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COMPARISON OF 0.7 MG AND 1 MG PROTAMINES ON ACTIVATED CLOTTING TIME AND BLEEDING IN OFF-PUMP CORONARY ARTERY BYPASS PATIENTS: A MULTICENTER STUDY

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Abstract

Background: Optimal anticoagulation management is crucial for graft patency and minimizing postoperative complications in off-pump coronary artery bypass grafting (OPCAB), a widely performed surgical procedure for coronary artery disease. The role of protamine in neutralizing heparin and its impact on activated clotting time (ACT) and postoperative bleeding remain unclear. This study compared the effects of two protamine doses (0.7 mg and 1 mg per 1 mg of heparin) on ACT and bleeding outcomes in patients who underwent OPCAB. **Methods**: This multicenter, single-blind, randomized controlled trial was conducted from February to April 2025 and included 50 patients undergoing OPCAB at Dr. Hasan Sadikin General Hospital and Santosa Hospital Central. Patients were randomized into two groups: Group 1 received 0.7 mg of protamine per 1 mg of heparin, and Group 2 received 1 mg of protamine per 1 mg of heparin. The primary outcomes were post-protamine ACT levels and postoperative bleeding at 1, 4, and 12 h. The secondary outcomes included the need for colloid and crystalloid fluid administration. **Results**: The results showed No significant difference was observed in the ACT between the two groups after protamine administration ($p = 0.541$). However, postoperative bleeding was significantly lower in the 0.7 mg group than in the 1 mg group at all postoperative time points ($p < 0.05$). The 1 mg protamine group required significantly more colloid infusion during the procedure ($p = 0.001$), suggesting greater hemodynamic instability associated with higher protamine doses. **Conclusions**: A protamine dose of 0.7 mg per 1 mg of heparin was associated with less postoperative bleeding than the standard 1 mg dose, without significant differences in ACT. These findings suggest that lower doses of protamine may be preferable in OPCAB to reduce bleeding risk while maintaining effective heparin neutralization. Further studies are needed to refine the protamine dosing protocols for cardiac surgery.

Keywords: ***Protamine, Off-Pump Coronary Artery Bypass Grafting, Activated Clotting Time, Postoperative Bleeding, Anticoagulation***

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. It is estimated that more than one million heart surgeries are performed annually worldwide. Among these, coronary artery bypass grafting (CABG) remains the most common procedure. CABG continues to be the gold standard for managing coronary artery disease, particularly in cases of triple-vessel disease (CAD 3VD) and left main stenosis (LMS) [1]. One of the surgical approaches used for revascularization is off-pump coronary artery bypass grafting (OPCAB). Although OPCAB is less frequently performed worldwide and requires more complex surgical techniques, it avoids the morbidities associated with cannulation, aortic clamping, cardioplegia, and the use of cardiopulmonary bypass (CPB) [2]. Optimal anticoagulation is critical during OPCAB to maintain graft patency and prevent graft occlusion in patients with CAD. However, the ideal anticoagulation strategy for OPCAB remains uncertain, varies widely, and is a subject of ongoing debate. Activated clotting time (ACT) is commonly used to monitor anticoagulation during OPCAB [3]. The target ACT is typically recommended to be between 250 and 300 s [4]. Unfractionated Heparin (UFH) is a commonly used anticoagulant in cardiac surgery because of its accessibility, efficacy, short duration of action, and ease of reversibility with protamine.

Bleeding during cardiac surgery can be caused by several factors, including incomplete surgical hemostasis, coagulopathy due to prolonged CPB duration, and insufficient heparin neutralization, often leading to transfusions [5,6].

Protamine is used in all cardiac surgeries to neutralize residual heparin and reduce postoperative bleeding risk. Protamine binds to free heparin, thereby preventing its interaction with antithrombin III [7]. Several studies have recommended a protamine dose of 1 mg for every 1 mg (100 IU) of heparin. This approach is considered straightforward but often results in excessive protamine administration. Protamine also has anticoagulant properties due to its effects on platelet function, coagulation factors, and stimulation of fibrinolysis. Excessive doses can increase the risk of bleeding [4-10].

