CASE REPORT

Clinical Case Reports   WILEY

The use of hydroxocobalamin for vasoplegic syndrome in left ventricular assist device patients

Brian Ayers[1] | Katherine Wood[1] | Jennifer Falvey[2] | Wendy Bernstein[3] | Igor Gosev[1]

[1]Division of Cardiac Surgery, University of Rochester Medical Center, Rochester, NY, USA

[2]Farmacy, University of Rochester Medical Center, Rochester, NY, USA

[3]Department of Anesthesiology and Perioperative Medicine, University of Rochester Medical Center, Rochester, NY, USA

Correspondence
Igor Gosev, University of Rochester Medical Center, 601 Elmwood Avenue, Box SURG, 14642 Rochester, NY, USA.
Email: igor_gosev@URMC.Rochester.edu

Abstract

We demonstrate evidence supporting the efficacy of hydroxocobalamin in reducing vasopressor requirements for LVAD patients with refractory vasoplegia. Further study is needed to substantiate these findings and determine its optimal use in practice.

KEYWORDS

cardiac, hydroxocobalamin, LVAD, vasoplegia, vasoplegic syndrome, ventricular assist device, vitamin B12

1 | INTRODUCTION

Vasoplegic syndrome is a well-recognized complication for cardiac surgery associated with significant morbidity and mortality. We describe six cases of hydroxocobalamin use for refractory vasoplegic syndrome during left ventricular assist device surgery. All patients demonstrated significantly improved hemodynamics while requiring fewer vasopressors. All patients survived to discharge.

Vasoplegic syndrome (VS) is a form of vasodilatory shock that is a well-recognized complication for cardiac surgery. It occurs in 9%-44% of cardiac surgery cases that use cardiopulmonary bypass (CPB) and is associated with an up to threefold increased risk of mortality.[1-3] VS is a state of persistent hypotension characterized by low systemic vascular resistance and an increased vasopressor requirement despite a high cardiac output and adequate fluid resuscitation (in the absence of infection or vasodilatory inotropes).[4] The proinflammatory state associated with left ventricular assist device (LVAD) implantation cases may be particularly susceptible,[5,6] with a mortality rate shown to be as high as 42% for cases complicated by VS.[7] Risk factors for developing VS include the preoperative use of ACE inhibitors, angiotensin

receptor blockers, beta-blockers, intravenous unfractionated heparin, preoperative EF <35%, and longer CPB time.[1,8,9]

Vasoplegic syndrome that is refractory to traditional catecholamines and second-line medications, such as methylene blue, remains exceedingly difficult to treat. Hydroxocobalamin as a single 5 g dose has become a promising new treatment option for such cases of refractory VS. Its use stemmed from observational cases of hypotension caused by vitamin B12 deficiency,[10,11] as well as the observed side effect of increased blood pressure when hydroxocobalamin has been used to treat cyanide poisoning.[11,12] Recently, there have been a number of isolated case reports describing the use of hydroxocobalamin for the treatment of VS in critically ill patient populations, including cardiac and liver transplantation surgery.[12-15] However, it's efficacy in LVAD surgery remains largely unknown. In this series, we describe our institutional experience using hydroxocobalamin in six cases of refractory VS during LVAD implantation surgery.

2 | CASE SERIES

Of the 114 LVAD patients implanted at our institution from July 2017 to July 2018, six (5.3%) patients received

perioperative hydroxocobalamin. The cohort consisted of critically ill patients with average INTERMACS profile of 2 (Table 1). Three patients were INTERMACS 1; two of whom were implanted directly off extracorporeal membrane oxygenation (ECMO) support. The majority had nonischemic

cardiomyopathy (83%) and most were implanted as destination therapy (66%).

