tranexamic acid cost 18 Euro. The

total costs of maintaining or restoring levels of hemoglobin thus amounts to 1092 Euro in the tranexamic group and 2325 Euro in the placebo group.

The total blood loss of women was less than that of men ($p = 0.04$) in this study. 3 previous studies have shown a tendency towards this finding (Duquenne et al. 1999, Benoni et al. 2000, 2001), which led some of the authors to ascribe it to the smaller stature of most women and they used block randomization by gender (Benoni et al. 2001) to avoid this confounding effect. The similar distribution of men and women in our study does not affect our results. There was no difference between the groups as regards thromboembolic episodes since none of the patients in the present study had any thromboembolic episodes clinically. This is in line with previous studies, but the numbers are far to small too draw any conclusion on potential thromboembolic hazards.

Thus, in conclusion, tranexamic acid effictively reduces the postoperative blood loss, the total blood loss and the need for blood transfusions in primary total hip arthroplasty.

No competing interests declared.

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