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Rescue of Nimodipine-Induced Refractory Vasoplegia With Hydroxocobalamin in Subarachnoid Hemorrhage: A Case Report

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Background: We report a case of refractory vasoplegia after nimodipine administration that was unresponsive to triple vasopressor therapy and was rescued by IV hydroxocobalamin.

Case Summary: An 84-year-old male presented comatose from a subarachnoid hemorrhage and developed severe hypotension unresponsive to three vasopressors following a single dose of enteral nimodipine. Multisystem point-of-care ultrasonography ruled out alternate etiologies of shock, indicating that this was likely a vasoplegic state caused by nimodipine. We administered 5 grams of IV hydroxocobalamin over 15 minutes due to the possibility of impaired nitric oxide metabolism as the driver of vasoplegia. This led to immediate improvement in hemodynamics and rapid discontinuation of vasopressors. The patient experienced chromaturia but no other adverse effects due to hydroxocobalamin.

Conclusions: Nimodipine administration is a standard practice for patients with aneurysmal subarachnoid hemorrhage to reduce unfavorable outcomes from cerebral vasospasm. Although mild hypotension is a common side effect of nimodipine, in rare cases, it may become profound, leading to refractory vasoplegia. There is no evidence-base for reversal agents for nimodipine-induced vasoplegia, and this case is the first to demonstrate successful use of hydroxocobalamin as a potential rescue therapy. We also propose an algorithm for treatment of vasoplegia with consideration of medications that act on nitric oxide–mediated vasodilation and their side-effect profiles.

Key Words: hydroxocobalamin; nimodipine; subarachnoid hemorrhage; vasospasm; vasoplegia

Cerebral vasospasm is a major cause of secondary neurologic injury after aneurysmal subarachnoid hemorrhage (aSAH). The secondary injury, delayed cerebral ischemia, occurs in 20–40% of patients (1), increases based on severity of the subarachnoid hemorrhage (SAH) (2, 3), and contributes to significant morbidity and mortality (4, 5). To reduce vasospasm-related mortality and unfavorable neurologic outcomes after aSAH, the American Stroke Association recommends the use of nimodipine, a dihydropyridine calcium channel blocker (5, 6). It remains the only Food and Drug Administration approved pharmacologic agent to reduce the mortality risk from vasospasm. It is recommended that nimodipine, at a dose of 60 mg every 4 hours, be initiated within 96 hours of aSAH and be continued for 21 consecutive days (5). As expected with a calcium channel blocker, mild hypotension is an expected side-effect of the drug, sometimes requiring dose reduction (30 mg every 2 hr) or concomitant vasopressor use (7, 8).

Although nimodipine-related hypotension commonly is mild, in rare cases, it may become more profound, leading to vasoplegic circulatory collapse (9). Vasoplegia is defined by significant hypotension (mean arterial pressure [MAP] < 60 mm Hg) in the setting of normal to high cardiac output (cardiac index > 2.2 L/min/m^2) and low systemic vascular resistance (typically < 800 dynes s/cm^5) despite high-dose vasopressor (equivalent to 0.5 mg/kg/min of norepinephrine) administration (10). It is thought to be secondary to nitric oxide (NO) accumulation, causing endothelial dysfunction and smooth muscle relaxation, leading to vasodilatory effect (9, 11). Vasoplegia is recognized in a variety of shock types: septic, anaphylactic, cardiogenic (often as a side-effect of cardiopulmonary bypass surgery) (12–14), as well as overdose from calcium channel blockers (15), but is rarely recognized as a consequence from nimodipine for vasospasm treatment in aSAH. Indeed, only one case series (four patients) exists in the literature describing

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refractory vasoplegia secondary to nimodipine administration (9). Two agents thought to be effective rescue therapies in refractory vasoplegia due to their NO scavenging effects are methylene blue (9–11, 15, 16) and hydroxocobalamin (a highly bioavailable form of vitamin B12) (12–14). There are no randomized controlled studies comparing their effects nor reports of hydroxocobalamin as a rescue therapy in nimodipine-induced refractory vasoplegia.

