

## Case Report

# Life Threatening Protamine Reaction During Bypass Surgery – A Case Report

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## Abstract

An anaphylactic reaction to protamine sulphate during cardiac surgery is a rare but known entity. Preoperative prediction and outcome of such a reaction is still unclear. We report a case of severe anaphylactic reaction to protamine sulphate in a diabetic while performing beating heart bypass surgery. We also reviewed the literature and discussed the management of such cases.

**Key words:** Protamine, Anaphylaxis.

## INTRODUCTION

Protamine is a basic polycationic peptide used for two purposes. It is mainly used to counteract the anticoagulant effects of heparin during cardiac surgery and also to reduce the absorption of insulin<sup>1</sup>.

## CASE REPORT

A 63 year old male, who was a known case of diabetes mellitus for 30 years, hypertension for 5 years, bronchial asthma for 10 years had been attending our hospital for over 11 years for control of diabetes. There was no history of any known drug or food allergy. He suffered an inferior wall myocardial infarction in 1998 and was thrombolysed. A coronary angiogram that time revealed single vessel disease involving the Right Coronary Artery (RCA-100% Stenosis) for which angioplasty was done. He had a repeat coronary angiogram done in January 2009 for recurrence of angina and positive stress test. It revealed severe triple vessel disease. He was advised Coronary artery bypass grafting (CABG) surgery. Echocardiogram revealed regional wall motion abnormality involving inferior wall with Left Ventricular Ejection Fraction (LVEF) of 50%. Coronary artery bypass surgery was done on beating heart (using Octopus 4.3) stabilizer using left internal mammary artery and saphenous vein grafts given to the left anterior descending, first diagonal, ramus intermedius, and posterior descending arteries. After the proximal anastomoses of the vein conduits to ascending aorta, protamine sulphate was given (slow infusion) to counteract

was stopped immediately. He responded to 10-15 minutes of cardiac massage and high dose adrenaline and nor-adrenaline infusion and bolus intravenous (IV) hydrocortisone. Once hemodynamics were stabilized he was shifted to Intensive Care Unit (ICU). In the ICU the patients haemodynamics were stable though with high inotropic support (Nor-adrenaline: 12 mcg/kg/min; adrenaline–0.05 mcg/kg/min; vasopressin–0.03 mcg/kg/min; Dobutamine–5 mcg/kg/min). After 2 hours in the ICU, his chest tube drainage was around 2300 ml and therefore a trial of small dose of protamine was tried through arterial line. 2 ml of slow IV infusion of protamine through radial arterial line was given again, leading to considerable fall of systemic BP and rise in pulmonary artery pressures (PAP). The airway pressure became high. He was taken back to operation room and cardiopulmonary bypass instituted and he was supported for an hour. In order to reduce the oozing, he was started on factor-VII (Nova –7 from Novartis) IV infusion. Systemic pressures were low even while coming off cardiopulmonary bypass and the patient was started on methylene blue IV infusion together with other inotropes. Over the next 5 days patient deteriorated and became comatose with renal failure and septicemia. On the 7th postoperative day he expired because of sepsis and renal failure.

## DISCUSSION

Protamine is a basic polypeptide isolated from sperm of salmon fish. Protamine is routinely used in cardiac surgery to reverse the anticoagulant action of heparin. It is also

the effect of heparin. Just after 10% of the calculated dose was given, the patient's airway pressure was found to be very high. Systemic Blood pressure (BP) and peripheral pulses were not recordable. Cardiac massage was given and protamine infusion

used to slow the absorption and thereby prolong the action of insulin.

The adverse reaction of protamine, starting from slight allergic

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reaction to severe anaphylaxis varies from 0.06% to 10.06%<sup>2</sup>. It has been reported commonly in 3 groups of patients. Firstly, patients with fish allergy; secondly, patients previously exposed to protamine and this includes cardiac surgical patients, third group involves diabetics who have received protamine zinc insulin. There is a subgroup of patients who may be theoretically exposed to the risk of protamine sensitivity, vasectomised or infertile patients, who develop antibodies to protamine due to sperm released to the blood stream. Reaction to protamine after

cardiac catheterization in diabetic patients, who were receiving NPH insulin, was reported by Stewart<sup>3</sup>. In contrast to 27% incidence reported by Stewart. Levy reported only 0.6-2% life threatening reaction to protamine, during cardiac surgery who have NPH-insulin dependent diabetics and 0.06% in non-insulin dependent diabetics<sup>4,5</sup>. The exact mechanism of protamine anaphylaxis is unclear, but many possible mechanisms have been proposed. Protamine-Heparin complexes activate the classical complement cascade with subsequent generation of

anaphylatoxins. Protamine binds with IgE and anti-protamine IgG antibodies<sup>6</sup>. The spectrum of cardiovascular manifestations of protamine reactions are systemic vasodilation with increase in cardiac output, acute pulmonary vasoconstriction, right ventricular dysfunction<sup>4,7</sup>.

