Case Report

The Use of Intravenous Hydroxocobalamin as a Rescue in Methylene Blue-resistant Vasoplegic Syndrome in Cardiac Surgery

Abstract

Vasoplegic syndrome is a well-recognized complication during cardiopulmonary bypass (CPB) and is associated with increased morbidity and mortality, especially when refractory to conventional vasoconstrictor therapy. This is the first reported case of vasoplegia on CPB unresponsive to methylene blue whereas responsive to hydroxocobalamin, which indicates that the effect of hydroxocobalamin outside of the nitric oxide system is significant or that the two drugs have a synergistic effect in one or multiple mechanisms.

Keywords: *Hydroxocobalamin, left ventricular assist device, methylene blue, vasoplegia*

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Introduction

Vasoplegic syndrome is a well-recognized complication during cardiopulmonary bypass (CPB) occurring in up to 25% of patients and is associated with increased morbidity and mortality, especially in the 5% nonresponsive to conventional vasoconstrictor therapy.[1-3] In such cases, refractory vasoplegia manifests itself as systemic hypotension (mean arterial pressure [MAP] <50 mmHg) despite increasing vasopressor and fluid support, increased cardiac index (>2.5 L/min/m^2), low systemic vascular resistance (SVR) (<800 dynes·s/cm^5), and normal or increased filling pressures. The cause of refractory vasoplegia is in part due to an inappropriately activated nitric oxide (NO) system. Under normal physiological conditions, NO is activated by NO synthase (NOS) in the cardiomyocyte and acts through the cyclic guanosine monophosphate (cGMP) mechanism to decrease vascular tone.[2] During times of physiological stress, however, an inducible form of NOS can be activated by inflammatory cytokines,[3] resulting in the continually activated NO system postulated to be the cause of refractory vasoplegia seen in CPB. Thus, treatment of CPB-associated refractory vasoplegia has been successful with inhibitors of the NO system.

Conventionally, methylene blue (MB) has been the treatment of choice due to its inhibition of cGMP and has been shown to be effective as both a preventive and rescue therapy.[3] However, there have yet been randomized control trials of MB that indicate optimum dosage, timing of administration, or target population, leaving the possibility that MB may not be effective for all patients. Recently, hydroxocobalamin has also been revealed to inhibit the NO system[4] and was successfully utilized for one case of CPB-associated refractory vasoplegia without attempting MB first.[5] This present case demonstrates that despite unresponsiveness to MB, hydroxocobalamin can be effective in refractory vasoplegia, thus not only supporting a second rescue modality for refractory vasoplegia but also suggesting an alternative method of managing refractory vasoplegia if MB should fail.

Case Report

A 62-year-old male with a history remarkable for type 2 diabetes mellitus, coronary artery disease status postcoronary artery bypass grafting, and automatic implantable cardioverter defibrillator presented for a left ventricular assist device (LVAD) as a bridge to transplantation.

During the preoperative optimization phase, the patient had the following vital signs: heart rate, 101 beats/min; noninvasive

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blood pressure (BP), 84/60 mmHg (MAP 68 mmHg); respiratory rate, 18; and an oxygen saturation of 98% on room air. Laboratory studies were remarkable for decreased renal function with a serum urea nitrogen 31 mg/dL (nl: 6–21 mg/dL) and a creatinine 1.7 mg/dL (nl: 0.8–1.3 mg/dL). Pulmonary function tests showed a total lung capacity of 6.06 (82% of predicted value), vital capacity of 3.46 (72% of predicted value), forced expired volume of 2.57 (70% of predicted value), and diffusion capacity of the lungs for carbon dioxide of 18.2 (63% of predicted value). Transthoracic echocardiography revealed a left ventricular ejection fraction of 10%, a moderately enlarged right ventricle with severe decrease in right ventricular systolic function, and mild valvular dysfunction. Right heart catheterization indicated elevated pulmonary arterial pressures (PAPs) at 53/28 mmHg (mean 36 mmHg) with pulmonary vascular resistance at 2.24 wood units. Subsequent to these findings, the patient was placed on a preoperative milrinone infusion of 0.5 mcg/kg/min and dobutamine infusion of 2 mcg/kg/min titrated by the cardiology service to optimize preoperative right ventricular function and improve diuresis with resulting increased BP to 98/62 mmHg (MAP 74 mmHg).

