

# TRANEXAMIC ACID REDUCES POSTOPERATIVE BLOOD LOSS IN CEMENTLESS TOTAL HIP ARTHROPLASTY

BY SATOSHI YAMASAKI, MD, KENSAKU MASUHARA, MD, PHD, AND TAKESHI FUJI, MD, PHD

*Investigation performed at the Department of Orthopaedic Surgery, Osaka Kosei-Nenkin Hospital, Osaka, Japan*

**Background:** Tranexamic acid, an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin, has been reported to reduce intraoperative and postoperative blood loss in patients undergoing total hip arthroplasty with cement. However, there have been few reports describing the effects of tranexamic acid on blood loss during and following total hip arthroplasty without cement.

**Methods:** We investigated the effects of tranexamic acid in twenty-one patients who underwent staged bilateral total hip arthroplasty without cement for the treatment of osteoarthritis of the hip. The average interval between the two procedures was  $16 \pm 16$  months. On one side, 1000 mg of tranexamic acid was administered intravenously five minutes before the skin incision. On the other side, tranexamic acid was not administered. Baseline hemoglobin and hematocrit values were obtained three weeks before each arthroplasty. The volume of postoperative blood loss was recorded at two-hour intervals for the first twelve hours and then again at twenty-four hours, and the values were compared between the two groups.

**Results:** The total intraoperative blood loss in the tranexamic acid group ( $607 \pm 298$  mL) was similar to that in the control group ( $633 \pm 220$  mL). The postoperative blood loss in the tranexamic acid group was significantly lower than that in the control group at all time-points during the first twenty-four hours ( $p < 0.001$  for all comparisons). The greatest reduction in blood loss was observed during the first four hours after surgery in the tranexamic acid group ( $p < 0.01$ ).

**Conclusions:** In patients undergoing total hip arthroplasty without cement, preoperative administration of tranexamic acid is associated with decreased postoperative blood loss during the first twenty-four hours, especially during the first four hours after surgery.

**Level of Evidence:** Therapeutic Level II. See Instructions to Authors for a complete description of levels of evidence.

Several techniques are available to minimize the likelihood of allogenic blood transfusion following total hip arthroplasty or total knee arthroplasty. These techniques include autologous blood donation, hypotensive anesthesia, and perioperative blood salvage. Tranexamic acid, a fibrinolytic inhibitor, has been used to reduce blood loss in patients managed with cardiopulmonary bypass surgery and total knee arthroplasty<sup>1-6</sup>. The use of this agent for patients undergoing total knee arthroplasty is attractive because the use of a pneumatic tourniquet substantially increases activation of local

fibrinolysis in the involved limb<sup>7</sup> and because increased fibrinolytic activity may increase bleeding after surgery<sup>4,8,9</sup>. In recent years, there have been several studies on the effectiveness of tranexamic acid for reducing intraoperative and postoperative bleeding in patients undergoing total hip arthroplasty with cement<sup>5,9-11</sup>. However, there have been few reports on its efficacy in those undergoing cementless total hip arthroplasty<sup>12,13</sup>. In the United States, tranexamic acid (Cyklokapron; Pfizer, New York, NY) has been approved by the Food and Drug Administration for the reduction of hemorrhage in patients with hemophilia but it has not been approved for the reduction of postoperative blood loss. A list of countries in which tranexamic acid has been approved, and the approved indications for its use, is shown in the Appendix.



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In the present study, we evaluated the intraoperative and postoperative blood loss in patients with osteoarthritis of the hip who underwent staged bilateral cementless total hip arthroplasty with and without the administration of tranexamic acid. The purpose of the present study was to evaluate the effectiveness of tranexamic acid in reducing intraoperative and postoperative blood loss.

## Materials and Methods

### Patients

Between December 1, 1997, and December 31, 2003, staged bilateral primary total hip arthroplasty was performed for the treatment of osteoarthritis of the hip joint in twenty-one patients at one institution. Patients with a history of severe ischemic heart disease, chronic renal failure, cirrhosis of the liver, and bleeding disorders, as well as those who were currently receiving anticoagulant therapy, were excluded from this study. The local hospital ethics committee approved the present study, and informed consent was obtained from each patient.

