Methylene Blue for Refractory Shock in Pediatric Patients

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Methylene Blue for Refractory Shock in Pediatric Patients

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Objectives:
- Review the pathophysiology of distributive shock
- Describe the rationale for using methylene blue in shock patients
- Evaluate the literature available utilizing methylene blue in shock patients
- Discuss the potential place in therapy for methylene blue

Patient Case

MJ is a 13 yo female who is afebrile with a HR 120, RR 28, BP 79/50, MAP 58. Upon physical exam, her extremities remain warm and her capillary refill is >3 seconds. Physician diagnoses her with distributive shock.

Which therapy would not be used in a patient with distributive shock?

A. Fluid bolus
B. Norepinephrine
C. Epinephrine
D. Methylene Blue
E. None of the above

12 hours later – MAP 57 mmHg despite adequate fluids and vasopressors

Current Medications:
- Norepinephrine 1 mcg/kg/min
- Vasopressin 0.04 units/kg/min
- Epinephrine 0.5 mcg/kg/min
- Hydrocortisone 2 mg/kg q6h, 1 mg/kg Q8H

Current vitals:

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>HR beats/min</th>
<th>RR breaths/min</th>
<th>BP 83/44 mmHg</th>
<th>MAP 57 mmHg</th>
</tr>
</thead>
</table>

Background:
Shock and MB

What other options do we have?
Epidemiology

- Mortality rate for adults with vasoplegia estimated up to 50%
- Mortality rate for adults with septic shock 30-50%
- Septic shock in pediatric patients
  - Consistently among top 10 causes of mortality in children
  - Mortality rate 14-24%
  - Healthcare costs of $1.9 billion annually in the U.S.

Types of Shock

- Hypovolemic
- Distributive
- Cardiogenic
- Obstructive

  - Sepsis
  - Anaphylaxis
  - Drug ingestion
  - Vasoplegia

Shock spiral

- Release of vasodilators
- Systemic inflammation

Distributive Shock Effects

- Systemic vascular resistance
- Cardiac output

Stages of Shock

- Compensated
  - Early shock
    - Tachycardia, tachypnea, capillary refill <3 seconds
- Uncompensated
  - Late shock
    - Tachycardia, tachypnea, hypotension, capillary refill >4 seconds
- Irreversible
  - Complete failure of compensatory mechanisms
  - Death in presence of resuscitation

Distributive Shock Treatment Options

- Fluid boluses
- Norepinephrine
- Epinephrine
- Vasopressin
- Dopamine
- Corticosteroids
- Phenylephrine
- Albumin
Methylene Blue for Refractory Shock in Pediatric Patients

<table>
<thead>
<tr>
<th>Methylene Blue</th>
<th>FDA indication</th>
<th>Drug-induced methemoglobinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing for methemoglobinemia</td>
<td>1 – 2 mg/kg</td>
<td>May repeat every 30 – 60 minutes</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Skin discoloration</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to methylene blue or any component</td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td>Cost</td>
<td>$75.00 for one 2mg/kg dose for a 25 kg patient</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of MB in Shock

- Increases oxygen delivery to ischemic tissue
- Increases macrophage activity
- Augments free radical scavenger capabilities

Randomized, Controlled Trials

- Adult trials
- Observational Studies
- Adult studies
- Care Series/Reports

Body of Literature

- Adult reports
- Pediatric reports

MB Randomized Trials

<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirov MY, et al. Crit Care Med. 2001.</td>
<td>n=20</td>
<td>Septic shock</td>
<td>↑ MAP</td>
</tr>
<tr>
<td>Memis D, et al. Anaesth Intensive Care. 2002.</td>
<td>n=30</td>
<td>Severe sepsis</td>
<td>2 mg/kg MB over 15 minutes, 0.25 - 2 mg/kg/hr MB for 4 hours</td>
</tr>
<tr>
<td>Levin RL, et al. Ann Thorac Surg. 2004.</td>
<td>n=56</td>
<td>Vasoplegic syndrome</td>
<td>1.5 mg/kg over 60 minutes</td>
</tr>
</tbody>
</table>

NO during shock

- Decreases responsiveness to vasopressors
- Alters distribution of blood flow
- Increases capillary leak
- Multiple organ dysfunction

