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ORIGINAL PAPER

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Tranexamic acid reduces blood loss after cementless total hip arthroplasty—prospective randomized study in 40 cases

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Abstract We investigated the effects of tranexamic acid in 40 patients who had received cementless total hip arthroplasty (THA) in a prospective, randomized study. In 20 patients, 1000 mg of whole-body tranexamic acid was administered intravenously 5 min before the operation started. The other 20 patients served as a control group and were operated on without tranexamic acid. Perioperative blood loss was similar in the tranexamic acid group and in the control group. Postoperative blood loss of the tranexamic acid group was significantly less than that of the control group at 2, 4, 6, 8, 10, and 12 h. Regarding time-related changes of postoperative blood loss, significant reduction was observed during the first 2 h after surgery in the tranexamic acid group ($P<0.001$). After the first 2 h, there was no significant difference between the tranexamic acid group and the control group. Preoperative administration of tranexamic acid decreased postoperative blood loss until 12 h and total bleeding in cementless THA by reduction of blood loss during the first 2 h after surgery.

Résumé Dans une étude prospective et randomisée nous avons enquêté sur les effets de l'acide tranéxamique chez 40 malades qui avaient reçu une PTH sans ciment. Chez 20 malades, 1000 mg/d'acide tranéxamique ont été administré par voie intraveineuse cinq minutes avant l'opération. Les autres 20 malades ont fait office de groupe témoin et ont été opérés sans acide tranéxamique. La perte de sang peropératoire était semblable dans le groupe acide tranéxamique et dans le groupe témoin. La perte de sang postopératoire du groupe acide tranéxamique était notablement plus faible que celle du groupe témoin à 2, 4, 6, 8, 10, et 12 heures postopératoires. En considérant les modifications de la perte sanguine en fonction du temps postopératoire, une réduction significative a été observée dans les deux premières heures dans le groupe acide tranexamique ($P<0.001$). Après les 2 premières heures, il n'y avait pas de différence entre le groupe acide tranéxamique et le groupe témoin. L'administration préopératoire d'acide tranéxamique a diminué la perte de sang postopératoire jusqu'à 12 heures et le saignement total dans les PTH sans ciment par réduction du saignement pendant les 2 premières heures après chirurgie.

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Introduction

In an attempt to decrease surgical bleeding and perioperative allogenic blood transfusion requirements, several techniques—such as autologous blood transfusion, intraoperative blood saving, and hypotensive anesthesia—have been developed. Additionally, administration of fibrinolytic inhibitors, such as tranexamic acid, has been used in cardiopulmonary bypass surgery [14, 20]. Previous reports on tranexamic acid in joint replacement surgery have demonstrated that tranexamic acid reduces postoperative, but not perioperative, bleeding [2, 3, 11]. As for total knee arthroplasty (TKA), the use of a tourniquet induces local fibrinolysis in the operative limb [10], and increased fibrinolytic activity may increase bleeding after surgery [13, 18]. In total hip arthroplasty (THA) fibrinolysis is similarly induced by surgical trauma [7]. Tranexamic acid given at the end of the operation does not reduce postoperative bleeding in cemented THA [4]. On the contrary, tranexamic acid given preoperatively reduces intraoperative and postoperative bleeding in cemented THA [9]. However, there were no reports on perioperative bleeding in cementless THA using tranexamic acid. The purpose of this prospective, randomized study was to evaluate whether or not tranexamic acid administrated before surgical incision reduces perioperative and postoperative bleeding in cementless THA.

Materials and methods

Between April 1, 2002, and June 30, 2002, primary THA was performed in our institution in 40 patients with osteoarthritis of the hip. Femoral head osteonecrosis and rheumatoid arthritis were excluded from the present study. The present study was approved by the local hospital ethics committee. Informed consent was obtained from each patient. Forty patients undergoing cementless THA were investigated in a prospective and randomized manner. In 20 patients, 1,000 mg of whole-body tranexamic acid (Transamin, Daiichi Pharmaceutical Co. Ltd., Japan) was administrated intravenously 5 min before the operation started. The other 20 patients served as a control group and were operated on without tranexamic acid. Randomization was carried out by a person not involved in the operation using a ticket drawn from an envelope containing an equal number of tranexamic acid and placebo tickets. The operating team was unaware of the contents of the solution administered.

