

Methylene Blue Administration for Distributive Shock States in Critically Ill Children

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ABSTRACT **Background:** Methylene blue (MB), an inhibitor of nitric oxide synthesis and its effects, is a potentially effective treatment against distributive shock states such as septic shock and vasoplegic syndrome. MB has been shown to alleviate vasoplegia and promote an increase in blood pressure, and it may reduce mortality. However, in the pediatric population, there are few case reports and only one controlled study on administration of MB use for vasoplegia, sepsis, or shock in general. **Objectives:** To summarize the experience of administering MB for vasoplegic shock in a tertiary care pediatric intensive care unit.

Methods: A retrospective chart review of seven pediatric cases treated with MB for vasoplegic shock was conducted. MB was administered as a bolus followed by continuous infusion. The authors measured blood pressure, vasopressor, and inotropic support. Patient outcome was monitored.

Results: The authors observed a favorable hemodynamic response with an increase in blood pressure and a reduction in vasopressor and inotropic support needed following MB administration in six patients. No side effects were observed. Three patients eventually died one to two days later, secondary to their underlying disease.

Conclusions: This case series adds to the small body of evidence in the pediatric population supporting the use of MB for distributive shock states and emphasizes the need for larger, randomized trials evaluating its role in vasoplegic shock treatment.

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KEY WORDS: methylene blue, shock, sepsis, septic shock, vasoplegia

nylate cyclase (sGC) [3]. Consequently, MB causes a decrease in vasodilatation and improved response to vasoconstrictors. In addition, MB is thought to counteract myocardial depression [3].

Vasoplegic syndrome is a common complication of CPB, which can lead to significant mortality and morbidity. Treatment with MB has been shown to alleviate vasoplegia, cause an increase in mean arterial pressure (MAP), and even reduce mortality [1,2,4]. The use of MB in adults with septic shock has been evaluated in two small randomized controlled trials [5,6] and in several case series and reports. One study has evaluated the addition of MB to norepinephrine in post CPB vasoplegia and found a favorable effect [7]. The cumulative evidence alludes to a significant improvement in MAP and a decrease in vasopressor use, although no clear survival benefit has been shown thus far. Importantly, in the pediatric population, there are only a few reports on administration of MB in sepsis or shock in general [7-12].

In this article, we present a collection of seven pediatric cases treated in our center with MB for vasoplegic shock during a 14-month period (April 2016–August 2017). The decision to administer MB was based on clinical features of vasoplegia (low blood pressure, low systemic vascular resistance) and lack of response to at least two vasopressor drugs and corticosteroids. The final decision was left to the discretion of the treating physician. All of our patients were treated identically with a protocol that included a loading dose of 1 mg/kg over 10 minutes and then a continuous infusion at a rate of 0.25 mg/kg/hour. This study was approved by the local ethics committee, which granted a waiver of informed consent due to the retrospective nature of the research.

PATIENTS AND METHODS

We conducted a retrospective chart review of seven pediatric cases treated with MB for vasoplegic shock. Patients ranged from newborn to 4.5 years of age. MB was administered as a bolus followed by continuous infusion. We measured blood pressure, pulse rate,

Previous reports have shown methylene blue (MB) to be effective in distributive shock states such as septic shock and vasoplegic syndrome during or after cardiopulmonary bypass (CPB) [1-3]. The effects of MB on the vascular bed are probably mediated through direct inhibition of the inducible nitric oxide synthetase and through the inhibition of enzyme soluble gua-

vasopressor, and inotropic support. Vasopressor support was later translated into vasopressor load units [13]. One vasopressor load unit ($\mu\text{g}/\text{kg}/\text{min}$) equals noradrenalin ($\text{mcg}/\text{kg}/\text{min}$) + dopamine ($\text{mcg}/\text{kg}/\text{min}$)/100 + adrenalin ($\text{mcg}/\text{kg}/\text{min}$) + vasopressin ($\text{U}/\text{kg}/\text{hour}$) \times 0.17. Hemodynamic data was compared between 2 hours prior to MB administration to 6 hours after the loading dose. Time to weaning of vasopressor support and MB treatment was recorded as was patient outcome.

