Tranexamic Acid Reduces Blood Loss in Off-Pump Coronary Artery Bypass Surgery

Reza Jalaeian Taghaddomi, MD,* Asadollah Mirzaee, MD,† Alireza Sharifian Attar, MD,* and Abbas Shirdel, MD‡

Objective: **This study was designed to evaluate the hemostatic effect of tranexamic acid in off-pump coronary artery bypass surgery.**

Design: **A prospective, randomized, double-blind, placebo-controlled study.**

Setting: **The Department of Anesthesiology and Cardiac Surgery, Medical Sciences University.**

Participants: **One hundred eight patients undergoing off-pump coronary artery bypass surgery were enrolled into the study. Eight patients were withdrawn, and 100 patients were divided into 2 groups.**

Interventions: **Fifty patients received tranexamic acid (bolus 1 g before skin incision and followed by maintenance dose of 400 mg/h during surgery), and 50 patients received saline.**

Measurement and Main Results: **Hematologic parameters, volume of blood loss, blood transfusion, and other clinical data were recorded throughout the perioperative period. Twenty-four-hour postoperative blood loss was significantly less in the tranexamic acid group compared with the control group (471 ± 182 *v* 844 ± 303). Patients in the tranexamic acid group received significantly less allogeneic blood (8 *v* 31 units).**

Conclusion: **Bleeding and hemorrhagic complications and the consequent need for allogeneic transfusion are still major problems after off-pump coronary artery bypass surgery. Tranexamic acid appears to be effective in reducing postoperative bleeding and the need for allogeneic blood products.**

KEY WORDS: tranexamic acid, off-pump coronary artery bypass, hemostasis

CONVENTIONAL CORONARY ARTERY bypass surgery via full sternotomy and cardiopulmonary bypass (CPB) with a decompressed and arrested heart provides good visibility and space to safely and adequately construct anastomoses to all coronary arteries; however, CPB induces a total body inflammatory response caused by activation of the complement system due to contact of the blood with the artificial surface of the CPB circuit. All organs are affected to a varying degree, potentially leading to dysfunction and/or damage of the brain, lungs, heart, bowel, kidneys, and coagulation system. Off-pump coronary artery bypass surgery (OPCAB) has gained interest since its reintroduction in the early 1990s by Buffolo et al and Benet et al and is the first-choice technique in an increasing number of surgical centers.[1,2]

Perioperative bleeding and coagulopathy are major complications of CPB, and, although avoidance of CPB has been shown to reduce these problems significantly, bleeding and hemorrhagic complications and the consequent need for allogeneic transfusions are still major problems after OPCAB.[3] There are different strategies including pharmacologic approaches to reduce perioperative bleeding in cardiac surgery. The use of fibrinolytic inhibitors (tranexamic acid, aprotinin, and aminocaproic acid) is one of the pharmacologic approaches that has shown beneficial effects in on-pump coronary artery surgery in a large number of controlled trials.[4-7]

In a meta-analysis conducted by Brown et al,[8] the effectiveness of antifibrinolytics in cardiac surgery was compared from 138 trials, and it was shown that they were effective in reducing blood loss and transfusions. In the recent multicenter BART study,[9] aprotinin and lysine analogs were compared in high-risk cardiac surgery patients. The trial was terminated early because of a higher rate of death in patients receiving aprotinin and precludes its use in high-risk cardiac surgery. However, only a few studies have been concerned with the use of antifibrinolytic drugs in OPCAB surgery.[10-14]

Casati et al[10] and Wei et al[12] evaluated the hemostatic effects of tranexamic acid in OPCAB and found it to be beneficial. Vanek et al[11] compared hemostatic effects of tranexamic acid versus aprotinin and concluded that it appeared to be a cost-effective and safe alternative to aprotinin.

The aim of this randomized, double-blind, placebo-controlled study was to evaluate the effects of tranexamic acid on the transfusion requirements and bleeding in a larger population of patients undergoing OPCAB surgery.

