

Dose of Protamine for Heparin Reversal in CABG Surgery

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ABSTRACT

Objective: To determine the dose of Protamine required for reversal of Heparin effect in Coronary Artery Bypass Grafting (CABG).

Study Design: Quasi-experimental study.

Place and Duration of Study: Adult Cardiac Surgery Unit, Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi Pakistan, from May to Dec 2022.

Methodology: Total 382 patients were included in this study through consecutive sampling and were divided into two groups (n=191 participants in each group). After induction of anesthesia, baseline Activated Clotting Time (ACT) was measured. About 300units/kg of unfractionated Heparin was given non-randomly before establishing Cardiopulmonary Bypass (CPB). After termination of CPB, Protamine was administered in doses of 1 mg/kg and 1.5 mg/kg to Group-A and Group-B respectively. Protamine was diluted in 20ml of saline, and administered at a rate of 100ml/hr. Once Protamine was administered, blood sample was taken after 5min for ACT measurement. If this ACT was within 10% of baseline, it was taken as sign for reversal of Heparin effect. Student t-test and Chi-square test were applied to compare the groups and level of significance taken was $p < 0.05$.

Results: Majority cases were males 287(75.1%), whereas 95(24.9%) were females. Statistically significant mean differences were noted between Cardiopulmonary Bypass (CPB) time, ACT after Protamine administration, and requirement for extra Protamine administration between two groups ($p < 0.05$). However, no significant differences were noted between age, weight and ACT before Heparin administration ($p > 0.05$). About 1mg/kg of Protamine reversed the Heparin effect in 116(60.7%) patients in Group-A, whereas 1.5mg/kg reversed the Heparin effect in 180(94.2%) cases in Group-B ($p < 0.001$).

Conclusion: Classical doses of 3mg/kg of Protamine in CABG patients may actually be exposing patients to higher than required doses of Protamine. Dose of 1mg/kg and 1.5mg/kg of Protamine was also found to be effective.

Keywords: Activated Clotting Time, Coronary artery bypass grafting, Heparin, Protamine.

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INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is the surgical procedure which is done to treat Coronary Artery Disease (CAD). CAD reduces the blood flow in coronary vessels. CABG restores the blood flow. Two types of CABG are common, Off-pump CABG and On-Pump CABG.

Open Heart surgery requires anticoagulation. Heparin is most commonly used medicine to prevent the thromboembolic phenomenon during open heart surgery. Its benefits include ease of availability, easy reversibility, cost-effectiveness, and a successful track record. Heparin is reversed by using Protamine. Protamine has cationic arginine that binds anionic Heparin. This makes it redundant, and the complex

formed does not have any anticoagulant effect.¹

The classical dose of Protamine given is 1mg/100units of Heparin given conventionally.² However; Protamine dosing represents a delicate balance to be kept in mind. If Heparin remains unbound, bleeding may increase. However, overdosing may expose the patients to side effects of Protamine. The side effects include paradoxical coagulopathy.³ Studies have concluded that patients receiving higher doses of Protamine required more fresh frozen plasma and platelet concentrates.⁴ One explanation is that Protamine affects platelets and Ghib-vWF interaction. Other possible reasons include decreased thrombin generation, factor-V and VII activation and clotting effect of factor VIII.⁵

The half-life of Heparin is 60-90 minutes, and fixed dose of 1mg, for every 100 units at the end of CABG might be proven high, as much of the Heparin

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is already out of the equation. Some studies have focused on, point-of-care systems using Heparin and Protamine titration.⁶ However, these studies have been proven too costly for 3rd world countries.

We planned to conduct this study based on fixed dosing; however, unlike previous studies, which focused on comparing 2.4-3 mg/kg of Protamine⁷, we used a dose of 1mg/kg and 1.5 mg/kg of Protamine in order to determine the minimum required dose of Protamine for Heparin reversal.

METHODOLOGY

This Quasi-experimental study was carried out at Adult Cardiac Surgery Unit, Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Pakistan, from May-December, 2022 after approval from Institutional Ethical Review Board under letter number (9/2/R&D/2022/173).

Sample size was calculated by WHO sample size calculator. Calculated sample size was 323 at 95% Confidence Level & 5% margin of error and taking prevalence of CABG as 30%.⁸ However, data was collected from 382 patients.

