Protamine adverse reactions in NPH insulin treated diabetics undergoing coronary artery bypass grafting

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Background
The routine use of protamine in cardiac surgery to neutralize heparin is usually associated with systemic reactions that result in substantial morbidity and mortality.
Aim
This study aimed to investigate the relationship between neutral protamine Hagedorn (NPH) insulin use and severe adverse reactions to intravenous protamine given after cardiopulmonary bypass.
Methods
After obtaining hospital ethics committee approval and after obtaining informed consent, 100 patients between 45 and 70 years of age of American Society of Anesthesiologist physical status II–III undergoing elective primary isolated coronary artery bypass grafting were included in this prospective study, which was conducted between May 2013 and June 2014. Patients were divided into two groups: the NPH group (50 patients), which included patients who were on NPH insulin preparation for more than 5 years before the study, and the non-NPH group (50 patients), which included patients on oral hypoglycemics. The incidence of protamine reactions was recorded for 30 min after protamine infusion. The incidence of severe hypotension, increased airway pressure, and cardiac arrest were compared using the χ^2-test. A P value less than 0.05 was considered significant.
Results
All patients (50 in each group) completed the study. There was no significant difference in patients' demographic data, preoperative comorbidities, and surgical factors between the two study groups. The number of patients who had hypotension was significantly higher in the NPH insulin group compared with the non-NPH group. For both groups, there was no significant difference with respect to bronchospasm, cardiac arrest, and increased pulmonary artery pressure.
Conclusion
This prospective study showed increased risk for hypotension among patients receiving NPH insulin for more than 5 years compared with those who were not exposed to NPH insulin.

Keywords:
bronchospasm, cardiac arrest, cardiopulmonary bypass, hypotension, neutral protamine Hagedorn insulin, protamine

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Introduction

Protamine is a cornerstone therapy in procedures with cardiopulmonary bypass (CPB), in which rapid reversal of heparin anticoagulation is obligatory for achieving surgical homeostasis. Usage of protamine in CPB is associated with the development of significant adverse effects, ranging from minor cardiovascular instability to life-threatening anaphylactic complications and fatal cardiovascular collapse [1]. Major adverse reactions after protamine exposure are liable to occur in 2.6% of cardiac surgical procedures [2], and these complications of protamine therapy are highly associated with serious postoperative outcomes [3,4].

Despite rarity of major reactions to protamine, anaphylaxis occasionally occurs in patients with a history of fish allergy [4], and it was found that neutral protamine Hagedorn (NPH) insulin use is the most common factor predisposing to anaphylactic reaction to protamine sulfate [2]. It could be anticipated that NPH insulin-dependent diabetic patients or NPH-treated diabetic patients are more prone than others to protamine reactions in the form of respiratory compromise, hypotension, and shock [5,6].

This study investigated the relationship between NPH insulin use and severe adverse reactions to intravenous protamine given after CPB.

Methods

After the institutional review board approval and after obtaining informed consent from all patients, 100 patients between 45 and 70 years of age of American Society of Anesthesiologist physical status II and III undergoing elective on-pump coronary artery bypass surgeries were enrolled in this prospective parallel group study, which was conducted during the period from March 2014 to May 2015.

Exclusion criteria were as follows: known sensitivity to fish, severe left ventricular dysfunction, a history of protamine allergy, bleeding that occurs without prior exposure to heparin and abnormal pulmonary hemodynamics, renal or hepatic dysfunction, emergency cardiothoracic surgery, thrombocytopenia less than 80 000 mm^{-3}, and being on heparin or other anticoagulants.

Patients were divided into two equal groups: the NPH group, which included 50 diabetic patients on NPH containing insulin preparations, and the non-NPH group, which included 50 diabetic patients on oral hypoglycemics with no history of protamine exposure. The patients in the first group had been on these treatments for more than 5 years before the study. The physician who recorded the adverse events was blinded to the study.

All patients were subjected the following: full history taking with special emphasis on allergic history, including previous fish allergy and previous adverse effect to any drug, and a history of diabetes, including control, duration, and management.

On hospital admission, all patients underwent preoperative laboratory tests such as complete blood count, renal function tests, liver function tests, coagulation profile, echocardiography, and coronary angiography. On the night of surgery, preanesthetic evaluation was carried out.

