CASE REPORT

Use of Continuous Infusion Hydralazine in a Pediatric Patient on Mechanical Circulatory Support

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Hydralazine is a direct peripheral arterial vasodilator used for acute hypertension. Usually administered as a bolus dose, continuous infusion has been described during pregnancy for preeclampsia and eclampsia and in limited reports in cardiac surgeries for afterload reduction. This case describes the use of continuous infusion hydralazine for afterload reduction in an infant receiving extracorporeal membrane oxygenation (ECMO) post-cardiac surgery. Postsurgery, the patient's mean arterial pressures (MAPs) could not be controlled despite escalating doses of vasodilatory medications including nitroprusside, nicardipine, and milrinone; hence, continuous infusion hydralazine was initiated. Although the initiation of a hydralazine infusion produced a decrease in MAP, the response was unsustainable. This case highlights an alternative method for managing systemic vascular resistance and cardiac output to allow for myocardial recovery after cardiac surgery and use of extracorporeal support. At the time of this writing, this is the first published case describing hydralazine administration via continuous infusion in pediatric patients. The use of continuous infusion hydralazine for afterload reduction provided a brief, non-sustained reduction in MAP in a post-cardiac surgery infant managed on ECMO support.

INDEX TERMS: afterload reduction, continuous infusion, extracorporeal membrane oxygenation, hydralazine, pediatric

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INTRODUCTION

Hydralazine is a direct-acting vasodilator used adjunctively for hypertension. Treatment with hydralazine is frequently limited by reflex sympathetic stimulation that increases heart rate and cardiac output.¹ Doses of intravenous hydralazine in pediatric patients generally range from 0.1 to 0.2 mg/kg administered every 4 to 6 hours. There is no information on the use of continuous infusion hydralazine for control of mean arterial pressure (MAP) in pediatric patients, and there is limited literature regarding its use for preeclampsia and cardiac surgeries in adults.^{2–5} We describe the use of continuous infusion hydralazine in an infant on mechanical circulatory support who did not have a satisfactory decrease in MAP with use of nitroprusside, nicardipine, and milrinone.

CASE REPORT

A 3-month-old, 4.2-kg female with a history of double-orifice mitral valve with moderate to severe stenosis and dysmorphic features presented to the cardiovascular intensive care unit for post-operative management status post resection of a supra-valvar mitral ring, resection of redundant mitral valve chordal tissue, and splitting of her papillary muscles. In the operating room she was unable to wean from bypass as a result of severely depressed right ventricular function and very high systemic vascular resistance (SVR) despite the utilization of reduced bypass flows and various inotropic supports (milrinone up to 0.5 mcg/kg/min, nicardipine up to 1 mcg/kg/min, nitroprusside up to 4 mcg/kg/min, and phentolamine 0.1 mg/kg bolus). She was subsequently cannulated on veno-arterial extracorporeal membrane oxy-

Figure. Relationship between MAP and medication administration or significant mechanical support events.

■ Milrinone ($\times 10^1$); ▲ Nitroprusside; ● Hydralazine; ◆ Map; ◆ Nicardipine ($\times 10^1$)

ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure

genation (ECMO) and transferred to the cardiovascular intensive care unit for continued care.

Immediately postsurgery the patient was managed with nicardipine 1 mcg/kg/min, nitroprusside 4 mcg/kg/min, and milrinone 0.5 mcg/kg/min. As a result of the highly variable hemodynamic state of the patient, the duration of titration for nicardipine was less desirable than the ability to quickly titrate nitroprusside. Nicardipine was then discontinued, nitroprusside was up-titrated to 8 mcg/kg/min, and milrinone at 0.75 mcg/kg/min was administered to reduce elevated MAP (goal: 45-55 mm Hg). Despite escalation of vasodilatory medications over the first 24 hours postoperatively, the patient remained hypertensive, with MAP values averaging 64 mm Hg (range: 55-81 mm Hg). The patient remained on ECMO with fluid management via ultrafiltration. ECMO flows during this time were a mean of 605 mL/min (548-650 mL/min).

