Methylene Blue to Treat Vasoplegia due to a Severe Protamine Reaction: A Case Report

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Protamine sulfate is used during coronary artery bypass graft surgery to reverse the anticoagulating effects of heparin. Vasoplegic syndrome is a state of endothelial dysregulation that produces profound vasodilatation that is refractory to vasopressors. This syndrome leads to systemic hypoperfusion and may progress to death. Up to 21% of patients after cardiac bypass may experience vasoplegia. Symptoms of vasoplegia may also be present in many different clinical settings.

This case report describes a 57-year-old woman who after cardiac bypass experienced a severe protamine reaction with profound hypotension, which was unresponsive to volume resuscitation and vasopressor therapy. A dramatic increase in blood pressure resulted almost immediately after administration of methylene blue. This patient had no prior risk factors for a protamine reaction other than her current cardiac surgery. A review of the pathophysiologic characteristics associated with vasoplegia and the pharmacodynamics of methylene blue will potentially enable anesthesia providers to utilize this lifesaving drug when needed.

Keywords: Methylene blue, protamine reaction, vasoplegic syndrome.

Protamine sulfate is a positively charged polypeptide extracted from salmon sperm. It is a series of arginine-rich basic proteins that bind to the acidic heparin molecule to reverse its activity.\(^1,2\) Administration of protamine is associated with adverse hemodynamic changes, ranging from mild hypotension to more severe changes such as elevated pulmonary artery pressure and decreased systemic vascular resistance resulting in profound hypotension due to nitric oxide release by the vascular endothelium. Transient mild hypotension may be related to the rate of administration.\(^1\) Manufacturer guidelines suggest that protamine be administered intravenously at 5 mg/min. However, during cardiac surgery, anesthesia providers frequently administer protamine over approximately 10 minutes, closely monitoring arterial blood pressure (BP).\(^1\)

Infusions are typically slowed or paused for temporary decreases in BP. If protamine results in an anaphylactic or anaphylactoid reaction, a massive overproduction of nitric oxide may occur. This typically manifests as a profound decrease in BP and systemic vascular resistance. It may also involve pulmonary hypertension and rightsided heart failure. The reported incidence of anaphylactic reactions to protamine range from 0.06% to 10.6%.\(^3,4\)

This vasoplegic syndrome, whose symptoms are listed in Table 1,\(^5,6\) typically does not respond to volume therapy and vasopressor therapy. A small number of published case reports describe catecholamine-resistant reactions to protamine that were successfully treated with methylene blue. However, many of these patients had other risk factors known to increase the likelihood of protamine reactions (Table 2).\(^1,3,6,8,10\) unlike the patient described in this case report.

This report demonstrates a life-threatening hemodynamic reaction to protamine, which was administered to reverse the anticoagulating effects of heparin during cardiopulmonary bypass surgery. The patient experienced severe hypotension, which was refractory to vasopressors and fluid resuscitation. Methylene blue was administered, and a dramatic increase in blood pressure was observed almost immediately. It is therefore prudent for the anesthesia provider to understand the pathophysiologic process of protamine reactions and vasoplegia and the usefulness of methylene blue as treatment.

Case Summary
A 57-year-old woman admitted for evaluation of unstable angina was scheduled for a 4-vessel coronary revascularization procedure. Her right coronary artery, left anterior descending artery, and ostial circumflex artery

Hypotension (mean arterial pressures < 50 mm Hg)\(^5,6\)
Normal or elevated cardiac index (> 2.5 L/min/m\(^2\))\(^5,7\)
Low systemic vascular resistance\(^6\)
Low filling pressures\(^5,6\)
Maintained hypotension despite use of high-dose vasopressors\(^5,6\)
Central venous pressure < 5 mm Hg and wedge capillary pressure < 10 mm Hg\(^5\)
Low peripheral resistance (800 dyne/s/cm\(^{-5}\))\(^6\)

Table 1. Signs and Symptoms of Vasoplegic Syndrome
were identified as having critical lesions associated with mild left ventricular dysfunction. Her only other remarkable medical history included hypercholesterolemia and hypertension. Surgical history included tonsillectomy with adenoidectomy and a cesarean delivery without complications. She had a weight of 79 kg and a height of 170 cm. Her BP was 151/70 mm Hg, heart rate was 58/min, and oxyhemoglobin saturation was 97%. Her medications included hydrochlorothiazide, metoprolol, nitroglycerin, and rosuvastatin. She was allergic to doxycycline. Her American Society of Anesthesiology (ASA) physical status classification was III. Laboratory values were normal, with a hematocrit of 43%.