All patients received a single dose of 5 g intravenous hydroxocobalamin. Intraoperative data are presented in Table 2. Five (83%) patients were undergoing primary LVAD implant, and one (17%) underwent pump exchange at the time of hydroxocobalamin administration. One patient underwent

TABLE 1 Characteristics of patients treated with hydroxocobalamin

Variable	Patient cohort (N = 6)
Characteristics	
Age (years)	53.2 ± 21.0 (21-73)
Male	4 (66%)
Height (meters)	1.7 ± 0.1 (1.6-1.9)
Weight (kg)	89.0 ± 31.9 (40-122)
BMI (kg/m^2)	29.9 ± 9.5 (15-40)
INTERMACS profile	2.3 ± 1.5 (1-4)
INTERMACS 1	3 (50%)
NYHA Class IV (N)	6 (100%)
Medical comorbidities	
Cerebrovascular disease	3 (50%)
Coronary artery disease	3 (50%)
Chronic lung disease	0 (0%)
Diabetes	2 (33%)
Chronic kidney disease	0 (0%)
Dyslipidemia	4 (66%)
Hypertension	3 (50%)
Ischemic cardiomyopathy	1 (17%)
Mechanical circulatory support	
Cardiopulmonary bypass	6 (100%)
ECMO	3 (50%)
Impella	1 (17%)
IABP	1 (17%)
Preoperative laboratory values	
Hemoglobin (g/dL)	9.9 ± 2.4 (7.6-13.1)
Creatinine (mg/dL)	1.1 ± 0.3 (0.6-1.4)
Total Bilirubin (mg/dL)	1.1 ± 0.5 (0.5-1.8)
Albumin (g/dL)	2.9 ± 0.3 (2.3-3.1)
WBC (10^3 cells/mm^3)	10.6 ± 4.9 (5.4-17.1)
Preoperative medications	
ACEi/ARB	3 (50%)
Beta-blocker	4 (66%)
Therapy strategy	
Bridge to transplant	2 (33%)
Destination therapy	4 (66%)

Note: Presented as no. (%) or mean ± SD (range).

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

TABLE 2 Intraoperative data before hydroxocobalamin administration

Variable	Patient cohort (N = 6)
Surgery type	
LVAD implant	5 (83%)
LVAD exchange	1 (17%)
Procedural data	
CPB time (minutes)	116.5 ± 48.2 (52-164)
Timing of B12 administration	
OR	2 (33%)
CVICU	4 (66%)
Time since leaving OR (hr)	7.1 ± 5.8 (2.5-17)
Blood products in OR	
Packed red blood cells (units)	3.7 ± 4.1 (0-11)
Plasma (units)	2.2 ± 2.6 (0-7)
Platelets (units)	1.3 ± 1.4 (0-4)
Cryoprecipitate (units)	0.5 ± 0.5 (0-1)
Hemodynamics before B12	
pH	7.4 ± 0.1 (7.3-7.44)
Temperature (celsius)	37.6 ± 0.5 (37-38.1)
Central venous pressure (mm Hg)	12.8 ± 4.5 (10-19)
Cardiac output (L/min)	7.3 ± 0.2 (7.0-7.5)
Cardiac index (L/min/m^2)	3.7 ± 0.4 (3.3-3.9)
Mean PA pressure (mm Hg)	23.3 ± 3.9 (11-33)

LVAD settings before B12	HeartMate 3 (N = 5)	HeartMate II (N = 1)
Flow	4.5 ± 1.0	4.4
Speed	5450 ± 640	9200
PI	3.0 ± 1.0	2
Power	4.3 ± 1.3	5.1

Note: Presented as no. (%) or mean ± SD (range).

Abbreviations: B12, hydroxocobalamin; CPB, cardiopulmonary bypass; CVICU, cardiovascular intensive care unit; OR, operating room; PI, pulsatility index.

a concomitant aortic valve replacement. All patients were adequately volume resuscitated at the time of hydroxocobalamin administration. Hydroxocobalamin was given intraoperatively in two (33%) cases while attempting to wean from CPB with persistent hypotension after methylene blue administration. Both patients were successfully weaned within 30 minutes following hydroxocobalamin administration. The other four (66%) patients were administered hydroxocobalamin postoperatively in the CVICU (range, 2.5-17 hours postoperative). One patient had an open chest at the time, which was successfully closed the following day.

