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Case series

Hydroxocobalamin for treatment of catecholamine-resistant vasoplegia during liver transplantation: A single-center series of 20 cases

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ABSTRACT

Introduction: Catecholamine-resistant vasoplegia is a potentially devastating complication during liver transplantation. Hydroxocobalamin has emerged as a treatment for vasoplegia associated with cardiac surgery, liver transplantation, and septic shock.

Presentation of case: We performed a retrospective review of patients who underwent liver transplantation between October 2015 and May 2020 to evaluate the efficiency of hydroxocobalamin in this setting.

Discussion: A total of 137 patients underwent liver transplantation, of which 20 received hydroxocobalamin for vasoplegia. Administration of hydroxocobalamin increased mean arterial pressure and reduced vasoactive drug requirements.

Conclusion: This case series adds to the previous individual reports describing the use of hydroxocobalamin during liver transplantation suggesting hydroxocobalamin can mitigate refractory hypotension from catecholamine resistant vasoplegia during liver transplantation.

1. Introduction

Catecholamine-resistant vasoplegia is a potentially devastating complication of liver transplantation [1]. Vasoplegia is characterized by refractory hypotension, normal to elevated cardiac index, decreased systemic vascular resistance, and a reduced response to vasoconstrictors. The mechanisms responsible for vasoplegia in this patient population are multifactorial and most likely include pronounced vasodilation of the splanchnic circulation, deficient endogenous vasopressin production, and abnormal nitric oxide metabolism [2].

Hydroxocobalamin has emerged as a treatment of catecholamine-resistant vasoplegia. The drug's use for vasoplegia was first described in cardiac surgery [3]. We and others have reported the utility of hydroxocobalamin in several cases of vasoplegia including patients undergoing cardiac surgery or liver transplantation [4–6]. A recent review analyzed the published cases and reported a total of 44 patients who received hydroxocobalamin in these settings [7]. The authors identified that 33 patients (75 %) who were "responders" to the medication as an indicated by clinically meaningful increases in arterial pressure. Several reviews regarding the use of hydroxocobalamin outside of liver transplant surgery have been published, but the efficacy of hydroxocobalamin in liver transplantation has yet to be fully elucidated, as only a few case reports and a single comparative review currently exist [8]. In this retrospective review, we examined our single-center experience in 20 patients undergoing liver transplantation who received hydroxocobalamin for treatment of catecholamine-resistant vasoplegia. This case series was completed following compliance with the PROCESS 2020 guidelines [10].

2. Cases

This case series was conducted at The Medical College of Wisconsin and Froedtert Hospital, a 689-bed tertiary care academic medical center in Milwaukee, Wisconsin. The Institutional Review Board of the Medical College of Wisconsin/Froedtert Hospital approved the review of cases (PRO00038110). Written informed consent was waived because of the

Abbreviations: MAP, mean arterial pressure; NEE, norepinephrine equivalents; MELD, Model for End-Stage Liver Disease.

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retrospective nature of the review. The review was registered with Research Registry registration unique identifying number researchregistry8141 (https://www.researchregistry.com/browse-the-registry#home/registrationdetails/62e3dec2352dfb0021c8b997/). Patients who underwent liver transplantation from October 2015 through May 2020 were identified. Patients were eligible for inclusion if they received hydroxocobalamin intraoperatively. Patients <18 years of age were excluded.

Intraoperative records were reviewed, and all data were extracted from the electronic medical record (Epic, Verona, WI). Intraoperative management including administration of hydroxocobalamin was based on the clinical assessment of each patient's hemodynamics by the attending anesthesiologist. Mean arterial pressures (MAP; radial artery catheter) and vasopressor requirements were recorded before and at 15-minute intervals after the initial dose of hydroxocobalamin. Standardization of hydroxocobalamin dosing was not possible because of the retrospective design. Doses ranging from 750 mg to 5 g were administered at the attending anesthesiologist's discretion. Vasoactive medications (phenylephrine, vasopressin, norepinephrine, and epinephrine) were converted to norepinephrine equivalents (NEE) at each time interval using the formula: NEE = norepinephrine (mcg/min) + dopamine (mcg/kg/min/)/2 + epinephrine (mcg/min) + phenylephrine (mcg/min)/10 + vasopressin (units/h) × 8.33.