All operations were performed with the patient in a lateral position using a posterolateral approach. Lumbar anesthesia with isobaric bupivacaine hydrochloride (10–15 mg) was given to all patients. All THAs were performed using the Spongiosa Metal II hip prosthesis (S&G Implants, Lübeck, Germany) with both components uncemented. All procedures were considered technically satisfactory and without complications, such as early infection or dislocation. Prophylactic antibiotic therapy consisted of intravenous administration of 1 g cephalosporin preoperatively and every 12 h for 3 days postoperatively. No patient had received low-molecular-weight heparin, because it is not yet authorized for thromboprophylaxis after arthroplasty in Japan. Three and 2 weeks before the operation, 400 ml blood (150 ml of erythrocytes; hematocrit 100%) was drawn from all patients on two occasions. Preoperative oral iron therapy (100–200 mg per day) was received for 3 weeks. The preoperatively donated autologous units were all retransfused postoperatively within 12 h.

We determined the perioperative blood loss by measuring the volume in the suction apparatus and estimating the swab contents. Two low vacuum drains were routinely used after the operations (Ortho PAS. system, Euroset, Italy). Postoperative blood loss was measured 2, 4, 6, 8, 10, 12, and 24 h after the operation and at removal of drains in 40 patients. The drains were removed on the second postoperative day. Total bleeding was calculated as perioperative plus postoperative blood loss. Time-related changes of postoperative blood loss (0–2 h, 2–4 h, 4–6 h, 6–8 h, 8–10 h, 10–12 h, and 12–24 h) was also measured for each patient to evaluate the period when tranexamic acid had an effect. Total blood loss was also calculated as compensated blood loss (perioperative transfused blood) plus noncompensated blood loss estimated from pre- and postoperative hematocrit levels [5]. The hemoglobin concentration in blood and hematocrit was recorded on preoperative day 1 and postoperative days 1, 7, and 14.

We used no routine screening for postoperative deep vein thrombosis (DVT), but all clinically suspected thromboembolic complications in the first 4 weeks were investigated using ascending phlebography.

All statistical analyses were done using SPSS 11.0 J software (SPSS Japan, Tokyo, Japan). Student's *t* test were performed to determine whether there were differences between the two groups with respect to demographic and blood loss at a significance level of $P<0.05$.

Table 1 Demographic data of each group. *PT* prothrombin time, *APTT* activated partial thromboplastin time, *Hb* hemoglobin, *Ht* hematocrit

	Control group	Tranexamic acid group
Age (year)	61.2±6.9	55.5±14.2
Body weight (kg)	54.5±8.7	52.6±11.5
Height (cm)	152.6±7.6	151.6±7.2
Gender (male/female)	18/2	19/1
Body mass index	23.4±3.7	22.8±4.6
Preoperative Hb (g/dl)	11.7±0.9	11.4±0.8
Preoperative Ht (%)	36.0±2.7	34.8±2.7
Bleeding time (minutes)	2.30±1.11	2.28±0.91
PT (seconds)	11.9±0.55	12.0±0.76
%PT (%)	94.6±6.4	95.5±11.8
Preoperative platelets (10^9/l)	224±50	244±68
APTT (seconds)	31.3±2.3	31.0±3.50
Surgery duration (minutes)	70.0±14.8	68.8±15.1

Data are presented as means±SD
No significant differences were found between the groups.

Table 2 Intraoperative and postoperative blood loss. *TBL* total blood loss (milliliter of erythrocytes; hematocrit 100%)

	Control group	Tranexamic acid group
TBL	522±121*	365±107*
Peroperative blood loss	640±215	570±191
Postoperation 2 h	367±158*	169±95*
4 h	509±207*	263±168*
6 h	594±257**	348±272**
8 h	669±271**	410±320**
10 h	719±301***	469±337***
12 h	774±320***	520±362***
24 h	890±353	655±418
Total bleeding	1667±401***	1350±477***

Data are presented as means±SD (millileter)
Significant differences between the group are described with *I<0.001, **P<0.01, ***P<0.05

Table 3 Time-related changes of postoperative blood loss

	Control group	Tranexamic acid group
Post operation 0–2 h	367±158*	169±95*
2–4 h	142±84	94±80
4–6 h	86±68	86±111
6–8 h	75±45	61±62
8–10 h	50±46	60±49
10–12 h	56±37	51±36
12–24 h	116±75	135±80

Data are presented as means±SD (milliliter)
Significant differences between the group are described with *$P<0.001$

Results

Table 1 summarizes the demographic data of the tranexamic acid and control groups. No significant differences were found between the two groups. There was no case that needed allogenic blood transfusion in either group.