### Preoperative Protocol

The baseline hemoglobin level, hematocrit, bleeding time, prothrombin time, activated partial thromboplastin time, and platelet counts were measured three weeks preoperatively at the time of autologous blood predonation (Table I). Then, 800 mL of blood was retrieved from all patients on two occasions within a three-week time-frame. Oral iron therapy (100 to 200 mg/day) was given for three weeks prior to the operation. The hemoglobin and hematocrit values were obtained again on the day before the operation (Table I).

### Tranexamic Acid Protocol

At the time of one of the total hip arthroplasties in each patient, 1000 mg of tranexamic acid (Transamin; Daiichi Pharmaceutical, Tokyo, Japan) was administered intravenously five minutes before the skin incision. At the time of the other total hip arthroplasty in the same patient, no tranexamic acid was

administered; the side on which the procedure was performed without tranexamic acid was used as a control. Tranexamic acid was given at the time of the first arthroplasty in ten patients and at the time of the second arthroplasty in eleven patients. The average interval (and standard deviation) between the two surgical procedures was  $16 \pm 16$  months (range, six to sixty-six months). The average age of the patients was  $62.2 \pm 7.2$  years at the time of the arthroplasty performed with tranexamic acid and  $62.1 \pm 7.2$  years at the time of the arthroplasty performed without tranexamic acid.

### Surgical Procedures

The same surgeon (K.M.) performed all arthroplasties through a standard posterolateral approach with the patient in a lateral position. Spinal anesthesia with isobaric bupivacaine hydrochloride (10 to 15 mg) was given to all patients. The ESKA cementless hip endoprosthesis (ESKA Implants GmbH, Lübeck, Germany) system was used for all arthroplasties. Prophylactic antibiotic therapy consisted of intravenous administration of 1 g of cephalosporin immediately preoperatively, followed by 1 g every twelve hours for three days postoperatively. All patients received their predonated autologous blood postoperatively. No patient received aspirin or any other chemoprophylaxis against venous thromboembolism. All patients wore compressive stockings on both legs for ten days postoperatively.

### Assessment of Intraoperative and Postoperative Blood Loss

We determined the intraoperative blood loss by adding the measured suction volumes and changes in the weight of the used surgical sponges. Two low-pressure vacuum drains (Ortho P.A.S.; Euroset, Medolla, Italy) were routinely used for forty-eight hours postoperatively. Postoperative blood loss was measured at two-hour intervals for the first twelve hours, at twenty-four hours postoperatively, and at the time of removal of the drains. Total blood loss was calculated as intraoperative blood loss plus postoperative blood loss. Time-related changes

TABLE I Preoperative Hematologic Data for Each Group\*

	Control Group (N = 21)	Tranexamic Acid Group (N = 21)
Baseline†		
Hemoglobin (g/dL)	12.7 ± 1.3	12.8 ± 1.3
Hematocrit (%)	38.5 ± 3.8	38.6 ± 3.6
Bleeding time (min)	2.0 ± 0.9	2.2 ± 1.0
Prothrombin time (sec)	11.7 ± 0.67	12.0 ± 0.76
Activated partial thromboplastin time (sec)	30.6 ± 2.9	30.4 ± 4.0
Platelet count (10 <sup>9</sup> /L)	250 ± 60	248 ± 54
Preoperative Day 1		
Hemoglobin (g/dL)	11.6 ± 0.8	11.8 ± 1.1
Hematocrit (%)	36.1 ± 2.2	36.7 ± 3.2

\*The data are presented as the mean and the standard deviation. No significant differences were found between the groups. †Baseline laboratory data were obtained three weeks preoperatively at the time of autologous blood predonation.