Mean arterial pressure was analyzed separately using linear mixed effects models with a random effect, which used a compound symmetry covariance structure, to account for the correlation in repeated measures from the participants. Both Model for End-Stage Liver Disease (MELD) and NEE were used in different models to predict mean arterial pressure. Analysis was done using SAS V9.4 (SAS Institute, Cary, NC). The two primary outcome measures were changed in mean arterial pressures and NEE after administration of hydroxocobalamin.

A total of 137 patients received liver transplants during the study period, of which 20 patients received hydroxocobalamin. Composite patient demographics, medical history, and medications are presented in Table 1, and individual patient information is presented in Table 2. MELD scores as a covariate for mean arterial pressure were not significant. Mean arterial pressures showed a significant reduction in covariate NEE (Table 3).

3. Discussion

The severity of hepatic disease in patients receiving liver transplantation varies between centers depending on the regional organ supply to demand ratio. When our study was conducted our facility had a high mean MELD score at transplant, and upon our review the liver transplant patients who received hydroxocobalamin had higher MELD scores than our center mean (Fig. 1). The lack of correlation between mean arterial pressure and MELD score in patients who received hydroxocobalamin most likely occurred because these patients had such profound abnormalities that the MELD score was no longer linearly correlated with disease severity. Nevertheless, hydroxocobalamin improved mean arterial pressures and lowered NEE in this particularly ill cohort (Figs. 2 and 3). The decline in NEE indicated reduced vasoactive drug requirements and was consistent with increased arterial pressure after administration of hydroxocobalamin to patients who were receiving large quantities of vasoactive medications. Hydroxocobalamin may also show clinical utility in patients who are experiencing adverse side effects of high-dose vasoactive medications (e.g. vasospasm, peripheral ischemia) by maintaining arterial pressure while allowing a concomitant reduction in doses of the drugs [4].Evidence for the use of hydroxocobalamin as treatment for catecholamine-resistant vasoplegia in liver transplantation remains sparse, consisting of only case reports [4,6,8], two small case series [5,6]. The activity of hydroxocobalamin as an off-label treatment for vasoplegia in cardiac surgery is more well-established, but the current retrospective analysis is the largest reported to date in which the utility of the drug has been examined in the liver transplant population. The precise mechanisms by which

Table 1
Patient demographics, medical history, and medications.

Total number	20
Mean MELD at transplant	39 ± 6
Status 1A	2 (10 %)
Male	13 (65 %)
Height (cm)	174 ± 8
Weight (kg)	90 ± 22
BMI	30 ± 8
Age	
≤54	10 (50 %)
55–64	6 (30 %)
≥65	4 (20 %)
Preoperative mechanical ventilation	7 (35 %)
Preoperative ICU admission	19 (95 %)
Preoperative CVVH/Dialysis	15 (75 %)
Previous abdominal surgery	5 (25 %)
Preoperative hematocrit	25 ± 3
Preoperative platelet count	73 ± 50
Racial ethnicity	
Caucasian	17 (85 %)
African American	2 (10 %)
Asian-American	1 (5 %)
Medications	
Intravenous vasopressors	6 (30 %)
Midodrine	13 (65 %)
Hepatic encephalopathy treatment	18 (90 %)
Beta-blockers	3 (15 %)
Diuretic	7 (35 %)
Insulin	8 (40 %)
Thyroid replacement	5 (25 %)
Opioid	6 (30 %)
Benzodiazepine	2 (10 %)
TPN	3 (15 %)
Cause of ESLD	
Primary biliary cirrhosis	2 (10 %)
Primary sclerosing cholangitis	1 (5 %)
Alcohol	9 (45 %)
Hepatitis B	1 (5 %)
NASH	4 (20 %)
Hepatitis C	2 (10 %)
Acetaminophen	1 (5 %)
Hepatic encephalopathy	13 (65 %)
Ascites	14 (70 %)
Portal hypertension	15 (75 %)
Esophageal varices	11 (55 %)
Atrial fibrillation	2 (10 %)
Coronary artery disease	4 (20 %)
Heart failure/cardiomyopathy	3 (15 %)
Hypothyroidism	5 (25 %)
Deep vein thrombosis	4 (20 %)
Diabetes mellitus	8 (40 %)
Seizure disorder	2 (10 %)
30-day mortality	1 (5 %)
90-day mortality	2 (10 %)
1-year mortality	3/20 (15 %)

Note: Data is expressed as numbers (percentages) or mean ± standard deviation.
Abbreviations: MELD, model for end-stage liver disease; BMI, body mass index; ICU, intensive care unit; CVVH, continuous veno-venous hemofiltration; TPN, total parenteral nutrition, ESLD, end-stage liver disease; NASH, non-alcoholic steatohepatitis.

