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Clinical Research

Risk Factors Associated with Difficult Reversal of Heparin by Protamine Sulfate in Cardiopulmonary Bypass: An Ignored Issue

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Background: The aim of this study was to evaluate risk factors associated with difficult heparin reversal by protamine after cardiopulmonary bypass.
Methods: Data from 120 consecutive patients who underwent open heart surgery from 2009 to 2017 were retrospectively reviewed. Patients were divided into 2 groups: (1) those in whom complete heparin reversal was achieved after a single infusion of protamine (group A, n=89); and (2) those who required more protamine for heparin reversal (group B, n=31).
Results: Female sex, prolonged bypass time (>200 min), long aortic cross-clamping time (>120 min), and a lowest rectal temperature <26°C were significant predictors of difficult heparin reversal. Larger amounts of fresh frozen plasma and platelet concentrate were transfused in group B than in group A.
Conclusion: Surgeons' efforts to reduce operative time and avoid deep hypothermia may be helpful for increasing the likelihood of easy heparin reversal, especially in female patients.

Keywords: Cardiopulmonary bypass, Coagulation, Heparin, Protamines

Introduction

Heparin is routinely neutralized with protamine sulfate to control blood loss at the completion of cardiopulmonary bypass (CPB). The activated clotting time (ACT), introduced by Hattersley [1] in 1966, is an objective clotting test used to evaluate the efficacy of heparin neutralization. In Korea, ACT has been widely used since the late 1970s, and its clinical outcomes have been reported [2,3]. Because ACT monitoring is considered to be the gold standard for heparin reversal by protamine, this issue has received little attention in the recent literature.

In clinical practice, some cases need more protamine due to a prolonged ACT. The objective of this study was to evaluate the risk factors associated with difficult heparin reversal and to determine whether the use of additional protamine was associated with postoperative bleeding and the amount of blood transfusion.

Methods

Study population

The medical records of 120 consecutive patients who underwent open heart surgery and aortic surgery using CPB at Jeju National University Hospital from 2009 to 2017 were retrospectively reviewed. These patients were divided into 2 groups: (1) those in whom complete heparin reversal could be achieved by a single infusion of protamine (group A, n=89); and (2) those who required more protamine to achieve complete heparin reversal because of a prolonged ACT (group B, n=31). The study was approved by the Institutional Review Board of Jeju National University Hospital (IRB approval no., 2019-07-011). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study.

Monitoring protocol of activated clotting time and routine blood transfusion

In the operating room, the initial ACT was measured using a whole blood micro-coagulation system (Hemochron Jr. Signature; Accriva Diagnostics, San Diego, CA, USA) after radial artery access for blood pressure monitoring. After median sternotomy, heparin was administered through a central venous catheter, with a routine amount of 300 IU/kg. Aortic cannulation was performed after confirming that the ACT had increased to over 400 seconds. We maintained the ACT from 400 to 600 seconds during CPB by adding heparin and checking the ACT every 30 minutes. After successful weaning from CPB, protamine sulfate was slowly given through a peripheral venous line at a dosage of 1.3 mg per 100 IU of initially administered heparin. The ACT was measured 10 minutes after the termination of protamine infusion. If the ACT was over 150 seconds and we were not sure of hemostasis, we added 50 mg of protamine and then 30 mg of protamine after the second ACT test.

We routinely prepared 5 units of packed red blood cells, 5 units of fresh frozen plasma, and 10 units of platelet concentrate. We transfused 3 units of packed red blood cells, 3 units of fresh frozen plasma, and 10 units of platelet concentrate in the operating room during CPB weaning.

Statistical analysis

All continuous data are expressed as mean±standard deviation and analyzed using IBM SPSS for Windows ver. 19.0 (IBM Corp., Armonk, NY, USA). The patients were divided into 2 groups. The independent Student t-test was used to compare parametric data between the 2 groups, while the Mann-Whitney U-test was used for nonparametric data. Categorical variables are expressed as the number of cases and percentage. The chi-square test or Fisher exact test was used to compare categorical variables between the 2 groups. The risk factors associated with difficult heparin reversal were analyzed using the Fisher exact test or Mann-Whitney U-test. In all analyses, p-values <0.05 were considered to indicate statistical significance.

Results

Patients' characteristics and operative data

Patients' characteristics are summarized in Table 1. Group A included 89 patients (61 men and 28 women) with a mean age of 57.8±17.8 years, while group B included 31 patients (14 men and 17 women) with a mean age of 62.0±13.2 years. There were significantly more female patients in group B (p=0.021), whereas there were significantly more patients with diabetes in group A (p=0.019) (Table 1). No statistically significant between-group differences were found in preoperative laboratory data or clinical conditions. However, the patients in group B had a significantly longer bypass time (p=0.020), cross-clamping time (p=0.016), and lower values of the lowest rectal temperature (p=0.021) than those in group A (Table 2).