PATIENT 1

A 4.5-year-old patient undergoing chronic hemodialysis treatment with chronic severe hypertension and hypertrophic cardiomyopathy underwent cadaveric kidney transplant and on arrival to the pediatric intensive care unit (PICU) developed a distributive shock state. Blood cultures were negative and the presumptive cause was vasoplegic reaction to anti-thymocyte globulin treatment. He was treated with rising doses of norepinephrine (0.4 $\text{mcg}/\text{kg}/\text{min}$), dopamine (10 $\text{mcg}/\text{kg}/\text{min}$), hydrocortisone, and empiric broad antibiotic coverage but remained hypotensive. An hour after the addition of MB the mean arterial pressure (MAP) rose by 25 mmHg and 3 hours later he was almost weaned from norepinephrine support. Due to the rapid response to MB the patient received a continuous infusion of MB for only one hour.

PATIENT 2

A 14-month-old toddler with intestinal failure due to microvillus inclusion disease presented with recurrent events of septic shock, acute renal failure, acute respiratory distress syndrome, and secondary hemophagocytic lymphohistiocytosis (HLH). Following a relapse of HLH the patient developed vasoplegic shock, which was non-responsive to vasopressor treatment. Although treated with epinephrine (0.15 $\text{mcg}/\text{kg}/\text{min}$), norepinephrine (0.3 $\text{mcg}/\text{kg}/\text{min}$), and vasopressin (0.04 $\text{U}/\text{kg}/\text{hour}$) he remained hypotensive. Following initiation of MB, the MAP rose significantly (by 30 mmHg) with a subsequent decrease in vasopressor support to a minimum 5 hours after initiation of MB treatment. MB infusion was continued for a total of 21 hours. Unfortunately, the patient died 3 days later.

PATIENT 3

A 2-month-old infant presented with severe Hirschsprung's enterocolitis, secondary septic shock, abdominal compartment syndrome, and multiorgan failure (MOF) despite treatment with epinephrine (0.3 $\text{mcg}/\text{kg}/\text{min}$), norepinephrine (0.27 $\text{mcg}/\text{kg}/\text{min}$), and vasopressin (0.04 $\text{U}/\text{kg}/\text{hour}$). After initiation of MB her MAP remained stable while on approximately 50% less vasopressor support. MB infusion was stopped after 35 hours.

PATIENT 4

A newborn presented immediately after birth with respiratory insufficiency due to meconium aspiration syndrome and vasoplegic shock secondary to *Escherichia coli* bacteremia. He was unresponsive to increasing vasopressor support with epineph-

rine (0.15 $\text{mcg}/\text{kg}/\text{min}$), norepinephrine (0.18 $\text{mcg}/\text{kg}/\text{min}$), vasopressin (0.04 $\text{U}/\text{kg}/\text{hour}$), and venoarterial extracorporeal membrane oxygenation (VA-ECMO) support. Following initiation of MB therapy, the MAP rose by 10 mmHg on a slightly lesser vasopressor support with a gradual general improvement. MB infusion was stopped eventually after 14 hours.

PATIENT 5

A 3.5-year-old patient, generally healthy, presented to the PICU with septic shock and MOF due to group A streptococcus toxic shock syndrome. One day later the hypotension worsened with clinical signs of vasoplegia despite aggressive treatment with dopamine (31.5 $\text{mcg}/\text{kg}/\text{min}$), epinephrine (0.3 $\text{mcg}/\text{kg}/\text{min}$), norepinephrine (0.3 $\text{mcg}/\text{kg}/\text{min}$), and vasopressin/ (0.02 $\text{U}/\text{kg}/\text{hour}$). MB treatment was initiated. Three hours after initiation of MB the MAP rose by 35 mmHg and he was weaned almost entirely from vasopressor support one day later. MB infusion was stopped after 48 hours.

PATIENT 6

A 1-month-old neonate who underwent supraglottoplasty and was hospitalized with septic shock and MOF due to *Pseudomonas aeruginosa* and *Escherichia coli* bacteremia. He was treated with VA-ECMO and continuous hemodialysis. MB was added to the vasopressor treatment due to severe lactic acidosis and hypotension unresponsive to full ECMO flows (>150 $\text{cc}/\text{kg}/\text{min}$) and extensive vasopressor support with epinephrine (0.1 $\text{mcg}/\text{kg}/\text{min}$), norepinephrine (0.15 $\text{mcg}/\text{kg}/\text{min}$), and vasopressin (0.03 $\text{U}/\text{kg}/\text{hour}$). Even though MB addition resulted in a rise in MAP (of 40 mmHg) and reduction of vasopressor support within three hours [Figure 1], the patient eventually died 2 days later. Total MB infusion time was 18 hours.