TABLE II Intraoperative and Cumulative Postoperative Blood Loss\*

	Control Group	Tranexamic Acid Group
Intraoperative blood loss (mL)	633 ± 220	607 ± 298
Postoperative blood loss (mL)		
2 hours	359 ± 167†	140 ± 70†
4 hours	481 ± 239†	212 ± 101†
6 hours	575 ± 270†	283 ± 143†
8 hours	633 ± 297†	344 ± 160†
10 hours	685 ± 313†	396 ± 173†
12 hours	727 ± 319†	444 ± 201†
24 hours	869 ± 363†	580 ± 237†
Total blood loss (mL)	1646 ± 469‡	1349 ± 478‡

\*The data are presented as the mean and the standard deviation. †The difference between the groups was significant ( $p < 0.001$ ). ‡The difference between the groups was significant ( $p < 0.01$ ).

in postoperative blood loss were measured every two hours for twelve hours and then again at twenty-four hours to determine the periods during which tranexamic acid had an effect. The hemoglobin level and the hematocrit were recorded on the first, seventh, and fourteenth postoperative days.

#### Assessment of Deep-Vein Thrombosis

We did not screen for postoperative deep-vein thrombosis before December 31, 2002, but we recorded the presence or absence of the Homans sign and edema of the legs for as long as four weeks postoperatively. Beginning on January 1, 2003, the D-dimer level was determined with use of enzyme-linked immunosorbent assay methods on the third postoperative day. When the D-dimer level was  $>5 \mu\text{g/mL}$ , venography of the involved limb was performed to check for the presence of deep-vein thrombosis.

#### Statistical Methods

All statistical analyses were performed with use of SPSS 11.0J software (SPSS Japan, Tokyo, Japan). Paired student t tests were used to determine whether there were differences between the two groups with respect to demographic data and blood loss. The level of significance was set at  $p < 0.05$ .

#### Results

There was no significant difference in the duration of the operation between the tranexamic acid group ( $66.9 \pm 14.7$  minutes) and the control group ( $70.1 \pm 12.7$  minutes). No patient required allogenic blood transfusion after any arthroplasty.

The values for intraoperative and cumulative postoperative blood loss are shown in Table II. The intraoperative blood loss in the tranexamic acid group ( $607 \pm 298 \text{ mL}$ ) was similar