TABLE 3 Change in patient hemodynamics and vasopressor requirements before and after administration of hydroxocobalamin

	Before B12	After B12	P-value
Hemodynamics[a]			
Mean arterial pressure	67.0 ± 3.5	76.1 ± 6.9	.050
Heart rate	113.3 ± 19.9	106 ± 21.4	**.026**
Cardiac output	7.2 ± 0.3	5.8 ± 1.0	.182
Cardiac index	3.6 ± 0.3	2.9 ± 0.6	.206
Vasopressors[b]			
Epinephrine	0.12 ± 0.04	0.11 ± 0.04	.363
Norepinephrine	0.11 ± 0.08	0.09 ± 0.09	.160
Phenylephrine	1.63 ± 1.20	1.25 ± 1.03	.097
Vasopressin	0.07 ± 0.03	0.05 ± 0.04	.113
Norepinephrine equivalents	0.50 ± 0.17	0.40 ± 0.19	**.048**

Note: Presented as mean ± SD.

Abbreviation: B12, hydroxocobalamin.

[a] Average during the hour before B12 compared to average during the hour after B12.

[b] Immediately before B12 administration compared to average during the hour after B12.

Bold values are statistical significant difference.

At the time of hydroxocobalamin administration, all patients were on epinephrine and norepinephrine, five (83%) were also receiving phenylephrine, and four (66%) were getting vasopressin. Four (66%) had been previously given methylene blue (2 mg/kg) at least 1 hour prior to hydroxocobalamin with initial increases in blood pressure but all failed to experience a sustained response to methylene blue, demonstrated by a return to persistent hypotension in the setting of continued high vasopressor requirements. No patients were experiencing right ventricular (RV) failure or LVAD outflow obstruction as assessed by intraoperative transesophageal echocardiogram.

The effect of hydroxocobalamin administration on patient hemodynamics and vasopressor requirements is shown in Table 3. The previously described and validated norepinephrine equivalent (NEE) score[16] was used to quantify each patient's vasopressor requirement over time. Patients demonstrated a trend toward increased MAP ($P = .050$) with simultaneous decrease in vasopressors ($P = .048$) as measured by NEE in response to hydroxocobalamin. The time series improvement in hemodynamics with concurrent vasopressor sparing effect is depicted in Figure 1. This effect appeared to persist with patients requiring 23% fewer NEE at 1 hour and 36% fewer NEE at 6 hours relative to time of hydroxocobalamin administration (Figure 2). All patients survived to discharge with low rates of postoperative complications. There were no cases of unplanned return to the operating room, hepatic failure, right ventricular failure, or infections. One patient developed renal failure requiring temporary dialysis. Mean stay in the intensive care unit was 16.8 ± 15.1 days, and average hospital total length of stay was 32.3 ± 21.7 days.