PATIENT 7

An 18-day-old neonate with epidermolysis bullosa was transferred to our PICU due to septic shock with methicillin resistant *Staphylococcus aureus* bacteremia. Shortly after his arrival to the PICU he required the support of norepinephrine (0.23 $\text{mcg}/\text{kg}/\text{min}$), dopamine (10 $\text{mcg}/\text{kg}/\text{min}$), epinephrine (0.42 $\text{mcg}/\text{kg}/\text{min}$), and vasopressin (0.05 $\text{U}/\text{kg}/\text{hour}$). He continued to exhibit signs of multiorgan dysfunction and hypotension. MB was started as a rescue therapy due to clinical signs of vasoplegia with a short-term rise in MAP allowing for a decrease in the doses of dopamine and epinephrine. Within one hour after this improvement, his oxygen saturation level and the MAP decreased. MB was stopped on the grounds of suspected elevation in pulmonary hypertension and inspired nitrous oxide was added. The distributive shock and hypoxemia continued to worsen without response to further therapeutic interventions and the patient eventually died a few hours later.

Table 1 summarizes the main patient characteristics of these patients. Figure 1 presents each patient's MAP and vasopressor

support before and after MB administration.

RESULTS

We observed distinct hemodynamic improvement after MB administration manifested both by an increased MAP and by a decrease in vasopressor and inotropic requirements. Five of the seven cases were patients with fluid-resistant catecholamine non-responsive septic shock and the remaining patients presented with vasoplegia, most probably due to systemic inflammatory responses (to HLH and anti-thymocyte globulin). Six of our seven cases responded rapidly with significant elevation of the MAP and weaning from vasopressor support. Three patients eventually died within several days of the primary process. The remaining four patients were discharged without further reported mortality. The initial effect of MB was seen within the first hour (after the loading dose) and continued to increase even after several hours. One patient did not show a response to MB. One patient experienced acute hypoxemia suspected to have resulted from a pulmonary hypertension worsening. However, even after cessation of MB and initiation of inotropic support we saw no improvement. No other side effects were observed.

DISCUSSION

We present a series of seven pediatric cases treated with MB for distributive shock states. Six out of seven patients demonstrate

a favorable hemodynamic response with an increase in blood pressure and a reduction in vasopressor and inotropic support following MB administration. Of note, the patients described were extremely sick and MB treatment was initiated as a last resort. Furthermore, two of these patients died several days after MB treatment while on minimal vasopressor support and not while on MB treatment.

All of our patients started MB treatment while on corticosteroid treatment. Prior case reports in the pediatric population have done the same, in line with the current sepsis guidelines treatment protocol [15]. However, two randomized controlled trials in adults excluded patients concurrently on corticosteroids, possibly due to the inhibitory effect of corticosteroids on cytokine release agonistic to the presumed MB mechanism of action [5,6]. The decision to stop MB treatment was based on cessation of vasoplegia signs, a significant decrease in vasopressor need, and were left to the treating physician's discretion.

Prior described cases in the literature include one case series of five neonates treated with a single dose of MB for vasoplegic shock due to sepsis with a subsequent rise in MAP and survival of three [8]. Three additional case reports [9,10,12], described the use of MB for vasoplegia post-CPB with a favorable hemodynamic response. To the best of our knowledge, the only randomized controlled trial in children was conducted in 40 post-CPB patients presenting with vasoplegia. This study compared the addition of MB to norepinephrine to norepinephrine alone.

