Evaluation and Comparison of Use of low-Dose Aprotinin and Tranexamic Acid in CABG: A Double–Blind, Prospective, Randomized Study of 150 Patients

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Abstract

Background- Cardiovascular operations are associated with an inherent bleeding tendency that sometime leads to severe bleeding and transfusion requirement. Pharmacologic intervention to minimize post-bypass bleeding and blood product transfusions has received increasing attention for both medical and economic perspectives.

Methods- In this double-blind, randomized, placebo-controlled clinical trial, three groups of patients, each comprising 50 patients undergoing on-pump coronary artery bypass grafting surgery (CABG) were blindly randomized to receive either low aprotinin, tranexamic acid, or placebo; the results were subsequently evaluated and compared between the groups.

Results- The following variables were similar in the groups, and there were no statistically significant differences in these variables: age (p value=0.308), sex (p value=0.973), hyperlipidemia (p value=0.720), hypertension (p value=0.786), smoking (p value=0.72), and diabetes (p value=0.960). The amounts of drainage from chest tubes were less in the aprotinin and tranexamic acid groups compared to the placebo group, and this was statistically significant (p value<0.001). There was no statistically significant difference in need for reoperation for bleeding between the three groups (p value=0.998). Complications following surgery in the three groups were statistically the same and not significantly different (Table below). All the complications had a good course, and all the patients were discharged from hospital uneventfully. There was no mortality in any group.

Conclusions- Low-dose aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement in CABG without importantly increasing mortality and morbidity
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Bleeding after cardiopulmonary bypass (CPB) is still a concern for coronary artery bypass grafting surgery (CABG) and an important factor affecting the morbidity and mortality in patients undergoing cardiac operations. Between 30% and 70% of open heart patients will require blood product transfusion.[1] Although small, the risk of transmitting hepatitis, human immunodeficiency virus, cytomegalovirus, or other infectious agents remains a concern.

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activity being the major contributors to the process.[2] Aprotinin, a serine protease inhibitor from the

bovine lung, and the synthetic antifibrinolytic drugs, tranexamic acid (TA) and ϵ-amino-N-caproic acid (EACA) given before CPB, have been shown to reduce mediastinal bleeding postoperatively.[3-7]

The antifibrinolytic drugs have been demonstrated to be equally effective as aprotinin in reducing bleeding and the need for allogeneic blood products, both in high-risk patients and routine patient populations undergoing cardiac operastions.[8]
Because antifibrinolytic drugs are much cheaper than aprotinin and are equally effective in reducing bleeding during cardiac operations and also given the recent reports on the adverse effect of aprotinin on graft patency and survival,[9,10] we studied a homogeneous patient population undergoing elective CABG to estimate the influence of low-dose aprotinin and TA on perioperative bleeding, need for allogeneic transfusion, and hemostasis.

Material and Methods

After institutional approval had been obtained for this double-blind, clinical, randomized trial, all patients scheduled for CABG in our center between 21 March, 2008 and 21 March 2009 were included in this study. The inclusion criteria were on-pump CABG and patients' acceptance, and the exclusion criteria were a history of hemorrhagic tendency and blood dyscrasia, history of plavix usage, known hepatic, renal and metabolic diseases, use of other anti-coagulation drugs like comadin for valvular disease and arrhythmias and streptokinase, emergency surgery, rheumatic heart disease, known allergy to aprotinin or transamine and prohibition for their use such as acquired visual defects and retinal disease, subarachnoid hemorrhage, disseminated intravascular coagulation, gall bladder disease, leukemia, embolization, and vein thrombosis.
The patients' demographic and clinical data such as age, sex, history of cigarette smoking, and other concomitant diseases were collected (Table I).

