Ultra-low dose aprotinin effects on reducing the need for blood transfusion in cardiac surgery

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ABSTRACT

Objectives: To assess the effects of ultra-low dose one million kallikrein inhibitor units (KIU) of aprotinin on bleeding and the need for transfusion after cardiac surgery.

Methods: We carried out this randomized clinical trial on 162 cardiac surgery patients in Shahid Madani Hospital, Tabriz, Iran from April 2004 to December 2005. The patients were randomly divided into 2 groups of 81 individuals. In the aprotinin group, 0.5 million KIU infused before and 0.5 million KIU during cardiopulmonary bypass. In the placebo group, 100 ml normal saline was infused as above. The need to use fresh frozen plasma (FFP), packed red blood cells (PRBCs) transfusion during, after operation, the rate of chest tubes drainage at 6, 12 and 24 hours after surgery were measured in 2 groups.

Results: Chest tubes drainage at 6 hours after surgery was 190 ± 24 ml in the aprotinin group and 266 ± 33 ml in the placebo group (p=0.066). The amount of bleeding at 12 and 24 hours was significantly different between 2 groups (p=0.048, p=0.009). The frequency of blood products transfusion in the aprotinin group was 68% and in the placebo group was 75% (p=0.02). The number of PRBCs and FFP units transfused were significantly lower in the aprotinin group (p=0.000, p=0.005). Total amount of blood and products transfusion in the aprotinin group was 2.56 ± 0.27 units and in placebo group it was 4.37 ± 0.27 units (p=0.0001).

Conclusion: Results indicate that the use of one million KIU of aprotinin in cardiac surgery is effective in reducing postoperative bleeding and transfusion requirements

Saudi Med J 2007; Vol. 28 (1): 49-53

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Received 20th May 2006. Accepted 3rd September 2006.

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Aprotinin is a natural protease inhibitor that exerts its antifibrinolytic effect through inhibition of plasmin and kallikreine.[1] Aprotinin prevents the activation of contact phase and protects the platelets damage caused by the increase of plasmin levels, and from a mechanical damage during the cardiopulmonary bypass (CPB). The net effect of aprotinin is to inhibit fibrinolysis and consumption of coagulation factors and finally reducing the bleeding.[2,3]

Through decreasing the bleeding after operation, aprotinin reduces the need for transfusion,[4] and reduces the risk of returning to operation room to control bleeding and also decreases the Intensive care unit (ICU)stay.[5] Two recommended regimens of aprotinin are as follows: 1. Administration of 2 million kallikrein inhibitor units (KIU) after anesthesia induction and 2 million KIU into the prime solution of pump and infusion of half of million unit per hour. 2. Administrating half dosage as mentioned in number one.

High dosage of aprotinin has side effects such as acute renal failure, allergic reactions, shock, myocardial infarction, heart failure, cardiac arrest, stroke and ventricular fibrillation and these side effects are rarely seen in low doses.[5] The high cost and side effects of conventional protocol (high dose) of aprotinin stimulate the assessment of the effectiveness of its lower doses.[6] Many reports used a prophylactic dosage of 2 million KIU aprotinin and showed its effect on reducing the postoperative bleeding,[7-11] but there were different results regarding the studies carried out on administrating one million units. Some studies haveshown the effectiveness of the drug on reducing the bleeding,[12-16] however, in other studies this dosage was not effective.[17] The aim of this study was to assess the effect of one million KIU of aprotinin on bleeding and the need for transfusion after cardiac surgery.

Methods. After ethics committee approval and written informed consent from the patients, we

included 162 patients who underwent elective surgery of coronary artery bypass grafting and valve surgery under CPB. The patients were randomly divided into 2 group of 81 patients. Aprotinin group received one million KIU aprotinin and the placebo group received normal saline in the same manner as the aprotinin group. The randomization process was carried out by forming "randomly permuted blocks" using an online software accessible on URL: http://www.Randomization.com. The patients were studied in Madani Heart Hospital from April 2004 to December 2005.

The patients requiring redo operation and with a known coagulopathies or receiving fibrinolytic drugs or heparin and antiplatelets drugs except aspirin before operation were excluded from the study.

Anesthesia methods used in patients were the same. In all of CABG patients, the left internal mammary artery (LIMA) was used with one or 2 more saphenous vein grafts.

Study drug administration. In the aprotinin group after the induction of anesthesia, one ml of aprotinin diluted in 10 ml of distilled water or saline was injected intravenously as a test dose, and in case of lack of hypotension and skin rash, the main dosage of the drug infused to 500,000 KIU of aprotinin diluted in 100 milliliter of saline were infused in 10-15 minutes and another 500,000 units were added to the prime solution of CPB.

The normal saline was injected in the placebo group instead of the test dose and the main dose in the same conditions and the same volume of normal saline was added to the prime solution. The patients, the anesthesiologist, surgeon, perfusionist and the nurses in the ICU were not aware of the allocation of the drug or the placebo to the patients (double blind).

Although taking the LIMA and saphenus vein out or suturing the atrium wall in valve procedures was carried out by different surgeons, from the viewpoint of surgical techniques and hemostasis, the same method was used. The type of the oxygenators, the degree of hypothermia and the combination of the prime solution and cardioplegin were the same in all of the patients.

