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Original Article

Low dose aprotinin increases mortality and morbidity in coronary artery bypass surgery*

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Abstract

BACKGROUND: The low dose aprotinin consistently reduces blood and transfusion requirement in adults during cardiac surgical procedures but its effectiveness in some ethnical groups were debated and controversy about its effect on mortality and morbidity precludes its routine use. This study was designated to determine whether a low dose of aprotinin causes more mortality and morbidity when used after coronary artery bypass grafting (CABG) surgery.

METHODS: In a clinical trial study, 380 patients in placebo and 273 patients in aprotinin group were enrolled. A test dose before skin incision and 2 million kallikrein inactivation units (KIU) during initiation of cardiopulmonary bypass (CPB) were given to patients. Differences in quantity of blood transfusion, morbidity and mortality were analyzed. Multivariable analysis was performed to determine risk factors for mortality.

RESULTS: Decreased blood product transfusions and increased rate of morbidity were found in the aprotinin group. Independent predictors for increased number of transfusion were aspirin continued before operation and small body mass index (BMI) but there was a significant difference in mortality and morbidity between two groups.

CONCLUSIONS: In patients undergoing CABG procedure, low dose aprotinin is effective in attenuating post bypass coagulopathy and decreasing blood product use, but it increases morbidity.

KEYWORDS: Aprotinin, Coronary Artery Bypass Graft, Blood Transfusion, Mortality.

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Cardiovascular surgery is associated with a significant consumption of allogeneic blood products often as a result of acquired hemostatic defect and incomplete hemostasis. Aprotinin has been repeatedly shown to reduce blood loss and transfusion requirements after cardiopulmonary bypass (CPB) in adults by multiple mechanisms, which include inhibition of fibrinolysis and preservation of platelet function through its antagonism of the actions of plasmin and kallikrein. Its effect are especially notable in patients considered at increased risk of bleeding such as those receiving aspirin, those with infective endocarditis, and those undergoing repeat sternotomy. Studies about the effects of aprotinin in some ethnical groups have not demonstrated consistent results, with improved hemostasis and reduced transfusion in some race and increased morbidity and mortality noted in some others ethnical groups.[1-3] Reasons for these inconsistencies could involve

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ethnic, patient selection, complexity of coagulopathies after CPB, and variability of dosage regimens. Pharmacological agents to reduce bleeding have gained much interest, since they are readily available, easy to administer, can be used prophylactically, do not require the use of costly equipment and appear to be very efficacious. The perioperative uses of aprotinin have gained acceptance around the world for prophylactic reduction of allogeneic blood transfusion in operation.[4-10] Mangano and associates found the use of aprotinin in patients undergoing coronary artery bypass grafting (CABG) to be associated with higher mortality and increased risk of renal and cardiac events in both short and long term studies.[5] Fergusson and associates compared aprotinin with two other lysine analogues in high risk cardiac surgery. The aprotinin group had higher hospital mortality than two other groups.[10] This finding resulted in controversies in aprotinin use in cardiac surgery all over the world. However, several problems have to be addressed for the clinical safety of aprotinin. Several studies have shown that response to aprotinin is related to internal fibrinolysis system of the patients.

The antifibrinolytic action of the aprotinin is based on different mechanisms. Aprotinin slows fibrinolysis and reduces factor VIIa formation by inhibiting plasmin and kallikrein respectively. This different pathway of aprotinin action may be fully effective in some ethnical group or partially effective in other races. The aprotinin inhibits these pathways by multiple enzymes and receptors and deficiency of these receptors may be related to ethnic and race, as there are ethnical variability in blood coagulation and fibrinolysis system in response to other drugs.[11, 12] To address this question, we performed a study in a single center in Kurdish population in Iran (Kermanshah, Kurdistan and Ilam).

