# Methylene Blue Use in Pediatrics

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## Abstract

Catecholamine-resistant shock, also known as vasoplegia, is a challenging entity with a significant risk of mortality. We seek to provide further data on the safety and effectiveness of methylene blue (MB) for vasoplegic shock in the pediatric population. We conducted a retrospective observational study of pediatric patients admitted to the pediatric intensive care unit or pediatric cardiac intensive care unit at Mount Sinai Kravis Children's Hospital from 2011 to 2021 who received MB for refractory shock. A list of patients was obtained by performing a pharmaceutical query from 2011 to 2021 for "MB." Chart review was performed to determine indication for use and to collect demographic and clinical data. There were 33 MB administrations: 18 administrations (16 unique patients) for vasoplegic shock, 11 for surgical dye, and 4 for methemoglobinemia. The median age was 5 years (interquartile range [IQR]: 0.08, 13). Ten patients required MB following congenital cardiac repair (62.5%); one administration for myocarditis, septic shock, postcardiac arrest, high output chylothorax, scoliosis repair, and one multisystem inflammatory syndrome in children. No patients experienced hemolytic anemia or serotonin syndrome following administration. The median dose of MB was 1 mg/kg. Vasoactive-inotrope score (VIS) improved in 4 out of 18 administrations at 1 hour. Mean arterial pressure (MAP) improved in 10 out of 18 administrations at 1 hour. Systolic blood pressure (SBP) improved in 8 out of 18 administrations at 1 hour. VIS, MAP, and SBP improved in 8 out of 18 administrations at 6 hours. MB may be safely considered as rescue therapy in catecholamine-resistant shock in pediatrics.

**Keywords**
- vasoplegic shock
- methylene blue
- vasoplegia
- pediatrics

## Introduction

Catecholamine-resistant shock, also known as vasoplegia, is a challenging entity with a significant risk of mortality. In pediatrics, there is a lack of evidence-based effective therapies, such as methylene blue (MB), for catecholamine-resistant shock. MB acts by inhibiting guanylate cyclase, thus inhibiting nitric oxide release.[1] In adult patients, the use of MB has been associated with improved mean arterial blood pressure (MAP)[2,3] as well as systemic vascular resistance.[2] The use of MB in pediatrics has been described in a recent systematic review with a total of only 102 patients under 25 years of age, illustrating data regarding the safety and efficacy of MB use in pediatrics is scant.[4] The aim is to observe the safety and effectiveness of MB use in pediatric patients with catecholamine-resistant shock.

## Material and Methods

We conducted a retrospective observational study of pediatric and adolescent patients admitted to the pediatric intensive care unit or pediatric cardiac intensive care unit at Mount Sinai Kravis

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Children's Hospital from 2011 to 2021 who received MB for refractory shock. Shock refractory to fluid resuscitation and vasopressor therapy is termed catecholamine-resistant shock.[5]

A list of patients was obtained by performing a pharmaceutical query from 2011 to 2021 for "MB." This population included one 34-year-old congenital heart disease patient who had been followed by pediatric cardiology. A chart review was performed to determine indication for use. Patients who received MB as surgical dye or for methemoglobinemia treatment were excluded.

Demographic data, including race, ethnicity, sex, and age, were obtained through the electronic medical record Face Sheet. Clinical data including laboratory and radiologic results were obtained and analyzed. Clinical data points included primary diagnosis, prior congenital cardiac diagnosis, MB dose, vitals pre- and postadministration, vasoactive-inotrope score (VIS) pre- and postadministration, adverse effects, intensive care unit length of stay (LOS), need for extracorporeal membrane oxygenation (ECMO) support, and mortality. VIS calculation may be visualized in ►**Fig. 1**.