Methylene Blue in the Literature

MB=methylene blue; MAP=mean arterial pressure; SV=stroke volume; CI=cardiac index
Methylene Blue for Refractory Shock in Pediatric Patients

Kirov, 2001 – Study Overview

**Objective**
- Evaluate the effects of continuous infusion of MB on hemodynamics and organ function in septic shock

**Design**
- Prospective, randomized, controlled, open-label pilot study

**Methods**
- 1:1 randomization (n=20) for MB or isotonic saline
  - Bolus 2 mg/kg over 15 minutes
  - Continuous infusion 0.25 mg/kg/hr, 0.5 mg/kg/hr, 1 mg/kg/hr, 2 mg/kg/hr each for a one hour period

**Endpoint**
- Hemodynamics and organ function assessed over 24 hours
- Survival rate at 28 days

Kirov, 2001 – Population

**Inclusion**
- Severe sepsis or septic shock
- Mechanical ventilation
- Pulmonary artery catheters in place

**Exclusion**
- < 18 years old
- Pregnant
- Receiving corticosteroid, immunosuppressant, or chemotherapy

Kirov, 2001 – Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methylene Blue</th>
<th>Isotonic Saline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic and vasopressor support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Norepinephrine</td>
<td>87%</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>- Epinephrine</td>
<td>81%</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>- Dopamine</td>
<td>40%</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MAP at 24 hours, mmHg</td>
<td>86.6 ± 15.3</td>
<td>69.9 ± 18.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Duration septic shock</td>
<td>58.9 ± 36.7</td>
<td>66.3 ± 44.3</td>
<td>0.73</td>
</tr>
<tr>
<td>- Duration vasopressor support, h</td>
<td>71.4 ± 14.2</td>
<td>93.3 ± 49.7</td>
<td>0.54</td>
</tr>
<tr>
<td>- Duration ventilation, h</td>
<td>84.4 ± 43.9</td>
<td>75.1 ± 57.1</td>
<td>0.72</td>
</tr>
<tr>
<td>- Resolution of shock</td>
<td>n=7</td>
<td>n=3</td>
<td>0.07</td>
</tr>
<tr>
<td>- Survivors at day 28</td>
<td>n=5</td>
<td>n=3</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Kirov, 2001 – Conclusions

**Author’s conclusion**
- Administration of MB:
  - ↑ cardiovascular function
  - ↓ requirement for adrenergic support
  - Maintains oxygen delivery and consumption
  - Has relatively small risk of toxicity

**Presenter’s conclusion**
- Small sample size
- Promising role for MB as adjuvant therapy for septic shock as it ↓ need for vaspressors
- Only minor adverse reactions seen

Memis, 2002 – Study Overview

**Objective**
- To assess the effect of methylene blue infusion on plasma levels of cytokines in severe sepsis

**Design**
- Prospective, randomized, double-blind, placebo-controlled study

**Methods**
- Computer-steered permuted block design (n=30)
  - 0.5 mg/kg/hr x 6 hours MB or isotonic saline

**Endpoint**
- Cytokine levels at 48 hours
- Hemodynamics and organ function over 48 hours

Memis, 2002 – Population

**Inclusion**
- Bacteriologically documented infection with at least two sepsis criteria
- One of the following conditions:
  - Hypocapemia
  - Oliguria
  - Lactic acidosis
  - Thrombocytopenia
  - Recent change in mental status

**Exclusion**
- < 18 years
- Pregnant
- Receiving corticosteroids, immunosuppressants, or chemotherapy
- Known irreversible underlying disease
Methylene Blue for Refractory Shock in Pediatric Patients

Memis, 2002 – Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methylene Blue</th>
<th>Isotonic Saline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP - End of MB infusion, mmHg</td>
<td>85±14</td>
<td>74±10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP - 48 hrs later, mmHg</td>
<td>75±12.5</td>
<td>74±14.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation duration, h</td>
<td>7±2</td>
<td>8±3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>26.6</td>
<td>26.6</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

