METHYLENE BLUE USE IN PEDIATRIC PATIENTS IN THE CARDIOVASCULAR INTENSIVE CARE UNIT

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Class of 2020

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Methylene Blue Use in Pediatric Patients in the Cardiovascular Intensive Care Unit

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The authors have disclosed that they do not have any potential conflicts of interest.

Funding Source: none

"Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

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Abbreviations: VIS vasoactive inotropic score

Keywords: vasoplegic syndrome, methylene blue, systemic vascular resistance, vasodilation, congenital cardiac surgery, congenital heart disease

Abstract:

Objective: 1) Compare trends in mean arterial blood pressures and vasoactive-inotropic scores of pediatric patients after treatment of hypotension with methylene blue compared to controls; 2) Describe the dose administered and the pathologies of hypotension cited for methylene blue use; 3) Compare the morbidity and mortality of pediatric patients treated with methylene blue versus controls.

Design: A retrospective chart review.

Setting: Cardiac ICU in a quaternary care free-standing children's hospital.

Patients: Thirty-two patients with congenital heart disease who received methylene blue as treatment for hypotension, fifty patients with congenital heart disease identified as controls.

Interventions: None.

Measurements and Main Results: Demographic and vital sign data was collected for all pediatric patients treated with methylene blue during a three year period. Linear regression models examined trends in mean arterial blood pressures twelve hours post methylene blue treatment and vasoactive-inotropic scores for twenty-four hours post treatment. Methylene blue treatment correlated with an increase in mean arterial blood pressure of 10.8mm Hg over a twelve hour period ($p< 0.001$). Mean arterial blood pressure trends of patients older than one year did not differ significantly from controls ($p=0.79$), but patients less than or equal to one year of age had increasing mean arterial blood pressures that trended toward significance compared to controls ($p=0.07$). Similarly, a statistically significant decrease in vasoactive-inotropic scores was observed over a twenty-four hour period ($\beta= -0.62$, $p< 0.001$, ECMO $\beta= -6.07$, $p= 0.029$). This difference remained significant compared to controls ($p=0.001$). Survival estimates did not detect survival differences between the groups ($p=0.5$).

Conclusion: Methylene blue may be associated with a decreased need for vasoactive-inotropic support and may correlate with an increase in mean arterial blood pressure in patients who are less than or equal to one year of age.

Contributors' Statement:

Dr Willis and Dr Scheffer conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Medical student Sarah Patel, contributed with data collection, analysis, and various background research and contributed to final manuscript edits. Dr. Mirea and team contributed to statistical analysis.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Introduction:

One well recognized risk associated with placing patients on cardiopulmonary bypass (CPB) during cardiac surgery is vasoplegic syndrome (VS). VS is a constellation of symptoms comprised of hypotension refractory to volume resuscitation and inotropic support, an adequate to high cardiac output state, and low systemic vascular resistance (SVR) (1,2,3,4). In adult patients placed on cardiopulmonary bypass the incidence of VS is as high as 4.8%- 8.8% (1,2). For at risk adult populations, such as those who have used heparin, ACE inhibitors, or calcium channel blockers pre-operatively, this incidence increases to 44.4%-55.6% (3). Additionally, adult patients who experience vasoplegia after cardiac surgery have an increased mortality of 10.7%-24% (1,3). Since this syndrome does not respond to conventional fluid and vasoactive therapy, patients who experience vasoplegic syndrome often experience poor systemic perfusion that can progress to multisystem organ failure and ultimately death (2).

In both children and adults, hypotension related to a vasoplegic state has multiple etiologies, including septic shock, burn injury, or cardiopulmonary bypass-induced vasoplegic syndrome. Various studies have demonstrated an increase in nitric oxide (NO) as the cause of this hypotension (4,6). Vascular endothelial and smooth muscle cells contain enzymes actively produce NO. Vasoplegia is hypothesized to result from the disruption of blood vessel endothelial homeostasis through increased inflammation and dysregulation of the nitric oxide/ cyclic guanosine 3', 5' monophosphate pathway (cGMP) (5). Published literature demonstrates decreased morbidity and mortality when NO synthesis is inhibited preventing microcirculation impairment (4). Pharmacologic treatments that inhibit NO synthase (NOS) have been developed in an attempt to decrease NO production in disease pathologies where the upregulation of NO causes hypotension. Initial animal and human studies testing nonspecific NOS inhibitors showed

NOS inhibition did reduce hypotension and increase systemic vascular resistance (SVR) (8). However, nonspecific NOS inhibition was also associated with severe adverse side effects including myocardial depression with decreased cardiac output, decreased oxygen delivery, and increased mortality, thereby making it unsafe for clinical treatment of vasoplegic syndrome (8).

