DOES TRANEXAMIC ACID REDUCE BLOOD LOSS IN OFF-PUMP CORONARY ARTERY BYPASS ?

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Abstract- Tranexamic acid is now used on a routine basis for on-pump coronary artery bypass grafting (CABG). We assessed the hemostatic effects of tranexamic acid to decrease bleeding tendency and transfusion requirements in patients undergoing off-pump coronary artery bypass surgery (OPCAB). A total of 66 patients were enrolled to elective OPCAB in a double-blind, prospective randomized study. Of these, 33 patients received tranexamic acid (15 mg/kg before the infusion of heparin and 15 mg/kg after protamin infusion), and 33 patients received only saline. Preoperative hematologic variables, postoperative bleeding and allogeneic transfusions were considered. D-dimer plasma levels were also evaluated to monitor the activation of fibrinolysis. Postoperative bleeding was significantly lower in the tranexamic acid group compared with the control group (320 ± 38 mL vs. 480 ± 75 mL at 12 hour, $P < 0.001$). The tranexamic acid group had significantly lesser need for allogeneic blood products (0.46 units/patients vs. 0.94 units/patients, $P < 0.001$). They had also lower post-operative D-dimer plasma levels. No postoperative thrombotic complications were observed in either group. The defective hemostasis occurs even in the OPCABG. Tranexamic acid effectively reduces postoperative blood loss and the need for allogeneic blood products after OPCAB is decreased.

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INTRODUCTION

Off-pump coronary artery bypass (OPCAB) surgery is associated with a reduced frequency of hemorrhagic disorders. But hemorrhagic complications are not completely eliminated and there is still a need for blood transfusion after OPCAB surgery. The protease inhibitors tranexamic acid is used to reduce blood loss after OPCAB.

The defective hemostasis following cardiopulmonary bypass is a serious complication in open-heart surgery, which results in an increase in bleeding and the requirement for allogeneic blood transfusion in many patients (1). The mechanisms of bleeding during and after cardio pulmonary bypass (CPB) surgery are supposed to be related to hemodilution, heparin administration, impaired platelets function, and increased fibrinolytic activity (2). In order to reduce CPB associated morbidity, OPCAB procedures have gained popularity. Although postoperative bleeding seems to be attenuated by the avoidance of CPB, hemorrhagic complications are not completely eliminated and there is still a need for blood transfusion after OPCAB surgery (3, 4).

In many centers, tranexamic acid is now used on a routine basis for on-pump CABG cases (5). The aim of this study is to evaluate the hemostatic effects of tranexamic acid in OPCAB surgery.

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MATERIALS AND METHODS

From Oct. 2002 to Nov. 2003, 66 consecutive patients who were scheduled for elective CABG with supposed off-pump techniques were enrolled in this prospective, double-blind, randomized study. The procedures were approved by ethics committee and all patients signed an informed consent.

Patients were randomly allocated to either the tranexamic acid group (T, n = 33) or the control group (C, n = 33). In the tranexamic acid group a loading dose of tranexamic acid (15 mg/kg) at the beginning of surgery, before the infusion of heparin, and another dose (15 mg/kg) at the end of the surgery, and after protamin infusion, were administered. In group C the same volume of saline solution was infused. 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. A standard preoperative data was collected prospectively for every patient undergoing CABG at our institution. The dataset was filled in consequence by the anesthetist, the surgeon, the perfusionist, and the nurses.

Inclusion criteria were primary bypass grafting, age 70 years or less, left ventricular ejection fraction 35% or more, body mass index (BMI) 25 or less, no administration of acetylsalicylic acid in the last 7 days before operation, and no heparin infusion before the operation. Exclusion criteria were the following: redo cardiac surgery, emergency CABG, left ventricular ejection fraction < 35%, hemoglobin less than 10 gr/L, platelet count less than 100000/mL, known coagulopathies' disorders, and renal insufficiency. Anesthesia was standardized for all patients. Anesthetic induction consisted of fentanyl 3 µg/kg followed by diazepam injection 0.1 mg/kg and sodium thiopental 2 mg/kg. Intubation was done after injection of succinylcholine 3 mg/kg. In patients with systolic hypertension more than 140 mmHg, lidocaine 1 mg/kg was tried before intubation. During surgery, halothane 0.5% with fentanyl 1-3 µg/kg/min was used. Maintenance of muscle relaxation was accomplished with pancuronium 2 mg/h routinely.