All patients were receiving 3 mg/kg (300 units/kg) of unfractionated heparin 2 minutes before placement of arterial and venous cannula and every hour one mg/kg of heparin were added to the pump. After reaching the activated clotting time (ACT) to 480 seconds, the patients underwent cardiopulmonary bypass. After the patients were separated from CPB, heparin was neutralized by protamine sulfate (1.5 mg of protamine for each mg of heparin) and ACT was kept to the approximate limit of 120-180 seconds, extra protamine was administrated if needed.

The patients transfusion protocol was as follows: as routine, patients whose hematocrit was higher than 40% after induction of anesthesia, one unit (450 ml) of blood was taken from the patient (acute normovolemic hemodilution) until it is re-transfused to the patient after weaning from CPB and hemostasis. Homologous red blood cells were transfused during CPB if the patient's hemoglobin concentration was less than 7 g/dl and postoperatively if less than 8 g/dl (and if less than 10 g/dl in hemodynamically unstable patients). Those patients who had bleeding more than 1000 ml at the first 6 hours after operation were transferred to the operating room in order to investigate the origin of the bleeding.

Sampling method. Data collection and analysis. Demographic data, heparin doses, activated clotting time, untoward reactions, blood products transfused intraoperatively and postoperatively, and mediastinal tube drainage at 6, 12 and 24 hours and also postoperative complications such as: plasma creatinine rise of more than 50%, myocardial infarction and hemodynamic instability, were recorded on a study protocol data sheet for each patient.

The collected data were statistically analyzed with the Statistical Package for Social Sciences version 12.0 (SPSS, Inc, Chicago, IL) software. The quantitative data in 2 independent groups, and the qualitative data were statistically analyzed using the student's t-test and chi-square (test or fishers exact test when appropriate) and a p-value of 0.05 or less was considered significant.

Results. Demographic data and preoperative variables were shown in **Table 1**. The 2 groups were similar in age, gender, body surface area, presence of diabetes mellitus, and relevant laboratory tests.

There were no differences between the groups regarding the type of operation, number of grafts in coronary artery bypass graft (CABG), CPB and operation time (**Table 2**). There was a significant difference between the least CPB temperature (p=0.003) but values were in the expected range (aprotinin group = 28.9 ± 2.9°C, and placebo group = 27.7 ± 1.8°C).

Mediastinal tube drainage at 6 hours postoperatively was not significantly different between the groups (p= 0.066), but drainage at 12 and 24 hours after operation was significantly less in the aprotinin group (**Table 3**). There was no difference between the groups in the number of units of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) given intraoperatively, but the number of units of PRBC and FFP transfused postoperatively in ICU were significantly less in the aprotinin group (p=0.003 and p=0.001). **Table 3** also shows the proportion of patients receiving PRBCs and FFP that was also significantly less in aprotinin group.

Postoperative mechanical ventilation time and ICU stay was the same in both groups. Also, there were no differences in the postoperative complications (**Table 4**). The total cost of PRBCs and FFP transfusion in both groups, and cost of aprotinin in aprotinin group are outlined in **Table 5**. The total cost of blood products with regards to the cost of aprotinin was not significantly different between the 2 groups.

Discussion. Although the chest tube drainage at 12 and 24 hours postoperatively was significantly reduced in aprotinin–treated patients, the important reduction in proportion of patients transfused and number of units transfused are a more sensitive indicator of the effect of aprotinin. These data support the use of ultra-low dose aprotinin during operation as an effective measure to reduce transfusion requirements.

The effectiveness of this dose has a physiological basis. The antifibrinolytic effect of aprotinin is thought to result from the direct inhibition of plasmin, whereas inhibition of kallikrein is involved to a lesser extent or possibly absent at this dose. Although aprotinin plasma concentration of 200 KIU/ml or greater are needed to inhibit kallikrein, plasma concentrations of 50 KIU/ml are required to inhibit plasmin. This level can be achieved with a loading dose of 1,000,000 KIU,[18] like our study. Hayashida and colleagues[19] showed that when minimal dose of aprotinin (one million KIU in the pump prime) was used, an increased levels of α 2-plasmin inhibitor, plasminogen activator-1, and decreased levels of D-dimer were observe after CPB as compared to the control group, thus supporting an antifibrinolytic effect.[19]

Some investigators suggested the safety and effectiveness of aprotinin in full dose therapy. The benefit of aprotinin–induced reduction in transfusion

Table 1 - Demographic variables in the 2 groups.

