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APROTININ: EFFECTS ON BLOOD LOSS AND FRESH FROZEN PLASMA REQUIREMENT IN CARDIAC OPERATIONS

H. TEIMOURI, M.D,[*] AND F. SABZI, M.D.[†]

From Imam Ali Heart Center, Kermanshah University, Kermanshah, Iran.

ABSTRACT

Background: Aprotinin has been used increasingly to reduce postoperative blood loss in open-heart operations; due to the potentialities for complications and high cost, it would seem reasonable to use aprotinin more selectively in small doses in the prime solution of the pump.

Methods: We prospectively studied the effect of preoperative low dose aprotinin [2 million units (230mg)] on blood loss and transfusion requirements in patients undergoing cardiopulmonary bypass. One-hundred and fifty patients were randomly assigned to two groups: prophylactic low dose aprotinin (group 1) and a non-medicated control group (group 2). The two groups were comparable in all demographic and operative variables.

Results: Postoperative chest tube drainage was significantly decreased in the aprotinin group compared with that in the control group (372.73 mL in group 1 and 482.2 mL in group 2, $p<0.05$). No significant difference was seen between the two groups in regard to transfusion requirement ($p>0.05$). The use of fresh frozen plasma (FFP) was significantly less in group 1 than in group 2 (469.87 mL versus 680.69 mL, $p<0.05$).

Conclusion: Prophylactic use of low-dose aprotinin immediately before cardiopulmonary bypass reduced the need for transfusion of blood & fresh frozen plasma (FFP) during the post operative period.

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INTRODUCTION

Control and modification of the adverse effects of cardiopulmonary bypass (CPB) on the hemostatic system continue to be an area of major interest. One of the pharmacologic agents used to preserve homeostasis during CPB, which appears to be the most promising is the serine protease inhibitor aprotinin. Prophylactic use of aprotinin has been shown to decrease postoperative blood loss and transfusion requirements in patients undergoing cardiac operations with extracorporeal circulation. Since the first description of high dose aprotinin for prophylaxis against excessive postoperative bleeding, numerous studies with different dose protocols have been conducted, with impressive results.[1-4] One point in common in these studies has been the application of aprotinin before and during CPB (cardiopulmonary bypass) to prevent platelet activation and fibrinolysis. By increasing the high dose of aprotinin, incidences of adverse effect on aorto-coronary bypass graft patency, anaphylactic reactions, renal impairment and disseminated intravascular coagulation after profound hypothermia have increased.[5-8] It has been reported that excessive postoperative bleeding is seen in 5% to 25% of patients undergoing CPB.[9] We confirmed the concept of low dose aprotinin use for reducing postoperative bleeding as in other studies. This prospective, randomized clinical study was performed to investigate the effect of aprotinin given in prime solution in the oxygenator on postoperative blood loss.

PATIENTS AND METHODS

This study was performed on patients scheduled for elective cardiac operation with CPB at the Imam Ali

* Assistant professor of cardiac anesthesiology, Shahid Madani Hospital, Lorestan University of Medical Sciences, Lorestan, Iran.
† Associate professor of cardiovascular surgery, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Table 1. Characteristics of patients compared by χ^2 or t- test.

Variable	Group 1 (N= 75)	Group 2 (N=75)	P value
First 24/hours chest tube drainage (ml)	372, 73±363. 63	482. 2±+345. 18	< 0.05
Blood transfused (ml)	528, 67±366. 98	597. 39±468. 60	>0.05
Fresh frozen plasma transfused (ml)	469, 87±343. 21	680. 69±436. 5	< 0.05
Cardiopulmonary bypass time (min)	46.44 ± 14.23	48.83 ± 11.76	>0.05
Number of bypass grafts	2.83± 0.74	2.91 ± 0.66	> 0.05
Cross clamp time (min)	45.5 ± 12.2	51.2 ± 13.1	> 0.05
Reoperation for post operative bleeding	15%	17.5%	> 0.05
Hemoglobin (g/dl)	13.41-2.3	13.6-4.2	> 0.05
Hematocrit (%)	40.2-4	40.4-4.2	> 0.05
Platelet (10/mm³)	212.2-68.4	214.5-56.7	> 0.05
Creatinine (mg/dl)	0.91-0.25	0.9-0.26	> 0.05
Death (number)	1	1	> 0.05
Intraaortic balloon pump used (number)	5	7	> 0.05
Neurological complication	1	2	> 0.05

Variables are expressed as mean ± standard deviation or percentage or number as appropriate.

