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# Methylene Blue for Postcardiopulmonary Bypass Vasoplegic Syndrome: A Cohort Study

## Abstract

**Background:** Methylene blue (MB) has been used to treat refractory hypotension in a variety of settings. **Aims:** We sought to determine whether MB improved blood pressure in postcardiopulmonary bypass (CPB) vasoplegic syndrome (VS) in a complex cardiac surgery population. Furthermore, to determine variables that predicted response to MB. **Setting and Design:** This was conducted in a tertiary care medical center; this study was a retrospective cohort study. **Materials and Methods:** Adult cardiac surgery patients who received MB for post-CPB VS over a 2-year period were studied. Mean arterial blood pressure (MAP) and vasopressor doses were compared before and after MB, and logistic regression was used to model which variables predicted response. **Results:** Eighty-eight patients received MB for post-CPB VS during the study period. MB administration was associated with an 8 mmHg increase in MAP ( $P = 0.004$ ), and peak response occurred at 2 h. Variables that were associated with a positive drug response were deep hypothermic circulatory arrest during surgery and higher MAP at the time of drug administration ( $P = 0.006$  and  $0.02$ ). A positive response had no correlation with in-hospital mortality ( $P = 0.09$ ). **Conclusions:** MB modestly increases MAP in cardiac surgery patients with VS. Higher MAP at the time of drug administration and surgery with deep hypothermic circulatory arrest predict a greater drug response.

**Keywords:** Cardiac surgery, methylene blue, vasoplegia

## Introduction

Vasoplegic syndrome (VS) occurs in approximately 5%–25% of patients who have cardiac surgery with cardiopulmonary bypass (CPB).<sup>[1]</sup> This syndrome is characterized by refractory arterial hypotension and low systemic vascular resistance. The pathophysiology of VS remains unclear, but contributing factors include initiation of the contact activation pathway and activation of the complement system.<sup>[2]</sup> In a cohort of over 2000 cardiac surgery patients, risk factors for VS included increased euroSCORE, procedure type, pre-CPB mean arterial blood pressure (MAP), CPB time, and the use of either beta blockers or angiotensin-converting enzyme (ACE) inhibitors before surgery.<sup>[3]</sup>

Methylene blue (MB) inhibits guanylate cyclase and can increase vascular smooth muscle tone.<sup>[4]</sup> It has been used off-label to treat refractory hypotension in a variety of settings including septic shock and post-CPB VS. To date, there are limited

clinical trials to support its use in cardiac surgery patients with VS. In one randomized nonplacebo-controlled trial that included 100 coronary artery bypass graft patients, MB was given to patients at high risk for VS and it reduced the rate of VS from 26% to 0%.<sup>[5]</sup> In a second randomized controlled trial that included 56 cardiac surgery patients with VS, MB administration decreased mortality by 7.1% compared to placebo.<sup>[6]</sup> A recent meta-analysis of randomized controlled trials concluded that MB effectively raises blood pressure in patients with VS.<sup>[7]</sup> However, it remains unclear which patients are most likely to benefit from MB and when the optimal window for administration might be.<sup>[8]</sup>

The purpose of our study was to review the use of MB in cardiac surgery patients with post-CPB VS at a single institution with a contemporary complex cardiac surgery population. We hypothesized that MB administration would be associated with a decrease in vasopressors and that patients who responded to MB might have decreased mortality compared to those who did not.

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## Materials and Methods

### Subjects

The Institutional Review Board at Emory University approved the study. All adult cardiac surgery patients who received MB after CPB between August 2010 and June 2012 were identified using pharmacy charge records and were included in the study. MB data were matched with data from the Institution's Society of Thoracic Surgeons database, which contains detailed perioperative data on all patients having cardiac surgery to obtain complete perioperative data for all patients.

### Vasoplegic syndrome

Patients were considered as having post-CPB VS if they had vasopressor doses that exceeded either of the following thresholds: norepinephrine dose >10 µg/min or vasopressin dose >0.04 units/min and persistent low systemic vascular resistance (<800 dynes/s/cm<sup>2</sup>) with a normal cardiac index. MB doses were between 1 mg/kg and 2 mg/kg for all patients, and the drug was given as bolus over approximately 10 min. Patients were considered to have a positive response to MB if they had a 20% decrease in either their norepinephrine or vasopressin dose within 2 h of drug administration without a concurrent increase in the dose of the other drug. The timing of maximal drug response (increase in MAP) was recorded for all patients in the cohort. Vasopressor management in our intensive care unit was targeted to maintain MAPs between 70 and 80 mmHg for most patients.

### Study variables

Baseline demographic data, medical comorbidities, and surgical data were collected for all patients. Variables were defined according to STS database specifications (www.sts.org). In addition, hemodynamic data and data about vasoactive drug administration were collected before and after MB administration. Finally, in-hospital mortality data were collected for all patients in the cohort.