There was concern for a non-sustained, rapid alteration to MAP with an intermittent hydralazine regimen, and the decision was made to initiate a hydralazine continuous infusion (1 mg/mL in 0.9% sodium chloride) at approximately 24 hours after ECMO cannulation to decrease MAP. Vasodilator medications and MAP were graphically evaluated and depicted in the Figure. Nitroprusside was weaned to 1 mcg/kg/min at the time of hydralazine initiation and stopped shortly after initiation of the hydralazine. Within 1 hour of starting the hydralazine infusion at 10 mcg/kg/min the patient's MAP fell from 81 to 45 mm Hg, and the patient was maintained at this

dose for 9 hours, with MAP values averaging 52 mm Hg (range: 45-58 mm Hg). ECMO flow during this time averaged 642 mL/min (623-687 mL/min). The patient remained tachycardic, with heart rates averaging 132 beats per minute (range: 102-152 beats/min). No other potential adverse events to hydralazine were observed during the treatment course.

At 33 hours postop MAP started to decrease; however, there was concern for inadequate cardiac output, and milrinone was maximized to 1 mcg/kg/min. The hydralazine infusion was slowly titrated up to 20 mcg/kg/min over the next 32 hours. The patient's MAP remained at a mean of 58 mm Hg (range: 50-67 mm Hg), with ECMO flows averaging 627 mL/min (573-667 mL/min). The patient was subsequently transitioned to nitroprusside 2 mcg/kg/min to reduce MAP, and the hydralazine infusion was stopped for approximately 2 hours for an attempted wean off of ECMO and subsequent mediastinal exploration. The nitroprusside was then titrated off and the hydralazine infusion reinitiated at 8 mcg/kg/min, resulting in a reduction of MAP from 64 to 45 mm Hg, while ECMO flows were maintained at 644 mL/min (627-656 mL/min). Mean arterial pressure remained decreased for approximately 4 hours, and the ECMO flow was decreased to 317 mL/min. Mean arterial pressure increased to an average of 58 mm Hg (40-67 mm Hg), and the nitroprusside was subsequently titrated up to 5 mcg/kg/min and the hydralazine dose was increased to 16 mcg/kg/min and maintained at this rate for the next 20

hours, with MAP averaging 60 mm Hg (46-77 mm Hg) and ECMO flows averaging 641 mL/min (609-662 mL/min).

ECMO flows were gradually reduced to 572 mL/min (547-631 mL/min) and an attempt was made to transition the patient off nitroprusside by increasing the hydralazine infusion to 40 mcg/kg/min. ECMO flows remained unchanged at 566 mL/min (510-580 mL/min), and the resultant MAP averaged 60 mm Hg (53-70 mm Hg). To further decrease MAP, the hydralazine was then reduced to 30 mcg/kg/min and the nitroprusside was reinitiated at 3 mcg/kg/min. The patient's MAP slowly declined over the next 40 hours, averaging 52 mm Hg (41-62 mm Hg), with ECMO flows remaining stable at 580 mL/min (553-614 mL/min). The nitroprusside was discontinued and the hydralazine infusion was decreased to 16 mcg/kg/min in anticipation of decannulation from ECMO support.

The patient's MAP continued to decrease to a mean of 46 mm Hg (38-57 mm Hg). The patient was decannulated from ECMO, and the hydralazine infusion was discontinued and the milrinone weaned to 0.5 mcg/kg/min. Epinephrine and vasopressin were initiated and the MAP remained decreased, averaging 47 mm Hg (41-57 mm Hg). Epinephrine and vasopressin were used periodically over the next 4 days as a result of reflex hypotension following ECMO cannulation and the previous heavy burden of vasodilatory agents. The patient's status improved, allowing for discontinuation of intravenous vasoactive medications. The patient was then transferred to the cardiac step-down unit and was ultimately discharged home from the hospital.