3 | DISCUSSION

Vasoplegic syndrome (VS) is a form of vasodilatory shock associated with an up to threefold increased risk of mortality
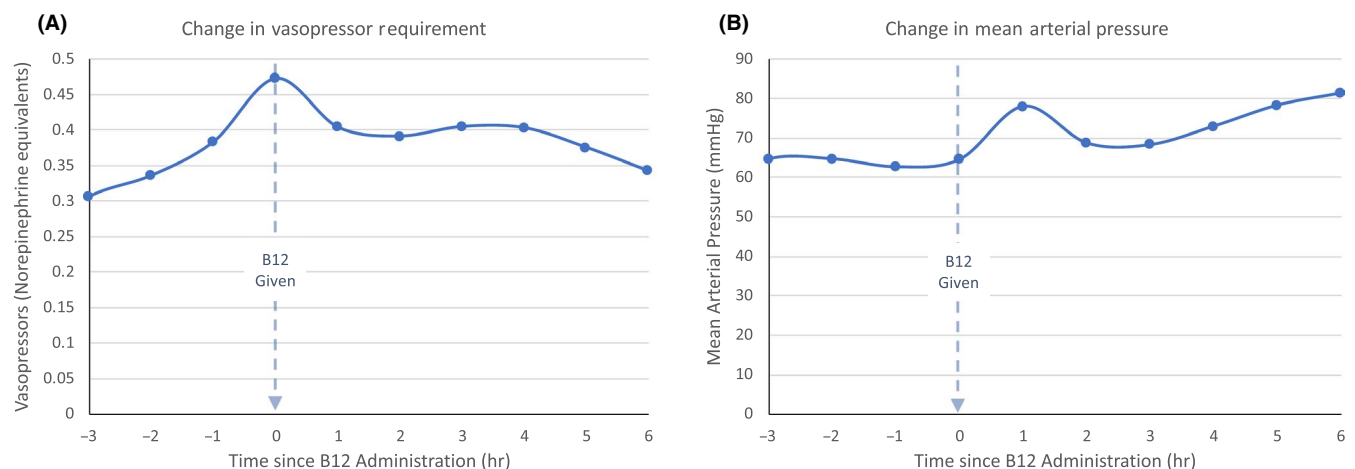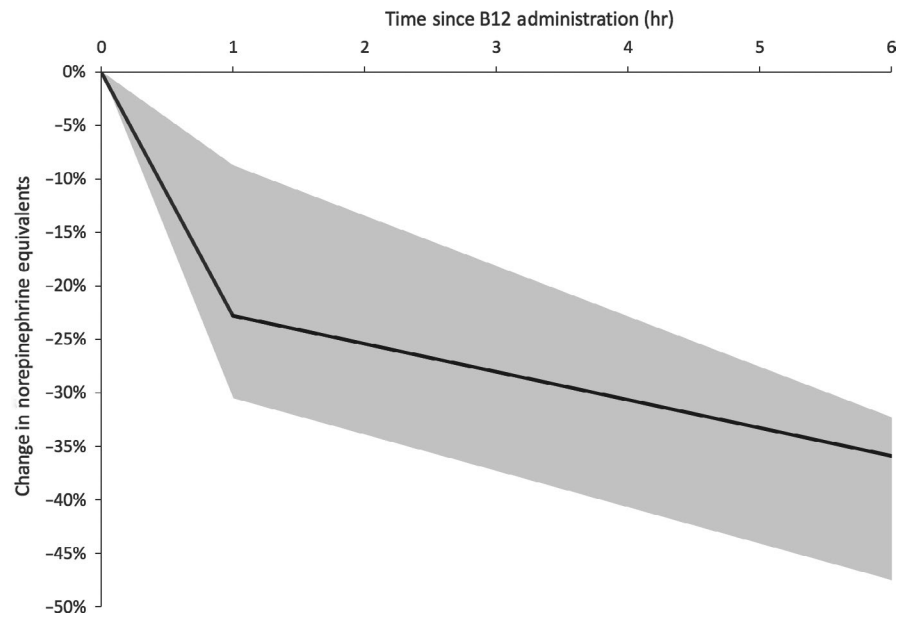

FIGURE 1 Time series data showing A, average vasopressor requirements and B, mean arterial pressure before and after hydroxocobalamin

FIGURE 2 Decrease in vasopressor requirements after administration of hydroxocobalamin (mean ± interquartile range)

in the postcardiopulmonary bypass patient population.[17] Methylene blue (MB) is the most commonly used treatment for VS that is refractory to traditional vasoconstrictors and catecholamines, but does not work for every case and is associated with a number of adverse side effects.[5,8,18] Hydroxocobalamin, an injectable form of vitamin B12, is a promising treatment for refractory VS. While still limited predominately to single-center institutional case series, there is growing evidence of the efficacy of hydroxocobalamin for the treatment of postcardiopulmonary bypass VS in cardiac surgery refractory to traditional therapies.[11-13,19,20] In this case series, we describe our experience using hydroxocobalamin to treat VS during LVAD surgery.