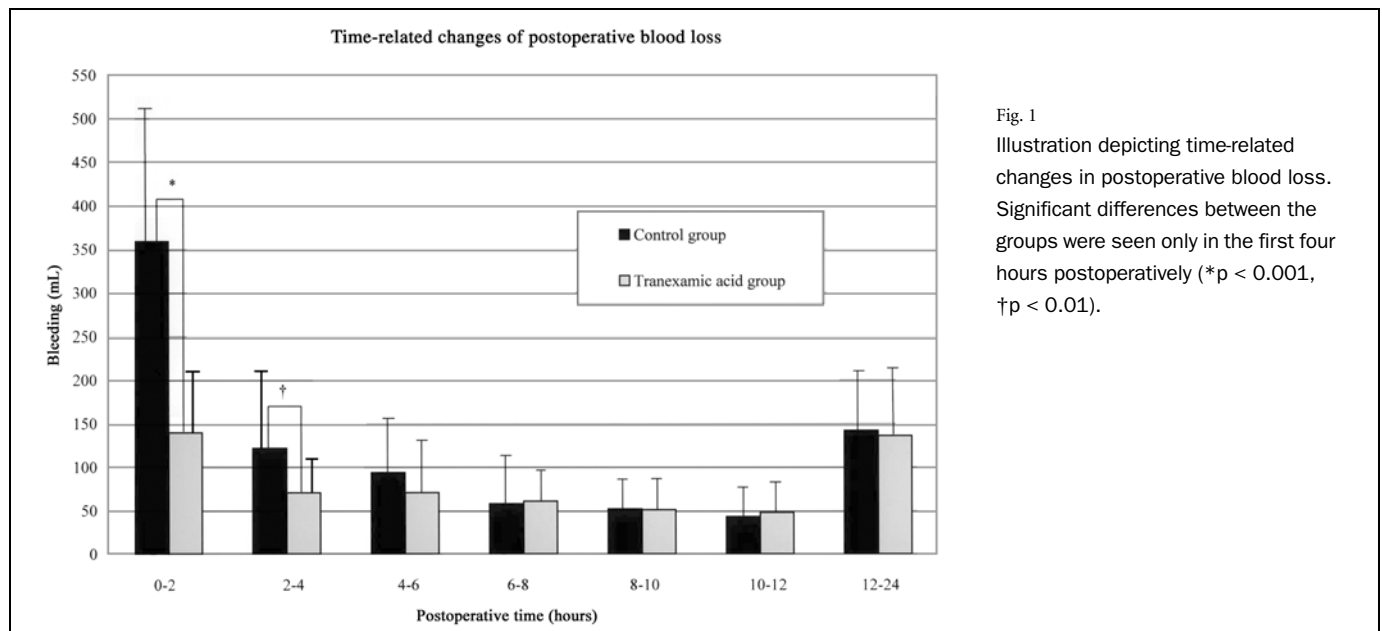


Fig. 1  
Illustration depicting time-related changes in postoperative blood loss. Significant differences between the groups were seen only in the first four hours postoperatively (\* $p < 0.001$ , † $p < 0.01$ ).

TABLE III Laboratory Analysis\*

	Preoperative Day 1	Postoperative		
		Day 1	Day 7	Day 14
Control group				
Hemoglobin (g/dL)	11.6 ± 0.8	10.4 ± 1.0†	11.0 ± 1.3†	11.3 ± 1.1†
Hematocrit (%)	36.1 ± 2.2	31.6 ± 3.1‡	33.8 ± 4.1†	35.3 ± 3.4‡
Tranexamic acid group				
Hemoglobin (g/dL)	11.8 ± 1.1	11.1 ± 1.2†	11.8 ± 1.1†	12.1 ± 1.2†
Hematocrit (%)	36.7 ± 3.2	33.7 ± 3.5‡	36.2 ± 3.1†	37.1 ± 3.5‡

\*The data are presented as the mean and the standard deviation. †The difference between the groups was significant ( $p < 0.01$ ). ‡The difference between the groups was significant ( $p < 0.05$ ).

to that in the control group ( $633 \pm 220$  mL). The cumulative blood loss in the tranexamic acid group was significantly lower than that in the control group at each postoperative interval ( $p < 0.001$ ), and the total blood loss in the tranexamic acid group ( $1349 \pm 478$  mL) was significantly lower than that in the control group ( $1646 \pm 469$  mL) ( $p < 0.01$ ).

The time-related changes in postoperative blood loss are shown in Figure 1. The tranexamic acid group showed significantly lower blood loss when compared with the control group only up to four hours after the operation.

The hemoglobin and hematocrit values on the first, seventh, and fourteenth postoperative days were significantly higher in the tranexamic acid group than in the control group (Table III).

When the twenty-one patients were interviewed and examined four weeks postoperatively, there were no clinical symptoms or signs of thromboembolic events such as deep-vein thrombosis or symptomatic pulmonary embolism. No perioperative complications occurred in association with any of the arthroplasties. Among those tested, the D-dimer levels on the third postoperative day were similar between the tranexamic acid group ( $2.11 \pm 0.73$   $\mu\text{g/mL}$ ) and the control group ( $3.01 \pm 1.33$   $\mu\text{g/mL}$ ). There was no case in which the D-dimer level was  $>5$   $\mu\text{g/mL}$ , and thus no patient underwent venography of the involved limb.

## Discussion

In an attempt to reduce bleeding and the need for allogenic blood transfusion, antifibrinolytic drugs such as tranexamic acid have been administered in association with a variety of surgical procedures<sup>1,8,9,14-17</sup>. Tranexamic acid is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin<sup>18</sup> and inhibits the activation of plasminogen by plasminogen activators.

