Original Article

Optimal Dose of Protamine for Heparin Reversal in Patients Undergoing Cardiopulmonary Bypass Surgery

Kanlayanee Yongyukantorn MD[1], Panthila Rujirojindakul MD[2], Orarat Karnjanawanichkul MD[1]

[1] Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand
[2] Bumrungrad International Hospital, Bangkok, Thailand

Objective: To compare the heparin reversal effect among three differential protamine doses in 1:1 ratio based on initial heparin dose (group 1), initial plus additional heparin dose (group 2), and total heparin dose (group 3) in patients undergoing cardiopulmonary bypass [CPB] surgery.

Materials and Methods: A retrospective review and follow up study was conducted in adult patients undergoing CPB surgery at a tertiary university hospital. The initial heparin dose, additional heparin dose, total heparin dose, protamine dose, baseline activated clotting time [ACT] and ACT after heparin reversal were obtained. Effective heparin reversal was defined as post reversal ACT within 10% of the baseline ACT value or between 80 to 150 seconds.

Results: Five hundred CPB surgical patients were included in the present study. Effective heparin reversal was achieved in 47.2%, 45.1%, and 55.6% of patients in groups 1, 2, and 3, respectively (p = 0.17). There was no difference in amount of blood loss and blood transfusion in 24 hours postoperatively.

Conclusion: There was no difference in effectiveness of heparin reversal, postoperative bleeding, and postoperative blood transfusion among these three differential protamine doses.

Keywords: Cardiac surgery, Dose, Heparin, Protamine

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Protamine is administered after cardiopulmonary bypass [CPB] to reverse heparin anticoagulation in open heart surgery[1,2]. Many methods have been used to calculate the optimal dosage of protamine. Using a heparin:protamine ratio of 1:1 to 1.3 is the most common choice and the simplest way based on the knowledge that protamine reverses anticoagulant activity of heparin by binding heparin to form an inactive complex in a 1:1 ratio[2]. However, many studies have shown that this ratio based on total heparin dose can cause serious complication from excess circulating protamine[3-5].

Excess protamine has been associated with coagulopathy, platelet aggregation, various hemodynamic changes, pulmonary edema, and increased risk of in-hospital mortality[6-8]. Berger et al[4] found that giving lower doses of protamine was effective neutralization while reducing postoperative blood loss and the incidence of re-operation from excessive bleeding when compared with a 1:1.37 ratio. However, the European Society of Anesthesiology guidelines still recommend this ratio due to the equivocal evidence[9]. The authors' institution still follows this recommendation. Due to concerns of excess circulating protamine and heparin clearance, some anesthesiologists gave the lower dose of protamine in 1:1 ratio based on initial or initial plus additional heparin instead of the ratio based on total heparin.

Thus, the present study aimed to determine the optimal dose of protamine needed for effective heparin reversal.

Materials and Methods

After approval from the Institutional Ethics Committee, the present study, a retrospective review of medical records, was conducted between January 2011 and December 2015. Patients aged between 18 to 75 years old that underwent open heart surgery using CPB circuit were included. Patients who had renal or liver failure, previous open heart surgery, active endocarditis, thoracic aortic aneurysm, cyanotic

Correspondence to:

Karnjanawanichkul O. Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, 15 Kanjanavanich Road, Hat Yai, Songkhla 90110, Thailand.
Phone: +66-74-451652, Fax: +66-74-429621
Email: oraratx@yahoo.com

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heart disease, preoperative use of anticoagulant, preoperative coagulopathy, intraoperative circulatory arrest, preoperative and postoperative use of intra-aortic balloon pump or extracorporeal membrane oxygenation, heparin resistance (receive fresh frozen plasma [FFP] after 6 mg/kg of heparin), and incomplete data were excluded, as were patients who died intraoperatively.

In all patients, baseline activated clotting time [ACT] was measured. The initial heparin bolus dose was 3 to 4 mg/kg. If the ACT was less than 400 seconds, 0.5 to 1 mg/kg of heparin was added. After the CPB, protamine was given to neutralize the heparin effects. Three differential doses of protamine were given. The patients were divided into three groups according to these doses.

Group 1: Protamine dose was equal to initial heparin dose.

Group 2: Protamine dose was equal to initial plus additional heparin dose (excluding CPB circuit).

Group 3: Protamine dose was equal to total heparin dose (the initial dose plus any additional dose given, including the CPB circuit).

ACT was done 10 minutes after the protamine was given. If it was prolonged, additional increments of 25 to 50 mg of protamine were given until the return of normal ACT.