Table 2
Mixed models for MAP, MELD, and NEE.

MELD			NEE		
Estimate	Standard error	*P* value	Estimate	Standard value	P value
70.84	1.80	–	75.26	2.26	–
0.03	0.28	0.9146	−0.17	0.08	0.0312

Abbreviations: MAP = Mean arterial pressure; MELD = Model for End-Stage Liver Disease; NEE = norepinephrine equivalency.

Table 3
Individual case information.

Patient	Age	BMI	Sex	MELD	Surgical technique	VVB	CVVH	ESLD cause	Portal HTN	Starting BP	Preoperative ICU care	SLK
1	52	26.6	Female	52	Conventional	Yes	Yes	PBC	Yes	86/59	Yes	No
2	45	20.5	Male	43	Conventional	Yes	Yes	PSC	Yes	69/31	Yes	No
3	67	31.4	Male	40	Conventional	Yes	Yes	ETOH	Yes	116/56	Yes	No
4	72	25.8	Male	43	Conventional	Yes	Yes	Hep. B	Yes	77/36	Yes	No
5	65	22.1	Female	37	Conventional	Yes	Yes	NASH	Yes	120/61	Yes	Yes
6	49	25.5	Male	Status 1A	Conventional	No	Yes	Hep. B	No	101/69	Yes	No
7	43	41.2	Female	Status 1A	Conventional	No	Yes	Drug	No	89/57	Yes	No
8	37	23	Male	43	Conventional	Yes	Yes	ETOH	Yes	91/49	Yes	Yes
9	59	31.9	Male	44	Conventional	Yes	Yes	Hep. C	Yes	103/36	Yes	Yes
10	69	33.4	Male	33	Conventional	Yes	No	NASH	Yes	88/46	Yes	No
11	54	49.0	Female	42	Conventional	Yes	Yes	PBC	Yes	119/59	Yes	No
12	53	33.1	Male	41	Conventional	Yes	No	ETOH	Yes	92/45	Yes	No
13	33	28.6	Female	38	Conventional	Yes	Yes	ETOH	Yes	71/30	Yes	Yes
14	60	24.3	Male	39	Conventional	Yes	Yes	ETOH	Yes	88/47	Yes	No
15	57	35	Male	29	Conventional	Yes	Yes	NASH	Yes	70/46	Yes	No
16	64	24.9	Male	30	Conventional	Yes	Yes	NASH/Cryptogenic	Yes	79/45	Yes	Yes
17	44	23.5	Male	30	Conventional	No	No	ETOH	Yes	114/64	No	No
18	56	21.2	Female	38	Conventional	Yes	Yes	ETOH	Yes	78/31	Yes	No
19	59	23.4	Female	30	Conventional	Yes	Yes	ETOH	Yes	100/52	Yes	No
20	33	36.3	Male	45	Conventional	Yes	Yes	ETOH	Yes	102/56	Yes	No

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease; VVB, Veno-venous bypass; CVVH, continuous veno-venous hemofiltration; ESLD, end-stage liver disease; HTN, hypertension; BP, blood pressure; ICU, intensive care unit, SLK, simultaneous liver kidney transplant, PBC, primary biliary cirrhosis, PSC, primary sclerosing cholangitis; ETOH, alcohol, Hep. B, hepatitis B, NASH, non-alcoholic steatohepatitis; Hep. C, hepatitis C.

