

# Methylene Blue Treatment of Vasoplegic Syndrome in Children after Cardiac Surgery

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## Background

- Vasoplegia is defined as hypotension refractory to volume resuscitation and inotropic support, an adequate to high cardiac output state, and low systemic vascular resistance or vasodilation.
- Vasoplegic syndrome has been reported in 4.8%- 8.8% of patients who were placed on cardiopulmonary bypass during cardiac surgery.<sup>1,2</sup>
- Adult patients who experience vasoplegia after cardiac surgery have an increased mortality of 10.7%-24%<sup>1,3</sup>
- Methylene blue has been used as a treatment for vasoplegic syndrome.
- Vasoplegia is hypothesized to result from the disruption of blood vessel endothelial homeostasis and dysregulation of the nitric oxide(NO)/cyclic guanosine 3', 5' monophosphate(cGMP) pathway.
- Methylene blue inhibits NO production, potentially reducing vasoplegia

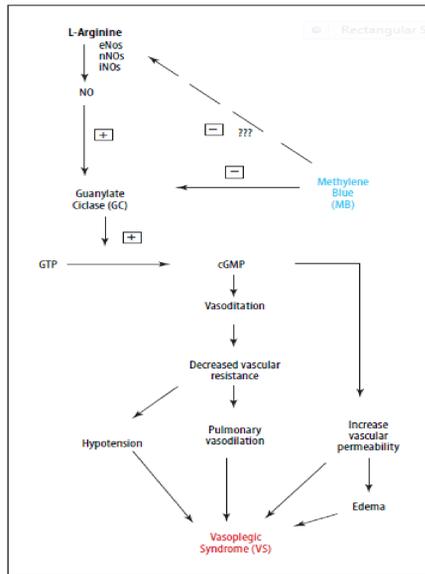


Figure 1. Possible mechanism of action of methylene blue (MB) competing with nitric oxide (NO) in the development of vasoplegic syndrome (VS).

## Objectives

### Specific Aim:

- Determine if using methylene blue to treat vasoplegia is associated with an increase in mean arterial blood pressure.

### Secondary Aims:

- Ascertain if there is an association between treatment with methylene blue and decreased need for inotropic support.
- Establish if there is a difference in morbidity and mortality between patients treated with methylene blue versus controls.

## Study Design

### Subjects:

- Patients treated with methylene blue in the Phoenix Children's Hospital CVICU from February 2013 - June 2016.
- Matched control subjects identified from pharmacy records during the same time period, received steroids and vasoactive inotropes standard of care for refractory hypotension.
- Thirty-two congenital heart disease patients who received methylene blue as treatment for hypotension were identified. Fifty patients with congenital heart disease identified as controls. Thirty-two identified patients as receiving methylene blue during the study period were identified. Four patients were excluded because methylene blue was used for diagnostic procedures and not for treatment of vasoplegia. Described uses of methylene blue included treatment of vasoplegia from cardiogenic shock (n = 7), post cardiopulmonary bypass vasoplegia (n = 16), ECMO decannulation hemodynamic instability (n = 2), and septic shock (n = 3).

### Study Design:

- Single-center retrospective cohort study using data collected during electronic medical record review.

### Statistical Analysis:

- Standard descriptive statistics for demographic information.
- Linear regression and mixed effect modeling to evaluate vital sign trends.
- Kaplan-Meier curves for survival, LOS, and duration of mechanical ventilation

## Results

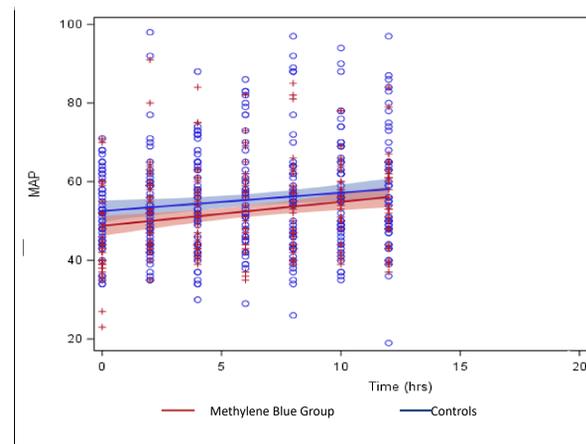


Figure 2: Linear regression model of mean arterial blood pressure vs. time for both the methylene blue cohort and the control cohort.

