Original Article

Evaluation of Hemodynamic Changes Due to Protamine Administration by Calcium Gluconate after Coronary Artery Bypass Grafting Surgery

MT Moeinvaziri[1], F Jahanmirinejad[1], M Salari[1], M Janati[2], J Kojuri[2], A Alipoor[3]

[1] Department of Anesthesiology, [2]Cardiovascular Research Center, [3]Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Iran

Background: Administration of Protamine sulfate for heparin neutralization after cardiopulmonary bypass may be associated with adverse reactions such as transient hypotension to cardiovascular collapse. Although catastrophic events are rare and occur only in 2.6% of cardiac surgeries, it is associated with adverse postoperative outcome. The aim of this study is to investigate whether bolus administration of calcium gluconate can minimize the adverse hemodynamic effects of protamine.
Patients and Methods: This randomized clinical trial (RCT) prospective study was conducted between Feb. 2006 to Dec. 2008. The patients were randomly allocated into three groups including group A (42 patients) who received only protamine after weaning from cardiopulmonary, group B (44 patients) concomitantly treated with protamine sulfate and calcium gluconate, and group C (40 patients) receiving calcium gluconate 5 minutes before administration of protamine. Hemodynamic variables such as systolic and diastolic blood pressures, mean of arterial pressure, central venous pressure and heart rate were obtained 0, 2, 4, 6, 8 and 10 minutes after protamine administration from each group.
Results: Systolic blood pressure in groups A (control) and C (calcium administration before protamine) 0,2,4,6,8 and 10 minutes after protamine administration initially decreased and increased subsequently (P=0.228). Also no statistically significant difference was found in diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), and heart rate (HR) in 0,2,4,6,8, and 10 minutes in any of the three groups.
Conclusion: In our study, hemodynamic changes in 10 minutes after protamine administration for heparin neutralization in patients with good left ventricular systolic function after coronary artery bypass grafting surgery were mild, and prophylactic calcium gluconate administration concurrent with or before protamine injection was not recommended.

Key words: Protamine, Heparine, Coronary Artery Bypass Graft Surgery

Introduction

Heparin is extracted from either porcine intestine or beef lung.[1] Heparin acts as an anticoagulant by binding to anti thrombin III (AT III), enhancing the rate of thrombin-AT 3 complex formation and also inhibiting other clotting factors.[2]

Correspondence:
M Janati
Cardiovascular Research Center, Faghihi Hospital, Shiraz, IR Iran
Tel: +98-711-2343529 Fax: +98-711-2343529
Email:janatim@sums.ac.ir

Protamine, a polypeptide isolated from fish sperm,[3] immediately reverses the effect of heparin by nonspecific polyionic-polycationic acid-base interactions. Protamine is a standard therapy for reversing heparin anticoagulation after cardiopulmonary bypass for coronary artery bypass grafting surgery. Protamine sulfate administration after cardiopulmonary bypass may be associated with adverse reactions such as transient hypotension, anaphylactic reaction, and cardiovascular collapse.[5]

Pulmonary hypertension, which appears to

be rather common in animals, may be an isolated finding without clinical consequence in humans. However, when pulmonary vasoconstriction is severe, it will lead to acute right-side heart failure and systemic hypotension.[5]
Although catastrophic events are rare, major adverse response related to protamine administration occurs only in 2.6% of cardiac surgical procedures.[6] These protamine reactions are highly associated with adverse postoperative outcome,[6] and are exaggerated in patients with myocardial dysfunction.

Protamine sulfate for reversing heparin anticoagulation is often accompanied by a small drop in systemic blood pressure and increase in pulmonary artery pressure but these complications are generally considered as benign and inevitable,[7-9] but major adverse effects related to protamine administration may be associated with in-hospital mortality.

