ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

COMPARISON OF PROTAMINE SULPHATE DOSE BY EXISTING FIXED DOSE METHOD AND CALCULATED DOSE METHOD ACCORDING TO ACTIVATED CLOTTING TIME OF PATIENTS UNDERGOING VALVULAR HEART SURGERIES

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Abstract

Background: To compare the fixed dose v/s calculated dose of Protamine Sulphate to achieve reversal of ACT (Activated clotting time) value after full dose of heparinization by protamine sulphate administration to as near as normal levels during valvular heart surgeries. **Material and Methods:** The study was done on 60 patients of ASA grade II & III scheduled for valvular heart surgery. All the patients were subjected to detailed pre-anaesthetic evaluation with clinical history and systemic examination. Routine investigations were done. All the patients were divided randomly into two groups, Group A and Group B. In Group A, protamine dose was given according to the calculated formula based on ACT. In Group B, Fixed dose of Protamine Sulphate, 1 mg protamine for each mg of heparin was given. **Results:** Group A and B showed significant difference in terms of protamine dose. In Group A the mean dose of protamine was 119.9 mg while in Group B the protamine dose given was 133.4mg (SD ± 17.98) based on fixed dose method. This difference in protamine dose was statistically significant (p-0.0104) .Using fixed dose method in Group B patients would have

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resulted in administration of extra protamine dose of 21 mg. There was increased amount of bleeding in Group B than in Group A patients. The average amount of total blood loss in group B was 1252.59ml (SD ± 267.95) and in group A was 1114.5ml (SD ± 212.02), which was significantly less in Group A patients. The amount of blood products transfused was also less in Group A than in Group B. **Conclusion:** ACT as a measure to calculate protamine dose for reversal of heparin resulted in reduced dose of protamine as compared to fixed dose of protamine used. This method can calculate protamine dose necessary to neutralise heparin more accurately. It also led to reduced amount of blood loss and decreased requirements of blood transfusion in perioperative period.

Keywords: Protamine Sulphate, ACT (Activated clotting time), Unfractioned heparin.

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Introduction

ACT remains the most widespread test in clinical practice for the calculation of adequate dose of protamine sulphate to be used. ACT is intended to monitor anticoagulant effect of unfractioned heparin. Target ACT value depends on specific dose & clinical scenario. Normal ACT value varies from 80-130 seconds. Normal ACT indicates that the tested blood contains either no heparin or that all heparin has been neutralised by protamine. Heparin remains the anticoagulant of choice for most of the cardiac surgeries. The action of hepain is well understood and one of the main advantage is the ease with which it can be neutralised.

Protamine remains the main stay of this process, although protamine has been associated with some adverse reactions. Rapid intravenous injection of protamine sulphate may cause a sudden fall in blood pressure, bradycardia, pulmonary hypertension, dyspnoea, transitory flushing and a feeling of warmth. Also, it can cause anaphylaxis reaction, resulting in respiratory distress. Overdose can even cause haemorrhage. Hyperheparinemia and bleeding has been reported in some patients after cardiac surgery, inspite of complete neutralisation of heparin by protamine sulphate (Heparin Rebound). Thus, accurate calculation of protamine dose is important in patients undergoing cardiac surgeries. This was a prospective, randomized study conducted in the Department of Anaesthesiology, Gandhi Medical College, and associated Hamidia hospital, Bhopal Madhya Pradesh, after approval from institute's ethical committee for the comparison of protamine sulphate dose by fixed dose method and calculated dose method according to ACT of patients undergoing valvular heart surgeries.

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Material and Methods

Study Design

This was a prospective, randomized study conducted in the Department of Anaesthesiology, Gandhi Medical College, and associated Hamidia hospital, Bhopal Madhya Pradesh, after approval from institute's ethical committee for the comparison of protamine sulphate dose by fixed dose method and calculated dose method according to ACT of patients undergoing valvular heart surgeries from March 2017 to August 2018.

Inclusion criteria

1. Age 20-50 years
2. Patient posted for heart valvular replacement surgeries.
3. ASA grade 2 and 3.
4. NYHA grade I, II & III

Exclusion criteria

1. ASA grade IV
2. NYHA grade IV
3. Patient undergoing double valve repair (DVR) or associated surgeries like CABG and revision heart surgeries.
4. Patients with renal and severe hepatic impairment, bleeding diastasis, PT > 14 seconds, INR > 1.5 neurological disorders, psychiatric disorders.
5. Known history of protamine sulphate sensitivity.

Informed Consent and Ethical Aspects

After explaining the protocol to all patients, a written and informed consent was taken from all patients. A detailed history, complete physical examination and routine investigations were done for all patients.

Sample Size

Sixty patients were selected for study, and informed consent was obtained from all of them. The patients were randomly allocated into one of the two groups: 30 patients in each group-: Group A and Group B.

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Group A: Protamine dose according to the calculated formula based on ACT.

