BRIEF REPORT

OPEN

Hydroxocobalamin in Refractory Septic Shock: A Retrospective Case Series

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OBJECTIVES: Refractory septic shock is associated with high morbidity and mortality. Hydroxocobalamin is used to treat postoperative vasoplegia; however, data supporting its use in the setting of refractory septic shock is limited and restricted to case reports. This study evaluates the effect of hydroxocobalamin on mean arterial pressure and vasopressor requirements in a series of patients with refractory septic shock.

DESIGN: Single-center, retrospective analysis.

SETTING: Urban, tertiary-care ICU.

PATIENTS: Adult ICU patients with refractory septic shock treated with hydroxocobalamin between August 2018 and January 2020.

INTERVENTIONS: Hydroxocobalamin 5 g IV infusion.

MEASUREMENTS AND MAIN RESULTS: Twenty-six patients were included for the analysis. Administration of hydroxocobalamin was associated with an increase in mean arterial pressure at 1, 6, and 24 hours postdose (+16.3, +14.3, and +16.3 mm Hg, respectively; $p < 0.001$). Increase in mean arterial pressure from baseline remained statistically significant when controlling for sex, age, and comorbid conditions. There was no change in the norepinephrine equivalents patients required 1 hour following hydroxocobalamin administration, but a statistically significant decrease in norepinephrine equivalent was observed at 6 and 24 hours postdose ($p < 0.001$).

CONCLUSIONS: Hydroxocobalamin provides sustained hemodynamic benefit at 24 hours in patients with refractory septic shock.

KEY WORDS: adult; critically ill; hydroxocobalamin; nitric oxide; septic shock; vasoplegia

Septic shock, a subset of sepsis, is associated with profound circulatory and cellular derangements. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L despite adequate volume resuscitation (1). Persistent hypotension despite high-dose vasopressor therapy is termed refractory septic shock. The burden of morbidity and mortality in patients with refractory septic shock is exceptionally high, with short-term mortality estimates exceeding 50%. Thus, effective therapies for this condition are desperately needed. Several agents such as angiotensin II, midodrine, and hydrocortisone/ascorbic acid/thiamine therapy, have been trialed in the setting of refractory shock with mixed success (2, 3).

Nitric oxide (NO) signaling has emerged as an attractive treatment target in the setting of shock. Inducible NO synthase (NOS) generates NO, which signals via soluble guanylyl cyclase to increase cyclic guanosine monophosphate,

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thus promoting vasodilation in sepsis. Nonselective NOS inhibitors (L-NG^G-monomethyl-arginine) have been developed for the treatment of shock (4). While these agents have been shown to increase MAP and reduce the need for vasopressors, they have been associated with increased mortality (5).

Hydroxocobalamin (vitamin B12a) is a NO scavenger that has seen use as a therapy for patients with postoperative vasoplegia (6). Evidence for hydroxocobalamin in the setting of septic shock is limited. One case report showed that in two patients with septic shock, administration of hydroxocobalamin reduced the requirement for vasopressor support (7). There is an ongoing randomized controlled trial to investigate a single dose of hydroxocobalamin versus placebo on vasopressor use at 3 hours (NCT03783091).

We aimed to characterize the impact of hydroxocobalamin on MAP and vasopressor requirements in a case series of refractory septic shock patients in the ICU.

MATERIALS AND METHODS

This was a single-center, retrospective case series of adult patients with refractory septic shock admitted from August 2018 to January 2020. Refractory septic shock was defined as septic shock requiring vasopressors at a dose of greater than 0.2 μg/kg/min of norepinephrine equivalents (NEs) as calculated in a prior study (3). The most common first-line vasopressor agent at the study site was norepinephrine, followed by addition of vasopressin at a starting dose of 0.04 U/min. Patients who received at least one dose of hydroxocobalamin were included, which was dosed at 5 g IV over 15 minutes. Patients were excluded if they received hydroxocobalamin for another indication or were not in the ICU at the time of drug administration. The decision to administer hydroxocobalamin was at the discretion of the attending provider of the ICU care team at the study site once the patient was failing to achieve MAP goal using two or more vasopressors. Hemodynamics were measured using various methods, including pulmonary artery catheters and echocardiography. Primary outcomes were the change from baseline in MAP and NE at 1, 6, and 24 hours after hydroxocobalamin administration. A mixed model with both fixed and random effects was used to quantify the difference seen in MAP and NE at 1, 6, and 24 hours compared with baseline while allowing for an individual random effect. Time was treated as a fixed effect variable. Age and gender were included as covariates. R Version 3.6.2 (lme4 and lmerTest packages) was used for analysis (Rstudio, Boston, MA). Institutional Review Board (IRB) exemption was obtained from the Mayo Clinic IRB (identification number 20-001371).

