Use of Intravenous Hydroxocobalamin without Methylene Blue for Refractory Vasoplegic Syndrome After Cardiopulmonary Bypass

DEFG 1 Vincent Peyko
ABDE 2 Michael Finamore

Corresponding Author: Vincent Peyko, e-mail: vpeyko@neomed.edu

Conflict of interest: None declared

Case series
Patients: Male, 71-year-old • Male, 71-year-old
Final Diagnosis: Vasoplegic syndrome
Symptoms: Refractory hypotension
Medication: —
Clinical Procedure: Cardiopulmonary bypass
Specialty: Anesthesiology

Objective: Unusual or unexpected effect of treatment

Background: Cardiac vasoplegic syndrome is a form of vasodilatory shock characterized by profound vasodilation and low systemic vascular resistance, which results in significant hypotension despite high cardiac output and appropriate fluid resuscitation. In up to 45% of patients, cardiopulmonary bypass (CPB) can precipitate vasoplegic syndrome. Vasoplegic syndrome after CPB that is refractory to other vasopressors, such as catecholamine and vasopressin, has been successfully treated with inhibitors of the nitric oxide (NO) system, such as methylene blue and hydroxocobalamin. Methylene blue has been the treatment of choice because of its effectiveness for both prevention and rescue therapy. Hydroxocobalamin has demonstrated efficacy in combination with methylene blue, and also on its own when vasoplegic syndrome is refractory to methylene blue.

Case Report: We present 2 cases that expand upon the existing evidence supporting the efficacy of hydroxocobalamin as a first-line option for inhibiting the NO system in vasoplegic syndrome that is refractory to other vasopressors. Specifically, we demonstrate the appropriate and successful use of hydroxocobalamin alone to treat refractory vasoplegic syndrome after CPB.

Conclusions: Refractory vasoplegic syndrome that occurs after CPB has been successfully treated with inhibitors of the NO system, such as methylene blue and hydroxocobalamin. The present cases expand upon the scant existing evidence of the efficacy of hydroxocobalamin as an appropriate option for refractory vasoplegic syndrome.

Keywords: Cardiopulmonary Bypass • Hydroxocobalamin • Methylene Blue • Vasoplegia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/930890

Authors’ Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

1 Department of Pharmacy, Mercy Health – St Elizabeth’s Boardman Hospital, Boardman, OH, U.S.A.
2 Department of Anesthesiology, Bel-Park Anesthesia Associated, Inc., Canfield, OH, U.S.A.

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)
**Background**

Profound vasodilation and low systemic vascular resistance (SVR) are characteristics of cardiac vasoplegic syndrome, which is a form of vasodilatory shock and can result in significant hypotension despite high cardiac output and appropriate fluid resuscitation [1,2]. After cardiopulmonary bypass (CPB), up to 45% of patients may exhibit vasoplegic syndrome [1-4]. The result is inadequate tissue perfusion and metabolic acidosis [2]. Significant morbidity and mortality can occur when treatment becomes refractory to vasopressors and the incidence may be increased in up to 5% of patients who do not respond to conventional vasoconstrictive therapy [3]. After cardiac surgery, reduced plasma levels of arginine vasopressin and excess nitric oxide (NO) production lead to vasodilation [2]. High-dose vasopressors are often required to maintain adequate blood pressure [1,2]. Complex interactions among plasma proteins, leukocytes, platelets, endothelial cells, and cytokines factor into this syndrome [2]. However, the primary clinical manifestation involves systemic hypotension [2]. Preoperative risk factors associated with higher incidence of postoperative vasoplegic syndrome include preoperative use of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, which increase the relative risk of vasoplegic syndrome by 1.37 and 1.31, respectively [5,6]. Use of vasopressors before or during CPB and longer duration of the procedure also confer increased risk of developing vasoplegic syndrome [1]. For each additional 30-minute interval on CPB, the risk of vasoplegic syndrome increases by 38% [5,6].

Resistance to vasopressors is thought to occur through 3 mechanisms: activation of adenosine triphosphate-sensitive potassium channels in the plasma membrane of vascular smooth muscle, vasopressin deficiency, and activation of inducible NO synthase [7]. Refractory vasoplegic syndrome that occurs after CPB has been successfully treated with inhibitors of the NO system, such as methylene blue [3].