Calculated Protamine Dose(mg) =

$$\frac{\text{Pre-Protamine ACT - BasalACT}}{\text{Post Initial Heparin Bolus ACT - Basal ACT}} \times \text{Initial Heparin Bolus(mg)}$$

(Note:- ACT value is measured in seconds)

Group B: Fixed dose of Protamine Sulphate, 1 mg protamine for each mg of heparin given.
The study was done on 60 patients of ASA grade II & III scheduled for valvular heart surgery. All the patients were subjected to detailed pre-anaesthetic evaluation with clinical history and systemic examination. Routine investigations were done (CBC, Fasting and post prandial blood sugar, Serum electrolytes Serum Urea & Creatinine, Coagulation profile, ECG, Echo cardiography, Chest X ray, Viral markers (HIV, HbsAg, HCV)
All the patients were divided randomly into two groups, Group A and Group B. In Group A, protamine dose was given according to the calculated formula based on ACT.

Calculated Protamine Dose(mg) =

$$\frac{\text{Pre-Protamine ACT - BasalACT}}{\text{Post Initial Heparin Bolus ACT - Basal ACT}} \times \text{Initial Heparin Bolus(mg)}$$

(Note:- ACT value is measured in seconds)

In Group B fixed dose of Protamine Sulphate, 1 mg protamine for each mg of heparin was given. Pre operatively, peripheral venous access using a 18 G cannula was secured. RL & NS @ 5ml/kg rate was given. The patient was connected to a multichannel monitor showing ECG, pulse rate, SpO2, respiratory rate, NIBP. After pre medication with IV glycopyrrolate (0.01 mg/kg), ondansetron (0.1 mg/kg), midazolam (0.05 mg/kg) and fentanyl (3 mg/kg), arterial line (radial or femoral) was inserted for invasive blood pressure monitoring and basal ACT values. All the base line parameters were recorded and after induction IJV was cannulated to monitor CVP. Before the purse string suture was applied to the aorta, we administered an initial dose of 3mg/kg heparin to maintain ACT values above 480 seconds during CPB. Before and after CPB, blood samples for ACT measurements were collected. During CPB blood samples were collected from the extracorporeal circuit. Heparin was not

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added to the prime. We measured basal ACT, pre protamine ACT & post initial Heparin Bolus ACT. ACT values were taken at every 30 minutes duration**.** Protamine sulphate was started after the removal of route vent cannula. In group A, protamine was given according to the mathematical formula based on ACT of patients and in group B fixed dose of protamine was given. Both the groups were observed for ACT values after administration of protamine sulphate, intra operative and post-operative amount of bleeding, need of any blood transfusion and, any protamine reaction. Demographic data (Age, Sex, Weight) was comparable in both the groups with p value >0.05. Difference in basal hemodynamic parameters (heart rate, blood pressure, mean blood pressure)and basal ACT was also insignificant with p value>0.05.

Results

Table 1: Nyha Grade

Nyha	**Group**		**Total**
	A	**B**	
II	19	18	37
III	11	12	23
Total	30	30	60

Number of patients in Group A with NYHA grade II was 19 and in Group B were 18. Number of patients in Group A with NYHA grade III was 11 and in Group B were 12.

Table 2: Mean Duration of Bypass

Group	**Mean Duration of Bypass (in minutes)**	**± Std. Deviation**	**P value**
A	114.8	18.07	0.759
B	116.2	17.18	

Mean duration of bypass in Group A patients was 114.8 min and in Group B patients was 116.2 min. There was no statistically significant difference in between two groups (P value – 0.759).

Table 3: Mean Basal ACT

Groups	**Basal ACT (in seconds)**	**± Std. Deviation**	**P value**

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A	113.4	11.09	0.48
B	111.2	12.63	

Mean basal ACT in Group A patients was 113.4 seconds and in Group B patients was 111.2 seconds. There was no statistically significant difference in between two groups (P value – 0.48).

Table 4: Mean Heparin Dose (Initial Bolus)

Group	Heparin (initial bolus in mg)	± Std. Deviation	P value
A	140.9	22.60	0.16
B	133.4	17.97	

Mean heparin initial dose in Group A patients was 140.9 mg and in Group B patients was 133.4 mg. There was no statistically significant difference in between two groups (P value – 0.16).

Table 5: Mean Protamine Dose

Group	Protamine Dose (IN MG)	± Std. Deviation	P value
A	119.9	21.37	0.0104
B	133.4	17.98	

Mean protamine dose in Group A patients was 119.9 mg and in Group B patients was 133.4 mg. There was statistically significant difference in between two groups (P value – 0.0104).

Table 6: Mean Final ACT

Group	Final ACT (In Seconds)	± Std. Deviation	P value
A	112.83	12.79	0.917
B	107.8	9.56	

Mean final ACT in Group A patients was 112.83 seconds and in Group B patients was 107.8 seconds. There was no statistically significant difference in between two groups (P value – 0.917).