This study was reviewed and approved by the Mount Sinai Institutional Review Board (HS #: STUDY- 21-01534). Demographic and clinical characteristics were summarized as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. All analyses were performed using Microsoft Excel.

$$\begin{aligned}\text{VIS} = {} & \text{Dopamine dose } (\mu g/kg/min) + \\ & \text{Dobutamine dose } (\mu g/kg/min) + \\ & 100 * \text{Epinephrine dose } (\mu g/kg/min) + \\ & 10 * \text{Milrinone dose } (\mu g/kg/min) + \\ & 10{,}000 * \text{Vasopressin dose } (U/kg/min) + \\ & 100 * \text{Norepinephrine dose } (\mu g/kg/min)\end{aligned}$$

**Fig. 1** Vasotrope inotrope score calculation.[26]

## Results

Thirty-three patient encounters of MB administration were identified. Of these, there were 18 administrations for vasoplegic shock, 11 for surgical dye, and 4 for methemoglobinemia. Of the 18 administrations for vasoplegic shock, 16 were unique patients. The median age was 5 years (interquartile range [IQR]: 0.08, 13). The median weight was 18.8 kg (IQR: 3.9–40.1). Of the 16 patients, three (18.8%) identified as African American, three (18.8%) as white, one (6.3%) as Pacific Islander, one (6.3%) as Asian Indian, one (6.3%) as West Indian, and seven (44%) as unknown/other race (►**Table 1**).

Ten patients required MB following congenital cardiac repair (62.5%), and two additional patients with congenital cardiac defects received MB outside of repair (one for shock state with high-output chylothorax and one propofol infusion syndrome following scoliosis repair). One administration was given in the setting of myocarditis, one septic shock, one refractory shock—cardiac arrest, and one multisystem inflammatory syndrome in children (MIS-C; ►**Table 1**). Overall, 75% of our cohort had a congenital heart defect. The MIS-C patient was a 6 year old who presented with fever and

**Table 1** Patient characteristics and demographics

| Patient | Age | Sex | Race | Diagnosis |
|---|---|---|---|---|
| 1 | 9 | M | Other/Unknown | Complete AV canal defect; mitral valve replacement |
| 2 | 18 | M | African American | Refractory shock |
| 3 | 2 wk | M | West Indian | HLHS |
| 4 | 11 | F | Other/Unknown | Chylothorax (AV canal defect) |
| 5 | 2 mo | F | Other/Unknown | Interrupted aortic arch |
| 6 | 34 | M | White | AV canal defect |
| 7 | 16 | F | Other/Unknown | Liver failure secondary to septic shock |
| 8 | 12 | F | Pacific Islander | Myocarditis |
| 9 | 16 | M | Other/Unknown | Tetralogy of Fallot; pulmonary valve replacement |
| 10 | 8 d | F | White | HLHS with critical aortic stenosis, aortic dissection; septic shock |
| 11 | 5 mo | F | African American | Tetralogy of Fallot, tracheal rings |
| 12 | 2 mo | M | Asian Indian | Tetralogy of Fallot with severe pulmonary stenosis |
| 13 | 5 | M | Other/Unknown | MIS-C |
| 14 | 3 wk | M | African American | Tricuspid atresia |
| 15 | 13 | F | White | Scoliosis repair |
| 16 | 9 d; 30 d | M | Other/Unknown | Total anomalous pulmonary venous return |

Abbreviations: AV, atrioventricular; F, female; HLHS, hypoplastic left heart syndrome; M, male; MIS-C, multisystem inflammatory syndrome in children.
Note: Age is listed in years unless otherwise specified.

 

**Table 2** Cardiac function before methylene blue administration

| Patient | Normal function | LV dysfunction | RV dysfunction | Methylene blue dose | Time after bypass |
|---|---|---|---|---|---|
| 1 | X | | | 1.5 mg/kg | 4 d |
| 2 | | X | X | 1 mg/kg | N/A |
| 3 | | | X | 1 mg/kg | 8 d |
| 4 | X | | | 1 mg/kg | N/A |
| 5 | | | X | 1 mg/kg | 16 d |
| 6 | X | | | 2 mg/kg | Within 24 h |
| 7 | | | X | 2 mg/kg | N/A |
| 8[a] | | | | 2 mg/kg | N/A |
| 9 | | X | | 1.5 mg/kg | Within 24 h |
| 10 | X | | | 1.5 mg/kg | Within 24 h |
| 11 | X | | | 1 mg/kg | Within 24 h |
| 12 | | X | | 1 mg/kg | 9 days |
| 13[b] | X | | | 1 mg/kg | N/A |
| 14 | | X | X | 1 mg/kg | Intraoperatively |
| 15 | X | | | 1.37 mg/kg | N/A |
| 16[c] | X | | | 1 mg/kg | 8 d, 23 d |