MAP=mean arterial pressure; MB = methylene blue

p<0.05 is significant

Memis, 2002 – Conclusions

<table>
<thead>
<tr>
<th>Author’s conclusion</th>
<th>Presenter’s conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No difference in cytokine levels</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>• Transient increase in MAP</td>
<td>• No loading dose</td>
</tr>
<tr>
<td>• No difference in survival outcome</td>
<td>• Low dose of MB used</td>
</tr>
<tr>
<td></td>
<td>• Only minor adverse reaction seen</td>
</tr>
</tbody>
</table>

Levin, 2004 – Study Overview

Objective

• To analyze the incidence of postoperative vasoplegic syndrome, to consider its prognosis, and to evaluate the effect of methylene blue on mortality

Design

• Prospective, randomized, placebo-controlled trial

Methods

• 1:1 randomization (n=56) to MB or placebo
• MB 1.5 mg/kg over 60 minutes

Endpoint

• Morbidity
• Mortality

Levin, 2004 – Population

Inclusion

• Patients having cardiac surgery
• Vasoplegic syndrome

Exclusion

• Off-pump coronary artery bypass surgery
• Bacterial endocarditis
• Aortic dissection
• Urgent or emergent procedures

Levin, 2004 – Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methylene Blue (n=28)</th>
<th>Placebo (n=28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, % (n)</td>
<td>0 (0)</td>
<td>21.4 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of vasoplegia &gt;48 hours, % (n)</td>
<td>0 (0)</td>
<td>28.6 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal failure, % (n)</td>
<td>0 (0)</td>
<td>14.3 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Respiratory failure, % (n)</td>
<td>0 (0)</td>
<td>14.3 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Supraventricular arrhythmia, % (n)</td>
<td>7.1 (2)</td>
<td>28.6 (8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sepsis, % (n)</td>
<td>0 (0)</td>
<td>25 (7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multi-organ dysfunction, % (n)</td>
<td>0 (0)</td>
<td>25 (7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Levin, 2004 – Conclusions

<table>
<thead>
<tr>
<th>Author’s conclusion</th>
<th>Presenter’s conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Placebo group</td>
<td>• Largest randomized trial to date</td>
</tr>
<tr>
<td>• Worse evolution</td>
<td>• No definition of when morbidity outcomes were assessed</td>
</tr>
<tr>
<td>• More sepsis</td>
<td>• Significant mortality benefit</td>
</tr>
<tr>
<td>• Higher mortality</td>
<td>• No discussion on hemodynamic variables or on weaning vasopressors</td>
</tr>
<tr>
<td>• No significant adverse effects</td>
<td></td>
</tr>
</tbody>
</table>
### MB Adult Observational Studies

<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preiser JC, et al. Crit Care Med. 1995.</td>
<td>n=14</td>
<td>At least one vasopressor</td>
<td>+ MAP</td>
<td>+ SVR</td>
</tr>
<tr>
<td>Andersen M, et al. J Crit Care. 1998.</td>
<td>n=10</td>
<td>At least two vasopressors</td>
<td>+ MAP</td>
<td>+ SVR</td>
</tr>
</tbody>
</table>

MAP=mean arterial pressure; SVR=systemic vascular resistance; CO=cardiac output

### MB Adult Observational Studies

<table>
<thead>
<tr>
<th>Citation</th>
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<th>Intervention</th>
<th>Results</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al. Korean J Intensive Care Med. 2008.</td>
<td>n=20</td>
<td>At least one vasopressor</td>
<td>+ MAP</td>
<td>+ SVR</td>
</tr>
<tr>
<td>Heemskerk S, et al. Intensive Care Med. 2008.</td>
<td>n=9</td>
<td>At least one vasopressor</td>
<td>+ MAP</td>
<td>+ SVR</td>
</tr>
</tbody>
</table>

MAP=mean arterial pressure; SVR=systemic vascular resistance; CO=cardiac output

### Juffermans, 2010 – Dose-Finding Study

**Objective**: To evaluate dose-dependency of MB in septic shock

**Methods**: n=15 adults (n=4), 3 mg/kg (n=6), 7 mg/kg (n=5) over 20 minutes

**Endpoints**: + MAP; + NO= nitric oxide; + CO=cardiac output

**Results**: Increases in dose → + positive effects → + splanchnic blood flow

**Conclusion**: + 3.3 mg/kg dose provides benefit while minimizing side effects

MB=methylene blue; MAP=mean arterial pressure; CO=cardiac output
To evaluate the use of MB in neonates with septic shock refractory to conventional therapy

