DOES A SINGLE BOLUS DOSE OF TRANEXAMIC ACID REDUCE BLOOD LOSS AND TRANSFUSION REQUIREMENTS DURING HIP FRACTURE SURGERY? A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY IN 67 PATIENTS

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Abstract- Extensive blood loss in total hip surgery is well known and is associated with a high transfusion rate of allogeneic blood. The aim of this study is to assess the effects of intraoperative tranexamic acid on post-operative bleeding and need for allogeneic transfusion during hip fracture surgery. We investigated 67 patients undergoing hip fracture surgery in a prospective, randomized, double-blinded study. 32 patients received tranexamic acid (TA) given in a bolus dose of 15 mg/kg before surgical incision. The remaining, 35 patients were allocated as control group. Postoperative bleeding, transfusions, complications, and hospital stay were recorded. The intraoperative bleeding was significantly lower in the TA group (652 ± 228 ml vs. 1108 ± 372 ml, P <0.003). Post operative drainage was lower in TA group (296 ± 85 ml vs. 375 ± 110 ml, P <0.195). There were no differences in coagulation parameters. The rates of transfused patients in TA and control groups were 37 % and 57 %. In TA group, hospital stay was 4.3 ± 1.6 days (vs. 5.8 ± 1.5 days in control group; P < 0.05). There is one in hospital mortality in control group. We conclude that tranexamic acid significantly reduces blood loss during hip fracture surgery.

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INTRODUCTION

Hip fracture is commonly encountered clinical problems, which are associated with a one year mortality rate of about 25% (1). In recent years, studies have documented a rapidly increasing incidence of hip fractures especially in elderly patients (2).

Surgery for hip fractures frequently requires blood transfusion, despite recent advances in techniques of orthopedic surgery and mechanical improvements of implants. Blood may be transfused before, during or following surgery. In the United State, surgery for hip fractures ranks second in total number of units of blood administered to patients according to diagnoses groups (3).

The use of allogeneic blood products increases the rate of transmission of infectious diseases, modulates the immune response, and increases the risk of postoperative infection. Numerous methods of controlling bleeding such as thromboplastic agents; topical freezing saline; deliberate hypotension; and administration of fibrinolytic inhibitors (such as aprotinin and tranexamic acid) have been used (4). Tranexamic acid has been used in urological, gynecological and thoracic surgery (5), but has not routinely been used in total hip surgery (6).

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In hip fracture surgery, however, tranexamic acid has not been used because its effectiveness is still unknown, and a few studies have been published. The goal of this prospective, randomized study was to determine the effect of a single bolus dose of tranexamic acid, given intravenously at the beginning of the operation, on blood loss as well as on need for blood transfusions in hip fracture surgery.

MATERIALS AND METHODS

The study was approved by the Ethical Committee of the hospital and informed consent was obtained from all patients. From Feb. 2004 to June 2005, 67 patients with a diagnosis of fracture of the hip necessitating hip surgery were recruited. We have included consecutive hip fractured patients with extracapsular fractures treated by plating and nailing, and intracapsular fractures, treated by hemiarthroplasty. We have excluded those patients with undisplaced subcapital fractures treated by pinning that have long been shown to be fractures with low level loss of blood. Other exclusion criteria were preoperative hemoglobin less than 10 $g \cdot L^{-1}$., platelets count less than $100 \times 10^{9} \cdot L^{-1}$ of blood, a known coagulopathies disorders, renal insufficiency (creatinine > 2 $mg \cdot dL^{-1}$), advanced hepatic dysfunction, and history of thromboemboli.

Patients were randomized using a random number technique. Caring personnel both the staff of the operating room and the intensive care unit (ICU) were blinded regarding the type and nature of treatment; the correct treatment option was assured by means of coded infusion syringes, prepared by a personal of the hospital pharmacy, not involved otherwise in the study.

Patients were allocated to either the tranexamic acid group (TA, n= 32) or the control group (n=35). In the tranexamic acid group, a single bolus dose of 15 $mg \cdot kg^{-1}$ was administered intravenously at induction of anesthesia. In control group, the same volume of saline solution was infused.

All operations were carried out by one team of surgeons on according to a standardized surgical protocol. Anesthesia was done via spinal route with bupivacaine 2-3 ml of 0.5% solution in all patients. If hypotension was occurred, it was treated with 5 mg ephedrine IV administration. They were given regular medication perioperatively. None of them received medications that influence surgical blood loss. Blood loss during surgery was measured by weighting swabs (the difference between the wet weight and the dry weight gave a representation of the blood loss during the procedure) and recording the amount returned through the suction apparatus. At the end of surgery, 2 vacuum drains were inserted into the patient, one deep and one superficial. These were used to record postoperative blood loss by measuring the drainage at 1, 2, 5, 12 and 24 hours after surgery.