Perioperative and postoperative blood loss is shown in Table 2. Perioperative blood loss was similar in the tranexamic acid group (570±191 ml) and in the control group (640±215 ml). Postoperative blood loss of the tranexamic acid group was significantly less than the control group at 2, 4, 6, 8, 10, and 12 h postoperatively. These findings are shown in Fig. 1. Total bleeding was significantly less in the tranexamic acid group (1350±477 ml) than in the control group (1667±401 ml) ($P<0.05$). Total blood volume (millimeter of erythrocytes; hematocrit 100%) was significantly less in the tranexamic acid group (365±107 ml) than in the control group (522±121 ml) ($P<0.001$).

Time-related changes of postoperative blood loss are demonstrated in Table 3. Those in the first 2 h after the

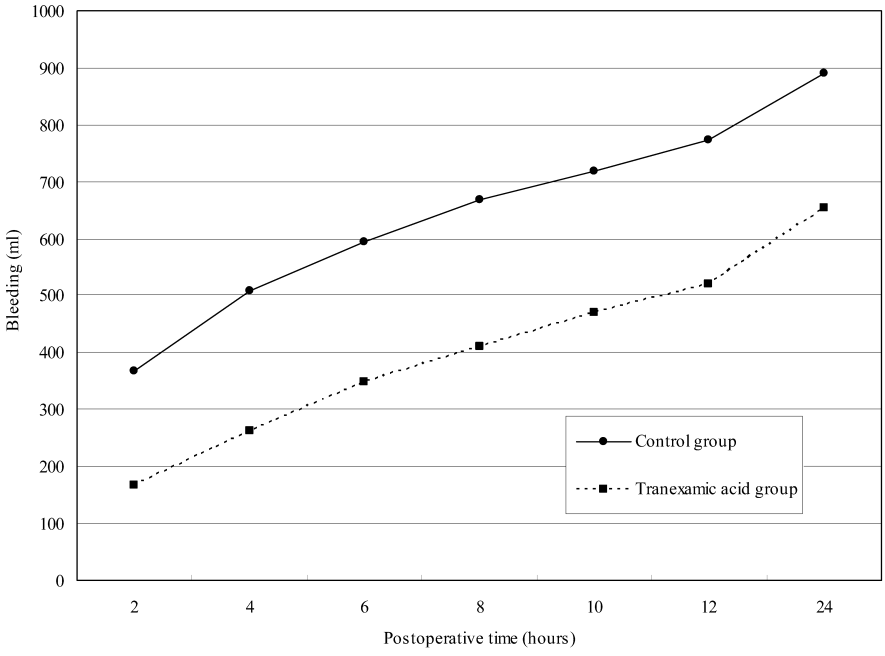

Fig. 1 Postoperative blood loss at 2, 4, 6, 8, 10, 12, and 24 h. Significant differences between the groups were seen at 2, 4, 6, 8, 10, and 12 h after the operation (2 and 4 h—$P<0.001$, 6 and 8 h—$P<0.01$, 10 and12 h—$P<0.05$). Total bleeding in the tranexamic acid group was less than in the control group ($P<0.05$)

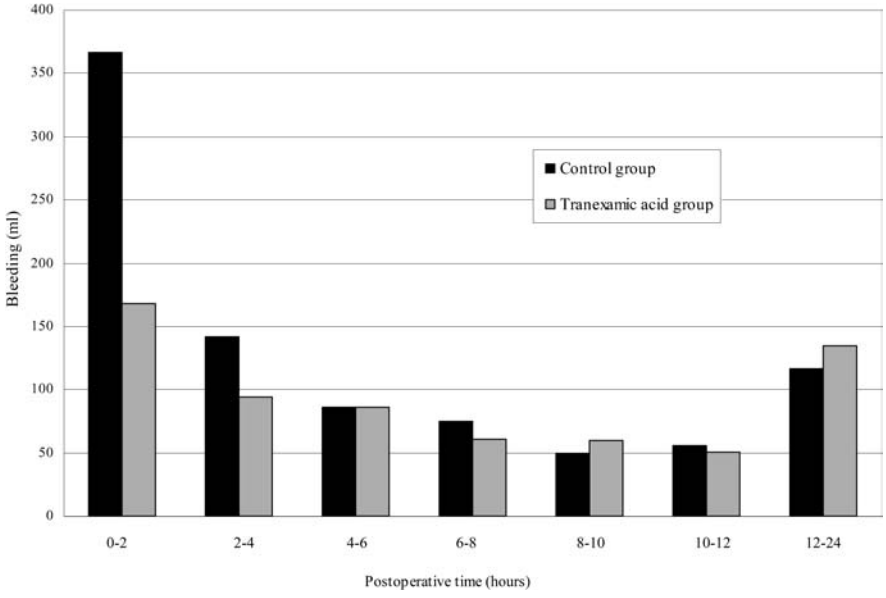

Fig. 2 Time-related changes of postoperative blood loss. Significant differences were seen in the first 2 h postoperatively ($P<0.001$)

