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

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ARTICLE INFO

Keywords:
Hydroxocobalamin
Liver transplantation
Vasoplegia
Norepinephrine
Vasopressin
Norepinephrine equivalents
Case report

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
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/l) × 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 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 %) |
| Miodrinone | 13 (65 %) |
| Hepatic encephalopathy treatment | 18 (90 %) |
| Beta-blockers | 3 (15 %) |
| Diuretic | 7 (35 %) |
| Insulin | 8 (40 %) |
| Thyroid replacement | 5 (25 %) |
| Opioid | 6 (30 %) |
| Benzbodiazapine | 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/cardiomopathy | 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 error | 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.**
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-resistant 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 beascertained. 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.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This work

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**Table 3**

| 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 | Hep. B     | Yes        | 116/56      | Yes                   | No   |
| 4       | 72  | 25.8| Male  | 43   | Conventional      | Yes | Yes | NASH       | Yes        | 77/36       | Yes                   | No   |
| 5       | 65  | 22.1| Female| 37   | Conventional      | Yes | Yes | NASH       | Yes        | 120/61      | Yes                   | No   |
| 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.)
was supported entirely by departmental funds.

**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/62e3dec2352dfb0621c88997/).

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.

References

[1] Y. Iwakiri, R.J. Groszmann, The hyperdynamic circulation of chronic liver disease: from the patient to the molecule, Hepatology 43 (2 SUPPL. 1) (2006) S121–S131.
[2] G. Wagener, G. Kovalevskaya, M. Minbax, F. Mattis, J. Emond, D. Landry, Vasopressin deficiency and vasulatory state in end-stage liver disease, J. Cardiothorac. Vasc. Anesth. 25 (4) (2011) 665–670.
[3] J.D. Roderique, K. Vandyck, B. Holman, D. Tand, B. Chui, B. Spiess, The use of high-dose hydroxocobalamin for vasoplegic syndrome, Ann. Thorac. Surg. 97 (5) (2014) 1785–1786.
[4] H.J. Woehlick, B.T. Boettcher, K.K. Lauer, D. Cronin, J. Hong, M. Zimmerman, et al., Hydroxocobalamin for vasoplegic syndrome in liver transplantation: restoration of blood pressure without vasospasm, A A Case Rep. 7 (12) (2016) 247–250.
[5] B.T. Boettcher, H.J. Woehlick, S.E. Reck, J. Hong, M. Zimmerman, J. Kim, et al., Treatment of vasoplegic syndrome with intravenous hydroxocobalamin during liver transplantation, J. Cardiothorac. Vasc. Anesth. 31 (4) (2017) 1381–1384.
[6] S.V. Sakpal, H. Reedstrom, C. Ness, T. Klinkhammer, H. Saucedo-Crespo, C. Auvenshine, et al., High-dose hydroxocobalamin in end-stage liver disease and liver transplantation, Drugs Ther. Perspect. 35 (9) (2019) 442–446.
[7] P.G. Charles, L.J. Murray, C. Giordano, B. Spiess, Vitamin B12 for the treatment of vasoplasia in cardiac surgery and liver transplantation: a narrative review of cases and potential biochemical mechanisms, Can. J. Anesth. 66 (12) (2019) 1501–1513.
[8] C. Crouch, A. Hendrickse, S. Gilliland, M.S. Mandell, Unexpected complication of hydroxocobalamin Administration for Refractory Vasoplasia in orthotopic liver transplant: a case report, Semin. Cardiothorac. Vasc. Anesth. 23 (4) (2019) 409–412.
[9] K. Gerth, T. Ehring, M. Braendle, P. Shelling, Nitric oxide scavenging by hydroxocobalamin may account for its hemodynamic profile, Clin. Toxicol. 44 (SUPPL. 1) (2006) 29–36.
[10] Y. Cai, A. Mack, B.L. Ladlie, A.K. Martin, The use of intravenous hydroxocobalamin as a rescue in methylene blue-resistant vasoplegic syndrome in cardiac surgery, Ann. Card. Anaesth. 20 (4) (2017) 462–464.
[11] F. Moccia, G. Berton, A. Florio Pla, S. Dragoni, E. Pupo, A. Merlino, et al., Hydrogen sulfide regulates intracellular Ca2+ concentration in endothelial cells from excised rat aorta, Curr. Pharm. Biotechnol. 12 (9) (2011) 1416–1426.
[12] Y. Fujita, Y. Fujino, M. Onodera, S. Kikuchi, T. Kikkawa, Y. Inoue, et al., A fatal case of acute hydrogen sulfide poisoning caused by hydrogen sulfide: hydroxocobalamin therapy for acute hydrogen sulfide poisoning, J. Anal. Toxicol. 35 (2) (2011) 119–123.
[13] P. Haouzi, B. Chenuel, T. Sonobe, High-dose hydroxocobalamin administered after H2S exposure counteracts sulfide-poisoning-induced cardiac depression in sheep, Clin. Toxicol. 53 (1) (2015) 28–36.
[14] M.R. Ebrahimkhani, A.R. Mani, K. Moore, Hydrogen sulphide and the hyperdynamic circulation in cirrhosis: a hypothesis, Gut 54 (12) (2005) 1668–1671.