Methods

This clinical trial study was approved by research ethics committee of Kermanshah University of Medical Sciences in September 2007. Informed consent was obtained before enrolling each patient in the study. Between September 2007 and September 2008, 653 patients scheduled to undergo first time CABG and were randomized in a double blinded clinical trial to receive low dose aprotinin (Hungary Corporation), 2 million KIU (Kallikrein Inactivator Units) or placebo. Aprotinin was presented in clear vials each containing 100000 KIU in 20 ml 0.9 % saline solution.[13,14] One of the anesthesiologist that not engaged in the patient care, made up the entire test solution and the trial drug was provided this anesthesiologist and was supplied in identical looking 500 ml bottles. 500 ml bags of sterile 0.9 % saline solution had a volume discarded (400 ml) and replaced with the same volume of test solution (400 ml aprotinin) so that all bags contained equal volumes (500 ml). These bottles were provided by anesthesiologist with sealed envelopes with the randomization codes to enable an individual patient's code to be broken in time of operation. With a computer generated random number, patients were consecutively allocated to one of the following two groups. Group A (n = 380), received 0.9% saline as placebo that was added to the pump prime. Group B (n=273), received 2000000 KIU aprotinin into the pump prime. These patients received a bag containing 400 ml aprotinin and 100 ml 0.9 saline solution that were added to the pump prime. The patients were selected according to similar risk of bleeding: patients undergoing CABG with left internal mammary artery (Lima) in combination with saphenous vein. The patients with right internal mammary (RIMA) graft harvesting were excluded from the study (risk of bleeding is higher in RIMA harvesting than saphenous vein graft). Other exclusion criteria were recent use of antiplatelet agents other than aspirin, allergy to aprotinin, history of sternotomy, congenital bleeding disorder. The patients were also excluded if they had recent thrombolytic therapy (less than 1 day) or heparin (less than 4 hours) or warfarin (less than 3 days) preoperatively. Other exclusion criteria were left ventricular ejection fraction less than 25%, impaired renal function (serum creatinine more than 2 mg/dl), combined valvular and CABG operation and diffuse and small coronary artery disease.

The conduct of the operation was performed according to technique of routine hospital anesthesia and we used a membrane oxygenator and cardiotomy suction for each patient. Bovine heparin was administered as a loading dose (300 IU/kg) and 20000 IU was added to the pump prime. Activated clotting time was maintained at more than 400 seconds before and after heparinization. Cell saver system and auto transfusion were not used. Homologous red blood cells were transfused during CPB if the patients hemoglobin was less than 7.0 g/dl and postoperatively if less than 8.0 g/dl or if there was excessive mediastinal bleeding. If the patient's condition warranted, platelets and fresh frozen plasma and cryoprecipitate were transfused. Variables such as age, weight, body mass index, blood products transfused intra operatively or post operatively and mediastinal tube drainage at 6 and 12 hours were recorded on a study protocol data sheet for each patient.

Electrocardiograms (ECG) changes between preoperative and postoperative period (performed on day one) with other's variable such as hemodynamic instability, cerebrovascular accident, renal and gastrointestinal complication and other complication were noted on the data sheet.

Preoperative and postoperative hemoglobin, creatinine phosphokinase myocardial band (CPK MB), troponin, and creatinine tests were also recorded. Evaluation of efficacy included the quantity of mediastinal tube drainage at 6 and 12 hours, incidence of reexploration for non surgical bleeding, proportion of patients requiring transfusion and comparison of the total number of blood units and each type of blood product (packed red cells, fresh frozen plasma, and platelet) transfused during the operation. Packed red blood cell concentrates were transfused when the hematocrit/hemoglobin (Hct/Hb) value was less than 0.20/7 g/dl. In the postoperative intensive care unit (ICU) the threshold for blood transfusion was a Hct/Hb less than 0.25/8 g/dl. The indication for postoperative platelets, fresh frozen plasma or cryoprecipitate transfusion was the presence of active bleeding (more than 200 ml/h) and a laboratory demonstrated coagulation defect (platelet count less than 80×10^9, PT or PTT more than 1.5 × control value or fibrinogen level less than 1 g/l. Diagnosis of clinically myocardial infarction was made on evaluation of ECG changes and increase in cardiac isoensymes or troponin. In-hospital mortality was defined as death from any cause after the CABG during hospitalization. Renal dysfunction required a postoperative serum creatinine level of more than 1.5 mg/dl with an increase over in preoperative baseline of at least 0.5 mg/dl. Cerebrovascular incidents included new onset stroke and coma.

Data analysis

Data were recorded by two dedicated nurses. The patients requiring reexploration for bleeding were excluded only if a documented site amenable to surgical repair was located. Categorical and continues variables were analyzed by χ^2 and student's t-test, respectively. Two groups of patients were compared to determine the effect of aspirin on the proportion of patients transfused and units of blood products transfused in each treatment group. The aspirin group was defined as those patients who received aspirin 6 days before operation and no-aspirin group included those patients who did not receive aspirin 6 days before operation. Multivariable logistic regression was performed to determine predictors of transfusion volume. Statistical test were performed using the SPSS software version 11.5 and considered significant if p value was less than 0.05.