DISCUSSION

This is the first report of continuous infusion hydralazine therapy in a pediatric patient. There was a marked, non-sustained decrease in MAP upon initiation of hydralazine. However, after the initial effects of hydralazine, the patient's MAP increased and remained elevated throughout the course, despite escalation of the hydralazine dose up to 40 mcg/kg/min and concomitant administration of other vasodilators. This initial decrease was also noted when the hydralazine continuous infusion was briefly interrupted and restarted, only to demonstrate lack of effect on up-titration of dose. Additionally, there appeared

to be no association with hydralazine dose and MAP outside of the initial reduction noticed at initiation. The patient was tachycardic throughout the postoperative course, averaging 132 beats per minute (range: 102-152 beats/min). No adverse drug reactions were suspected during the patient course.

Our limited experience is consistent with the results of previously published literature relating no significant alterations to MAP in patients receiving hydralazine. In a report by Swartz et al,³ 20 patients received hydralazine via continuous infusion following cardiopulmonary bypass. Continuous infusion hydralazine decreased SVR index but had a non-significant effect on arterial pressure. These data are consistent with the findings in a study by Oka et al⁴ in patients after open heart surgery who also noted significant decreases in SVR index with no significant reduction in MAP and with results of a study by Yoshimura and Kobayashi et al⁵ in sheep which illustrated a reduction in pulmonary hypertension without alter systemic arterial pressure. It is logical to assume that with no change in MAP and a decrease in SVR, cardiac output will increase.

The use of hydralazine in ECMO patients is not well described in the literature. An early study by Sell et al⁶ demonstrated that aggressive management with captopril, nitroglycerine, and hydralazine was beneficial in protecting against intracranial hemorrhage in neonates on ECMO. In their study Martin et al⁷ found that hydralazine failed to improve cardiac output in infants supported on ECMO. These data provide insight into the potential utilization of hydralazine to minimize hypertension while protecting cardiac output. The disposition of hydralazine during ECMO support has been described by Watt et al,⁸ who suggested that hydralazine pharmacokinetics may not be altered by the presence of ECMO, as has been reported with other pharmacologic agents.

In post-cardiac surgery patients there is the need to reduce SVR in an attempt to reduce myocardial workload. This becomes even more important in patients on ECMO with aortic cannulation, which causes elevated SVR, making it more difficult for the heart to rest. Although good responses can often be seen while utilizing other vasodilator therapies, such as nicardipine or nitroprusside, there are concerns with these agents that would make hydralazine therapy a potential option.⁹

Methemoglobinemia and cyanide toxicity can be concerns with long-term or large-dose nitroprusside therapy. Often solutions are made using sodium thiosulfate to prevent cyanide toxicity; however, the addition of thiosulfate can lead to potential thiocyanate toxicity and hemolytic crisis in those with G6PD deficiency.¹⁰ The patient in this case report was hemodynamically unstable, requiring frequent and immediate adjustments to therapy. Nicardipine takes significantly longer to titrate and longer for the effects to wear off when titrated down or off. Because of these concerns in this patient, nicardipine was a less desirable agent than nitroprusside and hydralazine.

This patient had a complicated postoperative course and required multiple modalities of support, including ECMO and vasodilatory pharmacologic therapy. The etiology of the elevated MAP is likely the use of ECMO, as during the patient's course, alternative causes of arterial hypertension, such as renal artery stenosis, were explored and ruled out. The patient's acetylase status was also unable to be assessed. On the rare chance that the patient may have been an ultrarapid acetylase, the patient may have been metabolizing hydralazine too rapidly for the drug to exert an effect. While the initial use of hydralazine continuous infusion was beneficial, the long-term use failed to obtain MAP control for a prolonged period of time.

CONCLUSION

Continuous infusion hydralazine initially lowered MAP in a pediatric patient supported on ECMO after undergoing cardiac surgery but was not effective for long-term MAP reduction.

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Abbreviations ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure

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