Michaels et al. revealed that no statistically significant changes in systhemic vascular resistance were seen when protamine was administered to patients with good left ventricular function after cardiopulmonary bypass. However, in patients with poor left ventricular function after cardiopulmonary bypass , an increased cardiac index may only partially compensate systemic vasodilatation following protamine administration ,thus in these patients protamine should be infused cautiously.[10] Also, other previous clinical and experimental studies[11-13] have suggested that protamine has a depressive effect on the left ventricular pump function. In this connection, Jastrzebski, Sykes and Woods[11] reported a decreased cardiac index in patients after protamine administration in the early post cardiopulmonary bypass period.

Shapria , et al.[9] showed that calcium administration can minimize the adverse hemodynamic effect of protamine by exerting positive cardiac inotropic and peripheral vascular effects.[14]

It seems that heparin neutralization with protamine causes myocardial dysfunction that can increase central venous pressure, pulmonary artery pressure and finally decrease systemic blood pressure. On the other hand, high intracellular level of calcium improves myocardial contractility by Digoxin through increased intracellular calcium in patients with heart failure. The present study was performed to clinically investigate whether increasing plasma calcium concentration and thereby intracellular calcium level could improve myocardial contractility during heparin neutralization by protamine in patients with good left ventricular function after for coronary artery bypass grafting surgery.

Patients and Methods

The study was conducted at Shiraz University of Medical Sciences affiliated hospital from Feb. 2006 to Dec. 2008, recruiting 126 patients undergoing coronary artery bypass grafting surgery. The study was approved by the university`s ethics committee and informed consents were obtained from all patients. Exclusion criteria included COPD, diabetes, hypertension, and left ventricular systolic dysfunction (EF less than 45%). Using systemic random allocation, the patients were divided into three groups of A or control (42 patients) who received only protamine after weaning from cardiopulmonary bypass (mean age 59.1±10.8, 73.8% males), B (44 patients) treated with protamine sulfate and calcium gluconate concomitantly, (mean age 57.4± 9.4, 75% males) and C (40 patients) receiving calcium gluconate 5 minutes before administration of protamine (mean age 55.6±9.2, 70% males). In the three groups There were no statistically significant differences among the three groups in regard to mean age (P=0.263) and gender (P=0.876).

After inserting radial arterial line, the patients were anesthetized using intravenous (IV) midazolam (40μg/kg), fentanyl (3μg/kg), morphine (0.13μg/kg), thiopental (5mg/kg) and pancuronium (0.15μg/kg). Anesthesia was maintained using 100% oxygen and Isoflorane throughout surgical procedure for all three groups.

In group A after weaning form cardiopulmonary bypass protaime sulfate was administered at a dose of 3mg/kg in 10 minutes. In group B protamine sulfate (3mg/kg) and calcium gluconate 10mg/kg were administrated in 10 minutes, but in group C initially calcium gluconate 10mg/kg was administrated in 10 minutes and after 5 minutes protamine 3mg/kg was given in 10 minutes. In the three groups, hemodynamic variables such as systolic and diastolic blood pressure, mean of arterial pressure, central venous pressure, and heart rate were obtained in 0,2,4,6,8 and 10 minutes following protamine injection.

Statistical analysis

The data were statistically analyzed using repeated measure ANOVA for comparing the mean in the three groups. One-way ANOVA and Chi-square were applied for evaluation of the difference between the ages and gender in the three groups respectively. Detection of differences between grading of indices was assessed with Friedman test. SPSS (statistical package for social sciences) version 10 was used for analysis and P value of less than 0.05 was considered significant.