In order for a pharmacologic agent to successfully inhibit NO, while avoiding serious adverse events, it would theoretically need to inhibit the NO pathway through a different mechanism. In cases of NO upregulation, methylene blue appears to inhibit soluble guanylate cyclase (sGC), a downstream biochemical messenger of NO, and ultimately decreases cGMP. cGMP is the final molecular messenger in the NO pathway; theoretically, decreasing cGMP might avoid the myocardial depression and other adverse side effects seen in nonspecific NO synthase inhibition. Levin et. al. used methylene blue as a treatment of CPB-induced vasoplegia in adults and showed a reduction in mortality in those who received the treatment (1,6). In a study treating adults with norepinephrine-refractory VS, Leyh et.al. demonstrated a subsequently higher SVR and decreased need for catecholamine therapy in methylene blue treatment group (2,6). According to these investigations, methylene blue effectively treats adult patients with vasoplegic syndrome.

Could methylene blue provide similar results when treating hypotension in pediatric patients in the cardiovascular intensive care unit? There is very limited data published on the use of methylene blue in pediatrics. Methylene blue is used, however, in pediatric cardiovascular intensive care units to treat patients experiencing CPB-induced VS refractory to traditional clinical management, based on the decreased mortality reported in the adult literature. Pediatric patients represent a subpopulation whose cardiac pathologies vary greatly from the adults examined in published studies. Due to the variability in cardiac pathology, we aim to describe

the type of pathologies for which methylene blue treatment was administered, as well as the impact methylene blue has on mean arterial blood pressure and vasoactive-inotropic score trends in pediatrics. Finally, wecompare the morbidity and mortality of patients who received methylene blue treatment to controls. In this way, our study investigates if methylene blue is a safe and effective treatment for hypotension in a pediatric population with congenital heart disease.

Materials and Methods:

A single center, retrospective study was performed by reviewing the electronic medical records of patients who were treated with methylene blue as well as a contemporary control group in the same cardiac intensive care unit of a quaternary care free-standing children's hospital from February 1st, 2013 to June 30th, 2016. This study was approved by the Institutional Review Board at Phoenix Children's Hospital and the Institutional Review Board waived the need for subjects to provide informed consent.

This study included any patient who received methylene blue as treatment for hypotension during the study period. As in adult studies, methylene blue was dosed according to weight using a dose of 1-2mg/kg per institutional pharmacy recommendations. Patients who received methylene blue for a diagnostic or radiographic procedure instead of treatment for hypotension were excluded. A clinically comparable control sample receiving traditional medical therapy for vasoplegia, which included treatment with a combination of epinephrine, vasopressin, and stress dose steroids, during the same time period was identified through a pharmacy database.

For both treated and control patients, trained investigators manually extracted demographic data, vital sign data, and vasoactive-inotropic scores during a designated collection period. As methylene blue has a half-life of five hours, mean arterial blood pressure (MAP) values were collected at the time the medication was administered and at 2, 4, 6, 8, 10, and 12 hours post treatment, more than two half-lives of the drug. Similarly, vasoactive-inotropic scores (VIS) were collected at the time of treatment and at 6, 12, 18, and 24 hours post treatment, more than four half-lives of methylene blue. The control cohort had similar electronic medical record data collected for assessment. Morbidity and mortality data for both groups was obtained from the Society of Thoracic Surgeons Database. Time-to-death in days was computed from the date of surgery to the date of death from all causes.

The distributions of demographic data, baseline clinical factors, cardiac surgical repair, and post-operative conditions were summarized using descriptive statistics within each treated and control patient group. Comparison between groups was performed using parametric (Pearson Chi-square test, T-test) or non-parametric (Fisher exact, Wilcoxon rank sum) tests as appropriate for the data distribution. Similar analysis compared the amount of fluid resuscitation and steroid treatment between patients in the methylene blue group and the control group. Univariate and multivariate mixed effect models were used to estimate the change in MAP and VIS over time while controlling for extracorporeal membrane oxygenation (ECMO) support. Post-operative ventilator support, post-operative complications, length of stay, and mortality were described and compared between the two groups using appropriate statistical tests as listed above. Overall survival was displayed for each group using Kaplan-Meier curves (Figure 3), and was compared between the two groups using the Log-rank test. All statistical tests were 2-sided

with significance evaluated at the 5% level. Analyses for this paper were performed using the statistical package SAS (SAS Institute 2011) and STATA (7).