RESULTS

A total of 45 patients were treated with hydroxocobalamin between August 2018 and January 2020 in our institution; 26 of which received hydroxocobalamin for the indication of septic shock.

The baseline patient characteristics are listed in **Table 1**. The median patient age was 69.5 years and patients were predominantly male (65%). The most common etiologies of septic shock were pulmonary infection (38%) and abdominal infection (38%), followed by device-related infections (12%) and skin/soft-tissue infections (12%). Urinary tract infection was the etiology of septic shock in one patient in the series. The majority of patients (69%) had positive blood cultures. At hydroxocobalamin administration, patients had a mean MAP of 62.5 mm Hg and a median NE dose of 0.41 μg/kg/min (range, 0.13–0.825 μg/kg/min) delivered using two vasopressors (range, 2–4). Patients had a median Acute Physiology and Chronic Health Evaluation (APACHE) IV predicted mortality score of 0.70 (range, 0.16–1). The median time from initiation of vasopressor therapy to hydroxocobalamin administration was 13.3 hours (range, 0.5–634 hr). At the time of hydroxocobalamin administration, patients had a median fluid balance of +4.94 L (range, −6.52 to +14.26 L). All patients received corticosteroids, one received methylene blue, and two received angiotensin II.

The distribution of MAP and NE values by time is shown in **Figure 1**. On mixed model analysis, MAP at 1 hour demonstrated a 16.3 mm Hg increase, at 6 hours, a 14.4 mm Hg increase, and, at 24 hours, a 16.3 mm Hg increase relative to baseline MAP. All time points demonstrated a significant increase relative to baseline MAP ($p < 0.001$). In a second model including both age and gender as covariates, results were similar. The increase in MAP was also seen if patients that received angiotensin II ($n = 2$) or methylene blue ($n = 1$) were removed from the dataset. The effect of hydroxocobalamin on vasopressor use is shown in **Table 2**. One hour following hydroxocobalamin administration, a

TABLE 1.
Baseline Characteristics for Patients Who Received Hydroxocobalamin

Characteristics and Outcomes	Result
Age, yr, median (IQR)	69.5 (26–84)
Female sex, *n* (%)	9 (35)
Etiology of septic shock, *n* (%)	
Respiratory	10 (38)
Abdominal	10 (38)
Skin and soft tissue	3 (12)
Device-related	3 (12)
Urinary	1 (4)
Positive blood culture, *n* (%)	18 (69)
Acute Physiology and Chronic Health Evaluation IV predicted mortality, median (IQR)	0.70 (0.16–1)
Comorbidities, *n* (%)	
Chronic kidney disease	12 (46)
Diabetes	9 (35)
Liver disease	9 (35)
Heart failure	7 (27)
Pulmonary disease	10 (38)
Acute kidney injury	18 (69)
Fluid balance at time of B12, L, median (IQR)	4.9 (–6.5 to 14.3)
Continuous renal replacement therapy, *n* (%)	21 (81)
Length of ICU stay, d, median (IQR)	7 (2–32)
Time from first vasopressor to B12 dose, hr, median (IQR)	13.3 (0.5–634)
Glucocorticoid exposure, *n* (%)	26 (100)
Methylene blue exposure, *n* (%)	1 (4)
Angiotensin II exposure, *n* (%)	2 (8)
Number of vasopressors prior to B12, median (IQR)	2 (2–4)
Vasopressors used prior to B12, *n* (%)	
Norepinephrine	26 (100)
Vasopressin	26 (100)
Epinephrine	8 (31)
Phenylephrine	4 (15)
Dopamine	2 (8)

IQR = interquartile range.