MATERIAL AND METHODS

Medical Faculty Ethics Committee approval and informed written consent from all patients were obtained. From October 2006 to September 2007, 108 consecutive patients scheduled for OPCAB were enrolled in the study. The exclusion criteria were as follows: a history of bleeding disorders, active chronic hepatitis or cirrhosis, chronic renal insufficiency (serum creatinine >2 mg/dL), preoperative anemia (Hb < 11 g/dL), previous cardiac surgery, and myocardial infarction <7 days before surgery. Also, patients receiving potent antiplatelet agents like adenosine diphosphate inhibitors (ticlopidine and clopidogrel) but not aspirin were excluded.

Eight enrollees were withdrawn from the study: 4 of them converted to on-pump surgery in the course of surgery and 4 of them due to the need for postoperative re-exploration for hemorrhage with the finding of an evident surgical source of bleeding. In 1 case, bleeding was from the distal anastomosis and in 3 cases from a branch of the left internal mammary artery (LIMA). Therefore, 100 patients were assessed in the study.

After enrollment in the study, the patients were divided into 2 groups randomly (group T and P). The envelope method with random numbers was used. An independent anesthesiologist prepared coded infusions with tranexamic acid/placebo and was not directly involved in the clinical treatment of randomized patients. Both the operating room staff and the intensive care unit staff were blinded regarding the study group.

In group T (n = 50), tranexamic acid, 1 g, was given 20 minutes before

*From the Departments of *Anesthesiology and ‡Hematology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashad, Iran; and †Department of Cardiosurgery, Chaem Hospital, Mashad University of Medical Sciences, Mashad, Iran.*

Address reprint requests to Reza Jalaeian Taghaddomi, MD, Department of Anesthesiology, Ghaem Hospital, Ahmad Abad Street, Mashhad, Iran. E-mail: r-jalaeian@mums.ac.ir

1053-0770/09/2303-0007$36.00/0

doi:10.1053/j.jvca.2008.09.018

skin incision and 400 mg/h during the entire surgical procedure. The patients from group P (n = 50) were infused with normal saline as a placebo.

Premedication was with intramuscular morphine (0.1 mg/kg) and oral diazepam (0.1 mg/kg). Fentanyl-based anesthesia (15-20 μg/kg) with a propofol infusion (50-80 μg/kg/min), midazolam, and pancuronium bromide was used in all patients. In both groups, lactated Ringer's solution, 500 mL, was used for volume expansion, followed by 5 mL/kg for basic needs and 7 mL/kg as third-space loss. Replacement for intraoperative blood loss was 3 times the amount of bleeding in both groups. A red blood cell transfusion was administered when hemoglobin decreased to less than 9 g/dL and/or hematocrit to less than 27%. A transfusion of fresh frozen plasma was instituted (to correct a suspected deficiency of coagulation factors) when chest tube bleeding increased to >150 mL/h or >100 mL/h for 2 consecutive hours.

All patients had surgery through a full median sternotomy. The LIMA was used in all cases with possible harvest of other grafts (great saphenous vein). A U-shaped stabilizer was used to dampen the movement of the beating heart .The verticalization of the heart was achieved by using a posterior pericardial suture.

The initial dose of intravenous heparin (100 IU/kg) was administered after harvesting the LIMA with a target activated coagulation time over 250 seconds. On completion of anastomoses, heparinization was partially reversed with a half-dose of protamine.

Patient characteristics and intraoperative variables including number of grafts, amount of bleeding, and infused blood were recorded in a questionnaire. Intraoperative blood loss was determined by measuring the weight change of moistened surgical gauzes and observing the fluid level of suction reservoirs.

Hematologic parameters (hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio), the amount of drainage, and the volume of infused blood products were recorded 4 hours and 24 hours postoperatively. In addition, the risk of perioperative myocardial ischemia and myocardial infarction were assessed based on the electrocardiographic changes, echocardiographic examination, and measuring CK-MB and troponin I levels in suspected cases. No routine investigations for deep venous thrombosis or pulmonary embolism were used, but clinical signs of thromboembolic complications were investigated.