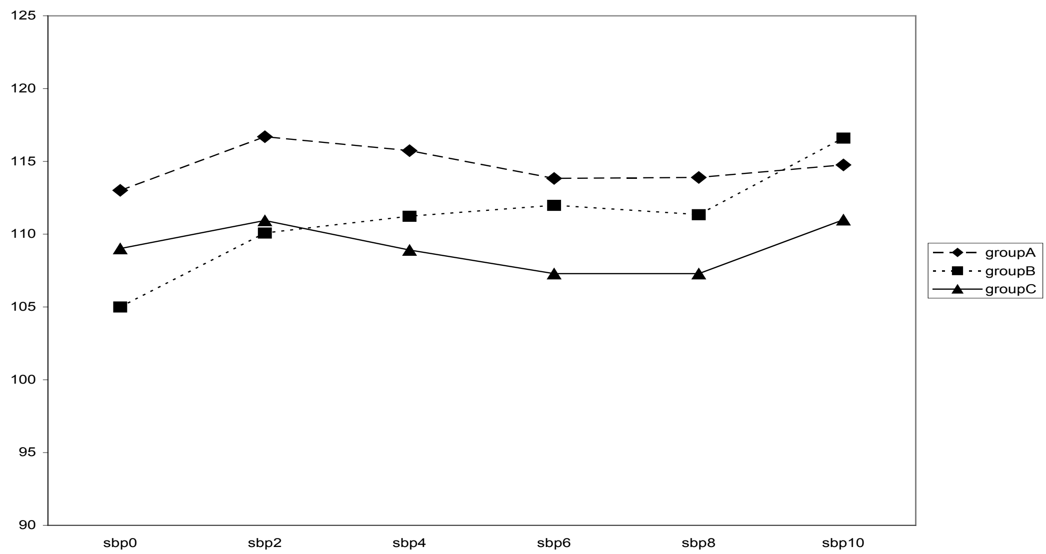

Figure 1. Trend of systolic blood pressure in the three groups

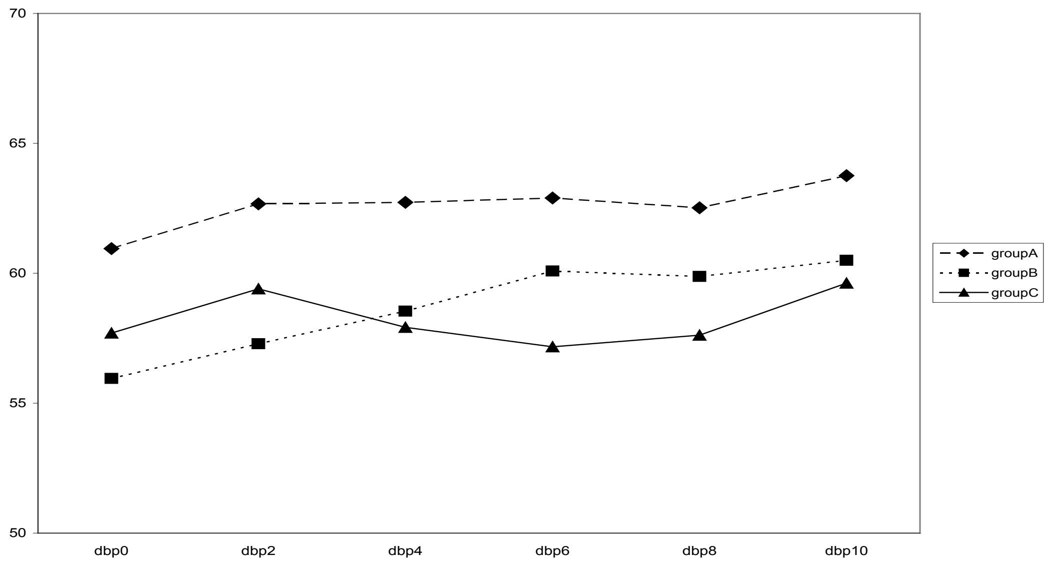

Figure 2. Trend of diastolic blood pressure in the three groups of study

Results

Systolic blood pressure in groups A (control) and C (calcium administration before protamine) in 0,2,4,6,8 and 10 minutes first decreased and later increased. In group B (concomitant administration of calcium and protamine) there was an increasing trend. However,these changes for three groups were not statistically significant (P=0.228) (Fig.1).

The mean of diastolic blood pressure in 0,2,4,6,8 and 10 minutes in group A was constant,and in group B it was first reduced but increased subsequently. In group C it initially increased and then became constant.