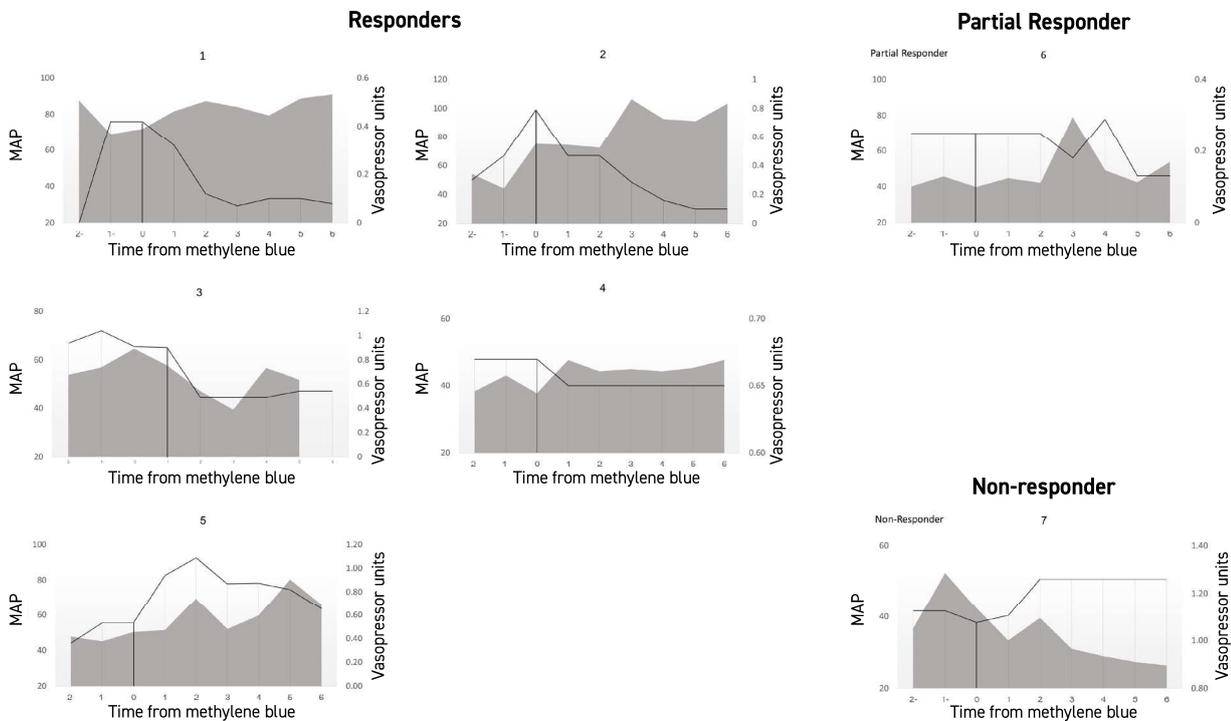
Table 1. Summary of patient characteristics

Patient #	Age	Primary diagnoses	Cause of shock	Pre MB support						MB duration	Hemodynamic effect				Side effects	Mortality (time)
				Peak dose of vasopressor				Steroids	ECMO		Vasopressor load		MAP			
				NA	A	Vaso	DA				Start	+3h	Start	+3h		
1	4.5 years	Post kidney transplant	ATG, vasoplegia	0.4			10	+		1	0.42	0.07	69	84		
2	14 months	MVID, HLH	HLH	0.15	0.3	0.04		+		21	0.47	0.29	44	106		+ (2d)
3	2 months	Hirschprung's	Toxic megacolon sepsis	0.27	0.3	0.04		+		35	1.04	0.49	54	47		
4	2 days	HLH	HLH	0.18	0.15	0.04		+	+	14	0.67	0.65	43	45		
5	3.5 years	Septic shock	Sepsis	0.3	0.3	0.04	31.5	+		48	0.53	0.87	45	52		
6	1 month	Septic shock	Sepsis	0.15	0.1	0.03		+	+	18	0.25	0.18	46	79		+ (2d)
7	18 days	Epidermolysis bullosa, sepsis	Sepsis	0.23	0.42	0.05	10	+		1	1.13	1.26	52	31	PHTN?	+ (1d)

Doses of adrenaline, noradrenaline, and dopamine are written in mcg/kg/min. Doses of vasopressin are written in u/kg/min

A = adrenaline, ATG = anti-thymocyte globulin, DA = dopamine, ECMO = extracorporeal membrane oxygenation, HLH = hemophagocytic lymphohistiocytosis, MAP = mean arterial pressure, MVID = microvillus inclusion disease, MB = methylene blue, NA = noradrenaline, PHTN = pulmonary hypertension, Vaso = vasopressin

Figure 1. Mean arterial pressure and vasopressor support



MAP is presented on a scale starting at 20 mmHg for ease of presentation and represented by the gray area. Vasopressor support is represented by the black line using vasopressor load units [13]. One vasopressor load unit ($\mu\text{g}/\text{kg}/\text{min}$) equals noradrenalin ($\text{mcg}/\text{kg}/\text{min}$) + dopamine ($\text{mcg}/\text{kg}/\text{min}$)/100 + adrenalin ($\text{mcg}/\text{kg}/\text{min}$) + vasopressin ($\text{U}/\text{kg}/\text{hour}$) \times 0.17. The dashed line represents the 5th percentile of MAP normal for age in pediatric intensive care patients [14]. The Y axis crosses at time of methylene blue administration

MAP = mean arterial pressure, VL = vasopressor load

The study showed reduced norepinephrine usage with the addition of MB and no side effects were recorded [7].