Results:

During the study period, methylene blue was administered on thirty-nine occasions to treat thirty-two unique patients. Of the thirty-two patients, four were excluded because methylene blue was used for diagnostic procedures and not for treatment of hypotension. The final sample treated with methylene blue included twenty-eight unique patients, with seven patients treated twice, resulting in a total of thirty-five methylene blue treatments. Indications for using methylene blue included hypotension secondary to cardiogenic shock in seven patients (25%), post cardiopulmonary bypass vasoplegia in sixteen patients (57%), ECMO decannulation hemodynamic instability in two patients (7%), and septic shock in three patients (11%). Methylene blue treatment doses in our study ranged from 0.3mg/kg- 2mg/kg with an average dose of 1.1mg/kg for our treatment cohort.

Among patients less than one year of age, those who were treated with methylene blue received surgery at a significantly younger age and had a lower mean weight at the time of surgery than did controls. However, among patients greater than one year of age, those treated with methylene blue were significantly older than controls, but the difference in weight did not reach statistical significance. Congenital heart disease diagnosis was comparable between groups, except for tetralogy of Fallot in ten (21%) of controls, but zero (0%) methylene blue patients (Table 1). The mean Society of Thoracic Surgeons (STAT) Category trended higher in the methylene blue patients than in controls, but was not statistically significant (p-value= 0.06).

Mixed effect model analysis of mean arterial blood pressure after controlling for vasoactive-inotropic scores revealed a statistically significant correlation between methylene blue use and an

increase in mean arterial blood pressure of approximately 10.8 mm Hg over a twelve hour period ($p<0.001$). Univariate linear regression analysis revealed an increase in mean arterial blood pressure over time ($\beta= 0.61$, $p< 0.001$) (Figure 1). Multivariate analysis accounting for blood pressure changes because of ECMO support continued to show a statistically significant increase in mean arterial blood pressure over time ($\beta= 0.65$, $p< 0.001$, ECMO $\beta= -4.37$, $p= 0.003$). When compared to a control group, however, there was no statistically significant difference between mean arterial blood pressure trends when analyzing all ages together. When divided and analyzed according to age less than or equal to one year and age greater than one year, there was a difference between the mean arterial blood pressure trends over time in the methylene blue group and the control group for ages less than or equal to one year, but this difference did not reach statistical significance ($p=0.07$).

Univariate linear regression analysis of vasoactive-inotropic scores (VIS) showed a significant downward trend in VIS for a twenty-four hour period after methylene blue use ($\beta= -0.65$, $p< 0.001$). Multivariate linear regression analysis controlling for ECMO support remained significant for decreasing VIS scores over time ($\beta= -0.62$, $p< 0.001$, ECMO: $\beta= -6.07$, $p=0.029$). Patients treated with methylene blue had a greater decrease in vasoactive-inotropic support over time than controls ($p=0.001$) (Figure 2).

Patients in the methylene blue group were extubated approximately twenty four hours sooner than those in the control group . However, patients in the methylene blue group had higher rates of reintubation than the control group ($p=0.009$). There was also a higher incidence of ECMO support and multisystem organ failure in the methylene blue group, but a lower incidence of cardiac arrest compared to controls. There were no reported adverse effects from methylene blue use. Mortality at thirty days post op and overall did not vary between groups, but at discharge,

methylene blue patients had a trend toward elevated mortality compared to controls, but this trend did not reach statistical significance. There was no difference in length of ICU stay or hospital length of stay between the two groups. There was also no difference in overall survival between groups.

Discussion:

Vasoplegia results in increased mortality because it often remains resistant to standard clinical interventions such as administration of intravenous fluid and the use of multiple inotropic medications leading to refractory shock and poor oxygen delivery in patients who experience it (2). If a patient's shock state is unable to be reversed, vasoplegic syndrome (VS) could lead to increased mortality in vulnerable populations such as pediatric patients undergoing cardiopulmonary bypass for cardiac surgery.

In our study, we demonstrated that methylene blue use was associated with an increase in mean arterial blood pressure over a twelve hour period and a decrease in vasoactive-inotropic scores over a twenty-four hour period. When compared with controls, the decrease in vasoactive-inotropic score maintained statistical significance. Although it did not reach statistical significance, there is also a possible difference in the mean arterial blood pressure trends over time between the methylene blue cohort and the control cohort in children less than or equal to one year of age. These results support the theory that methylene blue could be an effective treatment for vasoplegia in the pediatric population, although more prospective studies would be needed to verify causation.