Abbreviations: LV, left ventricular; N/A, not applicable; RV, right ventricular.
[a]Echocardiogram results not available.
[b]Received second dose 12 hours after initial administration.
[c]Received doses at separate intervals 3 weeks apart.

abdominal pain and was admitted to the ICU for hypotension. He required three vasoactive medications and received inotropic support for 4 days, with a total hospital stay of 8 days.

The median dose of MB was 1 mg/kg (range 1–2 mg/kg), and two patients required a second dose (one within 24 hours and one 3 weeks later). Fifteen patients had an echocardiogram done before administration (►**Table 2**). Eight of fifteen patients (53%) had documented normal function prior to administration, while seven (47%) had decreased function. Of the patients who underwent cardiac bypass, four out of ten administrations were within 24 hours following bypass.

No patients experienced hemolytic anemia or serotonin syndrome following MB administration. Three patients experienced increased bilirubin, but they were concurrently being treated for liver failure, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), or shock. Six (37.5%) patients did not survive to hospital discharge. Seven (43.8%) patients required ECMO during their hospital stays, with two patients receiving MB before ECMO cannulation. The average ICU LOS was 66.5 days (IQR 8.0, 80.8; ►**Table 3**).

Four administrations of 18 resulted in a decrease in VIS at 1 hour, while eight had no change, and two patients were deceased within 1 hour. Eight administrations resulted in a decrease in VIS at 6 hours (►**Table 4**). Ten of eighteen administrations resulted in an MAP increase at 1 hour, and eight increased at 6 hours with median MAP change of 11 (IQR: 5.5–20.5) and 3.5 (IQR: 2.75–13.75) at 1 and 6 hours, respectively. Of those with increased MAP, the median MAP increase at 1 hour was 17.5 mm Hg (IQR 11.75–21.75) and 13.5 mm Hg at 6 hours (IQR: 6.75–21.25). Five patients out of fourteen who survived had a decrease in MAP at 1 hour postadministration. Of these, one patient had an increase in VIS score at 1 hour, with the remaining having unchanged VIS score at 1 hour. Four of these five patients were postoperative cardiac patients, and one was a patient with MIS-C. At 6 hours, 6 out of 14 had a decrease in MAP with 3 patients having a corresponding increased VIS score. Eleven out of sixteen patients were postoperative cardiac patients, one was myocarditis and one was MIS-C. The remaining three patients were noncardiac: two with septic shock and one scoliosis repair with likely propofol infusion syndrome.

Gaies et al (2014) reported that a maximum vasoactive-inotropic score more than or equal to 20 predicts an increased likelihood of a poor composite clinical outcome.[6] Of the 11 postoperative cardiac patients, seven had an initial VIS score $\geq$ 20, three less than 20, and one not available prior to MB administration. Of our cohort, we had 10 cardiac patients who survived to 6 hours after administration. Of this cohort, of those with VIS $\geq$20, we found a trend toward an increase in MAP with four of six increasing (66.7%), while the cohort with VIS $<$20, had equivocal results.

Eight patients experienced an increase in systolic blood pressure (SBP) at both 1 and 6 hours. The median SBP change was 5 mm Hg at 1 hour (IQR: 8– 24.5) and 10.5 mm Hg at 6 hours (IQR: 5–19.5). Of those with increased SBP, the median SBP increase was 24 mm Hg (IQR: 11.75–37) and 16.5 mm Hg (IQR: 12.25–26.5) at 1 and 6 hours, respectively.

