Original Article

Evaluation and Comparison of Using Low-Dose Aprotinin and Tranexamic Acid in CABG: a Double Blind Randomized Clinical Trial

Mohammad Hassan Ghaffari Nejad, MD*, Bahador Baharestani, MD, Rostam Esfandiari, MD, Jafar Hashemi, MD, Abdollah Panahipoor, MD

Shaheed Rajaiee Cardiovascular Research Center, Tehran, Iran.

Received 16 March 2011; Accepted 26 July 2011

Abstract

Background: *Cardiovascular operations are associated with an inherent bleeding tendency that sometimes leads to severe bleeding and transfusion requirement. Pharmacological intervention to minimize post-bypass bleeding and blood product transfusions has received increasing attention from both medical and economic viewpoints.*

Methods: *This double-blind, randomized, placebo-controlled clinical trial recruited three groups of patients (each group consisting of 50 patients) undergoing on-pump coronary artery bypass graft surgery (CABG) and blindly randomized them to receive either low aprotinin, tranexamic acid, or placebo. The results were, subsequently, evaluated and compared between the groups. All the patients were operated on by one surgeon and the same surgery team.*

Results: *The following variables were similar between the groups, and there was no statistically significant difference between the groups in terms of 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 than the amount in the placebo group; the difference was statistically important (p value < 0.001). There was no statistically significant difference with respect to 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. All the complications (myocardial infarction, pericardial effusion, neurological complication and renal complication) had a good course, and all the patients were discharged from the hospital uneventfully. There was no mortality in any group.*

Conclusion: *Low-dose aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement in CABG without importantly increasing mortality and morbidity.*

J Teh Univ Heart Ctr 2012;7(1):15-18

This paper should be cited as: Ghaffari Nejad MH, Baharestani B, Esfandiari R, Hashemi J, Panahipoor A. Evaluation and Comparison of Using Low-Dose Aprotinin and Tranexamic Acid in CABG. J Teh Univ Heart Ctr 2012;7(1):15-18.

Keywords: *Aprotinin • Tranexamic acid • Coronary artery bypass*

***Corresponding Author:** : **Mohammad Hassan Ghaffari Nejad,** Consultant of Cardiovascular Surgery, Shaheed Rajaei Cardiovascular Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran. 1996911151. Tel: +98 21 23922160. Fax: +98 21 22042037. E-mail: gafer@rhc.ac.ir.*

Introduction

Bleeding after cardiopulmonary bypass (CPB) is still a concern for coronary artery bypass graft surgery (CABG) and an important factor in terms of morbidity and mortality rates in patients undergoing cardiac operations. Between 30% and 70% of open heart surgery 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. Coagulopathy is multi-factorial, and platelet dysfunction and plasmin-induced fibrinolytic activity are known as the major contributors to the process.[2] Aprotinin, a serine protease inhibitor from the bovine lung, and the synthetic anti-fibrinolytic drugs, tranexamic acid (TA) and e-amino-N-caproic acid (EACA), given before CPB have been shown to reduce mediastinal bleeding postoperatively.[3-7] Anti-fibrinolytic drugs have been demonstrated to be as effective as aprotinin in reducing bleeding and the use of allogeneic blood products, both in high-risk patients and routine patients undergoing cardiac operations.[8]

Anti-fibrinolytic drugs are much cheaper than aprotinin and equally effective in reducing bleeding during cardiac operations. Furthermore, given recent reports on the adverse effects of aprotinin on graft patency and survival,[9, 10] we sought to recruit a homogeneous patient population undergoing elective CABG in order to estimate the influence of low-dose aprotinin and TA on perioperative bleeding, need for allogeneic transfusion, and hemostasis.

Methods

After institutional approval was 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. All the patients were operated on by one surgeon and the same surgery team. The inclusion criteria were comprised of on-pump CABG and patients' consent, and the exclusion criteria comprised history of hemorrhagic tendency and blood dyscrasia, history of plavix use, 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 on the grounds of 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 1).

All the patients received 300 IU /Kg of bovine lung heparin. Additional heparin was administered for activated clotting times < 400 seconds. The activated clotting time was monitored every thirty minutes. After the patients provided informed written consent, they were blindly randomized into three groups of 50 persons. In group A (aprotinin), after the 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 the discontinuation of the pump; and in group C (control), 250 cc of normal saline was utilized as placebo after the induction of anesthesia.