Induction of anesthesia was accomplished with 3 mg of midazolam, 1 mg of pancuronium, 10 µg of sufentanil, and 120 mg of succinylcholine, followed by placement of a 7.5-mm endotracheal tube and a 20-gauge arterial line in the right radial artery. For monitoring purposes, a central venous catheter was placed in the right jugular vein and a catheter was placed in the pulmonary artery without incident. General anesthesia was maintained with sevoflurane (0.63% to 2.0%), pancuronium, midazolam, sufentanil, and a low-dose infusion of propofol. An aminocaproic acid loading dose of 7.9 g over 30 minutes was given, followed by a continuous infusion 1.1 g/h.

After the surgeon injected 24,000 U of heparin into the right atrium, standard cardiopulmonary bypass was established, and the surgeon successfully placed 4 coronary artery grafts. Aortic cross-clamp time was 117 minutes, and the patient was separated from bypass. Heparin reversal was initiated with protamine, 300 mg. The protamine infusion was administered intravenously (IV) through the patient’s central line and was titrated slowly while arterial BP was monitored.

After approximately 13 minutes, with 80% of the protamine infused, the systolic BP rapidly dropped from 120 to 62 mm Hg and proceeded to fall to 50 mm Hg. The pulmonary artery pressure increased from 17/8 mm Hg to 28/16 mm Hg. Heart rate increased from 74/min to 90/min. The protamine and propofol infusions were abruptly discontinued, followed by administration of a fluid bolus of 250 mL and 200 µg of phenylephrine, without improvement. A total of 1 g of calcium chloride was administered, and a norepinephrine infusion was initiated and quickly titrated to 20 µg/min. An additional 200 µg of phenylephrine was given as well as 32 µg of epinephrine. Two units of packed red blood cells were infused within 10 minutes as well as 500 mL of 5% albumin. After approximately 20 minutes of resuscitation efforts, the systolic BP remained at 50 to 60 mm Hg and the heart rate was 130/min (sinus tachycardia).

A severe protamine reaction was suspected, and 125 mg of methylprednisolone was given IV. No dermatologic reactions were noted at any time. Methylene blue, 500 mg, was administered IV and resulted almost immediately in a dramatic increase in the systolic BP to 100 mm Hg, which was sustained. The surgeon proceeded with wound closure. The patient was taken to the cardiac intensive care unit in stable condition. The remainder of her hospital stay was uneventful, and she was discharged 5 days later.

### Discussion

Methylene blue is an indicator dye that is commonly used to treat methemoglobinemia, priapism, and malaria (Table 3). Methylene blue is a competitive inhibitor of the enzyme guanylate cyclase and blocks the buildup of cyclic guanosine monophosphate (cGMP). This indirectly reduces the response of the vascular endothelium to the cGMP-mediated vasodilators, mainly, nitric oxide.

Vasoplegic syndrome may be present in a variety of clinical scenarios, including anaphylaxis, sepsis, systemic inflammatory response syndrome, renal failure, and hepatic failure. In each instance, activation and release of inflammatory mediators occurs. Nitric oxide overproduction in vascular smooth muscle causes massive vasodilatation, which is nonresponsive to vasoressor therapy. The exact pathophysiologic process that causes the overproduction of nitric oxide is not clear.

Anaphylaxis is diagnosed with a BP drop to below 90 mm

| Previous NPH insulin use (incidence as high as 2.8%)
| Fish allergy
| History of nonprotamine medical allergies
| Previous exposure to protamine
| History of vasectomy
| Decreased LV function
| Hemodynamic instability
| Heparin treatment
| ACE-inhibitor therapy
| Calcium channel blocker therapy

**Table 2. Risk Factors for Protamine Reactions or Vasoplegic Syndrome**

Abbreviations: LV, left ventricular; ACE, angiotensin-converting enzyme.

### Table 3. Common Indications for Methylene Blue

- Treatment of methemoglobinemia
- Treatment of malaria
- Treatment of pharmacologically induced priapism
- As a urinary antiseptic
- As an additive to stored blood bags to neutralize microorganisms
- In oncology for sentinel node detection
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Interference with pulse oximetry, causing false impression of decreased arterial saturation levels, which is transient.

May cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency and those with low levels of endogenous NADPH.

Dapsone-induced hemolytic anemia if given to patients taking dapsone.

Cardiac arrhythmias: nodal rhythm and transient isolated ventricular ectopy.

Angina and coronary vasoconstriction (with high doses).

Decreased cardiac output.

Decreased renal blood flow and mesenteric resistance.

Increased pulmonary artery pressure with decreased gas exchange.

Confusion.

Headache.

Vomiting and abdominal pain.

Hyperbilirubinemia and hemolytic anemia.

May turn skin bluish-gray.

Table 5. Methylene Blue: Adverse Reactions and Contraindications

Abbreviation: NADPH, nicotinamide adenine dinucleotide phosphate.
result in systemic hypoperfusion mediated by a common pathophysiologic pathway, which may be treated successfully with methylene blue. Therefore, it is prudent that the anesthesia provider be knowledgeable regarding indications and proper administration of methylene blue as a potential treatment of catecholamine-resistant vasoplegic syndromes.

REFERENCES

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