All patients were operated according to the standardized surgical protocol. After full midline sternotomy, the left internal mammary artery was harvested in all patients, together with saphenous vein anastomosis. Stabilization of the beating heart was established with the Octopus tissue stabilizer (Octopus 4.3 tissue Stabilizer; Medtronic Inc.; USA). Patients were heparinized according to body weight in a dose of 150 unit/kg and in the end of surgery; heparin was reversed with protamine in a ratio 1.3/1. A cell separator was not used. Intraoperatively no blood was retransfused. Before chest closure, mediastinal drains were inserted.

On arrival in the ICU, patients were placed on mechanical ventilation. All patients were evaluated for extubation every hour. All hemodynamically stable patients without excessive drainage and good arterial blood gas (ABG) were extubated. Blood loss was recorded at arrival in the ICU, 1, 4, 8, 12 and 24 hours after surgery. In every patient if drainage was more than 500 ml in first hour or 800 ml in two hours after operation, the patient was re-operated. The indications for whole blood transfusion were hematocrit less than 20% and/or hemoglobin < 7 g/dL during operation and hematocrit < 28% and/or hemoglobin < 9 g/dL in ICU and post ICU. The protocols for fresh frozen plasma (FFP) were prolonged PT (more than 1.5 times the normal range) and bleeding more than 200 mL/h. The protocol for platelet transfusion was platelet count less than 75000/mL, and bleeding more than 200 mL for longer than 2 hours.

Prophylactic measures were started in the first postoperative day with orally given aspirin (80 mg once per day) and subcutaneous injection of low-molecular-weight heparin. Perioperatively, routine hematologic (hemoglobin, hematocrit, platelet count) and hematochemical parameters such as creatinine were evaluated in all patients and the samples were analyzed by the central laboratory of the hospital for routine studies. In ICU stay, fasting blood sugar (FBS), hemoglobin, hematocrit, platelets, PT, electrolyte levels, and serum creatinine level were measured routinely. Oxygen hemoglobin saturation,

respiratory rate and serial ECG were continuously monitored. All patients had 48 hours ECG monitoring in ICU for evaluating myocardial ischemia. If there was suspicion of myocardial infarction (MI), we measured the level of CPK-MB and troponin I. Neurologic and pulmonary embolic events were examined by specialists every day.

In all patients, arterial blood samples were collected at four different time points to determine D-dimer: 1st preoperatively; 2nd at the end of surgery; hence 4 and 24 hours postoperatively. D-dimer which reflects the fibrinolytic status was measured using enzyme-linked fluorescent assay (ELFA) techniques (Minividas; ELFA; Biomerieux; France).

Statistical analyses were performed with the program package SPSS for windows, version 11.0 (SPSS Inc.). All values are expressed as mean ± SE. Comparisons of results between the two groups were done by the two-tailed unpaired *t* test for each normally distributed variable. Non-parametric evaluation was performed for variables not normally distributed (Mann-Whitney U test). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patients' clinical characteristics are shown in Table 1. No statistically significant differences were noted between the groups with respect to mean age, gender, body mass index, left ventricular function, mean duration time of the operation and number of grafts used for patient. Routine hematological and hematochemical data compared preoperatively and at the first postoperative day showed no significant differences between the two groups (Table 2).

Preoperative and postoperative mean levels of D-dimer were comparable in both groups. The increase in D-dimer levels after surgery was significantly inhibited in the T group (Fig. 1, $P < 0.05$).

Blood loss and transfusion requirements for the two groups are compared in Table 3. Postoperative bleeding was significantly lower in the tranexamic acid group compared with control group (320 ± 38 mL vs. 480 ± 75 mL, $P < 0.001$). Patients in the C group received more blood (0.94 units/patient vs. 0.46 units/ patient in T group, $P < 0.001$). The percentage of patients receiving any allogeneic blood products during or after operation was higher in T group (15%) than in C group (36%); ($P < 0.05$). Intra- and postoperative demographics were similar between two groups (Table 4). There was no difference between two groups regarding pulmonary dysfunction and neurological deficit. There was no hospital mortality in two groups.

DISCUSSION

Cardiopulmonary bypass has long been recognized as one of the major causes of the systemic inflammatory response, which may contribute to postoperative complications and multiple organ dysfunctions, such as the heart, brain, lung and kidney dysfunction (6).