### Statistical analysis

Statistical analysis was performed using SAS 9.3 (SAS Corp, Cary, NC, USA). Descriptive statistics were performed for patient characteristics. Continuous variables were described as the median value and interquartile range. Categorical variables were described as the number and percentage of patients. Mean norepinephrine, vasopressin, and epinephrine doses were calculated before and after MB administration and were compared using Student's *t*-test. The MAP was also compared before and after MB administration in the same way. The time distribution for maximal MB response was reported with a median value and interquartile range.

Pre- and intraoperative variables of interest as well as MAP at the time of drug administration were analyzed

with logistic regression to determine whether they were associated with a positive response to the MB. For all variables, odds ratios with 95% confidence intervals (CIs) were reported. In-hospital mortality was compared between patients who had a positive response to MB and those who did not using Chi-squared test.

## Results

A total of 88 patients met study inclusion criteria. Patient characteristics are shown in Table 1. The majority of patients in the cohort had either complex valve surgery or aortic surgery. The median CPB time was 148 min, and median intraoperative red blood cell transfusion was three units, reflecting a complex surgical population. Nearly 23.9% of patients in the cohort had deep hypothermic circulatory arrest for complex aortic repair.

Vasopressor doses and hemodynamic data before and after MB administration are shown in Table 2. MB was associated with a significant increase in MAP and decrease in norepinephrine dose of

**Table 1: Patient characteristics**

Variable	Median (Q1, Q3) or n (%)
Age	66 (57, 77)
Sex (% male)	64 (72.7)
Body mass index (kg/m <sup>2</sup> )	28 (25, 33)
Preoperative hemoglobin (g/dL)	12.4 (10.8, 14.4)
Preoperative creatinine (mg/dL)	1.1 (1.0, 1.4)
Preoperative bilirubin (mg/dL)	0.9 (0.7, 1.0)
Preoperative albumin (g/dL)	3.6 (3.3, 3.8)
Infectious endocarditis	6 (6.8)
Cerebrovascular disease	15 (17.1)
Chronic lung disease	25 (28.4)
Diabetes	31 (35.2)
Dialysis	2 (2.3)
Dyslipidemia	62 (70.5)
Hypertension	75 (85.2)
Preoperative ACE inhibitor	30 (34.1)
Preoperative beta-blocker	70 (79.6)
LV ejection fraction	55 (35, 60)
CPB time (minutes)	148 (111, 201)
Deep hypothermic circulatory arrest	21 (23.9)
Surgery type	
Isolated CABG	11 (12.5)
Isolated valve	33 (37.5)
Aortic surgery	27 (30.7)
Other	17 (19.3)
RBC transfusion (units)	3 (1, 6)
FFP transfusion (units)	2 (2, 6)
Platelet transfusion (units)	2 (1, 4)
In-hospital mortality	13 (14.7)

ACE: Angiotensin converting enzyme, CABG: Coronary artery bypass grafting, CPB: Cardiopulmonary bypass, FFP: Fresh frozen plasma, LV: Left ventricle, RBC: Red blood cell

approximately 2 mcg/min ( $P = 0.04$ ). There was no difference in vasopressin dose or epinephrine dose after MB ( $P = 0.54$ , and  $P = 0.45$ ). The median time until a maximum hemodynamic response was 2 h after drug administration (interquartile range 1.75–2.0 h). Of the 88 patients who received MB, 39 (44.3%) had a positive response. Patients with no response had an in-hospital mortality rate of 20.4% while those with a positive response had an 8.3% mortality rate ( $P = 0.09$ ).

Of the variables that were tested for association with MB response, two variables were found to have a significant association [Table 3]. Patients who had surgery with deep hypothermic circulatory arrest were more likely to have a positive response odds ratio (OR) =4.48 (95% CI = 1.54–13.06),  $P = 0.006$ , and patients who had a higher MAP when MB was administered were more likely to have a positive response OR = 1.04 (95% CI = 1.01–1.07),  $P = 0.02$ .

## Discussion

VS after cardiac surgery with CPB is a serious complication that is associated with a three-fold increase in mortality.<sup>[3]</sup> Often patients with VS require high-dose vasopressor therapy, which is associated with serious complications including arrhythmia, distal limb ischemia,

intestinal ischemia, and cardiac ischemia. In one study of patients receiving high-dose vasopressor therapy, only 17% of patients survived to 90 days.<sup>[9]</sup> The pathophysiology of VS after cardiac surgery is poorly understood but is generally thought to be related to inflammation induced by CPB and possibly preoperative medications including ACE inhibitors, calcium channel blockers, and intravenous heparin.<sup>[10]</sup> Both interleukin-1 and atrial natriuretic peptide are elevated after CPB and can cause increased levels of intracellular cyclic guanylate monophosphate (GMP). Further dysregulation of the cyclic GMP pathway in endothelial cells is thought to contribute to loss of vascular tone in VS.