The patient's age, weight, height, preoperative ejection fraction, the New York Heart Association [NYHA] classification, the American Society of Anesthesiologists [ASA] physical status, type of case (elective or emergency), smoking status, type of operation, CPB time, aortic clamp time, initial heparin dose, additional heparin dose, total heparin dose, protamine dose, baseline ACT, ACT after heparin reversal, 24-hour postoperative blood loss via chest drain, and 24-hour postoperative blood transfusion were obtained from the anesthetic record and hospital information system. The primary outcome was effective heparin reversal, which was defined as post reversal ACT within ±10% of baseline ACT or between 80 to 150 seconds. The secondary outcomes were 24-hour postoperative blood loss and blood transfusion in milliliter.

A pilot study was done for sample size calculation using the data of 50 patients between January and April 2015. Four hundred ninety samples were calculated by using 95% confidence interval, 80% power and 15% dropout, so we collected the data of 500 patients. Statistical analysis was performed using R software. Continuous variables were presented as median and interquartile range [IQR], while categorical variables were presented as frequency and percentage. Statistical comparison of the proportion of patients achieving heparin reversal between the three groups were done using a Chi-squared test while, comparison of blood loss and blood transfusion postoperatively were done using Kruskal-Wallis tests. A p-value less than 0.05 was considered as statistically significant.

Results

Five hundred patients were included. There were 259 patients (53.8%) in group 1, 51 patients (10.2%) in group 2, and 180 patients (36%) in group 3. Patient demographic data is shown in Table 1.

There was no difference between the three groups in terms of age, preoperative ejection fraction, NYHA classification, ASA physical status classification, elective or emergency case, smoking status, type of operation, CPB time, aortic clamp time, and intra-operative defibrillation use. There were differences in sex, weight, height, and body mass index [BMI] among groups. Most of the patients were in NYHA classification II, ASA physical status classification 3, elective case, and never smoking. The majority of patient had coronary artery bypass graft [CABG] surgery. The median CPB times for groups 1, 2, and 3 were 111, 109, and 114.5 minutes and the median aortic clamp times were 80, 75, and 82 minutes, respectively.

The results showed no statistically significant difference in terms of effective heparin reversal between groups ($p = 0.17$). The percentage of patients who achieved effective heparin reversal in group 1 was 47.2%, 45.1% in group 2, and 55.6% in group 3. There was also no difference in amount of blood loss and blood transfusion in 24 hours postoperatively (Table 2). Re-operation was performed in seven patients with no difference between the three groups. The major cause of re-operation was bleeding (85.7%).

Discussion

The present study showed no difference in the proportion of patients achieving effective heparin reversal among the three groups using a heparin, protamine dose ratio of 1:1 based on initial heparin dose (group 1), initial plus additional heparin dose (group 2), and total heparin dose (group 3). The median amount of blood loss and the median amount of blood transfusion postoperatively was similar in the three groups.

Although there were two studies that support the higher protamine dose[10,11], many studies showed lower protamine doses correlate with better outcomes[3-5,12].

Table 1. Comparison of demographic data between the three groups

Variables	Group 1 (n = 269)	Group 2 (n = 51)	Group 3 (n = 180)	*p*-value
Sex, n (%)				0.04*
Male	172 (63.9)	28 (54.9)	94 (52.2)	
Female	97 (36.1)	23 (45.1)	86 (47.8)	
Age (years), median (IQR)	58 (47, 65)	55 (47.5, 64.5)	59 (49.8, 67)	0.29
Weight (kg), median (IQR)	62 (55.8, 73)	57 (48.9, 64)	59.9 (52, 66.9)	<0.001*
Height (cm), median (IQR)	162 (155, 167)	156 (153.5, 165)	159 (152, 165)	0.002*
BMI (kg/m^2), median (IQR)	24.2 (21.7, 27.1)	22.6 (19.7, 24.6)	23.8 (21.3, 26.4)	0.01*
Preoperative ejection fraction (%), median (IQR)	63 (50, 65)	64 (50, 72)	65 (53, 69.8)	0.31
Preoperative NYHA class, n (%)				0.24
I	27 (10.0)	1 (2.0)	11 (6.1)	
II	129 (48.0)	27 (52.9)	103 (57.2)	
III	98 (36.4)	21 (41.2)	59 (32.8)	
IV	15 (5.6)	2 (3.9)	7 (3.9)	
ASA physical status, n (%)				0.73
3	239 (88.8)	44 (86.3)	161 (89.4)	
4	29 (10.8)	7 (13.7)	17 (9.4)	
5	1 (0.4)	0 (0.0)	2 (1.1)	
Case, n (%)				0.49
Elective	228 (84.8)	40 (78.4)	153 (85.0)	
Emergency	41 (15.2)	11 (21.6)	27 (15.0)	
Smoking status, n (%)				0.67
Never	150 (55.8)	31 (60.8)	113 (62.8)	
Current	11 (4.1)	1 (2.0)	5 (2.8)	
Quit	106 (39.4)	19 (37.3)	59 (32.8)	
No data	2 (0.7)	0 (0.0)	3 (1.7)	
Operation				
CABG	129 (48.0)	22 (43.1)	92 (51.1)	0.56
Valvular repair/replacement	114 (42.4)	28 (54.9)	77 (42.8)	0.24
Septal closure	46 (17.1)	9 (17.6)	27 (15.0)	0.81
Other operation	8 (3.0)	1 (2.0)	4 (2.2)	0.92
Anesthetic time (hour), median (IQR)	4.8 (4, 5.9)	4.8 (4, 5.8)	5.2 (4.1, 6)	0.42
Operative time (hour), median (IQR)	3.8 (2.9, 4.8)	3.7 (3, 4.5)	4 (3.1, 4.8)	0.48
CPB time (minute), median (IQR)	111 (83, 135)	109 (77.5, 136)	114.5 (83, 140)	0.77
Aortic clamp time (minute), median (IQR)	80 (56, 97)	75 (57.5, 104)	82 (59, 106.2)	0.45
Using intraoperative defibrillation, n (%)				0.46
No	239 (88.8)	43 (84.3)	163 (90.6)	
1 to 2 times	22 (8.2)	6 (11.8)	15 (8.3)	
>2 times	8 (3.0)	2 (3.9)	2 (1.1)	