We report a case of refractory vasoplegia secondary to nimodipine in a patient with an aSAH. We then describe the reversal of vasoplegia following administration of hydroxocobalamin, discuss proposed mechanisms of action, and suggest an algorithm for treatment of vasoplegia in the neurologically critically ill patient.

CASE PRESENTATION

An 84-year-old male with a history of hypertension, hyperlipidemia, prostate adenocarcinoma (on hormonal therapy), with no prior strokes or cerebral hemorrhages, was found down and presented to the hospital comatose with a Glasgow Coma Scale score of 3 (Hunt Hess 5). CT of the head revealed thick left cisternal subarachnoid blood extending into the sylvian fissure and cerebellar tentorium, with associated intraventricular hemorrhage (modified Fisher Scale score 4). Additional findings were traumatic bilateral holohemispheric subdural hematomas. CT angiogram of the head and neck demonstrated a left clinoid intracerebral artery aneurysm measuring 7 × 7 × 9 mm. This aneurysm likely ruptured, causing diffuse subarachnoid hemorrhage, loss of consciousness, and a traumatic fall that led to the development of bilateral subdural hematomas.

Based on the patient's age, poor neurologic examination, and discussions with the patient's family, neither surgical evacuation of SDH nor clipping or coiling of aneurysm for SAH was recommended. Medical management was initiated, and MAP was maintained between 70 and 90 mm Hg using a labetalol infusion.

On hospital day 3, nimodipine was started given the possibility that the inciting event was an aSAH. Fifteen minutes after the first dose of enteral nimodipine 60 mg, there was profound hypotension to a blood pressure of 76/40 (MAP 53 mm Hg) as measured by radial arterial catheter, along with bradycardia with heart rates in mid-50s. The labetalol infusion, previously at a low rate of 0.5 mg/min, was off for 2 hours prior to nimodipine administration. The patient was given 1L of crystalloid, and vasopressors were initiated for ongoing hypotension. The hemodynamic support rapidly escalated to triple vasopressor therapy equivalent to 0.59 μg/kg/min of norepinephrine (norepinephrine [0.23 μg/kg/min] + phenylephrine [2.6 μg/kg/min] + epinephrine [0.1 μg/kg/min]) (**Fig. 1**). He was also given a total of 2 grams of 10% calcium gluconate with minimal additional benefit. An arterial blood gas drawn during this time did not reveal any notable derangement or significant change from prior, with pH 7.41 and base deficit 6.1 mmol/L.

Given the rapid and profound development of hypotension, multisystem point-of-care ultrasonography (POCUS) was performed to elucidate the etiology of hypotension. A transthoracic echocardiogram revealed normal biventricular size, hyperdynamic systolic function, no regional wall motion abnormalities, and no pericardial effusion. The inferior vena cava size and distensibility on passive positive pressure ventilation were not suggestive of volume depletion or volume responsiveness, respectively. Anterior lung ultrasonography showed symmetrical bilateral pleural sliding with no evidence of pneumothorax. Since hypotension can be a late finding in elevated intracranial pressure and brainstem herniation, bilateral optic nerve sheath diameters were measured (< 5 mm) arguing against elevated intracranial pressure. Given cardiac, pulmonary, and neurologic etiologies of acute, severe hypotension were ruled out, the patient's hemodynamics in the setting of adequate intravascular volume and hyperdynamic myocardial function were consistent with a vasoplegic state. Nimodipine was the likely culprit: it was the only drug administered in an otherwise hemodynamically stable patient prior to hypotension ensuing. Due to presumed NO-mediated vasodilatory mechanism, the patient was administered 5 grams of IV hydroxocobalamin (Cyanokit; Meridian Medical Technologies, Columbia, MD) (17) over 15 minutes as a rescue therapy. Within minutes of administration of hydroxocobalamin, his MAP improved to 69 mm Hg, and all vasopressors were promptly weaned off. Nimodipine was subsequently discontinued with no recurrence of hypotension. Following 9 days of maximal medical support, despite