Before the induction of anesthesia, baseline laboratory tests results were obtained, including prothrombin time, activated partial thromboplastin time, hemoglobin, hematocrit, and platelet count.

General anesthesia followed the institutional standards. All surgeries were performed by the same surgical team. Standardized monitoring were applied in addition to transesophageal echocardiography.

Surgical procedure

After median sternotomy, CPB was instituted with 1500 ml crystalloid priming volume and mild hypothermia (32°C) with a Trillium Affinity oxygenator (Medtronic, Minneapolis, Minnesota, USA) and a Sarns CPB machine (Harrison, Mt. Clemens, Michigan, USA) at a flow rate of 2.6 $lmin^{-1}m^{-2}$.

Myocardial protection was accomplished using cold blood cardioplegia at 20°C. During CPB, homologous donor packed red blood cells were transfused if hemoglobin was below 6.5 gdl^{-1}.

On bypass, anticoagulation for extracorporeal circulation was accomplished using heparin 300 U/kg administered into the right atrium. Acelite activated clotting time (ACT) more than 400 was considered adequate for commencing CPB; if less, an additional dose of 100 U of heparin was given.

CPB was conducted with nonocclusive roller pumps, membrane oxygenators, arterial line filtration, and cold blood-enriched hyperkalemic arrest. Hemofiltration was used to maintain a minimum hematocrit of 22% during CPB as long as the blood reservoir volume was adequate. Systemic hypothermia to an esophageal temperature of 32°C was maintained during aortic cross clamping.

After completion of CPB and removal of the arterial cannula, heparin was neutralized with 1 mg of protamine sulfate for every 100 U of heparin administered. The anesthesiologist administrated the protamine into the central line by means of continuous infusion over a period of 15 min. Subsequently, a second dose of protamine 50 mg was administered if ACT remained above baseline ACT.

Recording protamine adverse effects

Patients were observed for protamine adverse reactions for 30 min after its intravenous infusion. Adverse events in which the administration of protamine followed by decrease in systemic mean arterial pressure (MAP) of at least 25% of baseline or decrease of more than 10% requiring inotropic medications, intra-aortic balloon, or reinstitution of CPB were considered the primary endpoints. Adverse events also included bronchospasm in the form of wheezing with a peak airway pressure increase of at least 3 cmH_2O, or need for bronchodilator therapy and cardiac arrest requiring inotropes, vasopressors, or reinstitution of CPB and cardiac massage. Increase in pulmonary artery pressure at least 25% of the baseline, generalized wheezing, and cardiac arrest were considered as secondary outcome measures.

At the end of surgery, patients were transferred to the ICU for postoperative care.

Sample size determination

Sample size was calculated on the basis of a previous study by Kimmel *et al.* [3] with an odds ratio of having adverse events with protamine reactions of 8.1 and a percentage of exposure in controls of 5.4%, α error of 5%, and power of the study of 80%. The minimum number of cases in each group was calculated as 34 patients, and hence we enrolled 50 patients in each group for possible dropouts.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using statistical package for social sciences software, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were carried out for numerical parametric data and presented as mean±SD, whereas categorical data were presented as number and percentage.

Variables such as demographic data and comorbidities were compared using the χ^2-test. A P value less than 0.05 was considered significant.

Surgical data such as cross clamp time, bypass time, number of grafts, and total heparin dose were compared using t-test.

Variables such as incidence of severe hypotension, increased airway pressure, increased PAP, and cardiac arrest were compared using the χ^2-test. A P value less than 0.05 was considered significant.

Results

There was no significant difference as regards demographic data, comorbidities, and surgical data between the two study groups (Tables 1 and 2).

The number of patients who had hypotension was significantly higher in the NPH insulin group compared with the non-NPH group (Table 3).

In the NPH insulin group, six patients experienced hypotension (decrease in systemic MAP of at least 25% of baseline), three of them required adrenaline 100 μg+1000 ml of fluids over 7 min, two patients required adrenaline+intra-aortic balloon pump+fluids, and one patient required reinstitution of CPB. In the non-NPH group, one patient experienced hypotension (decrease in systemic MAP of at least 25% of baseline); all required adrenaline and fluids.

For both groups, there was no significant difference with respect to bronchospasm and cardiac arrest.