Results

Seven hundred patients were included in the study. Twelve of those patients in the aprotinin group who were explored and found to have surgical bleeding were excluded from analysis. Fifteen patients were also excluded due to diffuse coronary artery disease, small coronary artery disease, antiplatelet agents other than aspirin, combined valvular and CABG operation, left ventricular ejection fraction (EF) less than 25%, impaired renal function, history of sternotomy, right internal mammary artery (RIMA) use and non-Kurdish patients in aprotinin group. Twenty patients were excluded from placebo group due to diffuse and small coronary disease, EF ≤ 25%, combined valvular and CABG operation and surgical bleeding (Diagram 1).

150 patients of each group were on aspirin preoperatively. Aprotinin and placebo groups were similar for age, weight, body surface area, gender and rate of urgent cases per group. There was no difference between groups in number of units of blood given on CPB, pump time and hemoglobin level (Table 1). Chest tubes drainage at 6 hours postoperatively was significantly less in the aprotinin treated group for the total population and significantly less in the aspirin and non aspirin group too. These differences in drainage remained significant at 12 hours (Table 2).

Table 3 shows the mean number of blood products transfusion (packed red blood cells, fresh frozen plasma, platelets). The proportion of patients with transfusion was significantly

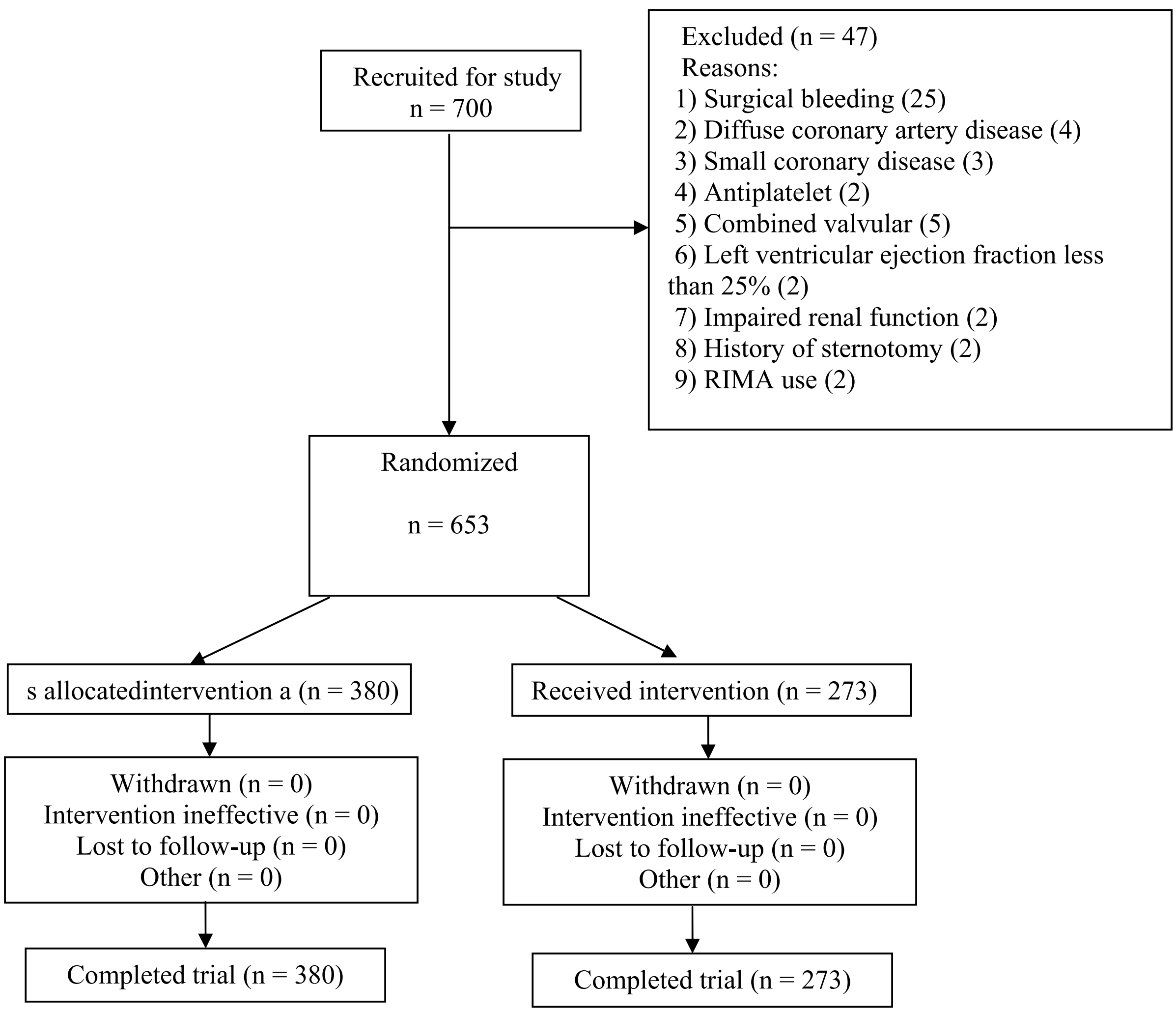

Diagram 1. Profile of the study

Table1. Preoperative factors in the two study groups

Variables	Aprotinin (n=273)	Placebo (n=380)	P -value
Age (year, mean with range)	60.8 (34-76)	63.2 (38-79)	> 0.05
Gender (% female)	30%	28%	> 0.05
Emergency case (%)	25%	27%	> 0.05
Pump time (minutes)	82.2 ± 2.1	85 ± 3.2	> 0.05
Preoperative hemoglobin (g/dl)	14.5 ± 1.1	14.5 ± 1.2	> 0.05

less in the aprotinin treated group when compared to placebo group. The same was true for the aspirin and no aspirin groups when the aprotinin group were compared with the placebo treated patients. The proportion of patients receiving platelets and fresh frozen plasma were significantly less in all aprotinin treated groups. Independent predictors for both risk of