Excessive bleeding during heart surgery is associated with an increased postoperative risk, even in low-risk patients. It is associated with complications such as stroke, acute kidney injury (AKI), prolonged ventilation, extended hospital and ICU stays, and increased mortality rates within 30 days. Moreover, excessive bleeding increases the need for blood transfusions, which further elevates the risk of morbidity and mortality. Some studies have also shown that excessive bleeding during and after surgery increases the likelihood of re-exploration [11].

Protamine administration is associated with immunological and inflammatory changes and can trigger an anaphylactic response characterized by hypotension, bradycardia, pulmonary vasoconstriction, and allergic reactions. These are the most frequently reported side effects, and excessive protamine doses may increase the risk of such adverse effects [5,7].

Recent studies in cardiac surgery patients suggest that protamine doses exceeding 1 mg per 1 mg of heparin are excessive and may interfere with hemostasis and coagulation, thereby increasing postoperative bleeding risk. Current literature tends to recommend lower protamine doses, typically less than 1 mg per 1 mg of heparin, especially in patients who do not undergo CPB [7,8]. A lower protamine dose may also reduce the risk of side effects. [5,7].

However, research on protamine dosing is relatively limited compared to that on heparin [8]. Few studies have focused on low-dose protamine in OPCAB procedures, highlighting the need for further research to determine its optimal dose. This study aimed to compare the effects of protamine doses of 0.7 mg per 1 mg of heparin (0.7) versus 1 mg per 1 mg of heparin (1) on ACT and postoperative bleeding in patients who underwent OPCAB.

METHOD

This study utilized an experimental design, specifically a single-blind randomized controlled trial (RCT), to compare the effects of two different protamine doses on the outcomes of patients undergoing off-pump coronary artery bypass grafting (OPCAB). The randomization process ensures unbiased allocation of participants into two groups, where one group receives treatment and the other does not, while maintaining blinding to minimize bias in outcome assessment.

The study population consisted of patients who underwent OPCAB surgery at Dr. Hasan Sadikin General Hospital and Santosa Hospital Central in Bandung. The sample was selected from individuals who met the inclusion criteria, and all participants were chosen consecutively as they arrived based on their eligibility. The sample size was determined through statistical calculations, ensuring a 95% confidence level and 90% power, which provided sufficient data to detect significant differences between the groups. A minimum of 21 patients per group was required, totaling at least 42 patients in both groups. The sampling technique used is consecutive sampling, where participants are selected in the order they present themselves, followed by randomization to assign them to the treatment or control group.

The inclusion criteria were patients aged ≥ 18 years who were undergoing OPCAB surgery at the aforementioned hospitals and who were willing to participate in the study with informed consent. The exclusion criteria were as follows: patients with a known allergy to protamine, those with pre-existing coagulopathy, and those who experienced complications, such as death during surgery or required the use of cardiopulmonary bypass (CPB). Patients who received heparin postoperatively for more than 12 h were also excluded.

The independent variable in this study was the dose of protamine, with two levels: 0.7 mg for every 1 mg of heparin and 1 mg for every 1 mg of heparin. The dependent variables included activated clotting time (ACT) and volume of postoperative bleeding. Covariates such as body weight, height, baseline hemoglobin levels, surgery duration, intraoperative blood loss, and fluid administration during surgery were also considered in the analysis. These variables were measured using routine blood samples, medical records, and

clinical observations. Data will be collected from patients who meet the inclusion criteria and provide informed consent for participation. Blood samples will be collected for routine tests, and baseline ACT levels will be recorded prior to surgery. Heparin was administered before grafting, followed by a post-heparin ACT check. If necessary, additional heparin was administered to achieve an ACT greater than 250 s. After grafting, protamine will be administered intravenously, and the ACT will be checked again after five minutes. Blood loss will be monitored at 1, 4, and 12 h postoperatively, and fluid administration will be recorded.