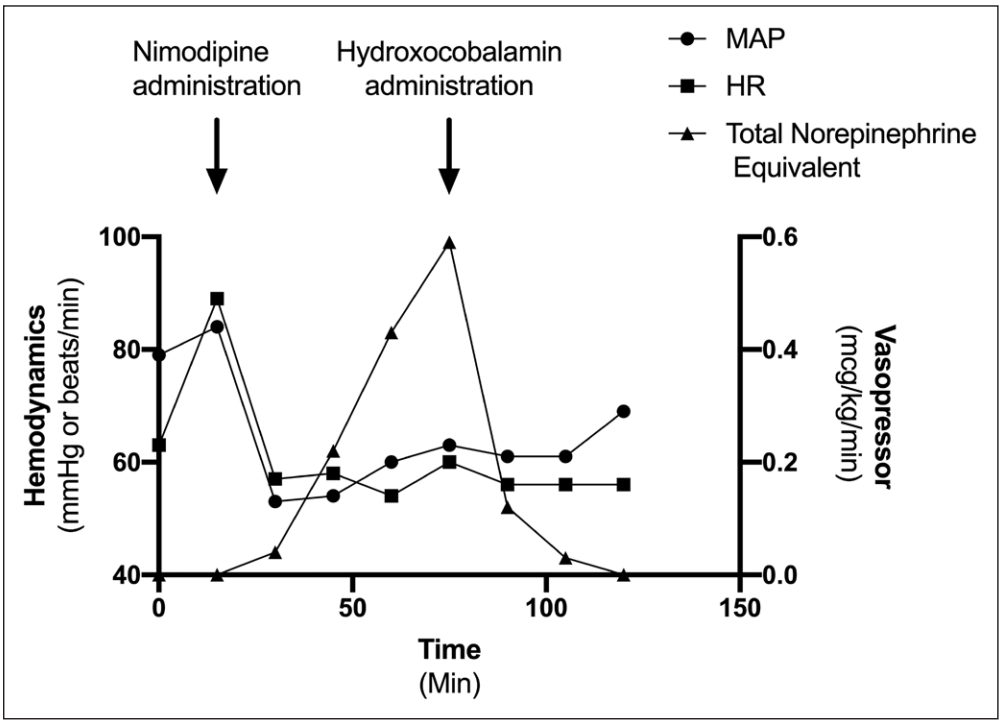

Figure 1. Hemodynamic changes and vasoactive drug doses in the 2 hr following the administration of the first 60 mg dose of enteral nimodipine. HR = heart rate, MAP = mean arterial pressure.

normotension, the patient's neurologic examination remained poor, and he was transitioned to comfort care.

DISCUSSION

Despite guideline-recommended use of nimodipine as a standard measure to reduce vasospasm-related morbidity and mortality from aSAH (7), hypotension is common. However, profound vasoplegic response to nimodipine remains a rare and underrecognized adverse effect. Here, we describe the case of a patient who developed severe hypotension unresponsive to three vasopressors after his first dose of nimodipine. A comprehensive evaluation using POCUS did not reveal any acute cardiovascular (Takotsubo's cardiomyopathy, acute right ventricular strain, pericardial tamponade, severe hypovolemia), pulmonary (pneumothorax), or neurologic (increased intracranial pressure) pathology leading us to diagnose a refractory vasoplegic state. Administration of IV hydroxocobalamin, 70 minutes after nimodipine administration, led to immediate improvement in hemodynamics and discontinuation of vasopressors, with purple discoloration of his urine as the only noted side-effect. Nimodipine has a terminal elimination half-life 8–9 hours and an initial rate of elimination of 1–2 hours, giving it an effective biological half-life of anywhere between 1.7 and 9 hours. The immediacy of increase in blood pressure along with ability to rapidly down-titrate vasopressors within 2–3 minutes of initiating the hydroxocobalamin infusion in the context of its pharmacokinetic properties, led to us surmise with confidence that the rapid cessation of vasoactive support was not just due to tapering of drug effect.