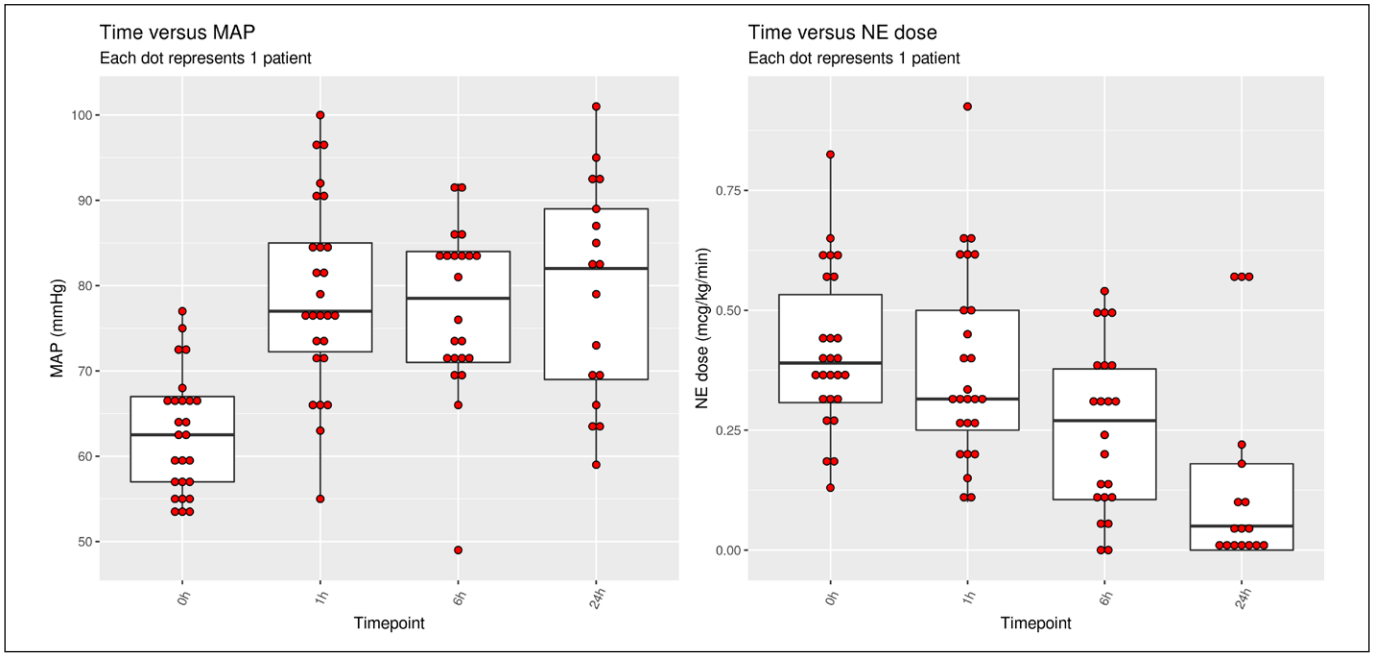

Figure 1. Boxplot of patient data over time. Each dot represents one patient. **A**, Mean arterial pressure over time. B, Norepinephrine equivalent dose over time. MAP = mean arterial pressure, NE = norepinephrine equivalent.

decrease of mean NE was noted, but it was not statistically significant (0.38 µg/kg/min [SD 0.20 µg/kg/min]; $p = 0.35$). However, at 6 and 24 hours, there was a statistically significant decrease in mean NE (0.25 µg/kg/min [SD 0.17 µg/kg/min] and 0.15 µg/kg/min [SD 0.21 µg/kg/min], respectively; $p < 0.001$). Patients