The collected data will undergo systematic processing using statistical software to ensure that they are clean, accurate, and ready for analysis. Descriptive statistics will summarize the numerical data, including the means, standard deviations, medians, and ranges for continuous variables and frequency distributions for categorical data. Inferential statistics will include hypothesis testing and comparison of the means of continuous variables between the two groups using t-tests or the Mann-Whitney U test for non-parametric data. For categorical variables, chi-square or Fisher's exact tests will be used. Statistical significance will be considered at $p \leq 0.05$. The research protocol will be submitted to an ethics review board for approval. All participants will be provided with detailed information regarding the study's purpose, procedures, potential risks, and benefits and will be asked to provide informed consent. The confidentiality of patient information will be strictly maintained, and participants will be free to withdraw from the study at any time, without consequence.

RESULTS

The study was conducted from February to April 2025 at Dr. Hasan Sadikin General Hospital and Santosa Hospital Central, Bandung, involving 50 patients who met the inclusion and exclusion criteria of the study. The patients were divided into two groups, each consisting of 25 individuals: one group received a protamine dose of 0.7 mg, and the other group received a protamine dose of 1 mg. The general characteristics of the participants based on age, sex, body weight, height, baseline hemoglobin, baseline ACT, heparin dose, final hemoglobin, and duration of surgery are summarized in Table 1.

In the 0.7 mg protamine group, the mean age was 58.36 ± 8.717 years, with 19 males (76%) and six females (24%) patients. The average body weight was 69.32 ± 15.774 kg and the average height was 163.04 ± 6.592 cm. The mean baseline hemoglobin was 12.69 ± 1.823 g/dL, and the mean baseline ACT was 131.08 ± 19.617 s. The mean heparin dose was 158.20 ± 35.381 IU, the mean final hemoglobin level was 9.52 ± 1.980 g/dL, and the mean surgery duration was 197.12 ± 36.874 min.

In the 1 mg protamine group, the mean age was 60.52 ± 8.032 years, with 22 males (88%) and 3 females (12%). The average body weight was 68.44 ± 13.389 kg and the average height was 166.12 ± 7.061 cm. The mean baseline hemoglobin was 12.35 ± 1.813 g/dL, and the mean baseline ACT was 141.64 ± 25.846 s. The mean heparin dose was 153.60 ± 28.156 IU, the mean final hemoglobin was 9.04 ± 1.906 g/dL, and the mean surgery duration was 199.52 ± 51.228 min.

Table 1. Comparison of Patient Characteristics Based on Protamine Dose

Variable	Protamine Dose (0.7 mg)	Protamine Dose (1 mg)	p-value
Age (years)	58.36 ± 8.717	60.52 ± 8.032	0.367
Gender			0.463
Male (%)	19 (76.0%)	22 (88.0%)	
Female (%)	6 (24.0%)	3 (12.0%)	
Body Weight (kg)	69.32 ± 15.774	68.44 ± 13.389	0.816
Height (cm)	163.04 ± 6.592	166.12 ± 7.061	0.045*
Hemoglobin Baseline	12.69 ± 1.823	12.35 ± 1.813	0.507
ACT Baseline (sec)	131.08 ± 19.617	141.64 ± 25.846	0.110
Heparin Dose (IU)	158.20 ± 35.381	153.60 ± 28.156	0.875
Final Hemoglobin (g/dL)	9.52 ± 1.980	9.04 ± 1.906	0.239
Surgery Duration (min)	197.12 ± 36.874	199.52 ± 51.228	0.705

*Note: p-values were calculated based on independent t-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. Statistical significance was set at $p < 0.05$.

For the analysis of numerical data, we used the independent t-test for normally distributed variables, such as age, baseline hemoglobin, and baseline activated clotting time (ACT), and the Mann-Whitney U test for non-normally distributed variables, including body weight, height, heparin dose, final hemoglobin, and surgery

duration. The p-values for age, body weight, baseline hemoglobin, baseline ACT, heparin dose, final hemoglobin, and surgery duration were all greater than 0.05, indicating no statistically significant differences between the two groups. However, the p-value for height was less than 0.05, indicating a statistically significant difference between the two groups, with the 1 mg protamine group having a higher average height than the 0.7 mg group.