In the NPH-treated group, one patient suffered cardiac arrest, requiring internal cardiac massage, adrenaline 100 μg, and reinstitution of bypass.

Table 2 Comparison between the NPH group and non-NPH group as regards number of grafts, cross clamp time, TBT, and total heparin dose

	Groups		Test	
	NPH group	Non-NPH group	*t*	*P* value
Number of grafts				
Mean±SD	2.7±1.3	2.8±1.2	0.357	0.722
Cross clamp time (min)				
Mean±SD	73.4±19.5	74.6±20.4	0.269	0.788
Total bypass time (min)				
Mean±SD	98.63±27.9	96.02±26.8	0.427	0.671
Total heparin dose (mg)				
Mean±SD	440±84.85	462±89.09	1.264	0.209

No significant difference as regards surgical factors. NPH, neutral protamine Hagedorn; TBT, total bypass time.

Table 1 Demographic data and comorbidities among the two study groups, the NPH group and the non-NPH group

	Groups [*n* (%)]		Test	
	NPH group	Non-NPH group	χ^2-test	*P* value
Age (years)				
Mean±SD	65.45±10.12	65.92±11.54	0.217	0.829
Sex				
Male	24 (48)	16 (32)	2.667	0.102
Female	26 (52)	34 (68)		
Weight (kg)				
Mean±SD	80.33±12.75	82.64±10.7	0.981	0.328
ASA II	26 (52)	34 (68)	2.667	0.102
ASA III	24 (48)	16 (32)	2.667	0.102
Smoking	14 (28)	16 (32)	0.190	0.663
Hypertension	14 (28)	16 (32)	0.190	0.663
Chronic obstructive airway disease	2 (4)	2 (4)	0.000	1.000
Peripheral vascular diseases	2 (4)	2 (4)	0.000	1.000
Previous myocardial infarction	4 (8)	7 (14)	0.919	0.338

No significant difference as regards demographic data. ASA, American Society of Anaesthesiologists; LVEF, left ventricular ejection fraction; NPH, neutral protamine Hagedorn.

Table 3 Comparison between the NPH group and the non-NPH group as regards protamine adverse reactions

	Groups [*n* (%)]		χ^2-test	
	NPH group	Non-NPH group	χ^2	*P* value
Severe hypotension	6 (12)	1 (2)	3.845	0.049*
Cardiac arrest	1 (2)	0 (0)	1.010	0.315
Increased airway pressure more than 3 cmH_2O (bronchospasm)	7 (14)	2 (4)	3.053	0.081
Increased pulmonary artery pressure >25% of baseline	1 (2)	0 (0)	1.010	0.315

Significant difference as regards hypotension among study groups. For both groups, there was no significant difference as regards bronchospasm, cardiac arrest, or increased pulmonary artery pressure. NPH, neutral protamine Hagedorn. *$P<$ 0.05 significant compared with non-NPH group.

In the non-NPH group, no patients suffered cardiac arrest.

In the NPH-treated group, seven patients had bronchospasm manifested by increased airway pressure more than 2 cmH_2O; two patients had bronchospasm in the non-NPH group. They required nebulized salbutamol and adrenaline intravenously in addition to hydrocortisone 100 mg.

Discussion

The number of patients presenting for cardiac surgery who are at risk of developing severe anaphylactoid reactions to protamine is rising in a short period because of increasing number of diabetic patients treated with insulin undergoing coronary artery surgery. This prospective study showed that the incidence of severe hypotension was significantly higher in patients treated with NPH insulin compared with the non-NPH group ($P<0.049$). There was no significant difference between the study groups as regards the incidence of bronchospasm, cardiac arrest, or increased pulmonary artery pressure.

Protamine–heparin complex causes complement activation by the alternative pathway with increased level of C3a, which produces systemic inflammatory type reaction with histamine release, increased capillary permeability, and hemodynamic derangements manifested by decreased systemic vascular resistance, bronchospasm, and flushing [7].

Anaphylactoid reactions secondary to protamine are caused by immunoglobulin (Ig)E-mediated reactions resulting in mast cell degranulation and histamine release or antiprotamine IgG-mediated complement activation developed through prior exposure to protamine during vascular surgery or cardiac catheterization [4].

