

# Ultra-Low Dose Aprotinin Effects on Reducing the Need for Blood Transfusion in Cardiac Surgery: A Double Blind Randomized Clinical Trial

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## Abstract

**Objective-** The recommended dose of aprotinin [3-6 million kallikrein inhibitor units (KIU)] reduces the rate of bleeding after open heart surgery and the need for the transfusion of blood products. However, issues have been raised due to the cost and some side effects of aprotinin, and the use of low doses has been noticed. Various studies have demonstrated the effectiveness of two million KIU doses, whereas there is controversy over one million KIU doses. The purpose of this study was to assess the effect of one million KIU aprotinin on bleeding and the need for transfusion after cardiac surgery.

**Methods-** A double-blind randomized clinical trial was conducted on 162 coronary artery bypass grafting (CABG) and valve surgery patients from April 2004 to December 2005. The patients were randomly divided into two groups of 81 individuals. In the aprotinin group, 0.5 million KIU aprotinin was infused before and again during cardiopulmonary bypass (CPB); and in the placebo group, 100 ml normal saline (NS) was infused before and during CPB. The need for the use of fresh frozen plasma (FFP) and packed red blood cells (pRBCs) transfusion during and after surgery and the amount of chest tube drainage at 6, 12 and 24 hours after surgery were measured in the two groups.

**Results-** The mediastinal and pleural drainage at 6 hours after surgery was  $190 \pm 24$  ml in the aprotinin group and  $266 \pm 33$  ml in the placebo group ( $p=0.066$ ). The amount of bleeding at 12 and 24 hours was significantly different between the two groups ( $p=0.048$  and  $p=0.009$ , respectively). The frequency of blood product 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 was significantly lower in the aprotinin group ( $p=0.000$ ) and  $p=0.005$ , respectively). The total amount of blood and products transfusion in the aprotinin group was  $2.56 \pm 0.27$  units and in the placebo group it was  $4.37 \pm 0.27$  units ( $p=0.0001$ ).

**Conclusion-** The results indicate that the use of one million KIU of aprotinin (ultra-low dose) in adult cardiac surgery is effective in reducing postoperative bleeding and transfusion requirements (*Iranian Heart Journal 2007; 8 (4): 11-16*).

**Key words:** cardiac surgery ■ blood transfusion ■ aprotinin

Aprotinin is a natural protease inhibitor that exerts its anti-fibrinolytic effect through the inhibition of plasmin and kallikrein.<sup>1</sup>

It also prevents the activation of contact phase reactants and inhibits platelet damage caused by the increase of plasmin levels and mechanical damage during cardiopulmonary

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bypass (CPB).

The net effect of aprotinin is to inhibit fibrinolysis and consumption of coagulation factors, finally reducing bleeding.<sup>2,3</sup> Through decreasing bleeding after operation, aprotinin reduces the need for transfusion<sup>4</sup> and reduces returns to the operating room to control bleeding and also decreases ICU stay.<sup>5</sup>

Two recommended regimens of aprotinin are as follows:

A) administrating 2 million KIU after anesthesia induction, 2 million KIU into the prime solution of the pump and infusion of half a million units per hour.

B) administrating in the order mentioned with half the dosages.

The 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.<sup>5</sup>

High cost and side effects of the conventional protocol (high dose) aprotinin necessitate an assessment of the effectiveness of lower doses.<sup>6</sup> Many reports have used prophylactic doses of 2 million KIU aprotinin and shown its effect on reducing postoperative bleeding,<sup>7-11</sup> but there are different results in the studies done on administering one million units. While some studies have shown the effectiveness of the drug on reducing bleeding,<sup>12-16</sup> the mentioned dosage has not been effective in some cases.<sup>17</sup>

## Methods

After the approval of the study by the Ethics Committee of the Research Deputy of Tabriz University of Medical Sciences, and obtaining written informed consent from all the patients, 162 patients who underwent elective surgery for coronary artery bypass grafting (CABG) and valve surgery under CPB between April 2004 and December 2005 were divided randomly into two groups of 81 patients: the aprotinin group received one million KIU aprotinin and the placebo group received

normal saline in a similar manner. Randomization was done by forming "randomly permuted blocks" in online software accessible on URL: (<http://www.randomization.com>.)