To our knowledge, there is an isolated case series describing four cases of vasoplegia refractory to vasopressor and fluid administration (with MAP < 55 mm Hg) after oral nimodipine administration. Each of these patients was treated with methylene blue with rapid resolution of hypotension, but no systematic evaluation for other neurocardiogenic sequelae of aSAH such as Takotsubo cardiomyopathy, impaired left ventricular function, and/or myocardial ischemia was performed (9). Methylene blue is a recognized therapy for vasoplegia refractory to vasopressors (9–11, 15, 16), and its use has also been described in amlodipine overdose (15). It blocks accumulation of cyclic guanosine monophosphate (cGMP) via inhibition of guanylate cyclase activity, acts as a NO scavenger, and inhibits endothelial NO synthase activity, thereby decreasing responsiveness of cGMP-regulated vasodilation activated by NO (11, 15).

Nimodipine may cause dysregulation of calcium signaling, leading to increase in NO release and activating cGMP resulting in significant vasodilation. Hydroxocobalamin, a highly bioavailable form of vitamin B12 that is approved for use in cyanide poisoning, is thought to act in a similar way to methylene blue on the NO system. Additionally, it is also thought to counteract hydrogen sulfide (H_2S)–induced vasodilation by directly binding

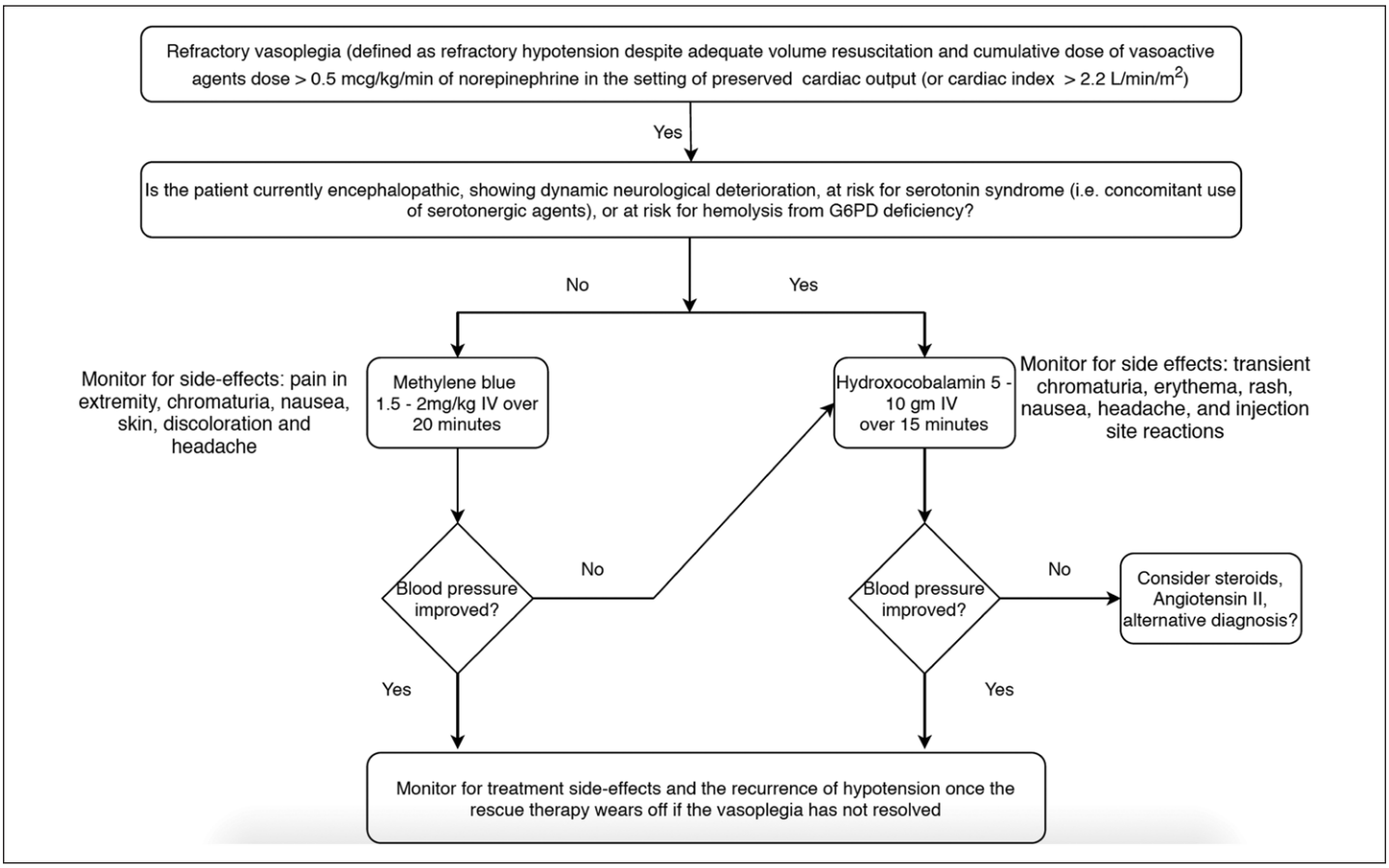

Figure 2. A suggested algorithm for the management of refractory vasoplegia in the neurologically critically ill patient based on side-effect profiles of rescue modalities and coexisting medical conditions. G6PD = glucose-6-phosphate dehydrogenase.

the H_2S to be excreted (12). To date, there is no literature describing the use of hydroxocobalamin in nimodipine-induced vasoplegia. However, there are a number of reports of hydroxocobalamin used in refractory vasoplegia after cardiopulmonary bypass (12–14). Interestingly, Cai et al (12) describe such a case of vasoplegia in the setting of cardiac surgery, refractory to vasopressors, fluid boluses, and methylene blue, which responded to hydroxocobalamin, suggestive of potentially a different or secondary mechanism of vasoplegia than impaired NO metabolism.