**Objective**
- To evaluate the use of MB in neonates with septic shock refractory to conventional therapy

**Design**
- Observational study

**Methods**
- n=5
- 1 mg/kg MB over 60 minutes

**Endpoint**
- MAP
- Heart rate
- Blood gas

MB=methylene blue; MAP=mean arterial pressure

**Heart rate**
- 

**Dopamine 10 mcg/kg/min**

**Methylene Blue 2 mg/kg load**

**Methylene Blue 1 mg/kg/h**

**↑**

**Refractory**

**Epinephrine 0.05 to 0.1**

**Vasoplegia**
- 1 mg/kg over 5

**Vasopressors weaned**
- Norepinephrine 0.1 mcg/kg/min

**↑ BP**

**MAP**

**Vasopressors**
- Vasopressin 0.0001 to 0.0003 units/kg/min
- Vasopressin 0.0001 to 0.0003 units/kg/min

**↓ need for larger, randomized controlled trial**

**MB=methylene blue; DOL=day of life**

**Taylor, 2005 – The Patient**

**Prior to surgery**
- Dopamine 10 mcg/kg/min
- Epinephrine 0.5 mcg/kg/min
- Milrinone 0.3 mcg/kg/min
- Methylene Blue 1 mg/kg/hr

**Post surgery**
- Epinephrine 0.05 to 0.1 mcg/kg/min
- Norepinephrine 0.1 mcg/kg/min
- Vasopressin 0.0001 to 0.0003 units/kg/min
- Milrinone 0.33 mcg/kg/min
- Methylene Blue 1 mg/kg/hr

**Author’s Conclusion**
- **↑ BP**
- **↑ HR in 4/5 neonates**
- No change in oxygen requirement or blood gases

**Presenter’s Conclusion**
- Diverse group of neonates
- Small sample size
- **↑ MAP**
- **↓ need for vasopressors**
- Need for larger, randomized controlled trial

**BP= blood pressure; HR= heart rate; MAP= mean arterial pressure**
## Methylene Blue for Refractory Shock in Pediatric Patients

### Taylor, 2005 – Case Report

**Intervention**
- 2 mg/kg MB load
- 1 mg/kg/hr for an unknown duration

**Result**
- Epinephrine and norepinephrine discontinued POD 1
- Vasopressin discontinued POD 2
- Milrinone discontinued POD 8

**Side Effects**
- None reported

**Key Point**
- Vasopressors discontinued within 2 days and inotrope discontinued day 8
- Post-operative course benign

### Flynn, 2009 – The Patient

- **14 yr old bilateral lung transplant**
- **Epinephrine 0.03 mcg/kg/min**
- **Vasopressin 0.002 units/kg/min**
- **Norepinephrine 0.5 mcg/kg/min**
- **Phenylephrine 0.75 mcg/kg/min**
- **Inhaled nitric oxide 20 ppm**

### Flynn, 2009 – Case Report

**Intervention**
- 1.5 mg/kg MB over 10 minutes

**Results**
- ↓ vasopressor drip rate before MB infusion ended
- NE off; phenylephrine off; Epi ↓ by half; vasopressin ↓ by a factor of 6
- No change in CVP

**Side Effects**
- None reported

**Key Point**
- MB aided in quick reversal of vasodilatory shock
- No deleterious effects noted
- Can be used concomitantly with NO

### Bhalla, 2011 – The Patient

- **5 yr old post cardiac transplant**
- **Epinephrine 0.222 mcg/kg/min**
- **Vasopressin 0.002 units/kg/min**
- **Méthylène blue 0.5 mcg/kg/min**
- **Norepinephrine 8 mcg/kg/min**
- **Dobutamine 15 mcg/kg/min**
- **Dopamine 17 mcg/kg/min**
- **Fluid boluses**

### Bhalla, 2011 – Case Report

**Intervention**
- 1 mg/kg MB over 5 minutes

**Results**
- ↑ MAP
- Epinephrine, Norepinephrine, and vasopressin weaned over 12 hours
- Skin discoloration
- Falsely low pulse oximeter reading