Patients requiring redo operations and the patients with known coagulopathies or patients receiving fibrinolytic drugs, heparin and antiplatelets drugs (except aspirin) before surgery were excluded from the study.

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

## 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. If there was no hypotension and skin rash, the main dosage of the drug was infused as 500,000 KIU of aprotinin which had been diluted in 100 milliliter of saline in 10-15 minutes and another 500,000 units were added to the priming solution of CPB.

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. The patients, anesthesiologists, surgeons, perfusionists and also the nurses in the ICU were unaware of the allocation (drug or placebo) of the patients.

## Surgical, anticoagulation, and transfusion protocols

Although harvesting the LIMA and saphenous vein or suturing the atrium wall in valve procedures were done 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 cardioplegia were the same in all of the patients.

All the patients received 3 mg/kg (300 units/kg) unfractionated heparin two minutes

before the placement of arterial and venous cannulae; and every hour, one mg/kg heparin was added to the pump. Two minutes after injecting heparin and when ACT reached  $\geq 480$  seconds, the patients were placed on CPB. 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 maintained in the range of 120-180 seconds via the administration of extra protamine as needed. The transfusion protocol in the patients was as follows: as a routine in patients whose hematocrit was higher than 40%, after the induction of anesthesia, one unit (450 ml) of blood was taken from the patient (acute normovolemic hemodilution) and 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 7.0 g/dl and postoperatively if less than 8.0 g/dl (and if less than 10 g/dl in hemodynamically unstable patients). Those patients who had bleeding more than 1000 ml in the first six hours after operation were returned to the operating room to find and control any source of bleeding.

### Sampling method, data collection and analysis

Demographic data, heparin doses, activated clotting times, untoward reactions, blood products transfused intraoperatively and postoperatively, and mediastinal tube drainage at 6, 12 and 24 hours as well as postoperative complications such as plasma creatinine rise more than 50%, myocardial infarction and hemodynamic instability were recorded on a study protocol data sheet for each patient by two independent groups. The qualitative data were statistically analyzed with student's t-test and chi-square, respectively. A *p* value of 0.05 or less was considered significant.

The collected data were statistically analyzed with SPSS 12.0 software.

## Results

Demographic data and preoperative variables are shown in Table I. The two groups were similar for age, gender, body surface area, diabetes mellitus and relevant laboratory tests. There were no differences between the groups regarding the type of operation, number of grafts in CABG, CPB and operation time (Table II).

There was a significant difference between the lowest CPB temperature ( $p=0.003$ ), but values were in the expected range (aprotinin group= $28.9\pm 2.9^{\circ}\text{C}$  and placebo group= $27.7\pm 1.8^{\circ}\text{C}$ ).

**Table I. Demographic variables in the two groups**

Variables	Aprotinin	Placebo	<i>p</i> value
Age (years)	52.6 $\pm$ 13.8*	54.1 $\pm$ 11.4	0.457
Sex (F/M)	40/60	39/61	1.000
Weight (kg)	67.5 $\pm$ 12.2	69.1 $\pm$ 15.8	0.481
Body surface area (m <sup>2</sup> )	1.72 $\pm$ 0.21	1.75 $\pm$ 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 $\pm$ 11.1	48.9 $\pm$ 9.4	0.403
Hematocrit (%)	42.8 $\pm$ 7.4	42.8 $\pm$ 5.7	0.963
Blood urea concentration (mg/dl)	16.3 $\pm$ 5.2	16.5 $\pm$ 8.3	0.840
Creatinine (mg/dl)	1.20 $\pm$ 1.12	1.44 $\pm$ 1.15	0.425
PT (sec) <sup>+</sup>	12.6 $\pm$ 0.8	13.3 $\pm$ 4.3	0.206
PTT (sec) <sup>++</sup>	40.1 $\pm$ 10.1	38.1 $\pm$ 10	0.248
Preop aspirin use	38%	43%	0.594
Time of aspirin cease (day)	1.9 $\pm$ 1.6	1.8 $\pm$ 0.4	0.454

\* Values are shown as mean  $\pm$  SD or percent.