Hydroxocobalamin also mitigates the effects of NO [8]. It has efficacy in combination with methylene blue when vasoplegic syndrome is refractory to methylene blue, and in its own right, as shown in several case reports and series [3,4,9-12]. We present 2 cases that add to the existing evidence about the efficacy of hydroxocobalamin as an appropriate option for vasoplegic syndrome refractory to other vasopressors. Quickly initiating appropriate treatment of refractory vasoplegic syndrome after CPB is vital because the mortality rate may be as high as 25% when the condition lasts for more than 36 to 48 h [5].

**Case Reports**

**Patient 1**

A 71-year-old man with a history remarkable for coronary artery disease (CAD) with recent ST-elevation myocardial infarction, systolic heart failure, hyperlipidemia, and chronic cellulitis in both lower extremities presented for a coronary artery bypass graft (CABG) and apical aneurysm repair.

Before surgery, the patient’s vital signs were as follows: heart rate, 78 beats/min; blood pressure, 119/65 mmHg; respiratory rate, 20 breaths/min; and oxygen saturation of 94% on room air. Laboratory studies were remarkable for decreased renal function with a serum creatinine of 1.3 mg/dL (reference: 0.7-1.2 mg/dL). The patient was on a beta-blocker, which increased the relative risk of vasoplegic syndrome.

Transthoracic echocardiography (TTE) revealed a decreased left ventricular ejection fraction (LVEF) of 30% with an aneurysmal apex, normal right ventricular size and function, mild mitral and tricuspid valve regurgitation, and mild aortic stenosis. Left heart catheterization showed severe triple vessel disease with 100% mid-left anterior descending coronary artery (LAD), 60% proximal obtuse marginal-3, and 70% mid-right coronary artery (RCA) stenosis.

A transesophageal echocardiogram (TEE) was performed immediately after intubation for intraoperative monitoring and diagnosis. The patient required boluses of vasopressor before initiation of CPB for a total of 20 mg of epinephrine, 2 units of vasopressin, and 200 mcg of phenylephrine to maintain a mean arterial blood pressure (MAP) of 65 mmHg. The retrograde autologous prime was the main reason for blood pressure supplementation. During CPB, hemodynamic stability was maintained without vasopressor support. After cross-clamp removal, epinephrine (3 µg/min) was initiated to assist with separation. Vasopressin (0.04 units/min) was started soon after echocardiography. That exam showed that the LVEF had increased to 45% and the right ventricular function remained normal. Cardiac output (CO) as calculated intraoperatively with echocardiography was 6.0 L/min.

Multiple boluses of vasopressin were administered and the infusion was increased to 0.06 units/min in an attempt to maintain a MAP above 65 mmHg. Calcium chloride was also given 30 min after cross-clamp removal and fluid resuscitation was guided by echocardiography. A Swan-Ganz catheter was placed before leaving the operating room. The entire procedure took 71 min and the patient still required multiple boluses of vasopressin at the completion of surgery. On arrival in the Intensive Care Unit (ICU), norepinephrine (6 µg/min) was started, vasopressin was increased to 0.08 units/min, and the epinephrine...
infusion rate remained unchanged. Stress-dose steroids were given for refractory hypotension related to potential corticosteroid insufficiency. The CO via the Swan-Ganz catheter was 5.6 L/min with a cardiac index (CI) of 2.9 L/min/m²; SVR was 859 dynes/sec/cm⁻5. Because the patient’s vasopressor requirements were increasing and his CI was adequate, hydroxocobalamin was administered for refractory vasoplegic shock. A total dose of 5 g was administered i.v. over 10 min. The SVR immediately increased to 1163 dynes/sec/cm⁻5 and peaked at 1638 dynes/sec/cm⁻5 several hours later with weaning of vasopressor support. Within 24 h, the norepinephrine infusion was discontinued and the epinephrine and vasopressor infusions were decreased; they were ultimately shut off later in the day, after hydroxocobalamin administration. The Swan-Ganz catheter was removed at this point.