The cardiac surgeons and cardiac surgery residents knew nothing about the groups. Heparin was reversed with protamine sulfate after the removal of all the cannulae. The amounts of mediastinal and plural blood shed were measured after six, twelve, and twenty-four hours, and the data were stored in a computer. Packed red cell was transfused for a hematocrit concentration < 30%, and fresh frozen plasma was transfused based on abnormal prothrombin times and bleeding rates. The platelet transfusion threshold was a platelet count ≤ 1,000,000.

Postoperative complications like postoperative myocardial infarction (based on rise in cardiac enzyme, change in ECG, and change in the ejection fraction estimated by echocardiography), neurological complications (estimated by clinical examination and CT-scanning), redo-operations for surgical bleeding and pericardial effusion, kidney complications (rise in serum creatinine and low urinary output < 0.5 cc per minute), and other complications were studied.

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

Results

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 (Table 1), and there was no important statistical difference between these variables.

The amounts of blood drainage from chest and mediastinal drains were significantly less in the aprotinin and transamine groups than the amount in the placebo group, and this was statistically important (p value < 0.001). Repeated measurement analysis of variances was employed for the comparison (Table 2).

Only 2 patients needed reoperation for bleeding: 1 in group B and 1 in group C; both of the cases were surgical bleeding and there was no statistically important difference

Published by "Tehran University of Medical Sciences" (www.tums.ac.ir)

Table 1. Patient's characteristics*

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

*Data are presented as mean±SD or n (%)

Table 2. Total amount of bleeding after coronary artery bypass graft surgery

Variable	Transamine	Aprotinin	Placebo	P value
Bleeding after 6h (cc)	115.3±88.7	109.2±86.7	240.0±182.9	<0.001
Bleeding after 12h (cc)	219.4±119.9	223.0±134.1	393.2±280.1	<0.001
Bleeding after 24h (cc)	355.9±178.7	382.3±217.7	540.8±346.9	<0.001
Bleeding after 48h (cc)	432.6±210.3	469.0±237.2	649.2±365.3	<0.001

*Data are presented as mean±SD

with regard to need for reoperation between the three groups (p value = 0.998) (Table 3).

Other complications after surgery in the three groups were statistically the same, with there being no statistically significant difference between the three groups (Table 3).

There were 8 cases of postoperative myocardial infarction (based on rise in cardiac enzyme, change in ECG, and change in the ejection fraction estimated by echocardiography): 4 in group C, 2 in group A, and 2 in group B (p value = 0.730) (Table 3).

Table 3. 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

*Data are presented as mean±SD or n(%)

Two patients in group C were re-operated on for pericardial effusion, and 2 patients (1 in the placebo group and 1 in the aprotinin group) had neurological complications. Renal complications were observed in 2 (4%) patients in the transamine group and 1 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. All the complications had a good course, and all the patients were discharged uneventfully from hospital (Table 3).

In the transamine group, 35 (70%) patients did not require blood transfusion, 4 patients needed one unit of packed cell, and 1 patient received six units of packed cell. In the aprotinin group, 19 (38%) patients received one unit of packed cell. In the placebo group, 23 (46%) patients received one unit of packed cell, 5 (10%) patients received two units, and 1 received four units of packed cell.

Discussion

A meta-analysis of multiple studies in the existing literature shows that aprotinin and anti-fibrinolytic drugs can reduce mediastinal chest tube drainage by 30% in comparison with placebos.[11] Whereas delivery protocols are uniform for aprotinin, they still vary widely for TA and EACA. The effect of TA and aprotinin on reducing blood loss after cardiac surgery is clear;[12] be that as it may, a meta-analysis of randomized studies of EACA versus placebo could not show a significant effect in reducing transfusion requirements.[13] TA has been shown to be both as effective as aprotinin in reducing coagulopathy-caused bleeding after CPB and cheaper than aprotinin.[12]

TA is emerging as the drug of choice for reducing coagulopathy-caused bleeding. In addition, concerns have been raised recently regarding the adverse effects of aprotinin on the renal system and final outcome.[10] We, therefore, designed the present study to investigate not only the benefits of low-dose TA and low-dose aprotinin in terms of reducing blood loss and allogeneic transfusion but also their effects on various coagulation factors.

