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Case Report Open Access

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% and no valvular abnormalities. Electrocardiogram (EKG) was normal sinus rhythm at 64 bpm.

2 mg midazolam IV was given preoperatively; he was brought into the operating room, an arterial line was placed and induced with another 2 mg midazolam, 740 micrograms (mcg) fentanyl and 6 mg etomidate and 10 mg pancuronium. Intubation and insertion of a right pulmonary artery (PA) catheter were accomplished uneventfully.

Initial cardiac index (CI) was 2.16 liters per minute per meter squared with pulmonary artery pressure (PAP) in the low 30's mmHg systolic and mid-teens diastolic with a central venous pressure (CVP) between 9 and 12 mmHg. SBP was above 100 mmHg after induction and during central line placement. Aminocaproic acid was started after central line placement with a 10 g bolus over 30 minutes then infused at 1 gram per hour. It was noted his mean arterial pressure (MAP) started trending below 60 mmHg. Prior to and during the first 20 minutes of cardiopulmonary bypass (CPB), he required 4 mg of phenylephrine. The MAP continued to remain in the high 50 mmHg range and required a norepinephrine (Ne) infusion of 10 micrograms per minute (mcg/min) to maintain MAP of 60 mmHg.

The four-vessel coronary artery bypass was completed and separation from CPB after two hours. The arterial blood pressure was in the 70-75/40-45 mmHg range. An epinephrine (EPI) infusion was started at 5 mcg/min and increased to 10 mcg/min to prevent further drop in blood pressure.

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 90bpm on Ne and VASO infusions. CI was 2.6 L/minute*m^2 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, pCO_2 of 45.1 mmHg, paO_2 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 adrenal 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.

CPB was reinstituted due to persistent hypotension, a worsening lactate of 11.3 despite the IABP use. After discussion, 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.

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

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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 LVAD, the right ventricle became hypokinetic 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^{-5}. At this time the ABG was a pH of 7.12 with a pCO_2 of 61.7 mmHg, a paO_2 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 pCO_2 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.

Methylene 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 (less than 800 dynes-s-cm^{-5}) in the setting of high doses of multiple vasoactive medications and a pH greater than 7.15 [4]. Our patient's pH did drop below 7.15; however, this was after hours of a low SVR state unresponsive to vasoactive medications.

The success of methylene blue for treating vasoplegic syndrome is well documented in case reports and in both treatment and prophylactic studies [5-7]. However, in the case here, methylene blue did not work. We believe he did have vasoplegic syndrome and no other causes of hypotension. Adrenal insufficiency and hypothyroidism could present similarly, but stress dose steroids were given to treat for potential adrenal insufficiency and there was no clinical evidence preoperatively of hypothyroidism and normal thyroid stimulating hormone levels were obtained in the ICU. The patient's presentation was not consistent with anaphylaxis. The sustained low SVR and high cardiac output state was more consistent with vasoplegic syndrome. The long initial CPB time, use of an angiotensin converting enzyme inhibitor, and use of a beta-blocker are known risk factors of vasoplegic syndrome [7]. In addition, the patient required high doses of prebypass vasoactive medications, which is associated with the highest odds ratio (OR 3.59) of all vasoplegia risk factors [6].

The incidence of methylene blue failure in vasoplegic syndrome is not known. However, in the study by Leyh et al. of his 54 enrolled patients with vasoplegic syndrome and treated with methylene blue, 3 did not respond and later died [6]. There was no further explanation or details in that study.

There may be an explanation for the failure of methylene blue that was seen in our case and presumably in the 3 cases in Leyh's study. Fernandes et al. describes a *Window of Opportunity* for methylene blue dosing [8]. In their review article, the window of opportunity describes, in a mouse sepsis model, three eight-hour windows of guanylatecyclase activity. Sepsis, like vasoplegic syndrome, is a state of profound refractory vasodilation. In the first eight hours, there is increased nitric oxide synthetase activity and upregulation of guanylate cyclase. The second eight hours there is an absence of guanylatecyclase expression and a down regulation of nitric oxide synthase. The third eight hour window occurs and there is an upregulation of guanylatecyclase and nitric oxide synthase.

Extrapolating this data to humans, presumably if methylene blue is given during a time of low levels of guanylatecyclase and nitric oxide synthase, then methylene blue would have no site of action and no clinical effect. We believe this is what occurred in our patient. There is no defined window of opportunity for humans, but in this case, methylene blue was given 6 hours after starting vasoactive medications and the presumed start of vasoplegic syndrome. The ICU team did not redose methylene blue. If later dosing yielded the hemodynamic improvement that methylene blue offers, then it would be strong clinical evidence that the window of opportunity for methylene blue dosing exists in humans.

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 have 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.

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