Table 1. Clinical characteristics and preoperative laboratory data

Characteristic	Group A (n=89)	Group B (n=31)	p-value
Age (yr)	57.8±17.8	62.0±13.2	0.229
Female sex	28 (31.5)	17 (54.8)	0.021
Body surface area (m^2)	1.63±0.29	1.63±0.18	0.980
Left ventricular ejection fraction (%)	58.7±11.5	60.1±12.6	0.594
Diabetes mellitus	31 (35)	4 (13)	0.019
Hypertension	46 (52)	18 (58)	0.540
Chronic renal failure	7 (8)	5 (16)	0.190
Atrial fibrillation	19 (21)	5 (16)	0.532
Hemoglobin (mg/dL)	12.9±1.7	12.8±1.7	0.783
Platelet count (10^3/μL)	225.0±77.5	201.3±64.9	0.129
Aspartate transaminase (IU/L)	31.4±28.3	33.2±24.3	0.754
Alanine transaminase (IU/L)	31.8±40.3	27.7±21.5	0.599
Total bilirubin (mg/dL)	0.67±0.34	0.68±0.30	0.866
Prothrombin time (international normalized ratio)	1.11±0.14	1.13±0.31	0.630

Values are presented as mean±standard deviation or number (%).

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Table 2. Operative data

Variable	Group A (n=89)	Group B (n=31)	p-value
Operations			
Aortic valve replacement	21 (23.6)	9 (29.0)	
Mitral valve replacement	14 (15.7)	6 (19.4)	
Double valve replacement	15 (16.9)	6 (19.4)	
Coronary artery bypass grafting	24 (27.0)	4 (12.9)	
Aortic surgery	5 (5.6)	4 (12.9)	
Repair of congenital heart disease	9 (10.1)	2 (6.5)	
Pulmonary embolectomy	1 (1.1)	0	
Cardiopulmonary bypass time (min)	144.4±58.7	190.8±100.3	0.020
Aortic cross-clamping time (min)	89.7±39.4	115.0± 50.9	0.016
Heparin-protamine profiles			
Initial ACT (sec)	114.6±15.4	125.0±47.0	0.071
Post-heparin ACT (sec)	480.4±89.9	495.5±104.5	0.443
Initial amount of heparin (mg)	182.9±47.0	191.9±74.4	0.436
Amount of protamine (mg)	238.8±62.3	231.6±37.2	0.548
Amount of cardioplegia (mL)	2,168.2±738.1	2,510.0±933.4	0.071
Amount of ultrafiltration (mL)	3,100.6±1,630.1	3,145.2±1,767.5	0.898
Lowest rectal temperature (°C)	31.48±2.98	29.99±3.25	0.021

Values are presented as number (%) or mean±standard deviation.
ACT, activated clotting time.

Table 3. Postoperative course and amounts of blood transfusion

Variable	Group A (n=89)	Group B (n=31)	p-value
Intensive care unit stay (day)	60.9±112.2	98.2±136.5	0.135
In-hospital days (day)	19.1±14.2	22.9±25.4	0.308
Amount of transfusion (packs)			
Packed red blood cells	7.14±6.1	11.10±11.0	0.064
Fresh frozen plasma	5.6±3.9	9.4±7.7	0.014
Platelet concentrate	10.8±4.5	15.0±9.2	0.021
Amount of tube drainage (mL)			
<12 hr	806.4±828.9	894.5±920.0	0.621
<24 hr	995.7±770.9	1,216.1±1,061.5	0.220
<48 hr	1,238.9±889.9	1,495.0±1,209.2	0.221
Total amount (mL)	2,970.1±2,215.3	3,588.7±3,192.1	0.246
Tube removal days (day)	4.3±2.4	5.36±4.6	0.134

Values are presented as mean±standard deviation.

Postoperative course and amounts of blood transfusion

There were no in-hospital deaths. No statistically significant between-group differences were found in the duration of the intensive care unit or hospital stay. The amount of transfused packed red blood cells in group B was larger than that in group A, but without reaching statistical significance (p=0.064). Furthermore, the amounts of transfused fresh frozen plasma and platelet concentrate in group B were significantly greater than those in group A (p=0.014 and p=0.021, respectively). The cumulative amount and duration of chest tube drainage in group B were 3,588 mL and 5.4 days, respectively. The corresponding values were 2,970 mL and 4.3 days in group A. However, those differences between the 2 groups were not statistically significant (p=0.246 and p=0.134, respectively) (Table 3).

