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# Case report of high-dose hydroxocobalamin in the treatment of vasoplegic syndrome during liver transplantation

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## Abstract

A 66-year-old man with cryptogenic cirrhosis secondary to nonalcoholic steatohepatitis presented for orthotopic liver transplantation. Following organ reperfusion, the patient developed vasoplegic syndrome, with arterial blood pressures of approximately 60-70/30-40 mm Hg (mean arterial pressure [MAP] <45 mm Hg) for >90 minutes. He required high-dose norepinephrine and vasopressin infusions, as well as i.v. bolus doses of norepinephrine and vasopressin to reach a goal MAP> 60 mm Hg. There was minimal response to a 2 mg/kg i.v. bolus of methylene blue. Following the administration of 5 g of i.v.hydroxocobalamin, the patient had a profound improvement in arterial blood pressure, with subsequent discontinuation of the vasopressin infusion and rapid reduction of norepinephrine infusion from 20 to 2 μg/min. While there have been several reports of the efficacy of hydroxocobalamin for vasoplegia after cardiopulmonary bypass, there have been only limited cases of hydroxocobalamin used in liver transplantation, and none with high-dose administration. We present a case of vasoplegic syndrome during liver transplantation that was refractory to high-dose vasopressors and methylene blue but responsive to high-dose i.v. hydroxocobalamin.

### Keywords

anesthesia/pain management; clinical research/practice; liver disease; liver transplantation: auxiliary; off-label drug use; physician education

## 1 | INTRODUCTION

Vasoplegic syndrome is a constellation of signs characterized by hypotension (typically mean arterial pressure [MAP] <50 mm Hg), low systemic vascular resistance, normal-to-high-cardiac output, and a reduced response to vasoactive medications.[1] While most closely

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DISCLOSURE

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associated with cardiac surgery and cardiopulmonary bypass,[2] vasoplegic syndrome is frequently seen in patients during liver transplantation, notably following reperfusion of the donor graft.[1,3] There have been several reported treatment methods for vasoplegic syndrome, including high-dose vasopressors, inotropes, corticosteroids, and methylene blue, all with varying results.[1,4,5]

We describe a case of vasoplegic syndrome during liver transplantation that was refractory to conventional therapy, yet effectively treated with high-dose intravenous (i.v.) hydroxocobalamin.

## 2 | CASE PRESENTATION

A 66-year-old man with a past medical history significant for cryptogenic cirrhosis secondary to nonalcoholic steatohepatitis and complicated by ascites and hepatic encephalopathy presented for orthotopic liver transplantation. Vanderbilt University Medical Center institutional review board policies were followed and approved for the publication of this case report. Additional past medical history included obstructive sleep apnea, left internal carotid artery dissection with subsequent cerebrovascular accident, and a spontaneous subdural hematoma after an episode of hematemesis. On the day of liver transplantation, his preoperative model for end-stage liver disease-sodium score was calculated at 19 (international normalized ratio 1.6, creatinine 0.72 mg/dL, total bilirubin level of 5.7 mg/dL, and sodium 136 mmol/L). The donor liver had a calculated donor risk index of 1.290.[6] The donor organ was from a 17-year-old black boy who died of anoxic brain injury.

The patient was transported to the operating room and placed on standard American Society of Anesthesiologists monitors. General anesthesia was induced with i.v. bolus doses of propofol, lidocaine, ketamine, and succinylcholine. An arterial cannula for invasive blood pressure monitoring was placed in the right radial artery and 2 central venous catheters, a multilumen access catheter, and a double-lumen catheter (Arrow® MAC™, Teleflex Reading, PA) were placed in the right internal jugular vein for volume resuscitation and infusion of vasoactive substances, all in sterile fashion under ultrasound guidance. A Belmont rapid infuser system (Belmont®, Belmont Instrument Corporation, Billerica, MA) was connected. A transesophageal echocardiography (TEE) probe was placed during the procedure for evaluation of cardiac function and a LiDCO arterial waveform analysis (LiDCO Ltd, Cambridge, UK) was used for continuous assessment of cardiac output.

General anesthesia was maintained with inhaled isoflurane and intravenous infusions of ketamine and sufentanil, with bolus doses of rocuronium for neuromuscular blockade. Norepinephrine and vasopressin infusions were used for vasopressor support. During the dissection and anhepatic surgical phases, the patient remained hemodynamically stable, requiring small volume resuscitation with 250 mL of 5% albumin and 4 units of fresh frozen plasma (FFP), which also aided in correction of his native coagulopathy. Methylprednisolone 500 mg i.v. was given during the anhepatic phase, per surgical protocol. The donor graft was implanted into the recipient using the piggyback technique after 5 hours and 30 minutes of cold ischemia time. Prior to reperfusion, the LiDCO arterial waveform

analysis showed a cardiac index of ≈4 L/min per $m^2$ and systemic vascular resistance (SVR) of ≈800 dynes-s/$cm^5$.