Protamine anaphylaxis is characterized by edema of skin, mucosa and viscera, decreased systemic vascular resistance, bronchospasm. Catastrophic pulmonary vasoconstriction is accompanied by right ventricular dilatation, pulmonary artery hypertension, decreased Left

administered in 10-mins. As regards our present case, the 2nd dose of protamine infusion (even in a very small dose) was found detrimental. Because of the large amount of chest drainage we gave protamine second time through arterial line. All the effects of protamine anaphylaxis in our patient is probably the effect of protamine-heparin complexes. Protamine alternatives are available.

Hexadimethrene bromide (poly-brene), was used in the past but not available now. Some times heparinases are used for reversal of heparin. rPF4 is one of the most promising drug used for heparin reversal. Drugs which can be used as a heparin-substitute, in predicted high risk cases of anaphylaxis without requiring any reversal are probably

one of the solutions to protamine reaction, Bivalirudin being one such drug.

## CONCLUSION

Protamine anaphylaxis has received very little attention from

surgeons. These reactions are more commonly seen by cardiac

surgeons than other clinicians, because of frequent use of protamine in cardiac surgery. Many times mild protamine reactions are noticed in the form of transient fall of systemic BP and rise of PAP. But potentially fatal anaphylaxis, like in our patient are rarely seen and we recommend following steps to overcome such a situation;

1. Avoid use of protamine in patients with history of previous protamine reactions, diabetics on protamine containing insulin and patients with fish allergy.

Ventricular (LV) filling pressures and systemic hypotension. This type of reaction appears to occur in patients with abnormal pulmonary haemodynamics<sup>8</sup>. Hypotension results because increase in cardiac output is not sufficient to overcome the decreased peripheral resistance. The precise mechanism that explains the protamine-mediated systemic hypotension is unknown. In experimental studies with canine pulmonary arteries revealed that protamine induces endothelium-dependant vasodilation and not vasoconstriction as documented earlier<sup>8</sup>. Heparin inhibits endothelium-dependent vasodilation to protamine. However this inhibitory effect can be overcome by higher doses of protamine, suggesting that protamine complexed with heparin does not induce vasodilation. The direct effect of protamine is vasodilation due to Endothelium derived relaxation factor /Nitric oxide release. Vasoconstriction may be temporary. It is possible that use of protamine may release thromboxane, which induces catastrophic pulmonary vasoconstriction. Protamine also depresses the myocardium by inhibiting cellular mechanism. Patients with LV dysfunction exhibit significantly decreased fractional shortening both during and immediately after protamine. Rapid injection of protamine induces cardiovascular effects. Hence not more than 50mg should be

2. Always administer protamine as a test dose (10% of the total dose) as slow IV bolus over a period of 10 minutes.
3. In case of any adverse reaction, stop the infusion. If the reaction is severe, like in our case, one should not continue the infusion.
4. One can try alternatives such as Bivalirudin in place of heparin or use protamine alternatives.

## REFERENCES

1. Kimmel S, Sekeres M, Berlin J, Ellison N. Mortality and adverse events after protamine administration in patients undergoing cardio-pulmonary bypass. *Anesth Analg* 2002;94: 1402-1408.
2. Weiler JM, Gelhaus M, Carter J, et al. A prospective study of the risk of an immediate adverse reaction to protamine sulfate during cardio-pulmonary bypass surgery. *J Allergy Clin Immunol* 1990; 85:713-719.
3. Stewart WJ, McSweeney SM, Kellett MR, et al. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; 70: 788.
4. Levy JH, Zaidan JR, Faraj BA. Prospective evaluation of risk of protamine reactions in NPH insulin-dependent diabetics. *Anesth Analg* 1986; 65: 739.
5. Levy JH, Schwieger IM, Zaidan JR, et al. Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; 98: 200.
6. Baur X, Bossert J, Koops F. IgE-mediated allergy to recombinant human insulin in a diabetic. *Allergy*. 2003 Jul; 58 (7): 676-678.
7. Morel DR, Zapol WM, Thomas SJ, et al. C5a and thromboxane generation associated with pulmonary vaso- and broncho-constriction during protamine reversal of heparin. *Anesthesiology* 1987; 66: 597-604.
8. Horrow JC. Protamine: A review of its toxicity. *Anesth Analg* 1985; 64: 358-361.