Risk factors associated with difficult heparin reversal

Risk factor analysis revealed that female sex, a prolonged CPB time (>200 minutes), a long duration of aortic cross-clamping (>120 minutes), and a lowest rectal tem-

Table 4. Statistical analysis of risk factors associated with difficult heparin reversal

Variable	Group A (n=89)	Group B (n=31)	p-value
Female	28 (31.5)	17 (54.8)	0.021
Age >65 yr	36 (40.4)	15 (48.4)	0.441
Body surface area <1.6 m^2	36 (40.4)	14 (45.2)	0.647
Left ventricular ejection fraction <40%	7 (7.9)	2 (6.5)	1.000
Diabetes mellitus	31 (34.8)	4 (12.9)	0.022
Hypertension	46 (51.7)	18 (58.1)	0.114
Chronic renal failure	7 (7.9)	5 (16.1)	0.187
Atrial fibrillation	19 (21.3)	5 (16.1)	0.532
Hemoglobin <12 mg/dL	30 (33.7)	8 (25.8)	0.415
Platelet count <150,000/μL	17 (19.1)	11 (35.5)	0.121
Initial activated clotting time >120 sec	27 (30.3)	14 (45.2)	0.134
Cardiopulmonary bypass time >200 min	21 (23.6)	12 (38.7)	0.020
Aortic cross-clamping time >120 min	19 (21.3)	13 (41.9)	0.026
Lowest rectal temperature <26°C	6 (6.7)	6 (19.4)	0.049

Values are presented as number (%).

perature <26°C were predictors of difficult heparin reversal (p=0.021, p=0.020, p=0.026, and p=0.049, respectively) (Table 4).

Discussion

CPB is the most integral component of cardiac surgery. Full anticoagulation during CPB is mandatory. Although complete reversal of heparin is vitally important after CPB is completed, in some cases, the ACT cannot be normalized by protamine infusion. Microvascular coagulopathy, clinically known as capillary oozing, is thought to be the most common cause of mediastinal bleeding resulting from CPB. However, its etiology is unclear, although it has been proposed that inappropriate doses of heparin and protamine are possible triggers [4]. Protamine has been administered empirically following the completion of CPB. Conventionally, it is known that heparin can be neutralized by protamine in a ratio of 1:1 or 1:1.3 and that 1 mg of heparin includes 100 IU [5-7].

In this study, female sex, prolonged operation time, and deep hypothermia were found to be risk factors for difficult heparin reversal. Yamamoto et al. [8] investigated the underlying reasons for prolonged ACT after protamine administration following CPB in cases of pediatric open heart surgery. They proposed low blood concentrations of coagulation factors (e.g., fibrinogen, antithrombin, and prothrombin) as possible reasons. Hoffman [9] suggested that the blood stream into the circuit and oxygenation membrane during CPB could induce repeated cycles of hemolysis and coagulation. This phenomenon could lead to a thromboembolic event. Akl et al. [10] proposed that the ACT may be determined by the metabolic rate of heparin, which could be affected by various factors, including different levels of sensitivity to heparin, cardiac output, total amount of blood supply, and perfusion velocity in each patient. Adhana et al. [11] proved that bleeding time and clotting time were significantly higher in women than in men in their study of 200 healthy volunteers. They suggested that increased estrogen levels could reduce platelet function and plasma fibrinogen levels. These studies seem to provide support for our hypothesis (or conclusions) regarding the risk factors of prolonged ACT.

The clinical importance of difficult heparin reversal is that a prolonged ACT might imply the need for a greater amount of blood transfusion. In this study, greater amounts of fresh frozen plasma and platelet concentrate were required for group B than for group A (p=0.014 and p=0.021, respectively). Ozkan et al. [12] retrospectively compared patients who underwent open heart surgery whose ACTs were 400–650 seconds with those with ACTs of 650 seconds or higher during CPB. They reported that drainage on postoperative day 1 (p=0.000), the postoperative blood transfusion amount (p=0.010), and intensive care duration (p=0.0015) were more favorable in the group with an ACT range during CPB of 400–650 seconds. Several studies have shown that monitoring and management of anticoagulation with ACT during CPB can minimize postoperative bleeding and the need for blood transfusion [13-15].

In conclusion, difficult reversal of heparin requiring additional protamine sulfate may lead to a requirement for a greater amount of blood transfusion in patients undergoing cardiac surgery using CPB. Surgeons' efforts to reduce

the operative time and avoid deep hypothermia may be helpful as ways to increase the likelihood of easy heparin reversal, especially in female patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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