Transfusions were given on a case-by-case basis with regard to age, cardiovascular status, hemoglobin concentration and blood loss. Most patients who had blood transfusions received these at a hemoglobin concentration between 80 and 100 g/L. No transfusions were administered after the second postoperative day. Perioperatively and in ICU, routine hematological (hemoglobin, hematocrit, platelet count, PT, PTT) and hematochemical parameters such as creatinine were analyzed in all patients. In all patients, arterial blood samples were collected at two different time points to determine D-dimer: preoperatively and 4 hours postoperatively. D-dimer which reflects the fibrinolytic status was measured using enzyme-linked fluorescent assay (ELFA) techniques (Minividas; ELFA; Biomerieux; France).

Patients had 24 hours ECG monitoring in ICU for evaluating myocardial Ischemia. If there was any doubt of MI, we measured the level of CPK-MB and troponin I.

Neurologic events and pulmonary embolic events were examined by specialists every day. All measurements are expressed as mean ± the standard error of the mean. Statistical analyses were performed with SPSS for Windows version 11.0 software (SPSS, Inc., Chicago, IL, USA). Comparisons of results between groups were carried out by the two-sample *t* test for each normally distributed variable. The nonparametric Mann-Whitney *U* test was used to analyze intraoperative and postoperative blood loss. A *P* value of less than 0.05 was considered to indicate a significant difference.

Table 1. Baseline and hematochemical data

Variable	Tranexamic acid group (n= 32)	Control group (n= 35)	*P* value
Gender, male/female	1.13	2.18	NS
Age, mean (SD)	51.81 ± 25.7	44.4 ± 26.16	0.247
Body Mass Index	22.7 ± 2.6	22.9 ± 3.4	NS
Hemoglobin (g/dL)			
Preoperative	11.1 ± 2.2	11.5 ± 1.3	NS
Postoperative	10.1 ± 1.4	8.9 ± 2.1	<0.05
Prothrombin time, seconds			
Preoperative	12.3 ± 0.7	12.1 ± 1.9	NS
Postoperative	14.2 ± 1.3	14.1 ± 1.2	NS
D-dimer, mg/L			
Preoperative	0.4 [0.3-0.5]	0.4 [0.3-0.5]	NS
Postoperative	0.5[0.4 -0.6]	0.9 [0.7-1.4]	<0.05
Mean time until surgery (hours)	4.5 ± 2.2	4.4 ± 2.6	NS
Hospital Stay, days	4.3 ± 1.6	5.8 ± 1.5	<0.05

Abbreviation: NS, not significant.

RESULTS

The data related to hematochemical are summarized in Table 1.No significant differences between the groups were found in the demographic data. The mean intervals between the onset of the hip fracture and surgery were 4.5 ± 2.2 hours in TA group. The two groups were similar in terms of age and, preoperative hemoglobin concentrations ($P = 0.24$). There was significant difference in postoperative hemoglobin in the two groups ($P < 0.05$). Preoperative median levels of D-dimer were comparable in both groups. The increase in D-dimer levels after surgery was significantly inhibited in the TA group ($P < 0.05$).

The data related to blood loss are summarized in Table 2. Perioperative blood loss was significantly lower in the TA group ($P < 0.03$). The total blood loss was 960 ± 483 mL in TA group and 1484 ± 724 mL in the control group ($P < 0.001$). The percentage of patients who received no allogeneic blood products during or after the operation was higher ($P < 0.01$) in the TA group (63%) than the control group (43%) (Table 3).

There was no difference between two groups regarding thrombotic complications, pulmonary dysfunction and neurological deficits. There was one in hospital mortality (up to 7 day after operation and before discharge) in control group due to failure of other organs.

Table 2. Perioperative and postoperative blood loss*

Variable	Tranexamic acid group (n= 32)	Control group (n= 35)	% Decrease in Blood Loss	*P* value
Perioperative blood loss (ml)	652 ± 228	1108 ± 372	41	0.003
Postoperative blood loss (ml)				
1 h	111 ± 76	139 ± 100	20	0.385
2 h	192 ± 78	246 ± 113	22	0.280
5 h	255 ± 59	323 ± 54	21	0.305
12 h	296 ± 40	375 ± 30	21	0.195
24 h	300 ± 54	390 ± 65	23	0.11
Total blood loss (ml)	960 ± 284	1484 ± 374	35.3	0.001

*Data are given as mean ± SD.

Table 3. Perioperative and postoperative total transfusion requirement

Variable	Tranexamic acid group (n= 32)	Control group (n= 35)	*P* value
Whole blood or PRBC received (no. of pts)	12	20	NS
Whole blood or PRBC (units/patient)	1.25	1.95	0.001
FFP received (no. of pts)	1	0	NS
Platelet received (no. of pts)	0	0	NS
Total number of patients transfused (%)	12 (37%)	20 (57%)	0.04

Abbreviations: PRBC, packed red blood cells; FFP, fresh-frozen plasma.