transfusion and number of transfusion were small body mass index and aspirin administered preoperatively within 6 days of surgery. Preoperative hemoglobin below 12 g/dl and age more than 70 years predicted a greater number of transfusions (Table 4). Treatment with placebo was found to be a statistically significant predictor of transfusion and greater number of transfusion.

Morbidity was not similar for each group. The rate of re-exploration for mediastinal hemorrhage (3% in aprotinin vs. 7% in placebo group, $p < 0.05$), cerebrovascular accident (1.1 vs. 4%), MI (6% in aprotinin vs. 3% in placebo group) and rate of increased creatinine level of more than 2 mg/dl (aprotinin 7% vs. 2 % placebo), mortality and intra aortic balloon pump using was different between two groups. Cardiac enzymes, CPKMB, and troponin were different between two groups when compared for MI (Table 5).

Discussion

Most of the previous studies used a high dose of aprotinin (6×10^6 KIU). However, by the use of a much lower dose of aprotinin rather than full dose, many investigators intended to reduce the cost per patient, maintain efficacy and extend the use of aprotinin to all patients needing cardiac surgery not just high risk patients such as those need repeated operation or complex procedures.[15]

Although the chest tube drainage was significantly reduced in aprotinin group patients, the important reduction in proportion of patients transfused and number of units transfused did not far outweigh the extremely high risk of mortality and morbidity in postoperative period. However, transfusion reduction is a more sensitive indicator of the effect of aprotinin. This would be especially true in patients on aspirin within 6 days before operation and in small patients.

Although safety was difficult to prove in previous study,[4-6] we showed in this study that aprotinin at this dose had a higher morbidity

Table 2. Chest tube drainage in the two study groups

Drainage	Aprotinin	Placebo	P -value
6 hours drainage (ml)			
Total	332 ± 32	536 ± 31	< 0.05
Aspirin group	434 ± 30	625 ± 41	< 0.05
No Aspirin group	341 ± 28	442 ± 31	< 0.05
12 hours drainage (ml)			
Total	459 ± 41	763 ± 31	< 0.05
Aspirin group	550 ± 31	830 ± 45	< 0.05
NO Aspirin group	450 ± 33	632 ± 28	< 0.05

