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Protamine Reaction in Cardiovascular Surgery

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Abstract

Coronary artery bypass grafting is the most performed cardiac surgery throughout the world today. The United States alone performs over 200,000 of these procedures every year. Protamine sulfate is administered to neutralize heparin given during these cases. Known hemodynamic effects are associated with protamine and on rare occasions, true anaphylaxis. A 10.7% chance exists of a protamine reaction occurring after its administration and five different risk factors that increase that chance is an allergy to fish, use of NPH insulins, previous vasectomy, previous exposure to protamine, and rapid administration of protamine. Treatment includes fluid resuscitation, administration of vasopressors, intra-aortic balloon pump, and methylene blue but this has not been studied. A heparin removal device as an alternative to protamine shows promise.

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Protamine Reaction in Cardiovascular Surgery

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Introduction

- Cardiopulmonary bypass grafting (CABG) is the most performed cardiac procedure done throughout the world today[1]
- 10.7% of patients receiving protamine experience a protamine reaction[2,3,4]
- Protamine is administered to neutralize the anticoagulant effects of heparin[4] Evidence shows that when a reaction does occur, there is an increased mortality risk[4]
- Reactions to protamine can be respiratory in nature such as wheezing, cardiovascular such as hypotension, impaired cardiac output, arrhythmias, pulmonary hypertension, or cardiac arrest, skin such as urticaria, flushing and angioedema, or hematologic such as bleeding[3]
- Protamine is administered routinely in many vascular procedures therefore anesthesia providers should know the risks associated with it and what to do if a reaction occurs
- Purpose: to discuss known risk factors that precipitate a reaction to protamine, how often a reaction may occur, appropriate treatment for when a reaction does occur, and if there are any alternatives to the administration of protamine available

Case Summary

- 80-year-old female, 165 cm, 77 kg, scheduled for elective CABG

Anesthetic evaluation

- PMH: CAD, HTN, MI with stent, PPM due to heart block, GERD, Hypothyroid, DDD, Parkinson's disease
- Labs: Na-139, K-4.6, Cl-105, CO_2-28, Gap-11, BUN-30, Crea-0.93, EGFR-58, Glucose-132, Calcium-9.8, Alk Phos-78, Albumin-3.8, WBC-4.7, RBC-4.03, Hgb-11.1, Hct-35.3, Plt-267
- Echo: EF 45%, moderate mitral regurgitation, moderate pulmonary hypertension
- Angiography: Left main 70-80% stenosis, RCA 80% stenosis, LAD 80-90% stenosis
- Medications: aspirin, omeprazole, potassium chloride, levetiracetam, escitalopram, levothyroxine, metoprolol, calcium carbonate, carbidopa/levodopa, acetaminophen, atorvastatin
- PSH: Cardiac stent placement, hysterectomy
- Premedication: None
- Anesthetic plan: GETA, A-line and CVL post-induction

Intraoperative course

- Monitors applied, preoxygenation
- Induction: 60 mg propofol, 5 mcg sufentanil, 50 mg lidocaine, 30 mg rocuronium for muscle relaxation
- Intubation: DL x 1, Grade I view, ETT 8.0
- Maintenance: Sevoflurane titrated to effect, IVP sufentanil, vecuronium for muscle relaxation
- Emergence: Postoperative ventilatory support, dexmedetomidine infusion @ 0.5 mcg/kg/hr
- Severe reaction after administration of protamine with BP dropping as low as 32/17 mmHg
- Treated with norepinephrine, epinephrine, vasopressin and calcium chloride
- Methylene blue was administered, and the patient was placed on an IABP
- Decision: to heparinize again and place the patient back on CPB
- Once ACT was 175 seconds, patient was closed and taken to the ICU on IABP

Postoperative course

- IABP was discontinued on POD 2. Extubated POD 3. Oxygen requirements began increasing on POD 8 which required BIPAP. Reintubated and eventually suffered cardiac arrest with CPR initiated and ROSC on POD 9. Comfort measures were later initiated, and patient passed on POD 9.

Risk Factors for a Protamine Reaction

- ❑ Allergy to fish[2]
- ❑ Use of NPH insulins[2]
- ❑ Previous vasectomy[2]
- ❑ Previous exposure to protamine sulfate[2]
- ❑ Rapid administration of protamine sulfate[2]

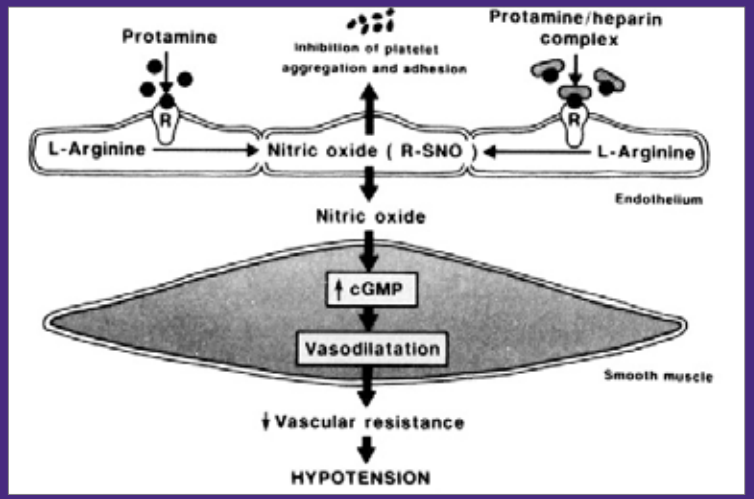

Figure 1. Demonstration of Protamine Pathophysiology Causing Hypotension[9]