The most important factors that cause

Table 1. Baseline characteristics (n=33 in each group)

Variable	Tranexamic group	Control group	*P* value
Age, years	44 ± 10	45 ± 10	NS
Gender (male/female)	12.1	15.1	NS
Body Mass Index (kg/m^2)	23.4 ± 2.6	23.4 ± 3.3	NS
Baseline Ejection fraction (%)	45 ± 8	40 ± 10	NS
Diseased vessels (no.)	2.1 ± 0.2	2.1 ± 0.5	NS
Coexisting illness, no. (%)			
Diabetes	5 (15.1%)	4 (12.1%)	NS
Previous myocardial infarction	9 (27.2%)	8 (25.14%)	NS
Hypertension	2 (6.06%)	1 (3.03%)	NS
Smoking	15 (45.4%)	13 (39.3)	NS
History of aspirin consumption, no. (%)	30 (90.1%)	31(94%)	NS

Abbreviation: NS, not significant.

Table 2. Preoperative and postoperative hematochemical data

	Tranexamic group (n= 33)	Control group (n=33)	*P* value
Hemoglobin (g/dL)			
Preoperative	12.3 ± 1.4	12.7 ± 1.5	NS
First postoperative day	10.6 ± 1.9	10.4 ± 0.8	NS
Hematocrit (%)			
Preoperative	41.6 ± 2.6	41.9 ± 3.2	NS
First postoperative day	33.4 ± 4.6	32.5 ± 3.6	NS
Platelet count (10^9/L)			
Preoperative	203 [164-247]	197 [155-221]	NS
First postoperative day	147 [133-195]	151 [130-185]	NS
Prothrombin time (seconds)			
Preoperative	12.4 ± 1.2	12.5 ± 1.3	NS
First postoperative day	14.4 ± 1.2	14.2 ± 1.5	NS
aPTT (seconds)			
Preoperative	31.5 ± 4.9	31.4 ± 5.2	NS
First postoperative day	33.5 ± 5.1	33.3 ± 5.6	NS
D-dimer (mg/L)			
Preoperative	0.4 [0.3-0.5]	0.4 [0.3-0.5]	NS
First postoperative day	0.5[0.4 -0.6]	1 [0.7-1.5]	< 0.05
Creatinine (mg/dL)			
Preoperative	0.8 [0.7-1.1]	0.8 [0.7-1.4]	NS
First postoperative day	1 [0.8-1.1]	1.1 [0.9-1.3]	NS

Abbreviation: NS, not significant.

haemostatic defects after CABG surgery are: inadequate surgical hemostasis, inadequate heparin reversal, complement activation, platelet dysfunction, and hyperfibrinolysis. Surgical incision and cardiac surgery cause increased concentration and activity of tissue plasminogen, which converts plasminogen to plasmin, and plasmin inactivates fibrin. However, platelet defects have been shown to be another important factor. Contact with a synthetic surface results in granules release, with subsequent reduced aggregation and adhesiveness of the platelets (7).

The performance of OPCAB might offer hemostatic advantages when it is compared with the need for CPB during CABG. During the recent years an increasing number of OPCAB procedures have been performed. Eliminating exposure of blood to the extracorporeal circuit could reduce hemostatic defects. However, significant bleeding and use

Table 3. Postoperative blood loss in milliliters and total transfusion requirement*

Variable	Tranexamic group (n= 33)	Control group (n= 33)	% Decrease in Blood Loss	*P* value
Postoperative blood loss (ml)				
0-2 h	90 ± 25	180 ± 37	55	<0.01
2-6 h	190 ± 41	290 ± 78	34	0.001
Total drainage	320 ± 38	480 ± 75	33	0.001
Mean total drainage time (hour)	10 ± 2	14 ± 2	-----	0.01
Whole blood or PRBC received (no. of pts)	5	8		0.07
Whole blood or PRBC (units/patient)	0.46	0.94		0.001
FFP received (no. of pts)	0	6		0.05
Platelet received (no. of pts)	0	0		NS
Total number of patients transfused (%)	5 (15%)	12 (36%)		

Abbreviation: NS, not significant.
* Data are given as mean ± SD unless specified otherwise.

Table 4. Operative and postoperative data (n=33)*

Variable	Tranexamic group	Control group	*P* value
Average grafts per patient	2.4 ± 0.3	2.3 ± 0.7	NS
Mean body temperature during surgery (^{o}C)	36 ± 0.6	36 ± 0.5	NS
Mean body temperature in ICU (^{o}C)	37 ± 0.6	37 ± 0.4	NS
Skin to skin surgery time (min)	182 ± 19	175 ± 34	NS
Ventilation time (hour)	6.1 ± 1.4	6.9 ± 2.4	0.07
ICU stay (hour)	10 ± 1.8	12 ± 3.2	< 0.05
Hospital stay (day)	4.8 ± 0.4	4.8 ± 0.9	0.09
Surgical re-exploration (bleeding)	0	1	NS
Myocardial infarction	0	0	NS
Renal dysfunction (creatinine > 2 mg/dL)	0	1	NS
Pulmonary dysfunction	0	0	NS
Major neurologic deficit	0	0	NS
Mortality	0	0	NS