Table 1.Patient Demographics

Variable	Transamine	Aprotinin	Placebo	sum	P value
Age(y)	54.6±10.4	53.6±9.1	54.2±9.7	54.5±9.4	0.973
Male%	41(82%)	40(80%)	35(70%)	116(77%)	0.308
Female%	9(18%)	10(20%)	15(30%)	34(23%)	

All the patients received 300 IU /Kg of bovine lung heparin. Additional heparin was administered for activated clotting times less than 400 seconds. The activated clotting time was monitored every thirty minutes. After having given written informed consent, all the patients were put in three groups randomly. In group A (aprotinin) after a test dose, 1 million units of aprotinin was added to the pump prime solution; in group B (transamine), 1 gr of transamine was added to the pump prime solution and another 1 gr was used intravenously after discontinuation of the pump; and in group C (control), 250 cc of normal saline was used as a placebo after the induction of anesthesia. Cardiac

surgeons and cardiac surgery residents knew nothing about the groups. Heparin was reversed with protamine sulfate after the removal of all the cannulae. Shed mediastinal and plural blood was estimated after six, twelve, and twenty-four hours and the data were stored in a computer. Packed red cells were transfused for a hematocrit concentration under 30%, and fresh frozen plasma was transfused based on abnormal prothrombin time and the rate of bleeding. Platelet transfusion threshold was a platelet count of 1000000 or less and bleeding tendency with one or more of the followings:

post-operative complications such as postoperative myocardial infarction (based on cardiac enzyme rise, ECG change, and ejection fraction change estimated by echocardiography), neurological complications (estimated by clinical examination and CT-Scanning), re-do operations for surgical bleeding and pericardial effusion, kidney complications (rising of serum creatinine and low urinary output under 0.5 cc per minute), and other complications.

The Data were expressed as mean± standard deviation. A comparison of the parametric data was done using an unpaired Student *t*-test for the quantitative data and K2 for the qualitative data. A p value < 0.05 was considered statistically significant.

Results

The patients in the three groups were compared. The distribution of sex (p value= 0.308), age (p value= 0.973), cigarette smoking (p value= 0.720), hyperlipidemia (p value= 0.707), diabetes (p value= 0.960), and hypertension (p value= 0.786) was the same in all the groups (Tables I, II), and there was no important statistical difference between these variables.

Table II. Risk factors

Variable	Transamine	Aprotinin	Placebo	Sum	P value
Cigarette smoking	31 (62%)	27 (54%)	29 (58%)	87 (59%)	0.720
Hyperlipidemia	16 (32%)	20 (40%)	18 (36%)	54 (36%)	0.707
Hypertension	25 (50%)	28 (56%)	25 (50%)	78 (52%)	0.786
Diabetes mellitus	40 (80%)	40 (80%)	39 (78%)	119 (79%)	0.960

The amount of blood drainage from chest and mediastinal drains was significantly less in the aprotinin and transamine groups compared to the placebo group, and this was statistically significant (p value <0.001). Repeated measurement analysis of variances was used in the following manner (Table III):

Table III. Amount of bleeding

Variable	Transamine	Aprotinin	Placebo	P value
Bleeding after 6h	115±88.7	109±86.7	240±182.9	0.001
Bleeding after 12h	219±119.9	223±134.1	393±280.1	0.001
Bleeding after 24h	355±178.7	382±217.7	540±346.9	0.001
Bleeding after 48h	432±210.3	469±237.2	649±365.3	0.001

Only 2 patients needed reoperation for bleeding: one in group B and one in group C; both of them were surgical bleeding and there was no statistically important difference in terms of need for reoperation between the three groups (p value 0.998) (Table IV).
Other complications after surgery in the three groups were statistically the same and not importantly different between the three groups (Table IV).
There were 8 (8%) cases of postoperative myocardial infarction (based on cardiac enzyme rise, ECG change, and ejection fraction change estimate by echocardiography: 4 in group C, 2 in group A, and 2 in group B (p value 0.730) (Table IV).