Supportive Evidence

- A retrospective analysis by Porsche et al assessed incidence and symptoms associated with protamine.[2] A reaction occurred between 0.06% and 10.7%.[2] Different reactions ranged from hypotension, increases in pulmonary artery pressure, bronchospasm, flushing, angioedema, erythema, and pruritus, chills, chest pain, or nausea and vomiting[2]
- A prospective study by Weiler et al examined incidence of protamine reaction.[3] 248 patients were given protamine, 26 experienced a reaction (10.7%).[3] A reaction was considered mild (20-29 mmHg decrease in SBP), moderate (30-49 mmHg decrease in SBP), or severe (50 mmHg decrease in SBP).[3] Eleven of the reactions were mild, 9 were moderate, and 4 were severe.[3] Patient risk factors and statistical significance were also significant for T2DM and received protamine-containing insulin[3]
- A SR by Nybo M et al examined incidence of anaphylactic reactions after the administration of protamine sulfate.[4] Nine retrospective studies found (0.19%) anaphylaxis, 16 prospective studies found anaphylaxis (0.69%).[4] Prior treatment with NPH insulin was the most common predisposing factor to suffer an anaphylactic reaction[4]
- Hecht P et al examined optimal protamine dosing.[6] Fixed-protamine: heparin ratio dose is one of the most common strategies utilizing 1 mg of protamine for every 100 units of heparin.[6] The ACT-based model is discussed incorporating a mathematical relationship to help determine the appropriate protamine dose based on ACT levels measured at baseline, before CPB, and pre-protamine as well as initial heparin dose and patient's weight.[6] The ACT-based model found on average a 40 mg reduction in protamine dose required[6]
- A randomized controlled trial assessed 12 Yorkshire female swine for heparin removal device efficacy compared to protamine administration.[8] Six were randomly allocated to a protamine group, which were given 1 mg of protamine for every 100 units of heparin and the other 6 were allocated to the heparin removal device group, that had a target of 90% heparin removal.[8] No statistically significant changes in hemodynamics were associated with use of the heparin removal device.[8] The study found that the heparin removal device was able to reverse systemic heparin anticoagulation by returning PT, APTT, ACT and heparin concentration to near baseline levels after an average run time of 31.5 minutes[8]
- A case study by Conti et al examined of the first use of a heparin removal device.[7] A 44-year-old woman with a history of diabetes that was on NPH insulin underwent a CABG.[7] A test dose of protamine was given, which resulted in a rapid decrease in SBP from 130 to below 40 mmHg, and an increase in the PAP to 52 mmHg, along with right heart failure.[7] Open cardiac massage and an epinephrine infusion were initiated, and hemodynamics were stabilized after 5 minutes.[7] The chest was closed and the patient was taken to the ICU with an ACT of 459 seconds.[7] Extensive bleeding occurred and the patient was taken back to the OR where the decision was made to use a heparin removal device.[7] After a run time of 25 minutes the ACT was 160 seconds, which was below the baseline of 192 seconds[7]
- A case study by Lutjen and Arndt examined a 57-year-old woman undergoing a CABG that suffered a protamine reaction. After 80% of the infusion, SBP dropped rapidly from 120 to 62 mmHg, and eventually to as low as 50 mmHg.[5] The PAP rose from 17/8 mmHg to 28/16 mmHg.[5] Aggressive treatment with vasopressors, fluids, blood products, and IV steroids maintained SBP between 50 and 60 mmHg.[5] Methylene blue, 500 mg IV yielded an immediate increase in the SBP to 100 mmHg.[5] The operation was completed, and the patient was transferred to the ICU in stable condition and discharged 5 days later[5]

Discussion

- Studies show that suggested treatment is supportive. Examples are diphenhydramine 50 mg IV to treat cutaneous manifestations, large volumes of fluid to replace intravascular loss, epinephrine up to 4 mcg/min, dopamine 5 mcg/kg/min, and isoproterenol 2 to 20 mg/min to support cardiac function. Intra-aortic balloon pump has also been utilized to support cardiac function[2]
- Methylene blue (500 mg) has successfully treated sustained hypotension after traditional supportive measures were unsuccessful[5]
- A fixed protamine: heparin ratio dose may be overdosing or underdosing the protamine leading to adverse outcomes[6]
- A heparin removal device which is an extracorporeal plasmapheresis filter that contains a resin which binds and immobilizes heparin from circulating heparinized blood, was utilized after patient suffered a reaction from protamine and was still bleeding after wound closure. Patient was brought back to OR and HRD was able to bring ACT to 160 seconds which was below the baseline of 192 seconds after a 25-minute run time[7]
- A bovine study demonstrated HRD was able to reverse heparin equal to protamine in an average of 31 minutes compared to a standard 15-minute infusion[8]

Case Critique

- Utilizing a fixed protamine: heparin ratio overdosing the protamine could have led to the reaction[6]
- The use of methylene blue was a positive, but it could have possibly been administered sooner
- A heparin removal device could have been utilized to reverse the heparin lowering the amount of time the patient required cardiopulmonary bypass but as of now it has not received FDA approval[7]
- Appropriate utilization of vasopressors and intra-aortic balloon pump to support cardiac function[2]
- Protamine was administered via micro drip over 15 minutes which aligns with research[2]

Recommendations for Practice

- Set guidelines to run protamine over at least a 5–15-minute time frame[2]
- Screen all patients who will be given protamine for risk factors of allergy to fish, use of NPH insulins, previous vasectomy, and previous exposure to protamine

Recommendations for Future Research

- Further studies on the use of methylene blue to treat hypotension after protamine administration
- Further studies on the use of a heparin removal device to determine efficacy and appropriateness of its use with known protamine allergies
- Further studies to assess appropriate dosing of protamine

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