**Side Effects**
- None reported

**Key Point**
- ↑ MAP 10 minutes post MB administration
- Short infusion time

### Rutledge, 2015 – The Patient

- **22 mo old with septic shock**
- **Norepinephrine 1 mcg/kg/min**
- **Vasopressin 0.04 units/kg/min**
- **Fluids 100 mL/kg**
- **Dopamine 20 mcg/kg/min**

MB = methylene blue; POD = postoperative day
**Methylene Blue for Refractory Shock in Pediatric Patients**

**Rutledge, 2015 – Case Report**

**Intervention**
- 1 mg/kg MB
- 0.25 mg/kg/hr MB x 25 hours

**Result**
- ↑ SBP 40%
- ↑ DBP 46%
- Dopamine weaned in 6 hours; norepinephrine weaned 14 hours
- Vasopressor weaned 5 hours after MB stopped

**Side Effects**
- Skin discoloration
- Urine discoloration

**Key Point**
- Long duration of MB infusion

**Adverse Effects**
- Blue-green discoloration of urine
- Blue discoloration of skin
- Skewing of pulse oximeter reading
- Methemoglobinemia

**Conclusions about MB**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients require less vasopressors</td>
<td>Evidence is from small case reports/studies</td>
</tr>
<tr>
<td>Improves MAP</td>
<td>No established regimen</td>
</tr>
<tr>
<td>Does not change oxygen consumption or delivery</td>
<td>No consistent demonstrated difference in mortality</td>
</tr>
<tr>
<td>No toxic side effects</td>
<td></td>
</tr>
</tbody>
</table>

**MB Dosing Recommendation**

1–3 mg/kg administered over 5-60 minutes

- No additional MB
- 1–3 mg/kg repeated bolus
- 0.25–1 mg/kg/hr

4–25 hours

**Patient Population for MB**

**Consider for Patients with:**
- Vasodilatory shock
- Decreased MAP
- ≤1 Vasopressor

**Do Not Recommend for Patients with:**
- G6PD deficiency
- Cold shock

**Conclusions**

- Patients require less vasopressors
- Improves MAP
- Does not change oxygen consumption or delivery
- No toxic side effects
- Evidence is from small case reports/studies
- No established regimen
- No consistent demonstrated difference in mortality
Methylene Blue for Refractory Shock in Pediatric Patients

MB Recommendation

Monitoring

- Mean arterial pressure
- Blood gas
- Lactate
- Serum creatinine
- Hemoglobin

What would you do?

Patient Case

- 12 hours later
  - MAP 57 mmHg despite adequate fluids and vasopressors
- Current Medications:
  - Norepinephrine 1 mcg/kg/min
  - Vasopressin 0.04 units/kg/min
  - Epinephrine 0.5 mcg/kg/min
  - Hydrocortisone 2 mg/kg x1, 1 mg/kg Q8H

Current vitals:

<table>
<thead>
<tr>
<th>Temp</th>
<th>HR</th>
<th>RR</th>
<th>BP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.8</td>
<td>122</td>
<td>39</td>
<td>83/44</td>
<td>57</td>
</tr>
</tbody>
</table>

Temp °C  HR beats/min  RR breaths/min  BP mmHg  MAP mmHg

Acknowledgements

- Carolyn Ragsdale, Pharm.D., BCPS, BCPPS
- Ronda Machen, Pharm.D., RD, BCPPS
- Molly Curran, Pharm.D.

Questions

Methylene Blue for Refractory Shock in Pediatric Patients

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Appendix A – Abbreviations

BP = blood pressure
CI = cardiac index
CO = cardiac output
CrCl = creatinine clearance
CVP = Central venous pressure
DBP = diastolic blood pressure
DOL = day of life
Epi = epinephrine
HR = heart rate
MAP = mean arterial pressure
MB = methylene blue
NE = norepinephrine
NO = nitric oxide
PaO₂:FiO₂ = ratio of partial pressure arterial oxygen and fraction of inspired oxygen
POD = postoperative day
PVR = pulmonary vascular resistance
SBP = systolic blood pressure
SV = stroke volume
SVR = systemic vascular resistance
Appendix B – Mechanism of Methylene Blue in Shock

Appendix C – Results: Driscoll, 1996

Appendix D – References