Reperfusion of the donor graft occurred ≈4 hours after incision and was well tolerated. A total of 80 μg i.v. of norepinephrine and 20 μg i.v. of epinephrine were administered in divided bolus doses during the first 5 minutes of the reperfusion period. Shortly thereafter, a persistent increased vasopressor requirement was noted, with norepinephrine dose increasing rapidly from 8 μg/min to 20 μg/min and addition of a vasopressin infusion at 0.04 units/min. Beyond this, numerous intermittent boluses of norepinephrine (8-32 μg i.v.) were required to achieve a target MAP of >60 mm Hg. LiDCO arterial waveform analysis demonstrated a supranormal cardiac index of ≈4-5 L/min per $m^2$, with a low SVR of <500 dynes-s/$cm^5$. Cardiac evaluation by TEE demonstrated hyperdynamic function with normal filling and without outflow obstruction or valvular regurgitation.

The decision was made to treat the underlying vasoplegic syndrome with methylene blue, a known nitric oxide scavenger and inhibitor of nitric oxide production. Methylene blue 2 mg/kg (170 mg) was infused over 15 minutes, with no significant improvement in MAP over the next 30 minutes despite continued infusions of vasopressors with intermittent boluses. The patient also received an additional 2 units of FFP and 220 mL of intraoperative cell salvage, with 400 mL of intravenous crystalloid administration during this time and calcium supplementation. Given the continued increase in vasopressor requirement and ongoing hypotension, refractory to standard therapy, we chose to administer high-dose hydroxocobalamin, to treat underlying vasoplegic syndrome. A 5-g Cyanokit (Meridian Medical Technologies, Columbia, MD) was infused over 15 minutes. This was followed by an abrupt increase in MAP to >80 mm Hg and concomitant decrease in vasopressor requirement (norepinephrine <10 μg/min) within 5 min of hydroxocobalamin administration, enduring for the remainder of the case and into the postoperative phase of care. Post-hydroxocobalamin administration, LiDCO arterial waveform analysis showed a cardiac index (CI) of ≈4-5 L/min per $m^2$ and improved SVR to >800 dynes-s/$cm^5$. Over the next half hour, the norepinephrine infusion was incrementally decreased to 2 μg/min and the vasopressin infusion was weaned off. After the surgery, the patient was transported to the surgical intensive care unit intubated with norepinephrine 2 μg/min as the only vasopressor. The surgery was otherwise uneventful, with an estimated blood loss of 3000 mL. The patient was resuscitated with a total of 6 units of FFP, 250 mL of intraoperative cell salvage, 1800 mL of crystalloid, and 250 mL of 5% albumin. Immediately postoperatively, hemoglobin and hematocrit were 9.2 g/dL and 25%, respectively, compared to a preoperative value of 12.6 g/dL and 36%, respectively. The patient was extubated on postoperative day 0, had an uneventful postoperative course, and was discharged home on postoperative day 4.

## 3 | DISCUSSION

Vasoplegic syndrome has been documented in both the cardiac surgery and organ transplantation literature.[1,2,4,7] The pathophysiology of vasoplegic syndrome is not completely understood, but is felt to be strongly associated with nitric oxide dysregulation[1] and immune-mediated cytokine trafficking.[8] First-line therapy for vasoplegic syndrome continues to be high-dose vasopressors.[1] In liver transplant recipients, vasopressor infusions

are frequently required after organ reperfusion to maintain adequate blood pressure to the graft and other organs. Prior studies have shown that lower hepatic artery flow is associated with lower graft survival and arterial complication risks.[9] This low-flow state in the liver can be multifactorial, with vasopressors being a factor in decreasing hepatic artery flow.[10] Furthermore, decreased hepatic artery flow intraoperatively is also associated with an increased risk of hepatic artery thrombosis.[11] Accordingly, these findings support the approach of targeted reductions of vasopressor doses in the postreperfusion period, balanced with the goal of using these medications to maintain adequate perfusion pressures and cardiac output for systemic perfusion.