 

**Table 3** Complications of methylene blue administration and associated mortality

| Patient | Complications: Hyperbilirubinemia | Complications: Hemolytic anemia | Complications: Serotonin Syndrome | ICU LOS (days) | Need for ECMO | Mortality (Y/N) |
|---|---|---|---|---|---|---|
| 1 | Y[a] | N | N | 53 | N | N |
| 2 | N | N | N | 4 | Y | N |
| 3 | N | N | N | 30 | Y | Y |
| 4 | N | N | N | 72 | N | N |
| 5 | N | N | N | 166 | N | N |
| 6 | N | N | N | 30 | N | N |
| 7 | N | N | N | 4 | N | Y |
| 8 | Y[b] | N | N | 26 | Y[c] | N |
| 9 | N | N | N | 20 | N | N |
| 10 | Y[d] | N | N | 9 | Y[e] | Y |
| 11 | N | N | N | 193 | N | N |
| 12 | N | N | N | 317 | Y[c] | Y |
| 13 | N | N | N | 4 | N | N |
| 14 | N | N | N | 24 | Y[e] | Y |
| 15 | N | N | N | 5 | N | N |
| 16[f] | N | N | N | 107 | Y[c] | Y |

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay.
[a]Bilirubin increased from 2.7 to 3.31 mg/dL in setting of shock.
[b]Hyperbilirubinemia in setting of septic shock and liver failure.
[c]History of ECMO, received MB after decannulation.
[d]Hyperbilirubinemia in setting of systemic inflammatory response syndrome and acute respiratory distress syndrome.
[e]Patient received methylene blue following ECMO cannulation.
[f]Received doses at separate intervals 3 weeks apart.

**Table 4** Vasoactive-inotrope score (VIS) before and after methylene blue administration

| Patient | VIS pre administration | VIS 1 h postadministration | VIS% change at 1 h | VIS 6 h postadministration | VIS% change at 6 h |
|---|---|---|---|---|---|
| 1 | 29.7 | 29.7 | 0 | 37.9 | +27.6 |
| 2 | 53 | 62 | +17.0 | 59 | +11.3 |
| 3 | 9.5 | 7 | −26.3 | 3 | −68.4 |
| 4 | 26 | 26 | 0 | 26 | 0 |
| 5 | 12 | 12 | 0 | 5 | −58.3 |
| 6 | 28.3 | 27 | −4.6 | 26 | −8.1 |
| 7 | 33 | Deceased | N/A | Deceased | N/A |
| 8 | 38.3 | 38.3 | 0 | 38.3 | 0 |
| 9 | 31.3 | 11.6 | −62.9 | 21.6 | −31.0 |
| 10 | 40 | 40 | 0 | 40 | 0 |
| 11 | 23 | 25 | +8.7 | 21 | −8.7 |
| 12 | 20 | 18 | −10.0 | 8 | −60 |
| 13 (first admin) | 5 | 5 | 0 | 9 | +80.0 |
| 13 (second admin) | 10 | 10 | 0 | 13 | +30.0 |
| 14 | X[a] | 10 | N/A | Deceased | |
| 15 | 5 | 7 | +40.0 | 3 | −40.0 |
| 16 (first admin) | 8 | 8 | 0 | 4 | −50.0 |
| 16 (second admin) | 25 | 26 | +4.0 | 37 | +48.0 |

Abbreviations: admin, administration; N/A, not applicable.
[a]X = Value not available.

 

**Table 5** Mean arterial pressure (MAP) pre- and postmethylene blue administration

| Patient | MAP preadministration | MAP 1 hpostadministration | MAP % change at 1 h | MAP 6 h postadministration | MAP % change at 6 h |
|---|---|---|---|---|---|
| 1 | 54 | 45 | −16.7 | 50 | −7.4 |
| 2 | 50 | 120 | +140.0 | 97 | +94.0 |
| 3 | 47 | 48 | +2.1 | 45 | −4.2 |
| 4 | 108 | 96 | −11.1 | 81 | −25.0 |
| 5 | 37 | 48 | +29.7 | 71 | +91.9 |
| 6 | 69 | 89 | +29.0 | 82 | +18.8 |
| 7 | 61 | Deceased | N/A | Deceased | N/A |
| 8 | X[a] | X[a] | N/A | X[a] | N/A |
| 9 | 44 | 65 | +47.7 | 61 | +38.6 |
| 10 | 33 | 96 | +190.9 | 40 | +21.2 |
| 11 | 52 | 50 | −3.8 | 66 | +26.9 |
| 12 | 50 | 65 | +30.0 | 56 | +12.0 |
| 13 (first admin) | 90 | 79 | −12.2 | 56 | −37.8 |
| 13 (second admin) | 57 | 79 | +38.6 | 55 | −3.5 |
| 14 | X[a] | 47 | N/A | Deceased | N/A |
| 15 | 81 | 95 | +17.2 | 82 | +1.2 |
| 16 (second admin) | 41 | 32 | −22.0 | 38 | −7.3 |
| 16 (second admin) | 53 | 57 | +7.6 | X[a] | N/A |