Inclusion Criteria: All patients who underwent On-pump CABG surgery irrespective of gender with age range of 30-80 years were included.

Exclusion Criteria: Patients presented in emergency, Off-pump CABG cases and patients on anticoagulants/anti platelets were excluded from the study.

In this study, "Heparin dose" was defined as 300 units of unfractionated Heparin per kg of body weight. Since 1mg of Protamine is classically used to reverse Heparin effects of 100 units, 3mg/kg is used to reverse 300units/kg of Heparin given in CABG. So, "Fixed dose of Protamine " was taken as 3mg/kg. Activated Clotting Time (ACT) was measured for determining the reversal of Heparin, and was considered "Corrected" if it was within 10% of baseline ACT (ACT measured before Heparin administration).

Non-probability consecutive sampling was used, and patients were distributed into two groups: Group-A (n=191) and Group-B (n=191). As the study design was quasi-experimental, random assignment to treatment condition was not followed. This distribution was on the basis of CPB time. If this time was equal to or more than 90 minutes, then patients were placed in Group-A. Similarly, if CPB time was less than 90 minutes, the patients were placed in Group-B. Group A received 1 mg/kg of Protamine for

Heparin reversal, whereas Group-B received 1.5mg/kg of Protamine right after CPB termination.

After administration of general anesthesia, blood sample was taken to determine baseline ACT. It was done before administration of Heparin. After completion of bypass surgery, surgeon allowed for neutralization of Heparin effect, Protamine dose was given at the rate of 1mg/kg or 1.5mg/kg depending on CPB time. This dose was diluted in 20ml normal saline, and infused at the rate of 100ml/hour. Once dose was administered, blood sample was taken after 5min for ACT measurement. If the recorded ACT was within 10% of baseline ACT, it was labeled as "Corrected ACT". If it was not achieved, additional dose of Protamine was administered.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 23:00. Means and standard deviations were calculated for continuous variables (e.g. age, weight, CPB, ACT). Frequency was calculated for categorical variables (gender, extra Protamine given). Chi-square was used for the comparison of extra Protamine given, and Student t-test was applied to find mean difference of Heparin dose and CPB time. The *p*-value ≤ was considered significant.

RESULTS

Out of total 382 patients, majority of the cases were males 287(75.1%). Mean of age, weight, Cardiopulmonary Bypass time (CPB time), ACT before and after Protamine administration have been shown in Table-I.

Table-I: Demographics and Intra-Operative parameters of study participants (n=382)

Variables	Mean±SD
Age (years)	60.13±7.37
Weight (kg)	73.84±10.21
CPB time (min)	100.59±29.28
ACT Before Heparin administration (sec)	106.52±11.00
ACT after Protamine administration (sec)	116.03±18.24

CPB=Cardiopulmonary Bypass; ACT=Activated Clotting Time

Table-II showed that mean difference of weight (*p*=0.64) and ACT before Heparin administration (*p*=1.00) were statistically insignificant between study groups. However, after Protamine administration, ACT was significantly higher in Group A than Group-B (121.13±21.61 sec vs 110.93±12.16 sec; *p*<0.001). CPB time also showed significant difference (*p*<0.001). However, this parameter was actually used to divide patients in two groups i.e. Group A and B and it was already expected.

Dose of Protamine For Heparin Reversal

Comparison in regards to requirement of extra Protamine as shown in Table-III, showed that the difference between two groups was statistically significant ($p < 0.001$). Extra Protamine was administered in 75(39.27%) and 11(5.76%) cases when a dose of 1mg/kg and 1.5mg/kg of Protamine was used respectively.

Table-II: Association of different doses of Protamine with independent variables (n=382)

Variables	Group-A (n=191) Mean±SD	Group-B (n=191) Mean±SD	p-value
Age (years)	60.04±7.39	60.22±7.38	0.81
Weight (kg)	73.60±10.31	74.08±10.13	0.64
CPB Time (min)	127±13.55	73.59±8.43	<0.001
ACT before Heparin administration (sec)	106.52±11.00	106.52±11.02	1.00
ACT after Protamine administration (sec)	121.13±21.61	110.93±12.16	<0.001

CPB=Cardiopulmonary Bypass; ACT=Activated Clotting Time

Table-III: Association of Extra Protamine given in different study groups (n=382)

Variables		Group A (n=191) (1mg/kg Protamine) Frequency(%)	Group B (n=191) (1.5mg/kg Protamine) Frequency (%)	p-value
Extra Protamine	Given	75 (39.27)	11(5.76)	<0.001
	Not Given	116(60.73)	180(94.24)	

DISCUSSION

Our results clearly showed that lower doses of Protamine (1.0 and 1.5 mg/kg) can reverse effects of Heparin in majority of patients (60.7% and 94.2%). If Protamine is used at 3mg/kg, this may expose the patient to unnecessary Protamine dose. Extra Protamine dose can always be given if desired ACT is not achieved.

