Vasoplegic Syndrome: Does the Timing of Methylene Blue Matter?

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Introduction

Vasoplegic syndrome is a perioperative event with severe and persistent hypotension with normal or elevated cardiac output, decreased filling pressures, and low systemic vascular resistance [1]. Methylene blue has been used with great success in treating vasoplegic syndrome [2,3], however, the ideal timing of dosing is not known. We report a case of vasoplegic syndrome during an on pump coronary artery bypass grafting (CABG) with no response to methylene blue and believe that prompt recognition of this syndrome and the timing of methylene blue dosing are paramount to success to reversing vasoplegic syndrome.

Case

A 63 year old male with chest pain was found to have multivessel disease and referred for elective three vessels CABG. He was 72 inches and 89 kilograms (kg) with a history of hypertension, hyperlipidemia, and benign prostatic hypertrophy (BPH). Medications included metoprolol 50 milligrams (mg) once a day, enalapril, hydrochlorothiazide, Zocor, Avodart and tamsulosin. Hydrochlorothiazide had been the only held morning medication. He had one prior uneventful surgical procedure 20 years prior.

Day of surgery vital signs were heart rate of 66 beats per minute (bpm), systolic blood pressure (SBP) of 132 millimeters of mercury (mmHg) and diastolic of 83 mmHg; normal laboratory findings with hematocrit of 40.5%. Preoperative transthoracic echocardiogram (TTE) showed mild concentric left ventricular hypertrophy with a mildly dilated left atrium. Left ventricular ejection fraction was 60-65% (TTE) showed normal wall motion initially, but hypokinesis soon developed after tachycardia to 110 bpm. No air was seen on TEE. An arterial blood gas (ABG) showed a pH 7.245, pCO2 of 45.1 mmHg, pO2 of 313 mmHg, bicarbonate of 19.7 mEq/L, and a base excess of -7.9 mmol/L. Serum ionized calcium was never less than 1 mmol/L. The hematocrit was 25%, thought not to be contributory.

CPB was re-initiated. VASO and Ne continued. In consideration of renal insufficiency, 125mg hydrocortisone was given intravenously. Despite no other signs or symptoms other than hypotension, anaphylaxis was considered and IV ranitidine and diphenhydramine were given; the latex Foley was replaced. After discussion the PA catheter was kept in place.

At 6 hours, an intra aortic balloon pump (IABP) was placed. CPB was weaned and the blood pressure was in the high 90/50’s mmHg. VASO continued, as weaning would result in a MAP of 50 mmHg and tachycardia of 120 bpm. TEE revealed no wall motion abnormalities. VASO and Ne continued at 0.04 U/min and 30 mcg/min, respectively.

Vasoplegia was considered and 200 mg methylene blue was given intravenously, 6 hours after the initial episode of hypotension. There was a brief rise in the MAP to the 70’s mmHg but lasted only three minutes.

With minimal change in the blood pressure, vasopressin (VASO) was started at 0.04 units per minute (U/min). A left femoral arterial line confirmed hypotension. Despite vasoactive medications, the blood pressure did not respond and remained in the high 80’s systolic with atrial and ventricular (AV) pacing at 80 beats per minute. The PAP was 20/10 mmHg and CVP was 4 mmHg. Transesophageal echocardiography (TEE) showed normal wall motion initially, but tachycardia and inferior and septal wall hypokinesis developed. Cardiopulmonary bypass was re-initiated. EPI was discontinued as the MAP was above 50 mmHg, with VASO and Ne continued.

The surgeons assessed the grafted vessels and regrafted the posterior descending artery after stating it was not competent. CPB was weaned after 30 minutes. At that time, the blood pressure was in the high 70/50’s with AV pacing at 90pm on Ne and VASO infusions. CI was 2.6 L/minute*m2 with a systemic vascular resistance (SVR) of 663 dynes-s-cm-5. Initial LV function appeared normal on TEE, but hypokinesis soon developed after tachycardia to 110 bpm. No air was seen on TEE. An arterial blood gas (ABG) showed a pH 7.245, pCO2 of 45.1 mmHg, pO2 of 313 mmHg, bicarbonate of 19.7 mEq/L, and a base excess of -7.9 mmol/L. Serum ionized calcium was never less than 1 mmol/L. The hematocrit was 25%, thought not to be contributory.