Abbreviations: admin, administration; N/A, not applicable.
[a]X = Value not available.

After 1 hour, six patients had a decrease in the heart rate (33.3%), and after 6 hours, 10 patients had a decrease in the heart rate (55.6%).

When stratifying by infant <1 year of age and children >1 year of age, the infants had a median MAP change of +4 mm Hg (IQR: 0.5–13) at 1 hour and +6.5 mm Hg (IQR: 0–12.25) at 6 hours. Those above 1 year had a median MAP change of +17 mm Hg (IQR: 9.5–21.25) at 6 hour, and a median change in MAP of –0.5 mm Hg (IQR: 9.75–1) at 6 hours (►**Table 5**).

Of those with decreased function on echocardiogram prior to administration, five of five had an increase in MAP at 1 hour, with a median change of 15 mm Hg (IQR: 11–21). Four of five had an increase in MAP at 6 hours, with a median change of + 17 mm Hg (IQR: 6–34). Of those with normal function, five out of eight and four out of eight had increased MAP at 1 and 6 hours, respectively. The median change in MAP in those with preserved function on echocardiogram was 1 mm Hg (IQR: 9–18.5) at 1 hour and –2 mm Hg at 6 hours (IQR: 4–7).

## Discussion

MB has been reported for the management of catecholamine-resistant shock in adults. Studies regarding its use for this indication in pediatrics are lacking with only case reports and small case series published in the literature. It is crucial to further explore its use to understand its efficacy, safety, and utility in pediatrics.

We describe a cohort which includes 16 pediatric patients, including four neonates, in the United States with refractory shock who received MB without any major side effects or complications. MB has been used in children with vasoplegia following cardiopulmonary bypass,[7–9] and Mehaffey et al have reported the use of MB in adult patients with vasoplegia after cardiopulmonary bypass with decreased operative mortality with early use.[10] In our cohort, 12 patients had a prior history of congenital cardiac disease (75%), 11 received MB following cardiotomy (69%), and 4 received it within 24 hours postoperatively (22%). The 12th patient was admitted for postoperative management following scoliosis repair and had an incidental history of Tetralogy of Fallot. MB has also been used in septic shock in a couple of pediatric patients in Chile and the United States.[9,11] In our cohort, two patients received MB for septic shock. Retrospective studies in the adult population have reported mixed results on efficacy.[10,12,13]

In our cohort, the VIS score improved in 4 out of 18 administrations at 1 hour and 8 out of 18 administrations at 6 hours. Abdelazim et al reported a similar decrease in norepinephrine infusion need for children who received MB for vasoplegia following cardiopulmonary bypass although the time of measurement after administration was not specified.[8]

After 6 hours, 10 patients had a decrease in the heart rate (55.6%), similar to Hassan et al, who reported a significant decrease in the heart rate after MB infusion. Eight patients

 

experienced an increase in SBP at both 1 and 6 hours. To our knowledge, no other pediatric MB studies with multiple patients have reported effects on SBP.

Of those who experienced an increase in MAP, the median MAP increase was 17.5 mm Hg at 1 hour (IQR: 11.75–21.75) and 13.5 mm Hg at 6 hours (IQR: 6.75–21.25). Hassan et al have reported similar results with a mean increase of 16 mm Hg in MAP at 1-hour post-administration in children with vasoplegia following bypass.[7] While 5 out of 16 had a decrease in MAP after 1 hour and 6 out of 16 at 6 hours, two had improved VIS at 6 hours.