In a low-risk patient population, TA was shown to decrease mediastinal bleeding after cardiac operations as early as 1990.[14] A similar result was reported in the studies by Karski and associates from Toronto.[15] The first significant study of a uniform patient population undergoing coronary

surgery was conducted by Roussou and colleagues,[16] who 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 gr bolus of TA followed by 8 gr during the procedure. Chest tube drainage in the control group was 1,114 ml versus 803 mL in the study group. A double-blind, randomized, placebo-controlled study was carried out by the Brook-Army Medical Center[17] on patients undergoing primary coronary artery operations. In that study, TA was commenced at 15 mg/Kg before CPB and was continued at 1 mg/Kg for five hours: The bleeding was reduced from 1,202 mL in the placebo group versus 1,020 mL in the TA group. Since then, multiple prospective studies have shown the efficacy of TA, by comparison with aprotinin or EACA.[9, 18] These studies mostly included patient populations that were at high risk for bleeding in conjunction with those of primary myocardial revascularization. Since 1998, there have also been a few studies containing placebo groups with primary myocardial revascularization; these investigations 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 resorting to antifibrinolytics.[18]

Consequently, it is a valid question to ask whether the addition of low-dose TA or aprotinin, as was administered in the present study, is beneficial. In light of our findings, both TA and aprotinin are beneficial in this setting. Our control patients bled only 540mL in twenty-four hours, but the use of TA and aprotinin significantly reduced this even further to 355 and 380 mL.

Conclusion

Both aprotinin and TA, even when administered in low doses, can significantly reduce blood loss and transfusion requirement in CABG without importantly increasing mortality and morbidity.

Acknowledgements

We would like to express our gratitude to Dr. H. Bakhshandeh for his statistical analysis for this paper.

References

1. Katsaros D, Petricievic M, Snow NJ, Woodhall DD, Bergen RV. Tranexamic acid reduces postbypass: a double blinded, prospective, randomized study of 210 patients. Ann Thorac Surg 1996;61:1131-1135.
2. Wong BI, McLean RF, Fremes SE, Deemar KA, Harrington EM, Christakis GT, Goldman B. Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. Ann Thorac Surg 2000;69:808-816.
3. Zabeeda D, Medalion B, Sverdlov M, Ezra S, Schakner A, Ezri T, Cohen AJ. Tranexamic acid reduces bleeding and the need for blood transfusion in primary myocardial revascularization. Ann Thorac Surg 2002;74:733-738.
4. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose response relationship of tranexamic acid. Anesthesiology 1995;82:383-391.
5. Royston D, Bidstrap BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 1987;2:1289-1291.
6. Horrow JC, Hlavacek J, Strong MD, Collier W, Brodsky I, Goldman SM, Goel IP. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 1990;99:70-74.
7. Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 1991;84:2063-2070.
8. Casati V, Guzzon D, Oppizzi M, Bellotti F, Franco A, Gerli C, Cossolini M, Torri G, Calori G, Benussi S, Alfieri O. Tranexamic acid compared with high dose aprotinin in primary elective operations: effects on perioperative bleeding and allogeneic transfusions. J Thorac Cardiovasc Surg 2000;120:520-527.
9. Misfeld M, Dubbert S, Eleftheriadis S, Siemens HJ, Wagner T, Sievers HH. Fibrinolysis adjusted perioperative low dose aprotinin reduces blood loss in bypass operations. Ann Thorac Surg 1998;66:792-799.
10. Westaby S, Katsumata T. Aprotinin and vein graft occlusion- the controversy continues. J Thorac Cardiovasc Surg 1998;116:731-733.
11. Fremes SE, Wong BI, Lee E, Mai R, Christakis GT, McLean RF, Goldman BS, Naylor CD. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. Ann Thorac Surg 1994;58:1580-1588.
12. Casati V, Guzzon D, Oppizzi M, Cossolini M, Torri G, Calori G, Alfieri O. Hemostatic effects of aprotinin, tranexamic acid and ϵ-aminocaproic acid in primary cardiac surgery. Ann Thorac Surg 1999;68:2252-2256.
13. Leupasis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery. Anesth Analg 1997;85:1258-1267.
14. Horrow JC, Hlavacek J, Strong MD, Collier W, Brodsky I, Goldman SM, Goel IP. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 1990;99:70-74.
15. Karski JM, Teasdale SJ, Norman PH. Prevention of Post-bypass bleeding with tranexamic acid and ϵ-aminocaproic acid. J Cardiothorac Vasc Anesth 1993;7:431-435.
16. Rousou JA, Engelman RM, Flack JE, 3rd, Deaton DW, Owen SG. Tranexamic acid significantly reduces blood loss associated with coronary revascularization. Ann Thorac Surg 1995;59:671-675.
17. Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary bypass operation. Anesth Analg 1997;85:963-970.
18. Hardy JF, Bélisle S, Dupont C, Harel F, Robitaille D, Roy M, Gagnon L. Prophylactic tranexamic acid and ϵ-aminocaproic acid for primary myocardial revascularization. Ann Thorac Surg 1998;65:371-376.