Evaluation and Comparison of Using Low Dose Aprotinin and Tranexamic Acid in CABGS: A Double –Blinded, Prospective, Randomized Study of 150 Patients

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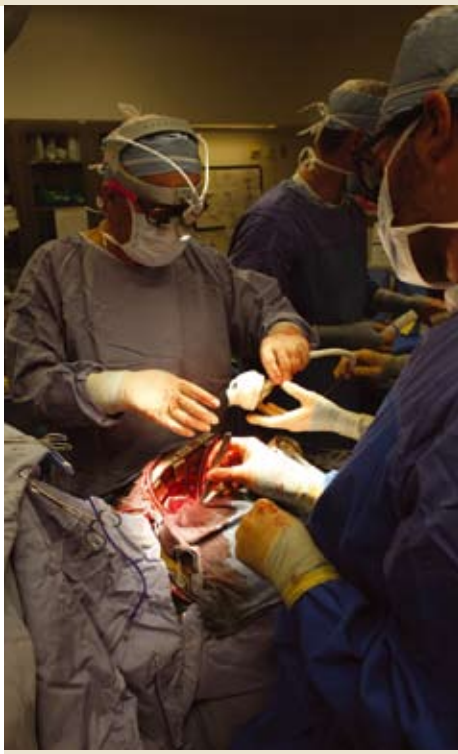

Abstract

Background. Cardiovascular operations are associated with an inherented bleeding tendency that some time 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 attention.

Methods: In this double-blind randomized placebo-controlled clinical trial, three groups of patients undergoing on-pump Coronary Artery Bypass Surgery(CABG), each group composed of 50 patients, were blindly randomized to receiving either low aprotinin, tranexamic acid or placebo, and then results were evaluated and compared in each group.

Results: The following variables were similar in groups and there were no statistically significant differences in these variables: Age(P=0.308), Sex(P=0.973), ypelipidemia(P=0.720),Hypertention(P=0.786),Smoking(P=0.72),Diabetes(P=0.960). The amount of drainage from chest tubes were less in aprotinin and tranexamic acid groups compared to placebo, and this was statistically important(P<0.001). There were no statistically significant differences in need for reoperation for bleeding in three groups(P=0.998). Complications following surgery in three groups were statistically the same and not significantly different (table below). All complications had a good course and all patients were discharged from hospital uneventfully. There were no mortality in any group.

Conclusions: low dose aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement in CABG surgery without importantly increasing mortality and morbidity.

Bleeding after cardiopulmonary bypass (CPB) is still a concern for CABG operation and an important factor affecting the morbidity and mortality in patients undergoing cardiac operation. 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 remain a concern. The coagulopathy is multifactorial with platelet dysfunction and plasmin-induced fibrinolytic activity the major contributors to the process (2). Aprotinin, a serine protease inhibitor from bovine lung, and the synthetic antifibrinolytic drugs, Tranexamic acid (TA) and-amino-N-caproic acid (EACA) given before CPB have been shown to reduce mediastinal bleeding postoperatively (3-7). The antifibrinolytic drugs have been shown to be equally effective as aprotinin in reducing bleeding and the use of allogeneic blood products, both in high risk patients and routine patients populations undergoing cardiac operastion(8).

Because antifibrinolytic drugs are much cheaper than aprotinin, and equally effective in reducing bleeding during cardiac operations and also recently mentioned

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 heamostasis.

Materials and Methods:

After institutional approval was obtained in a double blind clinical randomized trial all patients scheduled for coronary bypass surgery in our Center between the 21st of march 2008 and 21 march 2009 were included in this study. Inclusion criteria were: on pump CABG and patients' acceptance.

Exclusion criterias were: History of hemorrhagic tendency and blood dyscrasia, history of plavix usage, known hepatic, renal and metabolic diseases, use of other anti coagulation drugs like coumadin for valvular disease and arrhythmias and streptokinase, emergency surgery, rheumatic heart disease, known allergy to aprotinin or transamine and prohibition for their use like: acquired visual defects and retinal disease, subarachnoid hemorrhage, disseminated Intravascular coagulation, gall bladder disease, leukemia, embolization and vein thrombosis.

Patients demographic and clinical data as age, sex, history of cigarette smoking and other concomitant diseases were collected (Table 1).