Rescue medications for vasoplegia may have severe adverse effects. At clinically relevant concentrations, methylene blue may be associated with neurotoxicity and encephalopathy specifically in patients taking antidepressants (18–22), serotonin syndrome (especially with concomitant use of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, linezolid, meperidine, tramadol, etc.) (10, 23), hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency, hypertension, and headache (9, 10). The side-effect profile of hydroxocobalamin includes chromaturia, hypertension, erythema, headache, nausea, and rash, in addition to a false laboratory elevation of hemoglobin, creatinine, glucose, bilirubin, and alkaline phosphatase (10, 12, 24). Therefore, selection of antivasoplegic therapy must account for both patient and drug factors. Ortoleva and Cobey (10) propose a systematic approach to vasoplegia in the perioperative period surrounding cardiac surgery. Here, we propose a modified vasoplegia algorithm for the neurologically critically ill patient based on side-effect profiles of rescue therapies and coexisting medical conditions (**Fig. 2**).

Of interest, Bele et al (9) recommend administering an initial test dose of 15–30 mg of nimodipine prior to administration of the standard dosage of 60 mg of nimodipine, especially in patients on concurrent blood pressure medications that may increase the risk of vasoplegia, in order to evaluate the severity of potential hypotension. Although this is not a widely practiced strategy, it may be prudent to consider a lower first dose of nimodipine to evaluate response.

In conclusion, refractory vasoplegia is a potentially life-threatening adverse effect from nimodipine and may be mediated via impaired NO or H_2S signaling. Hydroxocobalamin may be the preferred modality of treating vasoplegia in patients with neurologic disease, G6PD deficiency, or those at risk of serotonin syndrome in comparison to methylene blue. Severe refractory hypotension following nimodipine in patients with aSAH should alert the intensivist to the possibility of vasoplegia, so that prompt intervention may be taken to preserve cerebral perfusion.

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

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