All six LVAD patients at our institution that received hydroxocobalamin for refractory VS in this study had a marked positive response. A single 5 g dose of hydroxocobalamin increased the cohort's MAP 14% in the first hour while simultaneously decreasing vasopressor requirements 23% on average. Five of the six patients experienced this immediate decrease in vasopressor requirements and the sixth patient's vasopressor score remained unchanged over the first hour. For this patient, hydroxocobalamin administration came at a time when the patient's vasopressors had been rapidly increasing (nearly threefold increase over the previous 60 minutes), suggesting hydroxocobalamin may have in fact attenuated the escalation of VS. In addition to the rapid effect of hydroxocobalamin, the response was also notable in that it persisted. All patients had sustained hemodynamics with a further decrease in their vasopressor score at 6 hours after hydroxocobalamin administration. Our work supports a recent study that found a similar positive response to hydroxocobalamin administration in a small cohort of LVAD patients experiencing VS.[21]

The mechanism of action for hydroxocobalamin's effect on VS is incompletely understood. Hydroxocobalamin has been shown to be a NO scavenger,[22] which is the same mechanism as that of methylene blue.[5] However, the interaction between hydroxocobalamin and MB is poorly understood.[13] Previous case reports have described a positive response to hydroxocobalamin in patients that had not responded to MB.[12,19] We saw a similar effect in our patient population. Four of the six patients received MB prior to hydroxocobalamin as a single 2 mg/kg bolus with one of the patients receiving an additional 0.5 mg/kg/hr infused over 6 hours. All four patients demonstrated an initial positive response to MB therapy, but the effect was not sustained and they returned to a state of VS. Hydroxocobalamin was subsequently given at least 1 hour after the administration of any MB and was associated with a sustained improvement in hemodynamics and vasopressor sparing effect. More research is needed to investigate whether these medications have a synergistic effect, or if there are patient-specific characteristics predictive of a positive response to either medication independently.

All our patients that received hydroxocobalamin survived to discharge with no incidence of RV or hepatic failure, and only one patient requiring temporary dialysis. We did not see any evidence of false blood leak alarm activation during dialysis for this patient. All potential adverse side effects of hydroxocobalamin, including the potential for falsely elevated laboratory values, should be carefully reviewed and communicated with all members of the treatment team before its clinical use to avoid confusion.[13] Hydroxocobalamin currently only carries approval from the Food and Drug Administration (FDA) for treatment of cyanide toxicity; all other clinical applications remain experimental. Our institutional practice in the setting of vasoplegic syndrome refractory to traditional

vasoconstrictors (catecholamines and vasopressin), is to first administer methylene blue and if patients remain hypotensive with high vasopressor requirements then administer hydroxocobalamin.

3.1 | Limitations

The main limitation of this study is that it is retrospective and observational in nature. While this is one of the largest reported LVAD cohorts to be treated with hydroxocobalamin, it is still a relatively small number of patients and the lack of complications or mortality seen in this study should be interpreted with caution. Moreover, given its retrospective nature, the treatment of VS and sequence of medications were not standardized across patients creating potential for biases and confounding effects. All patients that received methylene blue demonstrated persistent hypotension for at least 1 hour before hydroxocobalamin administration, but a cofounding effect cannot be ruled out. Prospective studies with standardized protocols are needed to account for the effect of other concomitant pharmacological agents, and larger cohort studies are needed to substantiate these findings and elicit any patient differences that are predictive of a positive response to hydroxocobalamin.

4 | CONCLUSIONS

In summary, vasoplegic syndrome is a common and severe complication for many cardiac surgery procedures that greatly increases patient morbidity and mortality. We demonstrate evidence supporting the use of hydroxocobalamin in LVAD patients and provide data demonstrating its association with a reduction in vasopressor requirements without associated adverse events. Further study is needed to substantiate these findings and determine the optimal use of hydroxocobalamin in clinical practice.

CONFLICT OF INTEREST
Dr Igor Gosev is a consultant for Abbott for work unrelated to the present manuscript. Abbott was in no way involved with the present work and his disclosure in no way influenced our scientific reporting of our findings.

AUTHOR CONTRIBUTIONS
BA: contributed to conception and design of study, acquisition, analysis and interpretation of data, and involved in drafting and revising the manuscript. KW, JF, and WB: contributed to conception and design of study and involved in drafting and revising the manuscript. IG: contributed to conception and design of study, analysis and interpretation of data, and involved in drafting and revising the manuscript.

