CASE REPORT

Extended Continuous Infusion of Methylene Blue for Refractory Septic Shock

Abhishek Jaiswal¹, Manish Kumar², Elizabeth Silver³

ABSTRACT

Objective: Highlight the utility of methylene blue (MTB) infusion for extended period for refractory vasoplegia.

Introduction: Hypotension refractory to vasopressor therapy in sepsis is associated with high mortality and limited therapeutic options. Dysregulated nitric oxide (NO) pathway seems to be a major driver, and, therefore, MTB, which inhibits inducible NO synthase activity and decreases cyclic guanosine monophosphate (GMP) accumulation by directly competing with NO by binding to soluble guanylyl cyclase, has been explored.¹–³ We describe a successful reversal of refractory septic shock with prolonged MTB infusion in a patient supported on multiple vasopressors at the highest clinical doses as well as venovenous extracorporeal membrane oxygenation (VV-ECMO).

Case description: We describe a successful reversal of refractory septic shock with prolonged MTB infusion in a patient supported on multiple vasopressors at the highest clinical doses as well as venovenous extracorporeal membrane oxygenation (VV-ECMO).

Conclusion and clinical significance: Current report suggests a potential role of MTB infusion in refractory vasoplegia even in advanced vasoplectic shock.

Keywords: Extra corporeal membrane oxygenation, Methylene blue, Refractory shock, Sepsis induced.

BACKGROUND

Patients in septic shock refractory to vasoactive agents have limited therapeutic options with poor prognosis. Dysregulated nitric oxide (NO) pathway seems to be a major driver, and, therefore, methylene blue (MTB), which inhibits inducible NO synthase activity and decreases cyclic guanosine monophosphate monophosphate (GMP) accumulation by directly competing with NO by binding to soluble guanylyl cyclase, has been explored.¹–³

CASE DESCRIPTION

A 38-year-old male was brought to our hospital for worsening lethargy and hypoxia. Initial assessment showed afebrile, lethargic male with tachypnea, bibasilar inspiratory crackles on chest auscultation, and hypoxia which improved on 15 L/minute oxygen supplementation. Investigations revealed metabolic acidosis (pH-6.95), blood sugar >1000 mg/dL, an anion gap of 31, and bibasilar infiltrates on chest imaging. Patient was started on intravenous (IV) fluid and insulin infusions, placed on noninvasive ventilation, and antibiotics. However, worsening hypoxia and breathing led to endotracheal intubation. Shortly thereafter, he became hypotensive, requiring boluses of IV fluid and vasopressor infusions (Fig. 1). His antibiotics were broadened and continuous venovenous renal replacement (CVVH) therapy was initiated for worsening metabolic acidosis, oliguria, and escalating the requirement of vasopressors. However, within 2 hours, he had a pulse electrical activity cardiac arrest. Bedside transthoracic echocardiogram showed hyper dynamic left ventricle without any pericardial effusion.

At 25 hours from presentation, and 4 hours after cardiac arrest, the patient was started on VV-ECMO support for ongoing hypoxia, inability to undergo CVVH due to hypotension. Continued hypotension despite improving hypoxia and acidosis with ECMO support along with multiple vasopressors prompted a trial of MTB. Following an IV bolus of MTB (172 mg), an infusion was started at 0.51 mg/kg/hour for next 10 hours, resulting in improved blood pressure, reintiation of CVVH, and decreased vasopressor requirement. Post infusion patient maintained hemodynamics on norepinephrine at 36 μg/minute, epinephrine at 0.25 μg/kg/minute, and vasopressin at 0.07 units/minute with improved urine output resulting in discontinuation of CVVH. However, 22 hours into MTB infusion discontinuation, he developed fever and hypotension prompting escalation of vasopressors infusions; and, due to continued hypotension despite maximum dose of multiple vasopressors, the MTB infusion was restarted with subsequent hemodynamic improvement. He was found to have Klebsiella pneumonia bacteremia and antibiotics were tailored per sensitivities. The MTB infusion was stopped after 54 hours and patient was off all vasopressors in next 6–7 days and eventually was discharged.

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Methylene Blue in Refractory Vasoplegia

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 14</th>
<th>Day 19</th>
<th>Day 60</th>
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<tbody>
<tr>
<td>38 y/o male presented with tachycardia, tachypnea, hypoxia, and blood glucose level &gt; 1000, pH 6.95</td>
<td>Chest X-ray revealed pneumonia, started on antibiotics</td>
<td>Blood culture: gram negative rods and antibiotics broadened, US abdomen showed gall stones, Underwent percutaneous cholecystostomy</td>
<td>CVVH started</td>
<td>MAPs continued to drop to 55-60 mmHg, Started on MTB infusion</td>
<td>MAPs dropped to 50 mmHg and phenylephrine reinitiated. MTB infusion restarted</td>
<td>Underwent bronchoscopy and cultures grew Klebsiella pneumonia</td>
<td>Discharged on Levofloxacin and Voriconazole to be finished as outpatient</td>
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<tr>
<td>De-saturated to 46% on 15 L/min, intubated for acute hypoxic respiratory failure</td>
<td>MAPs dropped to 50%: on maximal doses of norepinephrine, phenylephrine, epinephrine, vasopressin</td>
<td>Worsening hypoxia resulted in cardiac arrest. Resuscitated with 10 minutes of CPR</td>
<td>Patient started on VV ECMO support due to progressive hypoxia from multilocal pneumonia</td>
<td>Patient was able to come off of norepinephrine, phenylephrine, and MTB</td>
<td>MTB and other vasopressors titrated off with the addition of midodrine</td>
<td>Taken off VV ECMO</td>
<td>Tracheostomy performed because difficult to wean off ventilator</td>
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Figs 1A and B: (A) Timeline of the patient's significant events in the hospital from admission through discharge; (B) Effects of methylene blue on mean arterial pressures (MAPs) (arrows representing single-dose administration)

**Discussion**

Prolonged MTB infusion reduced vasopressor requirement, improved the overall hemodynamics and might have contributed to the survival of our patient with refractory septic shock. A successful experience with prolonged MTB infusion (44 hours) was reported in a less sicker patient requiring only modest doses of vasopressors, whereas our patient was far sicker with renal failure and refractory hypotension, despite multiple vasopressor infusions at maximal doses, correction of hypoxia, and acidosis with ongoing ECMO support.

**Conclusion and Clinical Significance**

Current report highlights the potential role of MTB infusion in refractory vasoplegia even in advanced septic shock.

**References**