Abbreviation: NS, not significant.
*Data are given as mean ± SD.

of allogeneic blood in OPCAB surgery were reported in some studies. Cartier and coworkers reported a mean postoperative bleeding of 525 ml, with a prevalence of patients transfused with allogeneic products of 31% (3). Ascione and coworkers described a mean bleeding of about 770 ml, with a not negligible use of allogenic products (8). It is well recognized that tranexamic acid reduces both, blood loss and the need for foreign blood-product transfusion following CABG with CPB (9, 10). Tranexamic acid exerted its antifibrinolytic effect by suppressing t-PA activity and thereby inhibiting secondary fibrinolysis. Tranexamic acid showed no effects on plasmin neutralization and the most important plasminogen activator inhibitor, PAI-1. However, tranexamic acid stabilizes ADP granules in platelets and inhibits platelet dysfunction. The effect of tranexamic acid on blood loss during

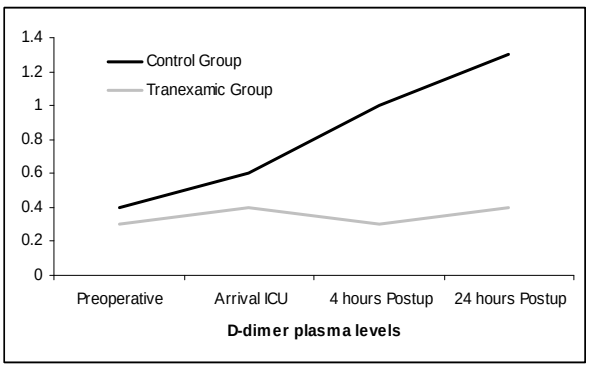

Fig. 1. D-dimer plasma levels (mg/L). Significant differences between two groups at 4 h and 24 hours postoperatively (Mann-Whitney U test, $P < 0.05$).

and after CPB coincided with other studies (11, 12). However, beneficial effects of tranexamic acid have not yet been established in OPCAB.

In this prospective, double-blind, randomized study we evaluated the effectiveness of tranexamic acid in OPCAB surgery. In order to investigate the effects of tranexamic acid coagulation and the fibrinolysis system in OPCAB patients, D-dimer was determined in all patients. We found significant higher values of D-dimer only in patients of the control group, whereas no significant changes were evident in the tranexamic acid group. Intergroup difference was already seen at the end of surgery and marked in the postoperative hours. This underlines that improved hemostasis is achieved at least partly by the antifibrinolytic action of tranexamic acid. In OPCAB, there is significant surgical trauma (such as sternotomy, harvesting of vein and artery, pericardiotomy), manipulation of the heart and exposure to heparin and protamine. These factors determine the activation of coagulation during OPCAB by release of tissue factor and activation of the extrinsic pathway (13). Recently, Casati *et al.* demonstrated the effectiveness of tranexamic acid in OPCAB surgery (14). Finally, the potential for hypercoagulability (15) to occur with the use of antifibrinolytic agents, as suggested by Cosgrove *et al* (16), was taken into account in this study. The possibility of thromboembolic complications and, in particular, graft occlusion with myocardial infarction caused by tranexamic acid, must be considered when

giving this drug to patients. Altogether, in recent studies (17), a Canadian group of investigators assessed saphenous vein graft patency with magnetic resonance imaging 5 to 30 days after surgery and they showed that the administration of tranexamic acid before cardiopulmonary bypass did not seem to compromise early venous graft patency rates. We found no evidence of hypercoagulability, such as an increased incidence of cerebrovascular accidents, deep venous thrombosis, or pulmonary emboli in our cases. A long-term study with larger number of patients may be necessary to clarify the issue of hypercoagulability. Mortality and other clinical outcomes were similar for the two groups, except for bleeding and transfusion requirements.

In summary, tranexamic acid effectively reduces postoperative bleeding tendency and then decreases the need for allogeneic blood products after OPCAB. The defective hemostasis occurs even in the absence of cardiopulmonary bypass, and the use of antifibrinolytic agents decreases post-bypass bleeding. Any potential increased incidence of thrombotic complications as a result of its use with CPB could not be clearly shown.

Conflict of interests

We have no conflict of interests.

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