Table 3. Transfusion requirements in the two groups of study

Variables	Aprotinin	Placebo	P -value
Total	2.5 ± 0.5	6.4 ± 0.66	< 0.05
Aspirin	3.2 ± 0.1	6.45 ± 0.6	< 0.05
No Aspirin	1.5 ± 0.33	4.5 ± 0.44	< 0.05
FFP			
Total	0.2 ± 0.1	4.2 ± 0.2	< 0.05
Aspirin	0.4 ± 0.2	3.5 ± 0.4	< 0.05
No Aspirin	0.1 ± 0.1	2.5 ± 0.5	< 0.05
Platelet			
Total	0.35 ± 0.2	1.1 ± 0.2	< 0.05
Aspirin	1.1 ± 0.5	2.1 ± 0.5	< 0.05
No Aspirin	0.5 ± 0.2/1	1.5 ± 0.1	< 0.05

and mortality. The antifibrinlytic effect of aprotinin is thought to result from the direct inhibition of plasmin, and in this dose, it also inhibits kallikrein, and kallikrein is involved to great extent and this inhibition reduces graft patency.[16] Hayashida and colleagues showed that when low dose of aprotinin was used, increased levels of Alfa 2 plasmin inhibitor, plasminogen activator and decreased levels of D-Dimmer were measured after CPB as compared to control, thus supporting antifibrinolytic not thrombogenic effect.[17] Reasons for these inconsistencies could involve ethnic, patient selection, increased complexity of coagulopathies after CPB, and variability of dosage regimens. The unsimilarity in rate of MI and increase in creatinine level between groups dose not support the safety of this aprotinin dose (Table 5). Although substantial increase in creatinine was reported in aprotinin treated patients; but occurrence of renal failure itself was not different between the groups. A similar trend was reported in another well known clinical trial and the evidences linking aprotinin to these side effects were strong.[18] The other previous study attempting to address systematically the issue of mortality found aprotinin to be associated with reduced mortality and slightly higher risk of myocardial infarction; however, those analysis unlike our study included a mixture of cardiac surgical procedures (mitral valve, aortic valve, CABG). In addition, others have indicated concerns about inaccuracies in patient numbers, discrepancies in odds ratios and inappropriate application of inclusion criteria, causing doubt on conclusions draw from these previous systematic analysis.[19-21] A report by Mangano et al. suggested that antifibrinolytic therapy, including aprotinin, increased mortality among patients undergoing CABG. The study used data from studies in which treatment groups assignment was described as randomized or controlled, thus treatment bias did not affect the results in this observational study.[5] In retrospective analysis of cardiac surgery population at risk for stroke, Ronald and Dunning observed a significant decrease in the occurrence of stroke among patients administrated low dose aprotinin relative to placebo group.[3] our investigation provided additional data describing the cerebrovascular effect of aprotinin. Other studies have shown high dose but not low dose aprotinin to

Table 4. Factors associated with risk of postoperative transfusion by logistic regression analysis

Variables	Odd ratio (95% CI)	P -value
Preoperative hemoglobin < 13	2.5 (1-4)	< 0.05
Age > 70 year	1.5 (0.6-2.5)	< 0.05
Aspirin	2.5 (1.5-4.5)	< 0.05
No Aspirin	5 (2.1-8.5)	< 0.05

Table 5. Comparison of postoperative complication between the two groups

Variables	Aprotinin (n = 273)	Placebo (n = 380)	P- value
Postoperative myocardial infarction	6%	3%	< 0.05
Postoperative cerebrovascular accident	1.1%	4%	< 0.05
Postoperative creatinine raising	7%	2%	< 0.05
Mortality	6%	2%	< 0.05
Intra-aortic balloon pump using	8%	3%	< 0.05

reduce the risk of stroke.[22]

Unlike previous studies[9,22-28] we showed that low dose aprotinin increased risk of post operative mortality, MI and graft thrombosis. The benefit of aprotinin-induced reduction in transfusion requirement and transfusion associated morbidity and mortality did not far outweigh the extremely high risk of mortality and morbidity, associated with low dose aprotinin administrations, as Westby pointed out in an editorial "Occluded grafts are a high price to pay for an average blood saving of 250 ml in the postoperative period".[15, 29-38] We are obsessed with use of platelet inhibitors to promote graft patency, yet in the operation room, with the onslaught of surgically induced thrombin formation, we are giving aprotinin that promote platelet adhesion and aggregation. A balance must be reached with these two opposing goals.[13, 14] Routine use of these hemostatic agents may lead to an increase in adverse events. One cannot discuss the benefit of this drug without discussing their potential risks. It would seem logical that along with increased efficacy there may be increased thrombotic risk. A more logical approach may be performed to reserve these pharmacologic therapies to Kurdish patients who are at high risk for transfusion.

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Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
FS, GM, AP, SD conducted the study and drafted the paper. HD helped in preparing and editing the manuscript.

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