Several studies have investigated the effect of tranexamic acid on intraoperative and postoperative blood loss in patients undergoing total hip arthroplasty with cement<sup>5,9-11</sup>, but the efficacy of such treatment has not yet been clearly established. Postoperative blood loss tends to be higher in association with total hip arthroplasty without cement than it is in association with total hip arthroplasty with cement<sup>19</sup>. In a previous case-

controlled study of patients undergoing cementless total hip arthroplasty<sup>12</sup>, we demonstrated that preoperative administration of tranexamic acid reduced total blood loss and postoperative blood loss primarily by reducing blood loss during the first two hours after surgery. In the present study of patients undergoing cementless total hip arthroplasty, in which each patient served as his or her own control, we found that preoperative administration of tranexamic acid did not reduce intraoperative blood loss but did reduce postoperative blood loss, primarily during the first four hours after surgery.

The half-life of 1000 mg of intravenously administered tranexamic acid has been found to be 1.9 hours<sup>20</sup>. Benoni et al. administered tranexamic acid at a dose of 10 mg/kg of body weight in order to maintain a minimum effective concentration in the blood. They showed that the concentration of tranexamic acid in the plasma remains above the minimum therapeutic level for approximately three hours after such intravenous administration<sup>1</sup>. Those findings are consistent with our observation that significant differences were seen as long as two hours postoperatively in our previous report<sup>12</sup> and as long as four hours postoperatively in the present study.

There have been few reports that have described the relationship between operative time and intraoperative blood loss. Salido et al. showed a significant relationship between operative time and the need for postoperative blood transfusion<sup>21</sup>. In the study by Ekbäck et al., the operative time was 120 minutes<sup>11</sup>. In agreement with our findings, which were based on a surgical procedure that was fifty minutes shorter than theirs, Ekbäck et al.<sup>11</sup> showed that the perioperative blood loss was significantly lower in the tranexamic acid-treated group than in the control group. Based on the finding that the half-life of 1000 mg of intravenously administered tranexamic acid is 1.9 hours<sup>20</sup>, we speculate that tranexamic acid might not be as effective for reducing perioperative blood loss when used in association with procedures of longer durations.

Our postoperative laboratory findings showed that the hemoglobin and hematocrit values on the first, seventh, and fourteenth postoperative days were significantly higher in the tranexamic acid group than in the control group. In addition, the hemoglobin and hematocrit values in the tranexamic acid group had recovered to the first-preoperative-day level by the


fourteenth postoperative day. Thus, preoperative administration of tranexamic acid was associated with a reduction in the length of time that the treated patients were anemic.

A theoretical concern associated with the use of tranexamic acid is its potential for inducing thromboembolic events<sup>22-24</sup>. Although tranexamic acid is an inhibitor of fibrinolysis, it does not affect coagulation. Lindoff et al. did not find evidence of an increased thrombotic effect in association with the use of tranexamic acid<sup>22</sup>. In addition, both Tanaka et al.<sup>23</sup> and Ho and Ismail<sup>24</sup> showed that the administration of tranexamic acid did not increase the risk of thromboembolic complications. Similarly, none of the participants in our previous case-controlled study<sup>12</sup> or in the present paired study had symptomatic deep-vein thrombosis or pulmonary embolism. Although tranexamic acid is considered to be contraindicated in patients with a history of thromboembolic disease, an increased risk of thromboembolism in such patients has not been shown in other clinical situations<sup>14-16</sup>.

In conclusion, the present paired study demonstrated that the administration of tranexamic acid just before surgery significantly reduces postoperative blood loss in patients undergoing primary cementless total hip arthroplasty, with the greatest reduction in blood loss occurring during the first four postoperative hours. However, further investigation is necessary to determine the optimal dose of this agent and the limits

of its effectiveness when used in association with procedures of increased duration.

### Appendix

 A table listing countries where tranexamic acid has been approved for selected indications is available with the electronic versions of this article, on our web site at [jbjournals.org](http://jbjournals.org) (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

Satoshi Yamasaki, MD  
Kensaku Masuhara, MD, PhD  
Takeshi Fuji, MD, PhD  
Department of Orthopaedic Surgery, Osaka Kosei-Nenkin Hospital, 4-2-78, Fukushima, Fukushima-ku, Osaka 553-0003, Japan. E-mail address for S. Yamasaki: [ys8483@okn.gr.jp](mailto:ys8483@okn.gr.jp)

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