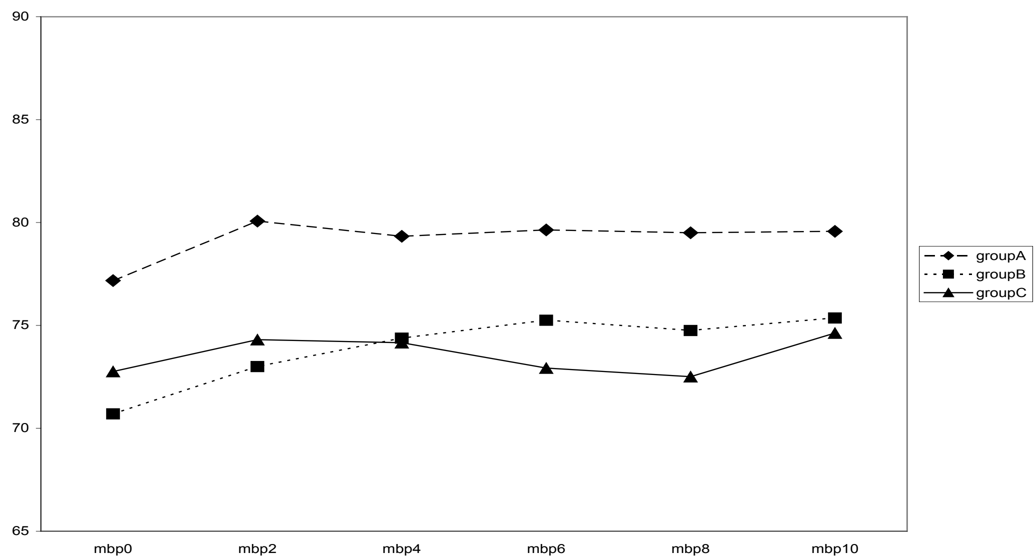

Figure 3. Trend of mean arterial blood pressure in the three groups of study

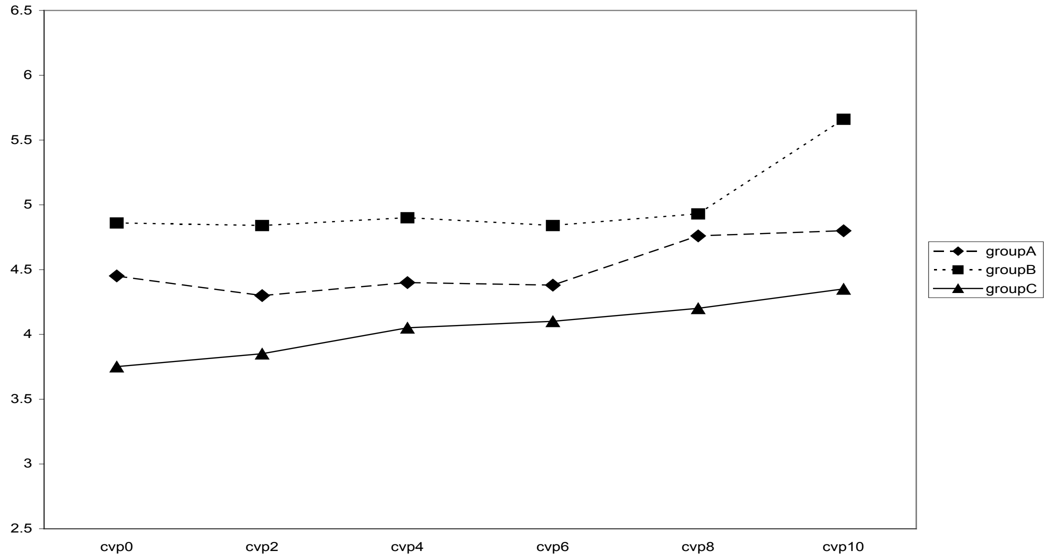

Figure 4. Trend of central venous pressure in the three groups of study

These changes were not statistically significant (P=0.462) (Fig. 2). Mean arterial pressure changes in the three groups were similar to diastolic blood pressure which were not statistically significant(p=0.763) (Fig. 3). Central venous pressure and heart rate changes for three groups were almost constant and statistically were not significant (P=0.712 and P=0.608, respectively) (Fig. 4,5). The mean and standard deviation of age for group A was 59.1± 9.4 and for group C 55.6±9.2 which were not statistically significant (P=0.263). The number of males in group A, B and C were 31 (73.8%), 33 (75%) and 28 (71%) respectively (P=0.867).