When Scheffer et al restricted subjects to less than 1 year, however, a larger increase in MAP was suggested, although without statistical significance.[9] Our cohort of patients had a larger increase in MAP 1 hour postadministration for patients who were older than 1 year of age but had a decrease in median MAP at 6 hours. Infants, on the contrary, had an increase in MAP with a median increase of 6.5 mm Hg. Driscoll et al had similar results with an increase in average blood pressure 5 hours following MB administration when used in refractory neonatal hypotension in septic shock.[14]

The overall mortality of our cohort was 6 out of 16 (37.5%). Of the eight patients with an improved VIS score at 6 hours, the mortality rate was 3 out of 8 (37.5%). Of the eight patients with an improved MAP at 6 hours, the mortality rate was 2 out of 8 (25%). There were six patients who had both an improved MAP and VIS score at 6 hours, of whom five survived to discharge (83.3%). Conclusions regarding the effect of MB on mortality are limited given the small sample size.

As MB is not routinely used in pediatrics, dosing has not been standardized. The five pediatric studies that have described MB dosing report ranges from 1 to 2 mg/kg/dose.[7,8,11,13,14] In the adult population, the literature has shown a range of 0.5 to 4 mg/kg/dose with continuous dosing of 0.25 to 2 mg/kg/h.[15–17] Our cohort of patients received bolus dosing with a range of 1 to 2 mg/kg/dose and median of 1 mg/kg/dose. No patients in our cohort received a continuous infusion of MB.

Commonly reported side effects of MB use include hyperbilirubinemia,[18] serotonin syndrome,[19] bluish discoloration of the skin and urine,[16,20,21] and hemolytic anemia in neonates.[22,23] Additionally, there is a risk of hemolysis and paradoxical methemoglobinemia in those with glucose-6-phosphate dehydrogenase deficiency.[24] A case report described an ex-35-week patient exposed to MB in utero for amniocentesis who subsequently developed hyperbilirubinemia requiring phototherapy and double-volume exchange transfusion.[18] In case reports of neonates with hemolytic anemia following MB, a need for multiple blood transfusions has been noted, with Howell–Jolly bodies found on peripheral smear.[22,23] No patients in our cohort experienced serotonin syndrome, and no neonates suffered from hemolytic anemia. However, it is difficult to comment on serotonin syndrome in our cohort. Out of the 18 administrations in our cohort, patients were pharmaceutically paralyzed in 10 of these administrations. In those who were paralyzed, there was no hyperthermia or diaphoresis. There was no inducible clonus or hypertonia, but this is difficult to assess in the setting of neuromuscular blockade. Only three patients had elevated bilirubin levels, all in the setting of liver failure, sepsis, and SIRS. Our experience demonstrates the use of MB without any major adverse effects in critically ill pediatric patients, adding to the safety profile of this rescue therapy. Both septic shock patients in our study, however, did not survive to discharge, prohibiting conclusions regarding the safety or efficacy of MB in septic shock.

Vasoplegia after cardiopulmonary bypass has 30 to 50% mortality,[25] while refractory septic shock in children has greater than 50% mortality.[5] Similarly, in our cohort of high-acuity patients, seven patients (46.7%) required ECMO support during their hospital stay. Of these, six did not survive to hospital discharge (85.7%). Two patients received MB before cannulation; two patients received it following cannulation, and three required MB following decannulation. Patient 16 received MB while cannulated on ECMO, and then several weeks later once decannulated for a separate episode of decompensation with hypotension. Insufficient data are available to determine whether MB affected the level of ECMO support.

Given our study's small sample size, heterogeneous population, and retrospective study design, it is difficult to draw strong conclusions regarding the effectiveness of MB. Nevertheless, this experience adds to the growing literature illustrating that MB could be safely considered as rescue therapy in critically ill pediatric patients without major side effects. Further prospective studies are needed to further elucidate the indications, optimal dosing, and efficacy of MB, and effect on ECMO use.

## Conclusion

MB could be safely considered as a rescue therapy in catecholamine-resistant shock in pediatrics.

### Conflict of Interest

None declared.

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