Table 4 Postoperative laboratory analyses. *Hb* hemoglobin, *Ht* hematocrit

	Preoperative day 1	Day 1	Day 7	Day 14
Control group				
Hb (g/dl)	11.7±0.9	10.6±0.7*	11.0±0.7*	11.3±0.8
Ht (%)	36.0±2.7	32.0±2.4*	33.9±2.3	34.9±2.4
Tranexamic acid group				
Hb (g/dl)	11.4±0.8	11.2±1.0*	11.8±1.1*	11.6±0.9
Ht (%)	34.8±2.7	33.9±2.9*	35.7±3.3	35.7±2.8

Data are presented as means±SD
Significant differences between the groups are described with * $P<0.05$

operation were significantly less than the tranexamic acid group. After the first 2 h, there were no significant differences between the tranexamic acid and control groups. These findings are shown in Fig. 2. Preoperative and postoperative laboratory findings are demonstrated in Table 4. Hemoglobin on postoperative days 1 and 7 and hematocrit on day 1 were significantly higher in the tranexamic acid group than in the control group. Among the 40 patients who were investigated 4 weeks postop-

eratively, there were no clinically reports of thromboembolic events.

Discussion

Several studies on peri- and postoperative bleeding using tranexamic acid have focused on cemented THA so far [4, 9, 12]. Regarding cemented THA, the femoral canal and possibly the acetabular bony beds are closed off by cement, and the pressurization of cement has a ceasing effect on blood loss from intramedullary circulation. Therefore, postoperative bleeding tends to be higher in the cementless THA than in the cemented THA due to spontaneous bleeding from intramedullary circulation. Thus, it is essential to examine whether or not tranexamic acid also reduces the perioperative and postoperative bleeding in cementless THA. In the present study, demographic data of both groups were closely matched, as shown Table 1 ($P>0.05$).

Regarding cemented THA, the effect of tranexamic acid on perioperative and postoperative blood loss has not yet been precisely established. Benoni et al. reported that tranexamic acid could not reduce perioperative and postoperative blood loss [4]. On the contrary, Ekbäck et al. described that tranexamic acid reduced perioperative and postoperative drainage bleeding [9]. Ido et al. also described that postoperative blood loss in the tranexamic acid group was significantly less than in the control group in cemented THA, but they did not describe perioperative blood loss [12]. In the present study, there was no significant difference of perioperative blood loss between the two groups, but postoperative blood loss was significantly less in the tranexamic acid group than in the control group when tranexamic acid was given 5 min before surgery.

Tranexamic acid is an inhibitor of fibrinolysis and it blocks the lysine-binding sites of plasminogen to fibrin [16]. It inhibits the activation of plasminogen by plasminogen activator. Regarding metabolism of tranexamic acid, the half-time of 1,000 mg of intravenously administered tranexamic acid was found to be 1.9 h [19]. Ali and Landymore reported that fibrinolysis was suppressed soon after the administration of tranexamic acid in patients undergoing cardiac surgery [1]. Benoni et al. administered tranexamic acid at 10 mg/kg body weight in order to maintain a minimum concentration in blood. They showed that the concentration of tranexamic acid in the plasma remains at or over the minimum therapeutic level only for about 3 h after intravenous administration [3]. Since a similar dose of tranexamic acid, 10–20 mg/kg body weight of the agent, was used in all previous reports, the difference could be mainly due to the delayed administration of tranexamic acid in the report by Benoni et al.

With respect to the timing of administration of tranexamic acid, Benoni et al. initially administered it at the end of the operation and again 3 h later, and could not demonstrate significant reduction of peri- and postoperative blood loss [4]. On the contrary, Ekbäck et al. reported that tranexamic acid initially given just before surgical incision and again 3 h later significantly reduced peroperative and postoperative drainage blood loss in cemented THA [9]. Nakao et al. reported that the concentration of plasminogen activator was increased by surgical intervention, especially between 30 min and 1 h after the start of operation [15]. Similarly, plasminogen activator was reported to increase in this type of operation [7].

In view of this, it can be considered that tranexamic acid given just before surgical incision could suppress the elevation of plasminogen activator, leading to the reduction of postoperative blood loss in cementless THA, as well as cemented THA. In addition, time related changes of blood loss in the first 2 h after the operation were significantly less in the tranexamic acid group than in the control group in the present study, which could be explained by the pharmacological action of the agent as described above. Accordingly, the second administration of tranexamic acid may have an additive effect on postoperative blood loss 3 h after the first administration.