In our report of case series, it seems that the effect of MB starts with the first loading dose but continues to increase even after 5 hours from administration. One patient responded rapidly after the loading dose and the continuous infusion was stopped after 2 hours. This result raises the question whether a continuous infusion can provide a better effect than a single dose. Prior reports have used either discrete loading doses of MB [8,10,11] or continuous infusion [9,12].

With regard to MB side effects, we did not see any clinical signs of serotonin syndrome in our series. Prior to MB initiation we inquired regarding G6PD deficiency and subsequently monitored hemoglobin levels and laboratory signs of hemolysis. Our treatment protocol included a relatively low loading dose and a subsequent continuous infusion. Evidence from prior studies suggested that the use of lower initial doses and continuous infusion might decrease side effects, including the effect on pulmonary hypertension. In our patient population methemoglobin levels and arterial blood gas calculated oxygen

saturation did not alter significantly. In one case, 2 hours after MB initiation and a short term improvement in MAP, the patient's blood pressure dropped again alongside a worsening in oxygenation. The treatment was stopped on the basis of a suspected diagnosis of pulmonary hypertension, but no improvement was seen after the cessation of MB and even after inspired nitrous oxide was started.

LIMITATIONS

There are several limitations to this case series. First, our case series retrospectively described the experience of a single center. We cannot fully eliminate the effects of further simultaneous treatments given around the time of MB initiation. Finally, the small number of patients and the retrospective nature of this report precludes a true estimation of MB effect on mortality in this context or statistical testing of the significance of the effect

CONCLUSIONS

We present a case series of seven patients treated with MB for

vasoplegic shock with a favorable hemodynamic response in the majority of the patients as measured by an increase in blood pressure and a reduction in the vasopressor/inotropic support. Our results add to the small body of evidence in the pediatric population supporting the use of MB in vasoplegic shock states. We believe that further controlled, prospective studies are needed to evaluate the efficacy of similar treatments and to identify the patients who may benefit from MB treatment.

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Capsule

Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I

Immune evasion is a major obstacle for cancer treatment. Common mechanisms of evasion include impaired antigen presentation caused by mutations or loss of heterozygosity of the major histocompatibility complex class I (MHC-I), which has been implicated in resistance to immune checkpoint blockade (ICB) therapy. However, in pancreatic ductal adenocarcinoma (PDAC), which is resistant to most therapies including ICB, mutations that cause loss of MHC-I are rarely found despite the frequent downregulation of MHC-I expression. Yamamoto et al. showed that, in PDAC, MHC-I molecules are selectively targeted for lysosomal degradation by an autophagy-dependent mechanism that involves the autophagy cargo receptor NBR1. PDAC cells display reduced expression of MHC-I at the cell surface and instead demonstrate predominant localization within autophagosomes and lysosomes. Notably, inhibition of autophagy restores

surface levels of MHC-I and leads to improved antigen presentation, enhanced anti-tumor T cell responses and reduced tumor growth in syngeneic host mice. Accordingly, the anti-tumor effects of autophagy inhibition are reversed by depleting CD8+ T cells or reducing surface expression of MHC-I. Inhibition of autophagy, either genetically or pharmacologically with chloroquine, synergizes with dual ICB therapy (anti-PD1 and anti-CTLA4 antibodies), and leads to an enhanced anti-tumor immune response. These findings demonstrate a role for enhanced autophagy or lysosome function in immune evasion by selective targeting of MHC-I molecules for degradation, and provide a rationale for the combination of autophagy inhibition and dual ICB therapy as a therapeutic strategy against PDAC.

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Eitan Israeli

If we all did the things we are capable of doing, we would literally astound ourselves.

Thomas Alva Edison (1847-1931), American inventor and businessman; developed many devices in fields such as electric power generation, mass communication, sound recording, and motion pictures