MB is a competitive inhibitor of guanylate cyclase that decreases intracellular levels of cyclic GMP. It binds to the heme moiety of the enzyme and inhibits cyclic GMP production increasing vascular tone. To date, there are two clinical trials of MB in cardiac surgery patients with VS.<sup>[5,6]</sup> Both studies showed improvements in hemodynamics with MB, and one of the studies showed a mortality reduction. However, it remains unclear which cardiac surgery patients are most likely to benefit from the drug and when it should be given.

In our cohort of 88 patients, MB administration (1–2 mg/kg) was associated with a modest increase in MAP of 8 mmHg and a decrease in norepinephrine dose of 2 µg/min. Factors associated with a positive response to MB were higher MAP at the time of drug administration and deep hypothermic circulatory arrest during surgery. To the best of our knowledge, these data are novel and important. First, the fact that higher MAP at the time of MB administration predicts response suggests that MB is a poor “salvage” agent and should be given before the onset of severe hypotension. Furthermore, to the best of our knowledge, MB has not been specifically evaluated in patients having deep hypothermic circulatory arrest. These patients are at particularly high risk for VS and might benefit more than regular CPB patients from the drug. Deep hypothermic circulatory arrest is associated with a profound inflammatory response during reperfusion, which may contribute to VS.<sup>[11]</sup> It is possible that MB may mitigate this response.

Our study has several important limitations. First, it is observational and lacks a control group. In our study, patient hemodynamics and vasopressor doses were compared before and after drug administration. It is possible that MAPs would have increased and vasopressors would have decreased without MB administration over time. Second, our study represents practices at a single center, and these may not be generalizable to other patients. In our intensive care unit, MAPs were targeted to be between 70 and 80 mmHg, and in other centers that have lower or higher MAP goals, experience with MB in VS may differ. Third, our study design did not allow us to determine

**Table 2: Vasopressor doses and mean arterial blood pressure**

Variable	Before MB	After MB	P
Norepinephrine dose (mcg/min)	12.5±5.9	10.4±6.5	0.04
Vasopressin dose (units/min)	0.09±0.04	0.08±0.04	0.54
Epinephrine dose (mcg/min)	7.4±4.6	6.9±4.4	0.45
Mean arterial blood pressure (mmHg)	74±19	82±13	0.004

MB: Methylene blue

**Table 3: Variables associated with methylene blue response**

Variable	OR (95% CI)	P
Age	1.02 (0.99-1.05)	0.29
Male sex	1.47 (0.56-3.85)	0.43
Body mass index	0.98 (0.92-1.05)	0.52
Preoperative creatinine (mg/dL)	0.75 (0.32-1.76)	0.50
Preoperative albumin (g/dL)	1.63 (0.50-5.31)	0.42
Diabetes	1.16 (0.48-2.81)	0.74
Hypertension	1.09 (0.34-3.56)	0.88
Preoperative ACE inhibitor	1.74 (0.71-4.23)	0.22
Preoperative beta-blocker	0.51 (0.20-1.32)	0.17
LV ejection fraction	1.03 (0.99-1.06)	0.06
CPB time	0.99 (0.99-1.01)	0.58
Deep hypothermic circulatory arrest	4.48 (1.54-13.06)	0.006
MAP (mmHg)	1.04 (1.01-1.07)	0.02

ACE: Angiotensin converting enzyme, CPB: Cardiopulmonary bypass time, LV: Left ventricle, MAP: Mean arterial blood pressure, OR: Odds ratio, CI: Confidence interval

whether MB improves mortality in cardiac surgery patients, which is a distinct and important clinical question. Finally, although there was a statistically significant increase in MAP and decrease in norepinephrine with MB, some may consider the magnitude of these changes to be clinically insignificant.

Our study also has important strengths. To the best of our knowledge, it is one of the largest observational studies of MB administration for VS in cardiac surgery patients to date. Furthermore, our study is the first to describe novel variables that are associated with improved MB response. These data could be important when selecting patients for future clinical trials.

In summary, in a cohort of 88 cardiac surgery patients with VS, MB was associated with an increase in MAP and decrease in norepinephrine dose that peaked approximately 2 h after drug administration. Patients who had surgery with deep hypothermic circulatory arrest and patients who received MB with a higher baseline MAP appeared to have the greatest response to the drug. Future studies are necessary to determine whether there is a definitive role for MB in cardiac surgery patients with VS.

### Conclusion

Methylene blue modestly increases blood pressure in cardiac surgery patients with VS and may be particularly effective in patients who have deep hypothermic circulatory arrest.

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### Conflicts of interest

There are no conflicts of interest.

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