ORCID
Brian Ayers https://orcid.org/0000-0003-3667-6873

REFERENCES
1. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. *Am J Med Sci*. 2015;349(1):80-88.
2. Shaefi S, Mittel A, Klick J, et al. Vasoplegia after cardiovascular procedures-pathophysiology and targeted therapy. *J Cardiothorac Vasc Anesth*. 2018;32(2):1013-1022.
3. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery—review of pathophysiology and update of treatment options. *Crit Care*. 2020;24(1):36.
4. Mehaffey JH, Johnston LE, Hawkins RB, et al. Methylene blue for vasoplegic syndrome after cardiac operation: early administration improves survival. *Ann Thorac Surg*. 2017;104(1):36-41.
5. Evora PR, Levin RL. Methylene blue as drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 2004;127(3):895-896.
6. Caruso R, Trunfio S, Milazzo F, et al. Early expression of pro- and anti-inflammatory cytokines in left ventricular assist device recipients with multiple organ failure syndrome. *Asaio J*. 2010;56(4):313-318.
7. Argenziano M, Chen JM, Choudhri A F, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg*. 1998;116(6):973-980.
8. Levin RL, Degrange MA, Bruno GF, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg*. 2004;77(2):496-499.
9. Mekontso-Dessap A, Houël R, Soustelle C, et al. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. *Ann Thorac Surg*. 2001;71(5):1428-1432.
10. Ganjehei L, Massumi A, Razavi M, Wilson JM. Orthostatic hypotension as a manifestation of vitamin B12 deficiency. *Tex Heart Inst J*. 2012;39(5):722-723.
11. Roderique JD, VanDyck K, Holman B, et al. The use of high-dose hydroxocobalamin for vasoplegic syndrome. *Ann Thorac Surg*. 2014;97(5):1785-1786.
12. Burnes ML, Boettcher BT, Woehlck HJ, et al. Hydroxocobalamin as a rescue treatment for refractory vasoplegic syndrome after prolonged cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2017;31(3):1012-1014.
13. Shapeton AD, Mahmood F, Ortoleva JP. Hydroxocobalamin for the treatment of vasoplegia: a review of current literature and considerations for use. *J Cardiothorac Vasc Anesth*. 2019;33(4):894-901.
14. Zundel MT, Feih JT, Rinka JRG, et al. Hydroxocobalamin with or without methylene blue may improve fluid balance in critically ill patients with vasoplegic syndrome after cardiac surgery: a report of two cases. *J Cardiothorac Vasc Anesth*. 2018;32(1):452-457.
15. Boettcher BT, Woehlck HJ, Reck SE, et al. Treatment of vasoplegic syndrome with intravenous hydroxocobalamin during liver transplantation. *J Cardiothorac Vasc Anesth*. 2017;31(4):1381-1384.

16. Vallabhajosyula S, Jentzer JC, Kotecha AA, et al. Development and performance of a novel vasopressor-driven mortality prediction model in septic shock. *Ann Intensive Care*. 2018;8(1):112.

17. Levin MA, Lin HM, Castillo JG, et al. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. *Circulation*. 2009;120(17):1664-1671.

18. Leyh RG, Kofidis T, Strüber M, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? *J Thorac Cardiovasc Surg*. 2003;125(6):1426-1431.

19. Cai Y, Mack A, Ladlie B, Martin A. The use of intravenous hydroxocobalamin as a rescue in methylene blue-resistant vasoplegic syndrome in cardiac surgery. *Ann Card Anaesth*. 2017;20(4):462-464.

20. Cheungpasitporn W, Hui J, Kashani KB, et al. High-dose hydroxocobalamin for vasoplegic syndrome causing false blood leak alarm. *Clin Kidney J*. 2017;10(3):357-362.

21. Cios TJ, Havens B, Soleimani B, Roberts SM. Hydroxocobalamin treatment of refractory vasoplegia in patients with mechanical circulatory support. *J Heart Lung Transplant*. 2019;38(4):467-469.

22. Gerth K, Ehring T, Braendle M, Schelling P. Nitric oxide scavenging by hydroxocobalamin may account for its hemodynamic profile. *Clin Toxicol (Phila)*. 2006;44(Suppl 1):29-36.