Table IV. Postoperative complications

Variable	Transamine	Aprotinin	Placebo
Myocardial infarction	2(4%)	2(4%)	4(8%)
Pericardial effusion	0	0	2(4%)
Neurological complications	0	1(2%)	1(2%)
Renal complications	2(4%)	1(2%)	1(2%)
Reoperation for bleeding	1(2%)	0	1(2%)
Mortality	0	0	0

Two patients in group C underwent redo surgery for pericardial effusion. Additionally, 2 patients (one in the placebo group and one in the aprotinin group) had neurological complications. Renal complications were 2 (4%) in the transamine group and one in each of the other groups; all the neurological and renal complications were reversed before the patients were discharged from hospital. There was no mortality in the three groups, and all the complications had a good course and all the patients were discharged uneventfully from hospital (Table IV).
In the transamine group, 35 (70%) patients did not need blood transfusion, 4 patients needed one unit of packed cells, and 1 patient received six units of packed cells; in the aprotinin group, 19 (38%) patients received one unit of packed cells; and in the placebo group, 23 (46%) patients received one unit of packed cells, 5 (10%) received two units, and 1 received four units.

Discussion

A meta-analysis of multiple studies has shown that aprotinin and antifibrinolytic are capable of reducing mediastinal chest tube drainage by 30% versus placebo.[11] Although delivery protocols are uniform for aprotinin, they still vary widely for TA and EACA. Whereas the effect of TA and aprotinin on reducing blood loss after cardiac operation is clear,[12] a meta-analysis of randomized studies of EACA versus placebo could not show a significant effect in reducing transfusion requirements.[13] Tranexamic acid has been shown to be as effective as aprotinin in reducing coagulopathy-caused bleeding after CPB and it is cheaper than aprotinin.[12]

TA is emerging as the available drug of choice to reduce coagulopathy-caused bleeding, and there is currently concern regarding the adverse effect of aprotinin on the renal system and final outcome.[10] We, therefore, designed the present study to glean knowledge about the benefit of using low-dose TA and low-dose aprotinin with respect to reducing blood loss and allogeneic transfusion and its effect on various coagulation factors.

In a low-risk patient population, TA was shown to decrease mediastinal bleeding after cardiac operation as early as 1990.[14] A similar result was found in studies by Karski and associates from Toronto.[15] The first significant study of a uniform patient population undergoing coronary operation was reported by Roussou and colleagues.[16] They retrospectively studied 415 patients undergoing CABG excluding emergency and redo operations. The first 209 patients were operated on without TA, and the subsequent 206 patients with a 2-g bolus of TA followed by 8-g during the procedure. Chest tube drainage in the control group was 1114 ml versus 803 mL in the study group. A double-blind, randomized, placebo-controlled study was reported from the Brook-Army Medical Center[17] on patients undergoing primary coronary artery operation. The dose of TA was 15mg/Kg started before CPB and 1 mg/Kg continued for five hours. The bleeding was reduced from 1202 mL in the placebo group versus 1020 mL in the TA group. Since then multiple studies have shown the efficacy of TA in prospective studies comparing patients receiving aprotinin or EACA.[9,18] These studies mostly included patient populations that were at high risk for bleeding mixed with those of primary myocardial revascularization. The few studies since 1998 with a placebo group with primary myocardial revascularization used high-dose TA or administered TA well into the postoperative period. With improved CPB and surgical techniques, blood loss is small after routine primary CABG even without the use of antifibrinolytics[18]. Therefore, it is a valid question to ask whether the addition of low-dose TA or aprotinin, as was the case in our study, is beneficial. In light of our findings, TA and aprotinin both are beneficial in this setting. Although the control patients only bled 540mL within a twenty-four hour period, the use of TA and aprotinin significantly reduced this even further to 355 and 380 mL.

Conclusion

Both aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement even in low doses in CABG without importantly increasing mortality and morbidity.

Conflicts of interest

None of the authors has any conflict of interest.

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