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Table 7: Mean Total Blood Loss

Group	Total Blood Loss (IN ML)	± Std. Deviation	P value
A	1114.5	212.02	0.0308
B	1252.6	267.95	

Mean blood loss in Group A patients was 1114.5 ml and in Group B patients was 1252.6ml. There was statistically significant difference in between two groups (P value – 0.0308).

Table 8: Mean Blood Transfusion

Group	Mean PRBC Transfusion (Units)	± Std. Deviation	P value
A	0.56	0.77	0.011
B	1.2	1.09	

Mean blood transfusion in Group A patients was 0.56 units and in Group B patients was 1.2 units. There was statistically significant difference in between two groups (P value – 0.011).

- Group A and B showed significant difference in terms of protamine dose. In Group A the mean dose of protamine was 119.9 mg (SD ± 21.37) using the mathematical formula based on ACT, while in Group B the protamine dose given was 133.4mg (SD ± 17.98) based on fixed dose method. This difference in protamine dose was statistically significant (p-0.0104). In all the cases in group A, the reduced dose of protamine was given and ACT returned to normal values and no further protamine dose was required. Only two cases in Group A had ACT >130 seconds.
- If we would have used the fixed dose method in Group A the average protamine dose given would have been 140.9mg. So the difference between these two protamine doses is 21 mg. This signifies that using fixed dose method in Group A patients would have resulted in administration of extra protamine dose of 21 mg.
- Regarding total blood loss, there was increased amount of bleeding in Group B than in Group A patients. The average amount of total blood loss in group B was 1252.59ml (SD ± 267.95) and in group A was 1114.5ml (SD ± 212.02), which was significantly less in Group A patients (p=0.0308).
- The amount of blood products transfused was also less in Group A than in Group B. In Group A 40% patients needed blood transfusion while in group B, 63.33% patients

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required blood transfusion. The average units of PRBC transfused in Group A and Group B was 0.56 and 1.2 units respectively, which was found statistically significant (p=0.0110).

- No adverse reaction of protamine and blood transfusion was seen in either of the groups.

Statistical Analysis

In the statistical analysis of our study, continuous variables were presented as mean for parametric data and median if the data was non parametric or skewed. Student-t test was applied for calculation of statistical significance. Categorical variables were expressed as frequencies and percentages. P <0.05 was taken to indicate a statistically significant difference. P value was calculated with the help of mean and standard deviation.

Discussion

Protamine is used in all the procedures requiring CPB to reverse the action of heparin. But the dose of protamine is not standardised and excess dose of protamine if administered can lead to adverse reaction such as bleeding. Inadequate doses of protamine can cause improper reversal of heparin and even Heparin Rebound is also seen to occur. So, the dose of protamine should be appropriate to neutralise heparin.

Most commonly protamine is given in a dose of 1mg for each mg (100U) of heparin. This dose could be in excess of what is required; as it is seen that heparin concentration decreases over a period of time during CPB. Bull and associates found that the response to heparin varied with individuals. Joel Umles et al in their study also found that reducing the dose of protamine to 2/3rd of the conventional dose of 1:1 for protamine and heparin was associated with adequate reversal of heparin and less amount of bleeding, clotting and heparin rebound episodes. Salvatone Suelzuet et al also found adequate reversal of heparin while reducing the dose of protamine to 2/3rd of conventional dose used.

There are many coagulation tests used to monitor circulating heparin levels, out of which ACT is the most common coagulation test used to monitor heparin levels and its reversal by protamine during CPB. Jack. A. Roth et al noted that the dose of protamine required to reverse the heparin was half when it was calculated using ACT rather than the standard protocol of using protamine dose as twice the heparin dose. Babka & co workers also noted that less protamine was required when ACT was utilised to calculate the dose and also the bleeding was significantly less as compared to the group receiving fixed dose of protamine.

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In our study, we have used a mathematical formula which is based on ACT of patient to calculate dose of protamine. We have found that the dose of protamine calculated by using this formula is significantly lower (p=0.0104) than the dose given by conventional fixed dose method of 1:1 for protamine and heparin. Despite giving lower doses of protamine in the study group, the post-operative results stayed the same; with ACT returning back to normal value and even there was less amount of bleeding and less requirement of blood and blood products in the post-operative period. Our results are in correlation with the study of Javier Suarez Cuenca et al, who also used the mathematical formula based on ACT to calculate protamine dose. They found that the dose calculated by this formula was significantly lower than that calculated by fixed dose method and also it was adequate to reverse the heparin with ACT returning to normal values. They also found that the amount of post-operative bleeding was less in the study group. Stephen A Kunz et al in their study also found that higher doses of intra-operative protamine relative to heparin were associated with greater risk of transfusion and post-operative bleeding.

Conclusion

Our study concluded that using ACT as a measure to calculate protamine dose for reversal of heparin resulted in reduced dose of protamine as compared to fixed dose of protamine used. This method can calculate protamine dose necessary to neutralise heparin more accurately. It also led to reduced amount of blood loss and decreased requirements of blood transfusion in perioperative period.

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