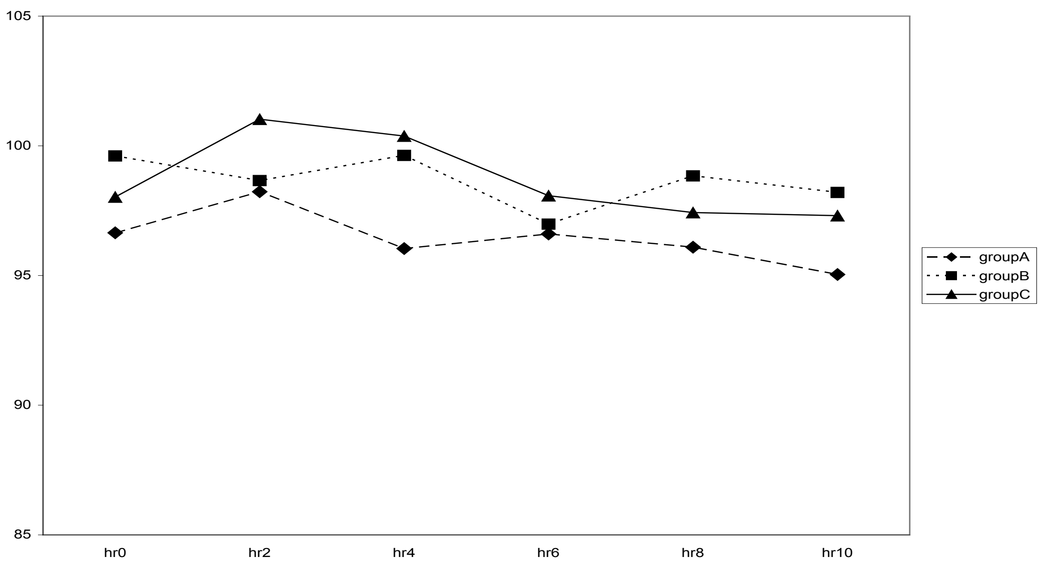

Figure 5. Trend of heart rate in the three groups groups of study

Discussion

From clinical and experimental observation, it is known that protamine neutralization of heparin causes increased pulmonary artery pressure, decreased systolic and diastolic pressure, myocardial oxygen consumption, cardiac output, heart rate and systemic vascular resistance. These multiple cardiovascular effects are mediated with complement activation, histamine release, thromboxane and nitric oxide production and antibody formation. Calcium chloride or calcium gluconate are the most frequently used adjunct to protamine for improving hemodynamic stability.

Gourine et al[5] suggested that protamine may have a negative inotropic effect that is apparent in patients with impaired left ventricular function.

On the other hand, Michaels et al[16] showed that hypotention was not developed after protamin administration in patiens with good left ventricular function.

Shapira et al[9] demonstarted an immediate and sustained enhancement of blood pressure occurred when calcium chloride was given as bolus injection or as a continuous infusion after cardiopulmonary bypass.

Vorasri muangmingsuk et al[17] suggested no measurable difference in heart rate or blood pressure in patients receiving calcium chloride either as a bolus before protamine administration or treated with protamine/calcium chloride.