Comparison of Clinical Characteristics Based on Protamine Dose

In the 0.7 mg protamine group, the average blood loss during surgery was 906.00 ± 372.581 mL, mean crystalloid volume administered was 1488.00 ± 390.854 mL, mean colloid volume was 996.00 ± 509.477 mL, and mean blood volume used was 24.72 ± 85.843 mL. No protamine was administered in this group. In the 1 mg protamine group, the average blood loss during surgery was 940.00 ± 418.828 mL, mean crystalloid volume administered was 1484.00 ± 363.639 mL, mean colloid volume was 1362.00 ± 307.977 mL, and mean blood volume used was 48.64 ± 119.815 mL. No additional protamine was added to this group.

Table 2. Comparison of Clinical Characteristics Based on Protamine Dose

Variable	Protamine Dose (0.7 mg)	Protamine Dose (1 mg)	p-value
Blood Loss (mL)	906.00 ± 372.581	940.00 ± 418.828	0.733
Crystalloid Volume (mL)	1488.00 ± 390.854	1484.00 ± 363.639	0.901
Colloid Volume (mL)	996.00 ± 509.477	1362.00 ± 307.977	0.001*
Blood Volume (mL)	24.72 ± 85.843	48.64 ± 119.815	0.641
Protamine Added (mL)	0.00	0.00	1.000

*Note: p-values were calculated as described above. Statistical significance was set at $p < 0.05$.

For the clinical data analysis, we used the Mann-Whitney U test due to the non-normal distribution of variables such as blood loss, crystalloid volume, colloid volume, and blood volume. The results show no significant differences in blood loss, crystalloid volume, or blood volume between the two groups, as indicated by p-values greater than 0.05. However, colloid volume was significantly higher in the 1 mg protamine group ($p = 0.001$).

Comparison of ACT and Postoperative Bleeding Based on Protamine Dose

In the 0.7 mg protamine group, the average ACT after heparin administration was 359.36 ± 81.611 s, and after protamine administration, it was 115.08 ± 24.789 s. The postoperative bleeding at the 1st, 4th, and 12th hours had means of 40.04 ± 26.036 mL, 103.04 ± 41.513 mL, and 207.60 ± 59.599 mL, respectively.

In the 1 mg protamine group, the average ACT after heparin administration was 442.24 ± 219.810 s, and after protamine administration, it was 111.16 ± 19.995 s. The postoperative bleeding at the 1st, 4th, and 12th hours had means of 116.92 ± 188.637 mL, 234.28 ± 262.957 mL, and 402.76 ± 331.772 mL, respectively.

Table 3. Comparison of ACT and Postoperative Bleeding Based on Protamine Dose

Variable	Protamine Dose (0.7 mg)	Protamine Dose (1 mg)	p-value
ACT After Heparin (sec)	359.36 ± 81.611	442.24 ± 219.810	0.372
ACT After Protamine (sec)	115.08 ± 24.789	111.16 ± 19.995	0.541
Postoperative Bleeding 1hr (mL)	40.04 ± 26.036	116.92 ± 188.637	0.0001**
Postoperative Bleeding 4hr (mL)	103.04 ± 41.513	234.28 ± 262.957	0.0001**
Postoperative Bleeding 12hr (mL)	207.60 ± 59.599	402.76 ± 331.772	0.0001**

*Note: p-values were calculated as described above. Statistical significance was set at $p < 0.05$.

The analysis of ACT post-protamine and postoperative bleeding revealed significant differences in bleeding volumes at the 1st, 4th, and 12th hours post-surgery, with the 1 mg protamine group experiencing significantly higher bleeding volumes ($p < 0.05$). However, ACT post-protamine did not differ significantly between the two groups ($p = 0.541$).

DISCUSSION

The present study explored the effects of two different protamine doses (0.7 mg and 1 mg per 1 mg of heparin) on activated clotting time (ACT) and postoperative bleeding in patients undergoing off-pump

coronary artery bypass grafting (OPCAB). Among the 50 patients included in the study, we observed statistically significant differences in height between the two groups ($p < 0.05$). While other characteristics, such as age, weight, and baseline hemoglobin, were relatively homogeneous between the groups, the observed difference in height may have implications for the pharmacokinetics of protamine administration. Taller individuals often have a larger body surface area (BSA) and greater intravascular volume, which can affect the distribution of heparin and protamine. Previous research has shown that BSA plays a significant role in determining the protamine dose required for effective heparin neutralization, suggesting that patients with higher BSA (often associated with greater height) may require slightly higher protamine doses to achieve optimal heparin reversal [5]. However, given that both groups had similar body weights and comparable heparin doses, the effect of height differences on the final outcomes was likely minimal, further supported by the lack of significant differences in weight, heparin dose, and ACT baseline values between the two groups.