The spectrum of protamine reactions includes systemic hypotension but the mechanism of protamine-mediated hypotension is unknown and protamine use may release thromboxane causing pulmonary vasoconstriction as well as depressing the myocardium by depressing the cellular mechanism [8].

Some studies were conducted on diabetic patients on NPH insulin preparations undergoing either cardiac catheterization or cardiac surgery; they reported the incidence of protamine adverse events and whether or not they were significant and showed methods of management or prevention.

For instance, Gottschlich and colleagues showed that only four participants experienced an adverse reaction due to protamine. Two were NPH insulin-dependent diabetic patients and two patients had a history of protamine exposure during cardiac catheterization. The occurrence of adverse reactions was 2.9% in NPH insulin-dependent diabetics versus 0.07% in nondiabetic patients ($P<0.05$) [9].

Stewart *et al.* [8] found that the incidence of protamine adverse reactions in NPH insulin-dependent diabetic patients undergoing cardiac catheterization was 27% (4/15) in the NPH-dependent diabetic patients versus 0.5% (3/636) in those with no history of NPH insulin use and there was one case of cardiac arrest ($P<0.001$).

In contrast to our study, a study by Weiler and colleagues showed a statistically significant increase in reactions in patients on protamine-containing insulin as compared with the rest of the patients. However, they could not prove whether diabetes alone was a risk factor or whether it was necessary for a diabetic patient to have a history of treatment with protamine-containing insulin for the risk for an immediate adverse reaction [10].

In another study, protamine re-exposure was associated with a 50-fold increase in adverse reactions [11], ranging from dyspnea and flushing to chest pain and respiratory arrest.

Kimmel *et al.* [3] found that in patients with a history of NPH insulin use and known pulmonary artery

pressure, there was no significant difference between the incidence of systemic hypotension and pulmonary hypertension, and they reported the risk for adverse events to be 2.6% ($P>0.15$).

A case report showed that a diabetic man on insulin preparation undergoing emergent off-pump coronary artery bypass grafting for acute myocardial infarction developed anaphylactic shock immediately after administering a small dose of protamine sulfate (40 mg) given through the central venous line. After 3 min of protamine administration, profound hypotension occurred [12].

Administration of protamine sulfate caused fatal anaphylactic reaction to a diabetic patient on NPH insulin undergoing femoropopliteal bypass surgery [13].

Another case report showed that a male patient who was diabetic on NPH insulin for 30 years developed severe anaphylactic reaction in the form of severe bronchospasm followed by cardiac arrest resuscitated with cardiac massage, high dose of adrenaline and then noradrenaline immediately following administering of 10% of the calculated dose of protamine sulfate while performing open heart bypass surgery [14].

In a previous study by Horrow and colleagues they showed that 13% of the patients had positive skin tests but showed no clinical reaction. The 100% incidence of IgG antibody raised serious doubts about the clinical application of the test [15].

Over the past 4 years, the fraction of population using insulin increased by 50%; this increase resulted from an increased number of type 2 diabetic patients treated with insulin [16]. This shows the extent to which the study of effects of protamine injection in patients treated with insulin is important.

The major limitation of our study was that the rate of protamine injection was not recorded, but generally the rate of injection was slow.

We would like to emphasize the fact that these outcomes should encourage researchers to conduct further studies with larger sample sizes, which would definitely add more to the scientific value and accreditation of our preliminary outcomes.

A study by Kambam and colleagues showed that patients who did not receive histamine receptor blockers presented with significant hemodynamic changes following protamine administration ($P<0.05$). This study could be helpful in prevention of the adverse hemodynamic effects associated with protamine administration by empirical administration of histamine blockers in susceptible patients [17]. We recommend the use of (a) protamine alternatives such as rPF4, which is one of the promising drugs used for heparin reversal in patients with a history of protamine reactions or diabetic patients on protamine-containing insulin, and (b) the use of a test dose of protamine (10% of the total dose) infused over 10 min; if there is any reaction, the infusion should be stopped and an alternative used.

Conclusion

This prospective study showed increased risk for hypotension among patients receiving NPH insulin for more than 5 years compared with those who were not exposed to NPH insulin.

The possibility of under-reporting by other authors and possibly noninclusion of significant hypotension may have led to underestimation of the true protamine reaction (hypotension) incidence. Caveat is of course contributing to such hypotension within this time period.

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Conflicts of interest

There are no conflicts of interest.

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