The patient was extubated the day after CPB, and over the next 3 days, low-dose dobutamine was used to augment CO to the kidneys and vasopressin was used at low doses as needed to maintain the MAP above 65 mmHg. On the fifth day after surgery, the patient was discharged from the ICU. On the eighth day after surgery, the patient was on room air, able to ambulate 400 feet, and discharged home.

Patient 2

A 71-year-old man with a history remarkable for CAD with recent non-ST-elevation myocardial infarction, mitral stenosis, peripheral vascular disease, and type 2 diabetes mellitus presented for a CABG and mitral valve replacement.

Before surgery, the patient’s vital signs were as follows: heart rate, 71 beats/min; blood pressure, 141/81 mmHg; respiratory rate, 16 breaths/min; and oxygen saturation of 96% on room air. Laboratory studies were remarkable for decreased renal function with a creatinine of 1.3 mg/dL (reference: 0.7-1.2 mg/dL) and glucose of 233 mg/dL (reference: 74-99 mg/dL). The patient was on a beta-blocker and an ACE inhibitor to maintain MAP prior to leaving the operating room. The length of surgery was guided by echocardiography.

The patient received 5 units of packed red blood cells, 2 units of fresh frozen plasma, 6 units of random donor platelets, and 15 units of cryoprecipitate secondary to a bloody surgical field and anemia. No bolus of vasopressors was required to maintain MAP prior to leaving the operating room. The length of CPB was 209 min. Norepinephrine was started at 6 µg/min and epinephrine at 7 µg/min.

Overnight in the ICU, the patient’s norepinephrine requirements increased from 6 µg/min to 14 µg/min with vasopressin started at 0.02 units/min. The epinephrine infusion rate remained the same. A noninvasive CO monitor placed on the patient showed an SVR of 620 dynes/sec/cm⁻5 and a CI of 2.7 L/min/m². Because his vasopressor requirements were increasing and his CI was adequate, hydroxocobalamin was administered for refractory vasoplegic shock (total dose 5 g i.v. over 10 min). SVR increased to 854 dynes/sec/cm⁻5 and the norepinephrine infusion was discontinued within 1 h. The patient was weaned off epinephrine over the next 48 h and off vasopressin over the next 72 h.
After surgery, the patient developed an acute kidney injury that required dialysis. He also developed new-onset atrial fibrillation that required amiodarone infusion on the day after surgery. He eventually developed junctional bradycardia that required dual-chamber pacemaker placement. The patient ultimately required a tracheostomy and placement of a percutaneous endoscopic gastrostomy (PEG) tube to facilitate complete recovery because he was still demonstrating signs of encephalopathy.

On the ninth day after surgery, the patient was transferred to a long-term acute care facility. Over the course of the following week, his tracheostomy was capped and he was eating on his own without use of the PEG tube. He continued to require dialysis.

**Discussion**

Patient 2 was on an ACE inhibitor and both he and Patient 1 were on beta-blockers before surgery, with vasopressors initiated prior to CPB, which increased the relative risk of vasoplegic syndrome [5]. Prolonged CPB time is considered to be >180 min and confers increased risk of post-CPB vasoplegic syndrome [5,13]. Patient 2 had a total CPB time of 209 min. A retrospective study of 2823 cardiac surgery cases by Levin et al demonstrated a mean CPB time of 164.4 min [6]. Because each additional 30-min interval on CPB increases the risk of vasoplegic syndrome by 38%, the risk was nearly 76% higher in Patient 2 than in the average patient in the study by Levin et al [5,6]. Thus, both our patients had increased risks of developing post-CPB vasoplegic syndrome, particularly Patient 2.

There is no universal definition for vasoplegic syndrome. Accepted definitions include SVR <800 dynes/s/cm², MAP <60 mmHg, CI >2.5 to 3 L/min/m², and ≥1 vasopressor after adequate fluid replacement [4]. Having ≥1 of these conditions within 24 h of CPB is generally accepted to constitute vasoplegic syndrome [4]. Patient 1 was receiving 3 vaspressors and his CI was 2.9 L/min/m² and MAP was <65 mmHg within 24 h post-CPB, constituting vasoplegic syndrome. Patient 2 met all criteria for vasoplegic syndrome because he was on 3 vasopressors and had a CI of 2.7 L/min/m², MAP <65 mmHg, and SVR of 620 dynes/s/cm² within 24 h after CPB.