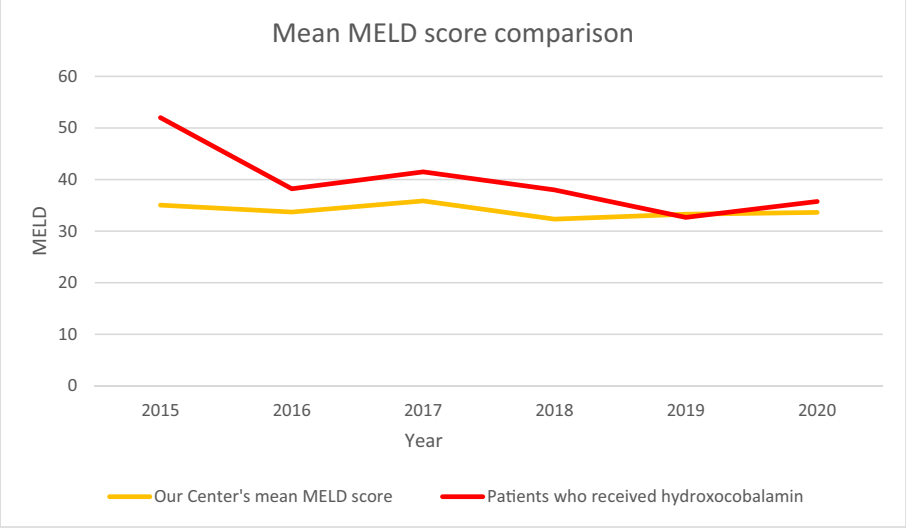

Fig. 1. Graphical comparison of our center's mean MELD score at transplant (yellow), and the mean MELD score of patients who received intraoperative hydroxocobalamin during liver transplantation (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

hydroxocobalamin increases arterial pressure are not fully understood. Hydroxocobalamin is a potent nitric oxide scavenger [10], but this effect is probably not the sole cause of the increase in arterial pressure associated with the drug because hydroxocobalamin may be efficacious when methylene blue is not [11]. Hydroxocobalamin is also a hydrogen sulfide scavenger, which plays a role in vascular smooth muscle relaxation through its interactions with adenosine triphosphate regulated potassium channels [12–14]. Hydrogen sulfide has also been implicated in the vasodilation commonly observed in patients with end-stage liver disease [15] and may play an important role in catecholamine-refractory vasoplegia as well.

Hydroxocobalamin was useful to increase arterial pressure and reduce NEE in the current study, but whether these beneficial actions positively influenced subsequent outcomes could not be ascertained. A temporal association between administration of hydroxocobalamin and the subsequent increase in mean arterial pressure was observed, but a direct cause-and-effect relationship could not be established with certainty, and it remains possible that other intraoperative factors may have influenced the results.

Few case reports regarding the role of hydroxocobalamin in liver transplants exist in the literature, and no larger reviews are available in this challenging patient population. Our findings confirm and extend the limited data indicating a role for hydroxocobalamin in the treatment of catecholamine-resistant vasoplegia in patients undergoing liver transplantation. Further investigation into the most appropriate dose and timing of administration of hydroxocobalamin is warranted in this challenging patient population.

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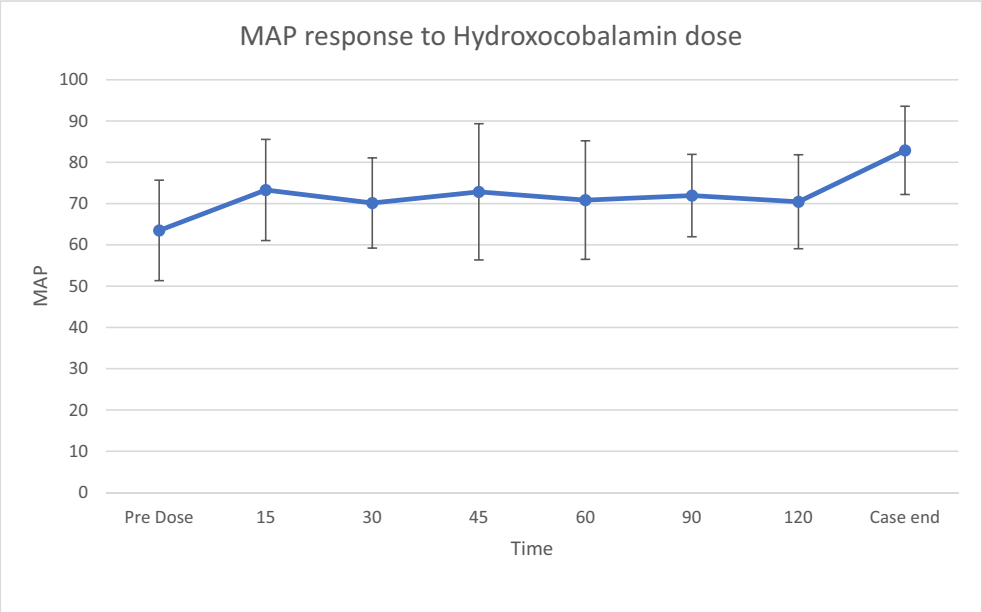