Heparin is used in CABG all over the world due to its strong anticoagulant property and easy availability. Due to its anionic chemistry, its anticoagulation can be easily reversed with Protamine Sulfate. However, Protamine comes with its own side effects ranging from systemic hypotension⁹ and allergic reactions to life threatening pulmonary vasoconstrictions,^{10,11} and the worst of these can be graft thrombosis,^{12,13} the very basis for which CABG was done in the first place. A cost effective method to correctly calculate dose required for Heparin reversal with Protamine is still not available,¹⁴ which highlights the importance of this study in third world countries like Pakistan.

In this study, 382 patients were given two different doses of 1mg/kg and 1.5mg/kg, and their Heparin reversal was observed with ACT after their administration. Main reason for using lower doses of Protamine is that Heparin concentration decreases with time, some studies quoting 40% reduction in Heparin concentration.¹⁵

Meesters and his colleagues,¹⁶ actually studied dose of Protamine required using conventional dosing and with a pharmacokinetic model. This model was used to calculate Heparin concentration present in body, and then giving Protamine 1mg/100 units of actual Heparin present in body. They found that there was significant reduction in requirement of Protamine (from 416±82 mg if fixed dosing is used, to 186±42 mg if Protamine is given based on actual amount of heparin present in body). However, such pharmacokinetic models are not easy to replicate in our set ups.

De Simone and his colleagues also found that administration of classical dose of Protamine to reverse effects of Heparin leads to excessive Protamine dose administration.¹⁷ Their study was quite interesting, and it used Hemostasis Management system which can be used to titrate Heparin and Protamine for accurate dose calculation. It is not cost effective to use this in Third World Countries.

As mentioned before, we used 1mg/kg and 1.5mg/kg of Protamine, and 1mg/kg was able to reverse Heparin effects in 116(60.7%) of cases, and 1.5mg/kg was able to reverse Heparin in 180(94.2%) cases. Hence, extra Protamine had to be given when desired ACT was not achieved. But important point is that extra Protamine administration is always a better option rather than exposing patient to side effects of Protamine.

Another study showed similar findings and they used 2/3rd of the dose required for reversal of Heparin effect (2mg/kg of Protamine).¹⁸ They found that this dose could completely reverse the effects of Heparin. This dose was higher to the dose we used in our study, however, it was still less than conventional dose of 3mg/kg of Protamine used in CABG surgery.

Dasgupta *et al.*,¹⁹ and his colleagues actually reported that even 0.5mg of Protamine /100 units of Heparin given (equivalent to our 1.5 mg/kg given), can reverse the effects of Heparin completely. But his study had some differences from our study. Main difference is that his study was in Off-pump CABG and therefore his patients were not exposed to cardiopulmonary bypass circuit. Other difference was

that 1.5 mg/kg of Protamine was not completely effective in our study.

LIMITATIONS OF STUDY

We used 1mg/kg Protamine (or 0.33mg Protamine /100 units of Heparin) when CPB time was ≥ 90 minutes, and 1.5mg/kg Protamine (or 0.5mg Protamine /100 units of Heparin) when CPB time was < 90 min. This study targeted only the On-pump CABG cases.

CONCLUSION

This study demonstrated that, the dose of 1mg/kg of Protamine might be proven effective in majority of cases. Furthermore, the increments of Protamine dose can always be given if ACT is not corrected. Our study demonstrated that doses of 1mg/kg and 1.5mg/kg of Protamine are quite effective.

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Conflict of Interest: None.

Authors' Contributions

Following authors have made substantial contributions to the manuscript:

SARAS & SSN: Concept, Drafting the manuscript, Critical review, approval of the final version to be published.

SMHK & SAH: Intellectual contribution, Concept, Final approval, Manuscript writing.

IBM & MUF: Data Collection, Data Analysis, Review of Article, Approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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