Dysregulation of NO homeostasis is thought to precipitate vasoplegic syndrome [4]. Hydroxocobalamin is 1 of 4 forms of vitamin B₁₂ found in humans [9]. It is typically used for cyanide toxicity and functions by cobalamin binding to cyanide to form cyanocobalamin, which is inactive and excreted through the kidneys [8].

It is not entirely known how i.v. hydroxocobalamin mitigates catecholamine-resistant vasodilatory shock, but it scavenge, binds, and prevents the formation of NO and hydrogen sulfide, which may also potentiate vasodilation and hypotension [9]. NO oxidizes the cobalt from hydroxocobalamin [9]. This complex of cobalt and NO may transfer NO to hemoglobin to reduce the NO level. Less NO and hydrogen sulfide may stabilize capillary membranes and restore vascular tone [7]. Hydroxocobalamin also likely exerts its vasopressor effects through inhibition of inducible NO synthase and guanylate synthase [4,14].

Methylene blue is a water-soluble dye that inhibits NO synthase and guanylate cyclase to reverse vasodilatation caused by excessive NO signaling [15]. Methylene blue has been the treatment of choice, given its effectiveness as both a preventive and rescue therapy [3,16-18]. However, drug shortages and drug-drug interactions through inhibition of monoamine oxidase to perpetuate serotonin syndrome may lead to the need for alternative therapy for vasoplegic syndrome that occurs after CPB [3].

Many case reports detailing hydroxocobalamin efficacy include concomitant use of methylene blue [3,7,8]. Methylene blue was given in addition to hydroxocobalamin in 54% of patients in the Armour et al case series and 45% in the Shah et al case series and there may be an advantage to the combination versus methylene blue alone [11,12,19].

Like the report by Roderique et al, our study demonstrates efficacy without concomitant methylene blue [4]. Both patients in the present case study received a single, 5-g dose of hydroxocobalamin given i.v., with very rapid hemodynamic responses, as MAP and SVR increased while the vasopressor requirement was reduced within hours. Hydroxocobalamin was chosen for refractory vasoplegic syndrome for our patients because of product availability and evidence from the literature supporting its safety and efficacy. A recently published retrospective study comparing hydroxocobalamin and methylene blue did not demonstrate differences between the ability to increase MAP, increase SVR, or lead to changes between groups in norepinephrine equivalents [20]. This equivalency suggests that either agent is appropriate for refractory vasoplegic syndrome that occurs after CPB. Unfortunately, a clinical trial comparing the drugs for treatment of vasoplegic syndrome was discontinued in 2020 due to lack of funding [21].

Both of our patients exhibited chromaturia and erythema, but otherwise, we report no significant adverse events (AEs) due to the administration of hydroxocobalamin in either case. A study of 136 healthy volunteers showed that chromaturia and erythema were the most common AEs in those that received 5- or 10-g doses of hydroxocobalamin [22]. Oxalate crystals were found in the urine of 61% of those that received 5-g doses and 56% of those that received 10-g doses [22]. There were no reports of photosensitivity, angioedema, or anaphylaxis [22].
Conclusions

The 2 cases in our report represent further evidence that hydroxocobalamin can be substituted for methylene blue to treat vasoplastic syndrome occurring after CPB that is refractory to other vasopressors and in situations in which methylene blue is contraindicated or unavailable, to reduce vasopressor demand and restore appropriate hemodynamic stability. Development of vasoplastic syndrome after CPB leads to death or a hospital stay of >10 days in 57.4% of patients [5]. Both of our patients avoided such outcomes, with vasoplastic syndrome resolving shortly after hydroxocobalamin utilization.

Conflict of Interest

None.