Fig. 2. Mean arterial pressure (MAP) response to hydroxocobalamin at 15-minute intervals. Time "0" represents MAP immediately before administration of hydroxocobalamin. (n = 20, mean ± SD).

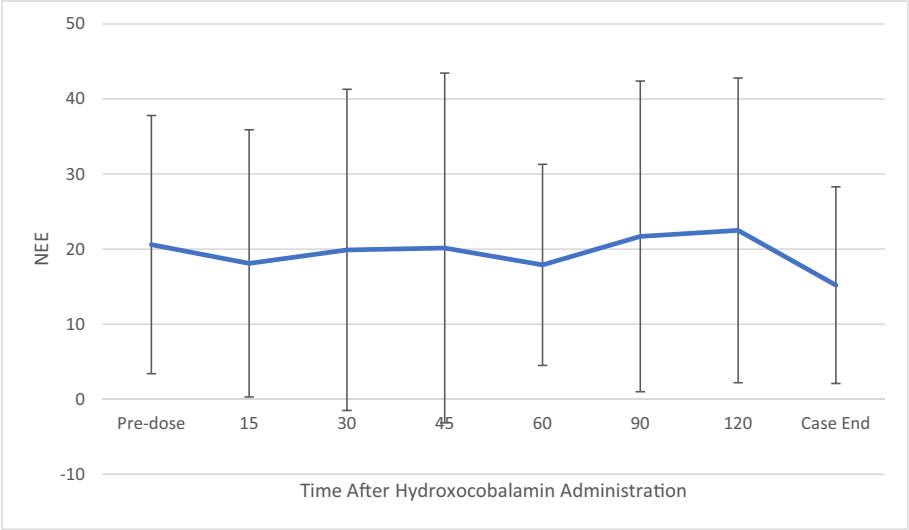

Fig. 3. Norepinephrine equivalents (NEE) response to hydroxocobalamin at 15-minute intervals. Time "0" represents NEE immediately before administration of hydroxocobalamin. (n = 20, mean ± SD).

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

This case series was conducted at The Medical College of Wisconsin and Froedtert Hospital, a 689-bed tertiary care academic medical center in Milwaukee, Wisconsin. The Institutional Review Board of the Medical College of Wisconsin/Froedtert Hospital approved the review of cases (PRO00038110). Written informed consent was waived because of the retrospective nature of the review, and registration with registry was not required.

Consent

This case series was conducted at The Medical College of Wisconsin and Froedtert Hospital, a 689-bed tertiary care academic medical center in Milwaukee, Wisconsin. The Institutional Review Board of the Medical College of Wisconsin/Froedtert Hospital approved the review of cases (PRO00038110). Written informed consent was waived because of the retrospective nature of the review, and registration with registry was not required.

Author contribution

Brent Boettcher: Participated in the anesthetics, data collection, case analysis and writing of the manuscript. Harvey Woehlck participated in the anesthetics, case analysis, and writing of the manuscript. Hemanckur Makker: Collected the data, case analysis. Paul Pagel: Data analysis,

writing of the manuscript. Julie Freed: Data analysis, writing the manuscript.

Registration of research studies

The review was registered with Research Registry registration unique identifying number researchregistry8141 (https://www.researchregistry.com/browse-the-registry#home/registrationdetails/62e3dec2352dfb0021c8b997/.

Guarantor

Brent T. Boettcher DO.

Declaration of competing interest

No benefits, in any form, have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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