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CPB was reinstituted due to persistent hypotension, a worsening lactate of 11.3 despite the IABP use. After discussion, vasoplosa was considered and 200 mg methylene blue was given intravenously, 6 hours after the initial episode of hypotension. There was a brief rise in the MAP to the 70’s mmHg but lasted only three minutes.

In light of persistent hypotension (MAP of 50 mmHg), tachycardia and inability to wean from CPB, a left ventricular assist device (LVAD) was placed. EPI infusion restarted up to 25 mcg/min in addition to Ne
and VASO along with boluses of phenylephrine (1000 mcg total) to keep MAP above 50 mmHg.

Total on-pump time now was 344 minutes; CPB was weaned. MAPs were in the 40 s, and PAP’s were 20 mmHg systolic. Despite the IVAD, the right ventricle became hypokinetid and dilated, the MAP dropped into the 20 s and CPB was re-initiated with placement of a right ventricular assist device (RVAD). Scopolamine, 0.4 mg IV and 2 mg IV midazolam were given to maintain amnesia and not decrease the MAP further as the blood pressure would not tolerate volatile agents at that time. With both ventricles assisted, the required high cardiac output state could be maintained. Mean pressure increased to 60-70 s and the heart rate continued in 120 s. SVR was 1061 dynes-s-cm⁻². At this time the ABG was a pH of 7.12 with a pCO₂ of 61.7 mmHg, a pO₂ of 76.8 mmHg, a bicarbonate of 20.6 mEq/L, and a base excess of -7.6 mmol/L. Protamine was given as the MAP was maintained in the 60-70 mmHg range. The high pO₂ was quickly corrected after ventilating the patient with separation of bypass.

The EPI was stopped and Ne and VASO continued. Twelve hours after induction, the patient was transferred to the ICU on a propofol infusion of 25 mcg/kg/min. In the ICU the MAP was 75 mmHg with the BIVAD at 4.5 L/min with the heart still AV paced at 90 beats per minute. Ne remained at 10 mcg/min and the VASO was weaned.

The next morning, the patient was responding to simple commands. He was weaned and the ventricular assist devices were removed after a week. The patient continued to recover and was discharged from the hospital with a left ventricular ejection fraction was 45%.

Discussion

This case demonstrates the severity of vasoplegic syndrome. The patient was weaned off CPB, only to have a low SVR and an unsustainable high cardiac output state. We believe that this could have been prevented with earlier administration of methylene blue.

Methylen blue is used in the treatment of vasoplegia as it is a soluble guanylatecyclase inhibitor. Methylene blue decreases the level of cyclic guanosine monophosphate and also inhibits the inducible and endothelial nitric oxide synthase, blocking the pathway for vasodilation and allowing vasoactive medications to work unopposed [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3]. Vasoplegic syndrome does not have a consistent definition in the literature, but in this case there was clearly severe hypotension with an initial normal cardiac output and a low systemic vascular resistance [3].

The timing of methylene blue dosing for vasoplegic syndrome has not been discussed in the literature. Preoperative prophylactic dosing as well as treatment dosing has been studied. In our case, late dosing was due to uncertainty of diagnosis and also trying other interventions, such as vessel regrafting, steroids and vasopressin, first. The clinical criteria for vasoplegic syndrome are not consistent across studies and therefore add to the difficulty of applying study results.

The early dosing of methylene blue should be tried in cases of suspected vasoplegic syndrome. In our case, there was no effect and timing may be the crucial factor. Methylene blue side effects are rarely reported with doses less than 5 mg/kg, other than causing a temporarily false depression of the oxygen saturation on pulse oximetry. Above 5 mg/kg arrhythmias, confusion, headaches, angina, or emesis has been reported and rarely neurotoxicity at doses above 5 mg/kg [9]. Methylene blue is very innocuous at doses of 2 mg/kg, especially when compared to the effects of stress dose steroids or increased doses of vasopressors [3]. Therefore, if there is an early suspicion of vasoplegic syndrome, early methylene blue is paramount, as the window of opportunity may be missed while trying other interventions which may result in further harm from medication side effects and continued untreated vasoplegia.

References