Our study was consistent with that of Vorasri et al[17] who did not find any statistically significant difference in blood pressure or heart rate in patients receiving calcium gluconate either as a blous before protamine administration or concurrently with calcium chloride injection. It is possible that amount of calcium administrated is not sufficient to increase plasma calcium concentration or there is no coordination between kinetic entrance of calcium into the cell and increase in plasma calcium concentration immediately after cardiopulmonary bypass which causes statistically significant difference in blood pressure, heart rate and central venous pressure.

The findings of the present study indicate that prophylactic calcium gluconate administration is not valuable before or concurrent to protamine sulfate in patients with good left ventricular function undergoing coronary artery bypass graft surgery.

Acknowledgements

The authors would like to thank Dr AA Nekooeian for preparation of the manuscript and the cooperation of clinical research of Nemazee hospital. The authors declare that they have no Conflicts of Interest.

References

1 Bailey JM, Lu W, Levy JH, et al. Clevidipine in adult cardiac surgical patients: A dose finding study. *Anesthesiology* 2002;**96**:1086-94. [11981147]

2 Hirsh J, Raschke R, Warkntin TE, et al. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995;**108**:258s-175s. [7555181]

3 Levy JH, Schwieger IM, Zaidan JR, et al. Evaluation of protamine at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989;**98**:200-4. [2755152]

4 Kimmel SE, Sekeres M, Berlin JA, et al. Mortality and adverse events after protamine administration in patients undergoing cardiopulmonary bypass. *Anesth Analg* 2002;**94**:1402-8. [12031996]

5 Weiss ME, Adkinson NF JR. Allergy to protamine. *Clin Rev Allergy* 1991;**9**:339-55. [1782626]

6 Kimmel SE, Sekeres MA, Berlin JA, et al. Adverse events after protamine administration in patients undergoing cardiopulmonary bypass. Risk and predictors of under reporting. *J Clin Epidemiol* 1998;**51**:1-10. [9467629]

7 Weiss ME, Nyhan D, Peng ZK, et al. Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med* 1989;**320**:886-92. [2648147]

8 Abe K, Sakakibara T, Miyamoto Y, et al. Effect of prostaglandine E1 on pulmonary hypertension after protamine injection during cardiac surgery. *Eur J Clin Pharmacol* 1998;**54**:21-5. [9591925]

9 Shapira N, Schaff HV, Piehler JM, et al. Cardiovascular effects of protamine sulfate in man. *J Thorac Cardiovasc Surg* 1982;**84**:505-14. [7121041]

10 Michaels IA, Barash PG. Hemodynamic changes during protamine administration. *Anesth Analg* 1983;**62**:831-5. [6603799]

11 Jastrzebski J, Sykes MK, Woods DG. Cardiorespiratory effects of protamine after cardiopulmonary bypass in man. *Thorax* 1974;**29**:534-8. [4428453]

12 Wakefield TW, Bies LE, Wrobleski SK, et al. Impaired myocardial function and oxygen utilization due to protamine sulfate in an isolated rabbit heart preparation. *Ann Surg* 1990;*212*:387-93. [2222010]

13 Wakefield TW, Wrobleski SK, Nichol BJ, et al. Heparin mechated reductions of the toxic effects of protamine sulfate on rabbit myocardium. **J Vasc Surg** 1992;**16**:47-53. [1619724]

14 Cote' CJ, Drop LJ, Daniels AL, et al. Calcium chloride versus calcium gluconate: comparison of ionization and cardiovascular effects in children and dogs. *Anesthesilogy* 1987;**66**:465-70. [3565811]

15 Gourin A, Streisand RL, Greineder JK, et al. Protamine sulfate administration and cardiovascular system. *J Thorac Cardiovasc Surg* 1971;**62**:193-204. [5560501]

16 Michaels IA, Barash PG. Hemodynamic changes during protamine administration *Anesth Analg* 1983;**62**:831-5. [6603799]

17 Muangmingsuk V, Tremback TF, Muangmingsuk S, et al. The effect on the hemodynamic stability of varying calcium choloride administration during protamine infusion in pediatric open-Heart Patients. *Anesth Analg* 2001,**93**:92-5. [11429346]