NYHA = New York Heart Association; ASA = American Society of Anesthesiologists; IQR = interquartile range; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; BMI = body mass index

* Statistically significant difference (*p*-value <0.05)

Table 2. Effectiveness of heparin reversal and 24-hour postoperative blood loss and blood transfusion

	Group 1 (n = 269)	Group 2 (n = 51)	Group 3 (n = 180)	*p*-value
Effective heparin reversal, n (%)	127 (47.2)	23 (45.1)	100 (55.6)	0.17
Postoperative blood loss (ml)†	380 (300, 560)	360 (265, 585)	420 (268, 571)	0.68
Postoperative blood transfusion (ml)†				
PRC	467 (276, 590)	505 (293, 708)	435 (252, 560)	0.14
FFP	505 (441, 602)	555 (470, 670)	505 (422, 617)	0.44
Platelets	375 (322, 436)	378 (342, 452)	381 (336, 448)	0.90

PRC = packed red cell; FFP = fresh frozen plasma

† Data presented as median (IQR)

Berger et al[4] found that giving a dose of 0.79 mg protamine to neutralize 1 mg exogenous heparin was associated with effective neutralization while reducing postoperative blood loss and incidence of reoperation for excessive bleeding when compared with 1.37 mg protamine. The studies of Miyashita et al[12] and Vonk et al[3] also found a lower protamine to heparin ratio improved hemostatic parameters and reduced the incidence of severe blood loss. The authors' study supported the use of lower protamine dose and suggested 1:1 heparin: protamine ratio base on initial heparin dose due to no difference in effectiveness of heparin reversal, 24-hour postoperative blood loss, and incidence of re-operation from excessive bleeding.

The authors accepted the success rate of heparin reversal of 47.2%, since there is wide range of response following empirical protamine dose. Previous studies illustrated that the lowest percentage of effective reversal using empirical dose was 45%[5].

The present study was limited by the retrospective study design. The sample sizes of each group were unequal. There were differences in sex, weight, height, and BMI among the three groups that may have affected the study results. The effectiveness of heparin reversal was determined by ACT, so the conditions such as hemodilution and hypothermia may prolong ACT and lead to false interpretation.

Conclusion

The authors found that there was no difference in effectiveness of heparin reversal, postoperative bleeding, and blood transfusion among patients who received different doses of protamine based on initial heparin dose, initial plus additional heparin dose, and total heparin dose. Thus, the dose equals initial heparin dose may be the best choice.

What is already known on this topic?

Giving a dose of 0.79 mg protamine for neutralization of 1 mg exogenous heparin was associated with effective neutralization while reducing postoperative blood loss and incidence of re-operation for excessive bleeding when compared to 1.37 mg protamine.

What this study adds?

There was no difference in effectiveness of heparin reversal, postoperative bleeding, and postoperative blood transfusion among three differential protamine doses in 1:1 ratio based on initial heparin dose, initial plus additional heparin dose, and total heparin dose.

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Potential conflicts of interest

The authors declare no conflict of interest.

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