In terms of clinical characteristics, the study found that the group receiving the 1 mg protamine dose required significantly more colloid during surgery than the 0.7 mg group ($p < 0.05$). This increase in colloid usage may reflect changes in hemodynamics owing to the systemic effects of protamine. Protamine has been shown to cause vasodilation and hypotension, particularly if administered too quickly, which likely necessitated additional fluid resuscitation, including colloids, to maintain a stable blood pressure and cardiac output [12]. Conversely, the group receiving 0.7 mg protamine required less colloid, suggesting more stable intraoperative hemodynamics. A lower dose of protamine may result in fewer cardiovascular side effects, thereby requiring less fluid to maintain hemodynamic balance. This aligns with current trends in cardiac surgery fluid management, which aims to avoid excessive fluid administration to minimize hemodilution and edema, demonstrating the importance of tailoring protamine doses to reduce unnecessary complications.

Regarding postoperative outcomes, the study revealed significant differences in bleeding volume between the two groups. The 1 mg protamine group experienced more bleeding at the 1st, 4th, and 12th postoperative hours than the 0.7 mg group ($p < 0.05$). This finding may initially appear counterintuitive, as a lower dose of protamine could theoretically leave residual heparin, thereby increasing the bleeding risk. However, our results are consistent with those of previous studies, indicating that higher protamine doses (such as the 1 mg/kg dose) are associated with increased bleeding [5]. The increased bleeding observed in the 1 mg group might be explained by the known anticoagulant effects of protamine, which include interference with platelet function, inhibition of clotting factors V and VII, and enhancement of fibrinolysis [13, 14]. These effects could lead to a higher likelihood of postoperative bleeding despite higher protamine doses because the system remains more anticoagulated. This observation is supported by studies showing that protamine doses above the optimal level can exacerbate bleeding, which aligns with the findings of Goedhart et al. and other studies comparing lower and higher protamine doses in cardiac surgery [15].

Moreover, thromboelastometry (ROTEM) analyses have shown that excessive protamine doses can prolong the clotting time and clot formation time, which may necessitate additional transfusions of plasma coagulation factors to maintain adequate hemostasis. These findings reinforce the need for careful protamine dosing, as excessive levels can impair thrombin formation and platelet function, contributing to increased postoperative bleeding [16-18]. Additionally, as seen in the study by Suelzu, protamine doses exceeding the optimal threshold of 0.67 mg/kg disrupt hemostasis, leading to undesirable outcomes such as delayed clot formation and increased blood loss [19].

The results of this study suggest that a lower protamine dose (0.7 mg/kg) is associated with less postoperative bleeding than the standard dose of 1 mg/kg, with no significant difference in ACT values post-protamine. These findings are consistent with those of previous studies highlighting the risks of protamine overdose and its adverse effects on hemostasis and postoperative recovery. Therefore, using a lower protamine dose may be beneficial in reducing bleeding complications during OPCAB surgery, although careful consideration of individual patient characteristics is essential for optimizing dosing and minimizing adverse outcomes.

CONCLUSION

In conclusion, the study found that a 0.7 mg dose of protamine did not significantly reduce the activated clotting time (ACT) compared to a 1 mg dose, as the p-value for ACT post-protamine was 0.541, leading to rejection of the first hypothesis. However, the second hypothesis was supported, as a lower protamine dose (0.7 mg) significantly reduced postoperative bleeding at the 1st, 4th, and 12th hours after surgery, with a p-value of less than 0.05, indicating that a reduced protamine dose is associated with less bleeding during off-pump coronary artery bypass surgery.

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AUTHORS' CONTRIBUTIONS
All authors contributed to the work, including data analysis, drafting, and review of the article. They approved the final version and were accountable for all the aspects.

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