Vitamin C for Vasoplegia After Cardiopulmonary Bypass: A Case Series

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Cardiac vasoplegia remains a significant contributor of morbidity and mortality in cardiac surgery patients after cardiopulmonary bypass. Effective therapeutic options for vasopressor-refractory vasoplegia are limited. We report 3 patients in whom we administered high-dose intravenous ascorbic acid (vitamin C), a cofactor for endogenous catecholamine synthesis, to treat vasoplegia refractory to epinephrine, vasopressin, and norepinephrine after surgery requiring cardiopulmonary bypass. Reductions in vasopressor requirements were observed in all 3 patients, and, in 2 patients, norepinephrine was completely discontinued within 24 hours. Ascorbic acid is a novel potential therapeutic option for cardiac vasoplegia that warrants rigorous prospective studies. (A&A Practice. 2018;11:96–9.)

**CASE DESCRIPTIONS**

**Case 1**
A 22-year-old man with hypertrophic cardiomyopathy underwent a transaortic and transapical septal myectomy. On postoperative day (POD) 2 in the intensive care unit, he remained vasodilated despite a cardiac index of 4.4 L·minute⁻¹·m⁻² and administration of epinephrine 0.02 µg·kg⁻¹·minute⁻¹, vasopressin 0.04 units/min, and escalating doses of norepinephrine. Once the norepinephrine infusion rate reached 0.1 µg·kg⁻¹·minute⁻¹, ascorbic acid 1500 mg IV every 6 hours was initiated. No other therapies were administered for his shock. His epinephrine, norepinephrine, and vasopressin were successfully weaned 4, 11, and 26 hours later, respectively. Ascorbic acid was discontinued when he no longer required vasopressor support, and he was subsequently discharged from the intensive care unit.

**Case 2**
An 18-year-old man with a HeartWare (Medtronic, Framingham, MA) left ventricular assist device as destination therapy for nonischemic dilated cardiomyopathy presented 16 months after initial implantation with pump thrombosis. He underwent HeartWare pump exchange during which he was estimated to have lost over 2 L of blood. He was transfused with 10 units of packed red blood cells, 4 units of fresh frozen plasma, 10 units of cryoprecipitate, 2 units of platelets, and return of 1200 mL from the cell saver. In the early postoperative period, he was adequately fluid resuscitated and the new left ventricular assist device was functioning properly. However, on POD 2, he required epinephrine 0.08 µg·kg⁻¹·minute⁻¹, vasopressin 0.04 units/min, and hydrocortisone 50 mg IV every 6 hours for hemodynamic support. Despite these interventions, he required escalating doses of norepinephrine to maintain adequate MAPs. Ascorbic acid 1500 mg IV every 6 hours was initiated when his norepinephrine infusion rate reached 0.12 µg·kg⁻¹·minute⁻¹. Thereafter, norepinephrine and vasopressin were successfully weaned 18 and 43 hours later, respectively. Ascorbic acid was continued for 96 hours and epinephrine infusion for inotropic support was successfully weaned thereafter at 116 hours. Serum lactate was successfully cleared shortly after ascorbic acid discontinuation.

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Case 3

A 67-year-old man with a complex cardiac history including severe mitral and tricuspid valve regurgitation and severe aortic valve stenosis underwent mechanical mitral, mechanical aortic, and tissue tricuspid valve replacements. Post-CPB transesophageal echocardiogram revealed a left ventricular ejection fraction of 20%, down from 30% preoperatively. He was centrally cannulated for venoarterial extracorporeal membrane oxygenation via femoral and ascending aortic sites. Due to rapid hemodynamic improvement, he was successfully weaned from extracorporeal membrane oxygenation on POD 3 and his chest was closed the day after. He continued to require vasopressor support despite a cardiac index of 2.75 L·minute⁻¹·m⁻². Epinephrine was maintained at 0.08 µg·kg⁻¹·minute⁻¹ and vasopressin at 0.04 units/min. However, he required increasing amounts of norepinephrine to maintain vascular tone. Norepinephrine continued to rapidly increase, and once it reached 0.3 µg·kg⁻¹·minute⁻¹, ascorbic acid 1500 mg IV every 6 hours was initiated. He also received hydrocortisone 50 mg IV every 6 hours and a bolus of methylene blue 100 mg IV. Despite these interventions, he remained in vasodilatory shock, and the decision was made to take the patient back to the operating theater for peripheral venoarterial extracorporeal membrane oxygenation cannulation via femoral sites. After this, ascorbic acid was continued for a total of 96 hours. His norepinephrine and epinephrine were able to be weaned to 0.03 and 0.05 µg·kg⁻¹·minute⁻¹, respectively. However, he still required triple vasopressor support at the time of ascorbic acid completion (96 hours). Twenty-four
hours after completion of ascorbic acid, he was still requiring full vasopressor support. Subsequent extracorporeal membrane oxygenation weans were unsuccessful, and he required initiation of continuous venovenous hemofiltration for acute renal failure. Because of medically refractory ventricular tachycardia episodes, the patient succumbed.