department of cardiovascular surgery between March 8, 2003 & June 7, 2004. Informed consent was obtained from all patients. Patients who received warfarin within 7 days of operation and those with any kind of bleeding diathesis were excluded from the study. One-hundred and fifty patients (90 males and 60 females) were randomly assigned to two groups. Group 1 was the low dose (280mg) aprotinin group; the patients received 2 million units of aprotinin in the prime solution of the oxygenator. Group 2 was a non-medicated control group. The operative procedure performed in all patients was coronary artery bypass grafting. All patients were operated on and cared for by the same team. The anesthetic management and conduct of CPB was standardized. The extracorporeal circuit consisted of a hollow-fiber membrane oxygenator (MAXIMA) and tygon tubing was used throughout the circuit. Before CPB, all of the patients were given 300u/kg bovine lung heparin, mild hypothermia, and cold crystalloid cardioplegia for induction and cold cardioplegia for maintenance were infused every 25 minutes for myocardial protection. The cardioplegic solution was returned to the circuits. Left internal mammary artery grafts were used routinely in all patients. The saphenous vein was harvested as needed. The left pleural space was opened during internal mammary harvesting and was emptied as far as possible by suction before chest closure. After systemic heparin administration, blood was routinely returned to the pump-oxygenator and reinfused. At the end of CPB heparin was reversed with protamine sulfate at a 1:1 ratio. The shed mediastinal blood was collected in a commercially available volumetric collection system and the amount was measured every one hour for the first day. The mediastinal and thoracic drains were removed when the total drainage was less than 100 mL over the previous 6 hours. Homologous packed red cells were administrated only when the hematocrit value fell to less than 25%. Patients received fresh frozen plasma (FFP) when excessive blood loss was accompanied by prolonged prothrombin time (greater than 1.5 times the normal value) and excessive blood loss (greater than 200mL/h for 2 consecutive hours). Auto-transfusion of shed blood was not used in any of the patients during the study. Reoperation for bleeding was undertaken if the blood loss exceeded 600 mL for 2 consecutive hours or overall blood loss exceeded 1500 mL. Cardiopulmonary bypass time, aortic clamp time, amount of total chest tube drainage, incidence of reoperation for bleeding, need for donor blood transfusion or fresh frozen plasma, use of aspirin, age of patient, ejection fraction and number of grafts were recorded for all patients. All results are expressed as the mean and standard deviation. Categorical variables were compared by χ^2 and continuous variables compared by Student t-test. A P-value less than 0.05 was considered statistically significant. Transfusions were evaluated intraoperatively and in the first 24 hours post-operatively as total amount in units of packed red blood cell, FFP and platelet concentrates used. Criteria for transfusion were strictly followed during the first post-operative day. Criteria for transfusion were Hemoglobin (Hb) less than 8g/dL during CPB or clinical condition (hypovolemia or tachycardia with anemia during CPB). Unfortunately criteria for transfusion of FFP were not strictly considered by ICU nurses and FFP was used for volume expansion. This is the only limitation of our study.

RESULTS

There were no statistically significant differences among the two groups with regard to age, sex, CPB time, duration of operation, aortic cross clamp time, blood transfusion, number of grafts and body mass index (BMI) (Table I). Four patients were reoperated on for excessive bleeding in both groups equally. There were no cases of renal impairment or allergic reactions to aprotinin. Postoperative chest tube drainage for 24 hours after operation and transfusion requirement is shown in Table II. Significantly reduced postoperative bleeding was found in group 1 that received aprotinin compared with that in the non-medicated control group ($p<0.05$) after the initial 24 hours. Preoperative use of aspirin did not affect the postoperative bleeding and transfusion requirement (Table II). The use of banked donor blood products postoperatively was not significantly different among the two groups, however the FFP requirement was significantly lower in the aprotinin group than in the control group (Table II) ($p<0.05$).

Table II. Demographic characteristic of patients compared by t test or χ^2.

	Group 1 (N= 75)	Group 2 (N=75)	P value
Weight(kg)	74.8-11.7	71.2-13.3	> 0.05
Age (y)	55.41 ± 9.25	54.73 ± 9.95	> 0.05
Male / Female	60/40 %	55/45 %	>0.05
Body mass index (kg/m^2)	28.4-3.2	27.5-4.1	>0.05

Variables are expressed as mean ± standard deviation or percentage or number as appropriate.

DISCUSSION

The efficacy of aprotinin as a hemostatic agent in the setting of cardiac operations is indisputable. It has proven to be more effective than tranexamic acid, ε-aminocaproic acid and desmopressin. Because of the potentiality for complications and high cost of aprotinin, it will be logical to use aprotinin in small doses.[10] In the present study, postoperative blood loss and FFP requirement differed significantly between aprotinin and control groups. Aprotinin by inhibiting excessive fibrinolysis and reducing plasmin levels allows replenishment of the platelet surface glycoprotein Ib receptors from intraplatelet pools. Michelson and Barnard[11] also showed that platelet recovers from plasmin as soon as it is neutralized by redistribution of the platelet glycoprotein Ib receptor. Also the endothelial cell plays an important role in the regulation of homeostasis. Protein C is a major regulatory protein of thrombus formation. It also prompts fibrinolysis by inactivating the plasminogen activator inhibitor. Aprotinin has been shown to inactivate protein C. Michelson and Barnard suggested that aprotinin contributes to preservation of endothelial cell function. It has been shown that a much lower dosage is required to inhibit the enezyme activity of plasmin as compared with plasma kallikrein. In the present study we used the low dose regimen (2 million U), because low dose aprotinin is sufficient to obtain the antiplasmin effect and to preserve glycoprotein Ib receptors.[11] These results suggest that aprotinin could be used in low dose with good efficacy. However the need for transfusion was similar in the two groups, but patients in the aprotinin group had less post operative bleeding. We think that this contradictory statement was caused by the inefficient observation of strict transfusion criteria by the ICU nurses.

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