References:

1. Shaefi S, Mittel A, Klick J, et al. Vasoplegia after cardiovascular procedures—pathophysiology and targeted therapy. J Cardiothorac Vasc Anesth. 2018;32:1013-22
2. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: Pathophysiology, risk factors, and treatment. Am J Med Sci. 2015;349:80-88
3. Cai Y, Mack A, Ladlie B, Martin A. The use of intravenous hydroxocobalamin as a rescue in methylene blue-resistant vasoplastic syndrome in cardiac surgery. Ann Card Anaesth. 2017;20:462-64
4. Roderique J, VanDyck K, Holman B, et al. The use of high-dose hydroxocobalamin for vasoplastic syndrome. Ann Thorac Surg. 2014;97:1785-86
5. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: Current concepts and management. Semin Thorac Cardiovasc Surg. 2010;22:140-44
6. Levin MA, Lin HM, Castillo JG, et al. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplastic syndrome. Circulation. 2009;12:1664-71
7. Landry D, Oliver J. The pathogenesis of vasodilatory shock. N Engl J Med. 2001;345:588-95
8. Patel J, Venegas-Borsellino C, Willoughby R, Freed J. High-dose vitamin B12 in vasodilatory shock: A narrative review. Nutr Clin Pract. 2019;34:514-20
9. Burns M, Boettcher B, Woehlich H, et al. Hydroxocobalamin as a rescue treatment for refractory vasoplastic syndrome after prolonged cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2017;31:1012-14
10. Zundel M, Feih J, Rinka J, et al. Hydroxocobalamin with or without methylene blue may improve fluid balance in critically ill patients with vasoplastic syndrome after cardiac surgery. J Cardiothorac Vasc Anesth. 2018;32:452-57
11. Armour J, Armour T, Juppa W, et al. Use of hydroxocobalamin (vitamin B12a) in patients with vasopressor refractory hypotension after cardiopulmonary bypass: A case series. Anesth Analg. 2019;129:e1-4
12. Shah P, Reynolds P, Pal N, et al. Hydroxocobalamin for the treatment of cardiac-associated vasoplegia: a case series. Can J Anaesth. 2018;65:560-68
13. Madhavan S, Chan SP, Tan WC, et al. Cardiopulmonary bypass time: Every minute counts. J Cardiovasc Surg (Torino). 2018;59:274-81
14. Lin Y, Yu T. Use of high-dose hydroxocobalamin for septic shock: A case report. AA Practice. 2019;12:332-35
15. Jentzer J, Vallabhajosyula S, Khanna A, et al. Management of refractory vasodilatory shock. Chest. 2018;154:416-26
16. Mazzeffi M, Hammer B, Chen E, et al. Methylene blue for postcardiopulmonary bypass vasoplastic syndrome: A cohort study. Ann Card Anaesth. 2017;20:178-81
17. Ozal E, Kuralay E, Yildirim V, et al. Preoperative methylene blue administration in patients at high risk for vasoplastic syndrome during cardiac surgery. Ann Thorac Surg. 2005;79:1615-19
18. Lenglet S, Mach F, Montecucco F. Methylene blue: Potential use of an antitique molecule in vasoplastic syndrome during cardiac surgery. Expert Rev Cardiovasc Ther. 2011;9:1519-25
19. Feih J, Rinka J, Zundel M. Methylene blue monotherapy compared with combination therapy with hydroxocobalamin for the treatment of refractory vasoplastic syndrome: A retrospective cohort study. J Cardiothorac Vasc Anesth. 2019;33:1301-7
20. Furnish C, Mueller S, Kiser T, et al. Hydroxocobalamin versus methylene blue for vasoplastic syndrome in cardiothoracic surgery: A retrospective cohort study. J Cardiothorac Vasc Anesth. 2019;33:1301-7
21. Clinicaltrials.gov. Bethesda (MD). National Library of Medicine (US). Identifier: NCT03446599. Hemodynamic effects of methylene blue vs. hydroxocobalamin in patients at risk of vasoplegia during cardiac surgery. 2018 Feb 27 [cited 2020 June 30]. https://clinicaltrials.gov/ct2/show/NCT03446599
22. Uhl W, Noltling A, Galleman D, et al. Changes in blood pressure after administration of hydroxocobalamin: Relationship to changes in plasma cobalamins-(III) concentrations in healthy volunteers. Clin Toxicol (Phila). 2008;46:551-59; discussion 576-77