**DISCUSSION**

Catecholamine-refractory vasoplegia remains a problematic complication after CPB that can lead to significant morbidity and mortality. Many salvage therapies have been suggested to be of benefit in the literature to maintain vascular tone, including methylene blue and hydroxocobalamin.7 These therapies continue to be used in practice, although they have limitations and risk. Methylene blue has a short duration, resulting in only transient MAP elevations, is associated with serotonin syndrome from monoamine oxidase inhibition, and has a maximal recommended dosage due to accumulation in tissues.7 Hydroxocobalamin is a newer agent with some promising results. However it will stain effluent from continuous renal replacement therapy red.7 This limits any transitioning to intermittent hemodialysis for several weeks, because the hemodializer will recognize this effluent as blood and cease operation. Ascorbic acid has minimal-to-no known adverse effects in the cardiac surgery population. Indeed, no observable side effects were realized in the patients reported herein.

We report the first use of ascorbic acid for cardiac vasoplegia in patients undergoing cardiac surgery. In healthy individuals, catecholamines are endogenously synthesized in the adrenal medulla.4 Ascorbic acid is a cofactor for dopamine β-hydroxylase and tyrosine hydroxylase in the biosynthesis of dopamine and norepinephrine, respectively. Hormonal synthesis, however, has been shown to be depressed in the setting of critical illness.5,5 Additionally, due to its water solubility, CPB has been shown to remove ascorbic acid from the blood, resulting in ascorbate deficiency.6 Because humans lack the ability to endogenously synthesize ascorbic acid, exogenous administration is theorized to increase adrenal stores, therefore increasing the production of catecholamines through these biochemical pathways. Furthermore, ascorbate has been proposed to scavenge reactive oxygen species, improve microcirculation, diminish induction of nitric oxide synthase, and increase the sensitivity to catecholamines through reduction of adrenergic receptors to a basic state.5,8,9

In septic shock patients, ascorbic acid has been shown to be associated with significant mortality benefit when coadministered with steroids and thiamine.8 The stress of surgery and insult of the CPB pump leads to release of a variety of inflammatory mediators mimicking the systemic inflammatory response syndrome seen in patients with septic shock, albeit in the absence of infection.1,10,11 We believe that this inflammatory state, known depletion of ascorbic acid in the CPB circuit, and ascorbic acid’s role in endogenous catecholamine synthesis describe its beneficial potential in vasodilatory shock states including cardiac vasoplegia. Indeed, 2 of our patients were rapidly liberated from norepinephrine infusions after vitamin C administration.

Given the lack of experience in post-CPB vasoplegic patients, we extrapolated the arbitrary dosing schema and 96-hour duration of ascorbic acid from the study by Marik et al10 of septic shock patients, because this high dose is proposed to restore adequate ascorbic acid serum concentrations in those who are deficient secondary to critical illness. Those authors found that all patients with available ascorbic acid concentrations drawn at baseline were indeed deficient. We only collected a baseline ascorbic acid concentration for case 2, which was low at 0.2 mg/dL. Due to the limited understanding between ascorbic acid concentrations and pathological consequences, a turnaround time of 3 days for this assay at our institution, and previous evidence describing depletion of ascorbic acid during CPB, the utility of measuring serum concentrations is unknown. In the absence of quantifying serum ascorbic acid concentrations, high-dose supplementation may potentially aid in reducing vasopressor requirements, specifically norepinephrine in the early stages of cardiac vasoplegia after CPB.

**CONCLUSIONS**

In 3 cases of cardiac vasoplegia after CPB necessitating epinephrine, vasopressin, and escalating norepinephrine doses to maintain MAP >65 mm Hg, we found reduced vasopressor support after administration of high-dose ascorbic acid. In 2 cases, complete liberation of norepinephrine was achieved within just 24 hours of ascorbic acid initiation. Prospective, randomized studies are warranted to evaluate the efficacy and determine the appropriate dosage and duration of ascorbic acid in the treatment of cardiac vasoplegia after CPB. 

**DISCLOSURES**

Name: Patrick M. Wieruszewski, PharmD.
Contribution: This author helped conceive and design the study, collect and interpret the data, review the literature, and draft the manuscript.

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