- Univariate and multivariate linear regression analysis showed a decrease in vasoactive inotropic scores (VIS) over time. (Univariate:  $\beta = -0.65$ ,  $p < 0.001$ ; Multivariate:  $\beta = -0.62$ ,  $p < 0.001$ )
- Patients treated with methylene blue had a greater decrease in vasoactive inotropic support over time when compared to controls.
- The Vasoactive Inotrope score has been proposed as a marker of illness severity after pediatric cardiac surgery

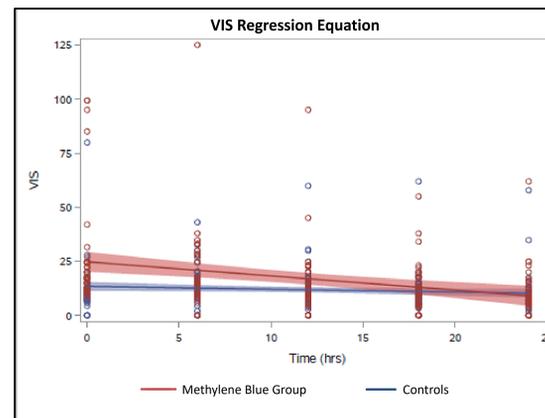


Figure 3: Linear regression model of VIS vs. time for both the methylene blue cohort and the control cohort. There was a statistically significant difference between the two regression models.

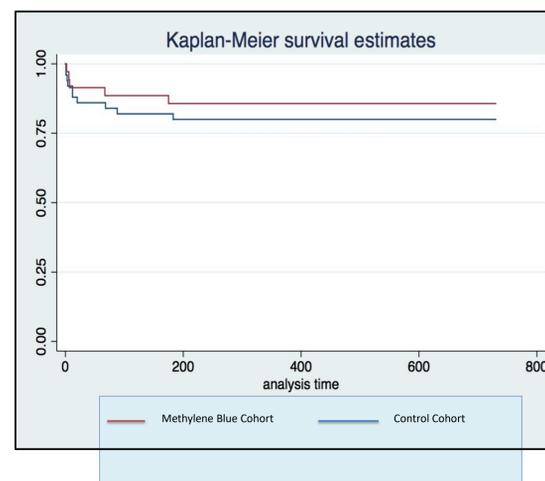


Figure 4: Kaplan-Meier survival estimates for the methylene blue cohort vs. the control cohort.

- Mean arterial blood pressure increased by approximately 10.8 mmHg over a twelve hour period ( $p = 0.0003$ ) after methylene blue administration.
- Univariate and multivariate linear regression analysis revealed an increase in mean arterial blood pressure over time. (Univariate:  $\beta = 0.61$ ,  $p < 0.001$ ; Multivariate:  $\beta = 0.65$ ,  $p < 0.001$ ).
- However, patients treated with methylene blue did not show a statistically significant change in mean arterial blood pressure trends when compared to controls.

Long rank test for equality between the two groups showed no significant survival difference.  
 $X^2 (1) = 0.46$ ,  $p = 0.5$   
 There was also no significant difference in length of hospital stay; however the methylene blue group had shorter lengths of intubation ( $p < 0.001$ ).

## Discussion

- Methylene blue use was associated with an increase in mean arterial blood pressure and a decrease in vasoactive inotropic scores over time
- The control cohort varied slightly in demographic characteristics, but did not have a statistically significant difference in fluid resuscitation or steroid use.
- There was no difference in survival between the two groups. However, the methylene blue group was able to be extubated nearly twenty-four hours sooner on average than patients in the control group.
- The association of methylene blue use with the ability to wean vasoactive medications, may have reflected less cardiopulmonary liability, and therefore allowed weaning toward extubation sooner than the control group.

## Limitations

- Sample size limitation: This was a single center, retrospective chart review with a small number of methylene blue patients. Our study sample size may have been too small to detect subtle differences in mean arterial blood pressure trends.
- Despite being clinically comparable, the control cohort was older with higher mean arterial blood pressures, which could have affected the ability to detect a difference in mean arterial blood pressure trends.

## Conclusion

- Methylene blue, used in the treatment of vasoplegia, may be associated with an increase in mean arterial blood pressure over time, but there was no statistically significant difference in mean arterial blood pressure trends between the methylene blue cohort and controls.
- Methylene blue is associated with a decreased need for vasoactive inotropic support when compared to the control cohort.
- There was no difference in survival estimates between the patients who received methylene blue and controls.
- There is a statistically significant decrease in ventilator days between the methylene blue cohort and the control cohort.

## References

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This study was approved by the Institutional Review Board at Phoenix Children's Hospital.