Table 1. Demographic and Perioperative Data

Variables	Tranexamic Acid Group	Control Group	*p* Value
Age (y)	54.7 ± 10.9	60.3 ± 10.2	0.068
Sex (M/F)	38/12	34/16	0.32
Weight (kg)	75.1 ± 14.0	74.8 ± 13.9	0.84
Height (cm)	164.6 ± 7.9	160.6 ± 124	0.17
Operation time (min)	176.5 ± 44.7	174.7 ± 32.6	0.87
No. of grafts	3.79	3.82	0.82
EF (%)	52.7 ± 11.1	54.1 ± 9.0	0.63
Aspirin, 80 mg/d (%)	88	92	0.66
Hemoglobin (mg/dL)	14.1 ± 1.4	13.8 ± 1.1	0.54
Platelets (10^9/mL)	201.4 ± 51.1	198.0 ± 45.0	0.80
PT	13.1 ± 0.88	12.9 ± 0.64	0.11
PTT	31.4 ± 0.5.3	31.2 ± 7.4	0.92
INR	1 ± 0.11	1 ± 0.04	0.08
Intraoperative bleeding (mL)	467 ± 170	531 ± 164	0.62
ACT at the and of surgery	162 ± 12	168 ± 13	0.81
ACT during surgery	272 ± 9	269 ± 10	0.78
ICU stay	2.1 ± 0.2	2.2 ± 0.1	0.90

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

Table 2. Hematologic Data 24 Hours After Surgery

Variable	Tranexamic Acid Group	Control Group	*p* Value
Hemoglobin (g/dL)	11.2 ± 0.96	11.1 ± 1.2	0.96
Hematocrit (%)	33.7 ± 3.1	34.4 ± 3.8	0.53
Platelets (10^9/L)	180.7 ± 48.0	171.9 ± 36.7	0.48
PT (s)	15.4 ± 2.9	14.7 ± 0.9	0.27
PTT (s)	39.7 ± 13.2	40.5 ± 9.1	0.81
INR	1.5 ± 0.74	1.3 ± 0.16	0.21
Creatinine (mg/dL)	1 (0.8-1.1)	0.9 (0.8-1)	0.83

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

RESULTS

No statistically significant differences were found between the 2 groups regarding the demographic and baseline hematologic data, including age, height, weight, sex, duration of surgery, number of grafts, ejection fraction, aspirin intake, hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio (Table 1).

The amount of intraoperative blood loss in the tranexamic acid group and the control group was 467 ± 170 mL and 531 ± 164, respectively, and there was no significant difference ($p = 0.62$). The activated coagulation time during and at the end of surgery showed no significant difference. Hematologic parameters were compared 24 hours postoperatively, and there was no significant difference between the 2 groups (Table 2). The amount of bleeding within 4 hours postoperatively in the tranexamic acid and the control groups was 87 ± 62 mL and 210 ± 195 mL, respectively, and the difference was significant ($p = 0.005$) (Table 3).

In the tranexamic acid group, no patient received allogeneic blood within 4 hours postoperatively, whereas in the control group in 11 patients 1 unit of packed red blood cells (PRBCs) and in 4 patients 2 units of PRBCs were transfused. There was

Table 3. Postoperative Bleeding and Perioperative Transfusions

Variables	Tranexamic Acid Group	Control Group	*p* Value
Bleeding, 0-4 hours (mL)	87 ± 62	210 ± 195	0.005
Bleeding, 4-24 hours (mL)	462 ± 118	570 ± 184	0.07
Total bleeding within 24 hours (mL)	471 ± 182	844 ± 363	<0.001
PRBC, intraoperative (U) (patients)	0	3 (3)	0.36
PRBC, 0-4 hours (U) (patients)	0	19 (15)	<0.001
PRBC, 4-24 hours (U) (patients)	8 (8)	9 (9)	0.5
Total number of transfused patients	8	31	0.003
FFP, 0-4 hours (U) (patients)	6 (2)	5 (2)	0.8
FFP, 4-24 hours (U)	0	0	1