In the present study, postoperative blood loss was significantly less in the tranexamic acid group than in the control group, when tranexamic acid was administered with the same dose and at the same timing as those in the report of Ekbäck et al. However, there was no significant difference in perioperative blood loss between the two groups, unlike Ekbäck's report. This might be due to the differences of races or of perioperative blood loss in the control group between the present study (640±215 ml) and Ekbäck's report (850±260 ml).

There is a concern that tranexamic acid may promote a hypercoagulable state, and several thromboses have been reported [17]. Christie et al. showed that cardiopulmonary embolism occurs during cement injection of the femoral component in THA [6]. However, some investigators have reported that tranexamic acid activates fibrinolysis but does not affect coagulation [8, 15]. Administration of tranexamic acid was not found to elicit DVT [8]. Ekbäck et al. described that tranexamic acid reduced fibrinolysis by a decreased D-dimer and increased plasmin-antiplasmin complex [9]. In the present study, apparent symptomatic DVT was not found in any case of the tranexamic acid group. Further investigation is necessary to prevent DVT when tranexamic acid is administrated.

In conclusion, tranexamic acid administered just before the operation reduced the postoperative blood loss within 12 h and total bleeding in cementless THA. Furthermore, the present time-course study revealed that postoperative blood loss for the first 2 h was significantly less in the tranexamic acid group than in the control group. However, further investigation is necessary to determine the dosage or timing of this agent to reduce peroperative and postoperative blood loss in cementless THA.

References

1. Ali IM, Landymore RW (1994) The use of tranexamic acid in cardiac operation (letter). J Thorac Cardiovasc Surg 107:1377
2. Benoni G, Fredin H (1996) Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomized, double-blind study 86 patients. J. Bone Joint Surg [Br] 78: 434–440
3. Benoni G, Carlsson A, Petersson C, Fredin H (1995) Does tranexamic acid reduce blood loss in knee arthroplasty? Am J Knee Surg Summer; 8:88–92
4. Benoni G, Lethagen, S, Nilsson P, Fredin H (2000) Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. Acta Orthop Scand 71:250–254
5. Charrois O, Kahwaji A, Vastel L, Rosencher N, Courpied JP (2001) Blood loss in total hip arthroplasty for destructive coxarthrosis. Int Orthop 25:22–24
6. Christie J, Robinson CM, Pell AC, McBirnie J, Burnett R (1995) Transcardiac echocardiography during invasive intramedullary procedures. J Bone Joint Surg [Br] 77:450–455
7. Dahl OE. The role of the pulmonary circulation in the regulation of coagulation and fibrinolysis in relation to major surgery (1997) J Cardiotholac Vasc Anesth 11:322–328
8. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications (1999) Drugs 5:1005–1032
9. Ekbäck G, Axelsson K, Ryttberg L, Edlund B, Kjellberg J, Weckström J, Carlsson O, Schött U (2000) Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth. Analg 91:1124–1130
10. Farmy NR, Patel DG. Hemostatic changes and postoperative deep-vein thrombosis associated with use of a pneumatic tourniquet. (1981) J Bone Joint Surg [Am] 63:461–465
11. Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylien J, Niemala H (1995) Tranexamic acid (Cyclokaplon) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 74:534–537
12. Ido K, Neo M, Asada Y, Kondo K, Morita T, Sakamoto T, Hayashi R, Kuriyama S (2000) Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg 120:518–520
13. Janssens M, Joris J, David JL, Lemaire R, Lamy M (1994) High-dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. Anesthesiology 80:23–29
14. Mongan PD, Brown RS, Thwaites BK (1998) Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularization. Anesth Analg 87:258–265
15. Nakao A, Sakoh T, Takimoto H, Itoh N, Yamamoto F, Sawada K (1979) Perioperative kinetics of plasminogen activator and antiplasmin, and antifibrinolytic action of trans-AMCHA. J Clin Exp Med 56: 998–1001
16. Nilsson IM (1980) Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol (R Coll Pathol.) (Suppl) 14:41–47
17. Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, Burrows FA (1997) The efficacy of tranexamic acid versus placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. Anesth Analg 84:990–996
18. Risberg B (1985) The response of the fibrinolytic system in trauma. Acta Chir Scand Suppl 522:245–271
19. Sano K, Hakumizu H, Kojima T, Akimoto K (1976) Absorption and excretion of tranexamic acid in human; Clin Pharmacol Ther 7:375–382
20. Shore-Lesserson L, Reich DL, Vela-Cantos F, Anmar T, Ergin MA (1996) Tranexamic acid reduces transfusions and mediastinal drainage in repeat cardiac surgery. Anesth Analg 83:18–26