+PT=prothrombin time; ++PTT=partial thromboplastin time

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 III).

**Table II. Comparison of operative variables in the two groups**

Variables	Aprotinin	Placebo	<i>p</i> value
Type of surgery CABG	47(60%)*	59 (78%)	0.189
Valve surgery	25 (30.9%)	13 (16.3%)	
Number of grafts	2.9 ± 0.43	3±0.89	0.558
Aortic X-clamp time (min)	60 ± 20	58±24	0.593
CPB time (min)	103 ± 26	100±36	0.621
Least temp. during CPB (°C)	27.7 ± 1.8	28.9±2.9	0.003

X-clamp: cross clamp; CPB: cardiopulmonary bypass

\* Values are shown as mean± SD or number (percentage)

**Table III. Mediastinal drainage and transfusion requirements in the two groups**

Variables	Aprotinin	Placebo	<i>p</i> value
Drainage at 6 hrs (ml)	190±24*	266±33	0.066
Drainage at 12 hrs (ml)	360±37	478±46	0.048
Drainage at 24 hrs (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%	0.31
FFP	52%	69%	0.043
Total transfusions	68%	75%	0.02

\*PRBCs: packed red blood cells

++FFP: fresh frozen plasma

\*Values are shown as mean± SD or number (percentage)

There was no difference between the groups in the number of units of packed red blood cells (pRBCs) and FFP given intraoperatively, but the number of units of blood and FFP transfused postoperatively in the ICU was significantly less in the aprotinin group ( $p=0.003$  and  $p=0.001$ , respectively). Table III also shows the proportion of patients receiving pRBCs and FFP, which was also significantly less in the aprotinin group. Postoperative mechanical ventilation and ICU stay was the same in both groups. Also there were no differences in postoperative complications (Table IV).

**Table IV. Prevalence of postoperative complications in the two groups**

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

SBP: Systolic blood pressure \* Values are shown as mean± SD or percentage

The quantitative data in the total cost of pRBCs and FFP transfusion in both groups and cost of aprotinin in the aprotinin group are outlined in Table V. The total cost of blood products with regard to the cost of aprotinin was not significantly different between the two groups.

**Table V. Cost of aprotinin and blood products transfusions**

Variable	Aprotinin	Placebo	<i>p</i> value
Drug / patient cost *	\$47.03	0	-
pRBCs <sup>+</sup> / patient cost *	2.78\$	7.29\$	0.001
FFP <sup>++</sup> / patient cost *	13.7\$	29.42\$	0.003
Total transfusion cost (with regarding drug cost)	63.51\$	59.11\$	0.493

\* Cost of drug or blood product used in each patient.

+ pRBCs: packed red blood cells

++ FFP: fresh frozen plasma

## Discussion

Although the chest tube drainage at 12 and 24 hours postoperatively was significantly reduced in aprotinin-treated patients, the important reduction in the proportion of patients transfused and number of units transfused is 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 physiologic basis. The anti-fibrinolytic effect of aprotinin is thought to result from the direct inhibition of plasmin, whereas inhibition of kallikrein is involved to a lesser extent or is possibly absent at this dose. Although aprotinin plasma concentrations 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,<sup>18</sup> like that in our study. Hayashida et al.<sup>19</sup> showed when a minimal dose of aprotinin (one million KIU in the pump prime) was used, increased levels of  $\alpha$ 2-plasmin inhibitor, plasminogen activator-1, and decreased levels of D-dimer were measured after CPB as compared to a control group, thus supporting an anti-fibrinolytic effect.<sup>19</sup>

Some investigators have suggested the safety and effectiveness of aprotinin in full dose therapy. The benefit of aprotinin-induced reduction in transfusion requirement and transfusion-associated morbidity and mortality far outweighs 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.<sup>20</sup>

In another prospective, non-blinded 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.<sup>21</sup>

However, many variables can be considered when cost analysis is undertaken and this analysis 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

postoperative bleeding and transfusion requirements.

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