In cases of vasoplegic syndrome that are refractory to treatment with fluid resuscitation and standard doses of vasoactive agents, the infusion of methylene blue has been suggested as a viable treatment option, due to its inhibition of guanylate cyclase and nitric oxide scavenging effects.[1,12] Methylene blue inhibits the activity of the cyclic guanosine monophosphate system and releases cyclic adenosine monophosphate, both of which enhance the vasoconstrictive effects of endogenous and exogenous catecholamines.[1, 13] While methylene blue may be of benefit for reperfusion syndrome in liver transplantation,[3] not all patients respond. Furthermore, some patients are not candidates due to the risk of serotonin syndrome from use of antidepressants that affect serotonin and catecholamine uptake.[14]

Intravenous hydroxocobalamin is a well-recognized treatment of acute cyanide toxicity in Europe and has been approved recently in the United States for the same indication.[15] The understood mechanism of hydroxocobalamin therapy in this setting involves direct binding to cyanide to form cyanocobalamin, which deactivates the effect of cyanide and allows for subsequent renal excretion of the cyanocobalamin compound.[15] The mechanism behind the hemodynamic effects of hydroxocobalamin is less clear. There is a consistent increase in blood pressure, primarily diastolic blood pressure, associated with hydroxocobalamin use in humans and animals that appears to be related to its effectiveness as a scavenger of nitric oxide.[16] There may be some additional effects related to hydroxocobalamin binding to hydrogen sulfide, thus inhibiting the binding of adenosine triphosphate-sensitive potassium channels, leading to hypotension.[17] Further downstream modulation of cytokine pathways has also been implicated, which may explain the prolonged effects of hydroxocobalamin in experimental models of septic shock.[18]

The primary adverse effect of hydroxocobalamin administration is increased blood pressure which, in the case of vasoplegic syndrome, is beneficial. Other named adverse reactions to hydroxocobalamin include transient chromaturia, erythema, rash, nausea, headaches, and injection site reactions.[15] The patient had an increase in his blood pressure and transient chromaturia with red/blue urine following hydroxocobalamin administration.

Severe refractory hypotension following reperfusion of a liver graft should be managed in a stepwise fashion. Vasopressors and intravascular volume resuscitation should remain the first-line treatment, along with high-dose steroid administration, which is standard in liver transplant. In instances of refractory vasoplegia, alternatives such as methylene blue and hydroxocobalamin should be considered as third- and fourth-line therapy, respectively.

While both methylene blue and hydroxocobalamin function as nitric oxide scavengers, methylene blue is more cost effective, at approximately $223.73 for 50 mg/10-mL vial, compared to $985.58 for 5 g of hydroxocobalamin.[19] This makes methylene blue a more practical treatment option for vasoplegia. In patients who fail methylene blue therapy or have contraindications to methylene blue, hydroxocobalamin can be considered as next-line therapy. This therapy should be considered instead of methylene blue in patients at risk for serotonin syndrome.[14]

In this report we present a case of vasoplegic syndrome during liver transplantation that was refractory to high-dose steroids, fluid resuscitation, high-dose vasopressors (norepinephrine and vasopressin), and methylene blue. Our patient subsequently demonstrated a profound blood pressure response to a single administration of high-dose intravenous hydroxocobalamin accompanied by a sustained decrease in vasopressor requirements that started within minutes of the medication infusion and persisted postoperatively. While alternative causes for resolution of vasoplegia in this instance are possible, the prompt hemodynamic improvement after hydroxocobalamin administration points to hydroxocobalamin as the most likely factor.

To date, there are 2 reports illustrating the hemodynamic benefits of hydroxocobalamin, with and without trialing methylene blue, in the setting of liver transplantation.[4, 20] The previously published case reports demonstrated the use of hydroxocobalamin in liver transplantation with lower doses of hydroxocobalamin (125-mg and 250-mg bolus doses), followed by hydroxocobalamin infusions (250-500 mg/h) for vasoplegia. Boettcher et al[4] reported lower doses of hydroxocobalamin, but a more limited duration of response, thus requiring the initiation of a hydroxocobalamin infusion. While definitive studies need to be performed regarding both mechanism and dosing strategies, the present case should raise the awareness of transplant surgeons and anesthesiologists concerning a safe and potentially beneficial therapy in a subset of liver transplant recipients who are failing conventional therapies to treat postreperfusion vasoplegic syndrome.

## Abbreviations:

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| **FFP** | fresh frozen plasma |
| **i.v.** | intravenous |
| **MAP** | mean arterial pressure |
| **SVR** | systemic vascular resistance |
| **TEE** | transesophageal echocardiography |

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