Before induction of general anesthesia, a left radial arterial line was placed under ultrasound guidance with lidocaine local infiltration. Induction comprised 2% lidocaine (100 mg), etomidate (30 mg), fentanyl (500 mcg), and succinylcholine (100 mg). A rapid sequence induction was chosen to obtain rapid airway access in the setting of ventricular failure and attenuated the myoclonic response elicited by etomidate. Maintenance was accomplished with isoflurane, vecuronium, and fentanyl.

A transesophageal echocardiogram was placed immediately postintubation for intraoperative monitoring and diagnosis. Postinduction, it was noted that the patient required increasing bolus doses of vasopressors to maintain a MAP within 20% of the preoperative baseline of 98/62 mmHg (MAP 74 mmHg). Ultimately, 400 mcg of epinephrine and 22 units of vasopressin were administered in a combination of boluses in addition to infusions before the initiation of CPB. During CPB, vasopressor requirements continued to increase and dobutamine and milrinone infusions were halted. Despite infusions of vasopressin 0.04 μ/min, norepinephrine 0.25 mcg/kg/min, and significant boluses of epinephrine and vasopressin, the patient remained hypotensive whereas attempting to separate from CPB even after successful implantation and function of the LVAD, subsequent improvement of PAP to 41/19 mmHg (mean 27 mmHg), and improvement of the right ventricular function. Due to significant refractory hypotension, two bolus doses of MB were administered (1 mg/kg) to no avail with systemic BPs 61/54 mmHg (MAP 56 mmHg) and 44/41 mmHg (MAP 42 mmHg) after the first and second doses of MB, respectively. Finally, the decision was made to administer hydroxocobalamin (Vitamin B12) for refractory vasoplegia. A total dose of 5 g of hydroxocobalamin was administered intravenously through the CPB circuit, and within 15 min of administration, the patient was weaned from vasopressor support and separated successfully from CPB with a BP of 79/68 mmHg (MAP 71 mmHg). On arrival to the Intensive Care Unit, the patient was weaned completely from norepinephrine and did not require additional vasopressor boluses. On postoperative day 6, the patient was transferred to the cardiac step-down floor with LVAD flow of 4.5 L/min.

Discussion

Hydroxocobalamin is a highly bioavailable form of vitamin B12. Proposed mechanism of the drug may include the NO system like that of MB[4] as well as a second mechanism involving hydrogen sulfide (H_2S)-induced vasodilation.[6,7] As a factor independent of NO, H_2S has been proposed in animal models to be released by endothelial tissue and act by modifying endothelial potassium channels consequently inducing hyperpolarization and vascular relaxation.[6] Hydroxocobalamin binds to H_2S to be excreted, and thus this drug has been approved for H_2S toxicity.[7] Hydroxocobalamin is currently available as a lyophilized form and is approved for cyanide poisoning at a dose of 5 g in 15 min by intravenous infusion for a maximum dose of 10 g. No recommendations have been made for vasoplegia. In terms of treatment for vasoplegia, studies in anesthetized rabbits demonstrate moderate pressor effect of hydroxocobalamin resulting increase in SVR, BP, and decrease in cardiac output (4). However, cyanocobalamin, a typical B12 formulation sold over the counter, did not induce the same effects of increased BP and SVR.[8] In healthy human volunteers, hydroxocobalamin was associated with increased BP up to 4 h with the maximum increase of 27 and 25 mmHg in systolic and diastolic pressure, respectively.[9] Similar to MB, hydroxocobalamin has also not been studied in randomized controlled trials for vasoplegia. Thus, its parameters of effect are largely unknown. The drug's side effects may include a papular rash, headache, nausea, pruritus, chest discomfort, dysphagia, and decrease in lymphocytes.[9] Due to its red coloring, hydroxocobalamin may also falsely elevate hematocrit and pulse oximetry.

Hydroxocobalamin was utilized in this case to be an effective treatment for refractory vasoplegia. Thus far, two additional cases have reported success with hydroxocobalamin, one without MB after CPB and the other during liver transplantation,[5,10] This is the first reported case of vasoplegia on CPB unresponsive to MB whereas responsive to hydroxocobalamin, which potentially indicates that the effect of hydroxocobalamin outside of the NO system is significant or that the two drugs have a synergistic effect in one or multiple mechanisms.

More research is indicated to elucidate the mechanism of vasoconstriction by hydroxocobalamin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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