DISCUSSION

Bleeding during hip fracture surgery is an important problem. An excessive bleeding from femur canal into peripheral compartments occurs immediately after fracture and before surgery. The mechanisms of bleeding during and after hip surgery are supposed to be defective surgical hemostasis, platelets dysfunction (drug-induced), consumptive coagulopathies and increased fibrinolytic activity.

Extensive blood loss in relation to surgery is associated with a high risk for patients, especially because of cardiovascular complications; therefore fractures of the hip frequently require the transfusion of blood. Allogenic blood transfusion carries the risk of immunological and non-immunological adverse effects, such as transfusion reactions and transmission of infectious agents (AIDS and hepatitis viruses). Allogenic blood transfusion has furthermore a high medical cost (7). In other hand, Geriatric hip fracture patients who receive allogeneic red blood cell transfusions are at higher risk for developing a postoperative urinary tract infection than are those patients who are not transfused (8).

In an attempt to decrease surgical bleeding and perioperative allogenic blood transfusion requirements, several techniques- such as autologous blood transfusion, perioperative blood salvage, deliberate hypotension, and administration of fibrinolytic inhibitors have been developed (4). However, these approaches also have some disadvantages, such as the time limit of blood preservation, the use of expensive devices, and the insufficient blood correction in intraoperative blood saving. Altogether, the use of a pneumatic tourniquet as well as surgery enhances coagulation and fibrinolysis. Tranexamic acid saturates the lysine binding sites of human plasminogen, displacing plasminogen from the fibrin surface, which results in inhibition of fibrinolysis (5).

It is useful in a wide range of hemorrhagic conditions such as cardiac surgery, acute upper gastrointestinal bleeding, oral surgery, liver transplantations and gynecologic bleedings (9).

Bone bleeding from the femoral canal at hip surgery was reduced by administration of tranexamic acid. Our results had some differences with other studies, which have shown reduced bleeding in total hip arthroplasty (THA) (8). Ido *et al.* (6) reported a significant reduction in postoperative blood loss in patients undergoing THA. Benoni *et al*. (11) showed that administration of tranexamic acid at the end of surgery does not reduce postoperative blood loss. In other orthopedic procedures, authors have shown tranexamic acid to be of use in reducing blood loss and transfusion requirements in knee arthroplasty and scoliosis surgery (12-14).

The volume of blood lost in these procedures may be lesser or greater than during hip fracture surgery and a direct comparison with the results of these studies is of limited value. Dose, duration, time of administration of the tranexamic acid in relation to surgery, and number of times the drug is administered may be the reasons for these discrepancies.

Some authors believed that postoperative blood loss in patients undergoing total knee arthroplasty (TKA) and total hip arthroplasty (THA) is one of the most important factors affecting their postoperative status. The fibrinolytic system is temporarily activated by use of a tourniquet, and blood loss is reduced due to local fibrinolysis. Benoni *et al*. (15)

administered tranexamic acid intravenously before tourniquet release and then 3 hours later in patients undergoing TKA, and reported that the intra and postoperative blood loss was reduced to one-third as a result. But in contrast to elective hip or knee surgery; in hip fracture, the fibrinolytic system is activated by trauma and increased during surgery. Therefore we used a single bolus dose of 15 mg/kg given intravenously at induction of anesthesia. The half-life of tranexamic acid is approximately 2 hours, which would cover the duration of surgery. Jansen (13) and Tanaka (16) demonstrated a 40–58% decrease in blood loss when TA was given pre- and intraoperatively. 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 (17).

The potential for hypercoagulability to occur with the use of antifibrinolytic agents was taken into account in this study. As TA inhibits fibrinolysis, therefore the administration of TA causes concern for an increase in the incidence of thromboembolic events. Benoni *et al*. (18) suggested that TA does not affect the risk of DVT because it inhibits fibrinolysis in the wound but not in the general circulation, indicating that TA does not induce a general prothrombotic state. Some investigators have suggested that tranexamic acid activates fibrinolysis but does not affect coagulation. Therefore, use of tranexamic acid seldom leads to thrombosis. In our study further diagnosis of DVT or pulmonary embolism was not made without clinical suspicion. We did not screen for postoperative thrombosis, but all clinical events up to a minimum of 6 weeks after the operation were recorded.

In conclusion, we have experienced a significant reduction of total blood loss in hip fracture surgery with using TA compared with non-TA. We did not register any thromboembolic complications. The blood-sparing effect of TA has a high cost- benefit ratio.

Conflict of interests

The authors declare that they have no competing interests.

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