Variables	Aprotinin	Placebo	*P*- value
Age (years)	52.6 ± 13.8*	54.1 ± 11.4	0.457
Gender (female/male)	40/60	39/61	1.000
Weight (kg)	67.5 ± 12.2	69.1 ± 15.8	0.481
Body surface area (m^2)	1.72 ± 0.21	1.75 ± 0.21	0.340
Diabetes mellitus	15%	17.7%	0.803
Hypertension	34.6%	51%	0.071
Functional Class (II/III/IV)	23/11/2	19/10/3	0.821
Ejection fraction (%)	50.7 ± 11.1	48.9 ± 9.4	0.403
Hematocrit (%)	42.8 ± 7.4	42.8 ± 5.7	0.963
Blood urea concentration (mg/dl)	16.3 ± 5.2	16.5 ± 8.3	0.840
Plasma Creatinine (mg/dl)	1.20 ± 1.12	1.44 ± 1.15	0.425
PT (sec)	12.6 ± 0.8	13.3 ± 4.3	0.206
PTT (sec)	40.1 ± 10.1	38.1 ± 10	0.248
Pre-operative aspirin use (frequency)	38%	43%	0.594
Time of the aspirin cease (day)	1.9 ± 1.6	1.8 ± 0.4	0.454

Values were shown as mean ± SD or percent
PT - prothrombin time, PTT - partial thromboplastin time

Table 2 - Comparison of operative variables in the 2 groups.

Variables	Aprotinin	Placebo	*P*-value
Type of surgery			0.189
Coronary artery bypass graft	47 (60%)	59 (78%)	
Valve replacement surgery	25 (30.9%)	13 (16.3%)	
Number of grafts	2.9 ± 0.43	3 ± 0.89	0.558
Aortic cross clamp time (min)	60 ± 20	58 ± 24	0.593
CPB time (min)	103 ± 26	100 ± 36	0.621
Lest temperature during CPB (°C)	27.7 ± 1.8	28.9 ± 2.9	0.003

CPB - cardiopulmonary bypass, Values were shown as mean ± SD or number (percentage)

Table 3 - Mediastinal drainage and transfusion requirements in 2 study groups

Variables	Aprotinin	Placebo	*P*-value
Drainage at first 6 hours (ml)	190 ± 24*	266 ± 33	0.066
Drainage at first 12 hours (ml)	360 ± 37	478 ± 46	0.048
Drainage at first 24 hours (ml)	555 ± 56	805 ± 76	0.009
PRBCs (Unit)	1.06 ± 0.11	1.92 ± 0.20	0.0001
FFP (Unit)	1.52 ± 0.20	2.46 ± 0.26	0.005
Total transfusions (Unit)	2.56 ± 0.27	4.34 ± 0.37	0.0001
Percent of patients requiring transfusions:			
PRBCs[+]	59%	64%	0.310
FFP[++]	52%	69%	0.043
Total transfusions	68%	75%	0.020

Values were shown as mean ± SD or number (percentage)
PRBCs - packed red blood cells, FFP - fresh frozen plasma

Table 4 - Prevalence of post-operative complications in the 2 groups.

Variables	Aprotinin	Placebo	*P*-value
Mechanical ventilation time (hours)	15 ± 14	14 ± 10	0.630
ICU stay (hours)	69 ± 29	72 ± 31	0.421
Neurological complications	2 (2.5%)	0 (0%)	0.738
Post-operative myocardial infarction	1 (1.3%)	2 (2.5%)	0.867
Plasma creatinine rise more than 50%	1 (1.3%)	2 (2.5%)	0.867
Re-exploration for bleeding	1 (2.5%)	5 (6.2%)	0.206
Hypertension (SBP>140 mmHg)	15 (18.5%)	20 (25.3%)	0.384
Hypotension (SBP<90 mmHg)	15 (18.5%)	11 (13.6%)	0.378

Values were shown as mean ± SD or percentage
ICU - intensive care unit, SBP - systolic blood pressure

Table 5 - Cost of aprotinin and blood products transfusions

Variables	Aprotinin	Placebo	*P*-value
Drug/patient cost	$47.03	0	-
PRBCs/patient cost	$15.90	$7.29	0.001
FFP/patient cost	$7.60	$29.42	0.003
Total transfusion cost (with regarding drug cost)	$70.53	$59.11	0.112

Cost of drug or blood product used in each patient
PRBCs - packed red blood cells, FFP - fresh frozen plasma

requirement, and transfusion–associated morbidity and mortality, is far outweigh the side effects of aprotinin administration.

Although determination of detailed and actual hospital costs was not available in this university hospital, this study showed no more cost imposition when ultra-low dose of aprotinin was used. In a retrospective study, low-dose aprotinin was shown to be effective in redo coronary operations in reducing cost.[20] In another prospective, nonblinded study comparing high–dose, low-dose, and no aprotinin used in patients undergoing open heart surgery, costs were significantly reduced when low-dose aprotinin was used.[21] However many variables can be considered when cost analysis is undertaken and may vary between countries and institutions. The costs of blood products as well as aprotinin may vary widely between hospitals.

Finally, our results indicate that the use of one million KIU of aprotinin (ultra-low dose) in adult cardiac surgery is effective in reducing post operative bleeding and transfusion requirements.

Acknowledgments. *This study was supported by the Research Deputy of Tabriz University of Medical Sciences. We are gratefully thank the Research Authorities of the University and Mrs Mahmoodian, Mrs. Sherkati, Mrs. Donboli, Mrs. Salek and especially Mr. Mosharkesh, who is in-charge of the computers of the research center of Madani Heart Hospital.*

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