TABLE 2.
Outcomes Following Administration of Hydroxocobalamin

Characteristics and Outcomes	Result	*p*
Lactate before B12, mmol/L, mean (SD)	6.44 (4.43)	–
Lactate after B12, mmol/L, mean (SD)	6.21 (5.94)	0.75
NE before B12, µg/kg/min, mean (SD)	0.41 (0.17)	–
NE after B12 (+1 hr), µg/kg/min, mean (SD)	0.38 (0.20)	0.35
NE after B12 (+6 hr), µg/kg/min, mean (SD)	0.25 (0.17)	< 0.001
NE after B12 (+24 hr), µg/kg/min, mean (SD)	0.15 (0.21)	< 0.001
MAP before B12, mm Hg, mean (SD)	62.5 (8.1)	–
MAP after B12 (+1 hr), mm Hg, mean (SD)	80.1 (11.9)	< 0.001
MAP after B12 (+6 hr), mm Hg, mean (SD)	78.6 (9.8)	< 0.001
MAP after B12 (+24 hr), mm Hg, mean (SD)	82 (12.7)	< 0.001
Patient disposition, *n* (%)		–
Home	2 (8)	
Facility	5 (19)	–
Died	19 (73)	–

MAP = mean arterial pressure, NE = norepinephrine equivalent.
Dashes indicates no significance testing was performed.

receiving hydroxocobalamin had a median ICU stay of 7 days (range, 2–32 d). Seven patients survived to hospital discharge, while 19 patients died (73%).

DISCUSSION

The central physiologic abnormality in refractory shock is believed to be an impaired vascular response to catecholamine stimulation. This inappropriate vascular response is mediated by exuberant inducible NOS signaling, activation of adenosine triphosphate-sensitive potassium channels on vascular smooth muscle, and an absolute or relative deficiency of angiotensin II, cortisol, or vasopressin (2). Given this insensitivity, catecholamine-sparing therapies have seen significant scientific interest.

Hydroxocobalamin (CyanoKit) has a Food and Drug Administration indication for the treatment of confirmed or suspected cyanide poisoning. It is also used off-label for postoperative vasoplegia that can develop after the cession of cardiopulmonary bypass. Hydroxocobalamin increases vascular tone by acting as a sink for circulating NO and hydrogen sulfide (H_2S). Mechanistically, NO oxidizes the cobalt atom of hydroxocobalamin forming a Co-NO complex that can subsequently transfer NO to hemoglobin or glutathione (8). H_2S is produced by bacteria during septic shock resulting in vasodilation and hydroxocobalamin has been shown to bind and reduce the circulating volume of H_2S as well (8). Hydroxocobalamin is generally well tolerated but is associated with chromaturia that may last several weeks (6). This side effect can be of concern for the critically ill as it has the potential to interfere with hemodialysis machines in the form of causing false blood leak alarms.

Data from two case series provide the rationale for its use in this context. The first demonstrated that 24 of 33 patients with vasoplegia secondary to cardiopulmonary bypass had at least a 33% reduction in vasopressor dose 30 minutes after hydroxocobalamin administration (9). The second demonstrated a 14 mm Hg increase in MAP 30 minutes after hydroxocobalamin administration (10).

Our data suggest that hydroxocobalamin can be used as a rescue therapy in patients already receiving high-dose vasopressors for septic shock. Hydroxocobalamin may provide a sustained hemodynamic benefit to patients, providing clinicians' critical time to pursue definitive measures such as source control. MAP increase was noted after an hour of B12 infusion, although NE equivalents did not change. This may have been due to concern from treating clinicians about the time duration of effect of B12 and, therefore, avoidance of rapid weaning of vasopressors. Over a 24-hour period, the MAP continued to be increased compared with baseline and NE showed a decrease that was significant. To our knowledge, this is the largest case series assessing the effect of hydroxocobalamin on MAP and vasopressor usage in patients with septic shock. This study has a few important limitations, mainly the retrospective nature of the study and the small sample size (26 patients). In addition, the timing of hydroxocobalamin administration in the disease course was variable between patients, and it is unclear how this influences outcomes. In all cases, corticosteroids were administered before hydroxocobalamin; however, the two therapies were only separated by 1–3 hours in a few patients. Given that this did not apply to the majority of the study group, this is unlikely to be a confounding variable. This reflects clinical practice and escalation of care measures based on real-time patient assessment. The mortality rate was high in this cohort, similar to APACHE IV predicted mortality.

CONCLUSIONS

Our series indicates that hydroxocobalamin is a viable rescue therapy option in patients with severe septic shock. However, larger studies are warranted to assess the efficacy and safety of hydroxocobalamin in the setting of refractory septic shock.

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The authors have disclosed that they do not have any potential conflicts of interest.

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