All patients received 300 IU /Kg of bovine lung heparin. Additional heparin was administered for activated clotting times less than 400 seconds. The activate clothing time was monitored every 30 minutes. After we obtained written informed consent all patients were put in three groups randomly. In group A (aprotinin) after test dose 1 million units of aprotinin was added to pump prime solution. In group B (transamine) 1 gr of Transamine was added to pump prime solution and another 1 gr was used intravenously after discontinuation of pump. In group C (control) 250 cc of normal saline were used as placebo after the induction of anesthesia. Cardiac surgeons and cardiac surgery residents didn't know anything about the groups. Heparin was reversed with protamine sulfate after removal of all cannulaes. Shed mediastinal and plural blood, were estimated after 6, 12 and 24 hours and data were stored in a computer. Packed red cell was transfused for a hematocrete concentration under 30% and fresh frozen plasma was transfused based on abnormal prothrombin time and the rate of bleeding. Platlete transfusion threshold was a platelet count of 1000000 or less and bleeding tendency with one or more of the followings:

Post-operative complications like post-operative MI (based on cardiac enzyme rising, ECG changing and EF changing estimated by echocardiography), Neurological complications (estimated by clinical examination and CT-Scanning), redo operation for surgical bleeding and pericardial effusion, kidney complication(rising of serum creatinin and low urinary out put under 0.5 cc per minute) and other complications were studied.

Data was expressed as mean+/_ standard deviation. comparison of parametric patients' data was done using an unpaired student's t-test for quantitative data and K2 for qualitative data. P-value of less than 0.05 was considered significant.

Results:

We compared patients in three groups .Sex (P Value0.308), Age (P Value0.973), Cigarette smoking (P Value 0.720), Hyperlipidemia (P Value 0.707), Diabetes (P Value 0.960) and Hypertension (P Value 0.786) distribution were the same in all groups, (Table 1,Table 2) and there were no important statistical differences in these variables.

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%)	

Table 2.Risk Factors

Variable	Transamin	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 were significantly less in aprotinin and transamine groups compare to placebo group, and this was Statistically important.(P Value <0.001),We used repeated measurement analysis of variances in this manner.(Table 3)

Only two patients needed reoperation for bleeding, one in group B and one in group C, both of them were surgical bleeding and there were no statistically important difference in need for reoperation in three groups.(P Value 0.998). (Table 4)

Table 3.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

Other complications after surgery in three groups were statistically the same and not importantly different in the three groups. (Table 4)

There were 8 cases of post operative myocardial infarction 8% (based on cardiac enzyme rising, ECG changing and EF changing estimate by echocardiography ,4 in group C, 2 in group A and 2 in group B.(P Value 0.730) (table 4)

Table 4.Post operative complications

Variable	Transamine	Aprotinin	Placebo
Myocardial Infarction	2(4%)	2(4%)	4(8%)
Pericardial Effusion	0	0	2(4%)
Neuralgic 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

2 patients in group C were reoperated for pericardial effusion, two patients; one in placebo group and one in aprotinin group had neurological complications. Renal complications were 2 in transamine group (4%) and one in each other group, all neurology and renal complications were reversed before patients being discharged from hospital. There were no mortality in three groups and all complications had a good course and all patients discharged uneventfully from hospital. (Table 4)

In transamine group 35 patients (70%) didn't need blood transfusion, 4 patients needed 1 unit of packed cell and one patient received 6 units of packed cell, in aprotinin group 19 patients (38%) received 1 unit of packed cell and in placebo group 23 patients (46%) received 1 unit of packed cell, 5 Patients (10%) received 2 units and one received 4 units of packed cell.

Discussion:

Meta-analysis of multiple studies has shown aprotinin and antifibrinolytics to reduce mediastinal chest tube drainage by 30% versus placebo (11). Although delivery protocols were uniform for aprotonin, they still vary widely for TA and EACA. Whereas the effect of TA and aprotonin 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 as effective as aprotinin in reducing coagulopathy-caused bleeding after CPB and cheaper than aprotinin (12).

As TA is emerging as the presently available drug of choice to reduce coagulopathy-caused bleeding and because there are some concerns regarding adverse effect of aprotinin on renal system and final outcome (10), we designed our study to glean knowledge about the benefit of using low-dose TA and low-dose aprotinin in terms of reducing blood loss and allogeneic transfusion and its effect on various coagulation factor.

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 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 5 hours.The bleeding was reduced from 1202 mL in 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 that had a placebo group with primary myocardial revascularization used high-dose TA or administration of TA well into 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 addition of low-dose TA or aprotinin as given in our study is beneficial. From our findings, TA and aprotinin both are beneficial in this setting. Although control patients only bled 540mL in 24 hours, 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 coronary artery bypass surgery without importantly increasing mortality and morbidity.

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