During our evaluation we noted that the increase in mean arterial blood pressure only trended toward statistical significance when ages were stratified. In children older than a year, the increasing mean arterial blood pressure trends observed over time may have resulted from

normal cardiac recovery and improvement of low cardiac output syndrome after cardiopulmonary bypass, since both the control and treatment cohort linear regression models had similarly increasing slopes that were not statistically different. In ages less than or equal to one year, however, the control cohort linear regression model did not show any trend toward increasing mean arterial blood pressures, but the methylene blue cohort had an initial lower average mean arterial blood pressure and a statistically significant trend up in mean arterial pressures over a twelve hour period. Although this subgroup analysis was a smaller sample, the difference in the two regression models suggests that there may be a correlation between the use of methylene blue and increasing mean arterial blood pressures in children less than or equal to one year of age.

Both our treatment cohort and our control cohort were very heterogeneous in certain demographic characteristics, specifically in age and weight, but are very typical of the clinical patient population. Normal values for vital signs such as mean arterial blood pressure vary greatly between ages, which can make statistical interpretation of these vital sign trends difficult. In our study, heterogeneity of age resulted in variability of mean arterial blood pressure data that limited our interpretation of vital signs trends unless age groups were stratified. Ideally, we would have examined all vital sign trends stratified by age to improve the accuracy of our interpretation. However, our population was too small to appropriately power such a subgroup analysis. Our study may have detected a statistically significant difference in the mean arterial blood pressure trends of the two cohorts for patients less than or equal to one year of age if we had a larger sample size.

Attempting to identify the control group without introducing bias may also have contributed to the difference seen in mean arterial blood pressure trends between the methylene

blue cohort and the control cohort. There are multiple factors that control mean arterial blood pressure and vasoactive-inotropic scores. In an attempt to limit cofounding factors, a control group was selected using a pharmacy database that identified patients who received both vasoactive-inotropic treatment and stress dose steroids to treat refractory hypotension after cardiac surgery to find a clinically comparable cohort. The control cohort varied slightly in demographic characteristics, but did not appear statistically different in fluid resuscitation or steroid use (Table 2). This control cohort, however, was older than the methylene blue group and so was more likely to experience a low cardiac output state from cardiopulmonary bypass instead of true vasoplegia. These imprecisions may have been enough to alter mean arterial blood pressure trends preventing the detection of a mean arterial blood pressure difference between the two cohorts.

For adult patients who experienced vasoplegic syndrome, multiple studies have demonstrated an overall reduction in mortality in patients who were treated with methylene blue (1,2,6). However, unlike the adult studies, our study did not find any statistically significant survival difference between the methylene blue cohort and the control cohort. Our study did demonstrate, however, that methylene blue was not associated with increased mortality. Patients treated with methylene blue were also extubated sooner than patients in the control cohort. Speculatively, methylene blue treatment may have been associated with less cardiopulmonary liability, increasing the clinician's confidence to wean toward extubation sooner than the control group. Despite faster extubation times, the methylene blue group also had higher rates of reintubation. In addition, our study showed a higher incidence of ECMO support and multisystem organ failure in the methylene blue group as compared to controls, but this is likely a result of the high incidence of refractory hypotension and severe shock that led to the use

ofmethylene blue. There was no difference between the two groups in their need for ICU care or hospital length of stay and no adverse side effects directly attributable to methylene blue in any of our cases, indicating it is a potentially safe treatment for vasoplegic syndrome.

Our study was designed as a retrospective chart review and therefore had limitations inherent with this design. We examined blood pressure trends of any pediatric patient that was given methylene blue for hypotension, regardless of the pathology. Accurately pinpointing the justification for methylene blue treatment retrospectively was difficult, especially given the complex nature of the patients' disease processes, resulting in multiple reasons for hypotension cited in the electronic medical record. We could not accurately limit our patient selection to patient with cardiopulmonary bypass-induced vasoplegia without introducing selection bias and therefore decided to look at all patients who were treated with methylene blue during the study period. Furthermore, limiting our sample size to only those patients who received methylene blue as treatment for post cardiopulmonary bypass vasoplegic syndrome would have resulted in a sample size too small to appropriately power our study.

Furthermore, the definition of vasoplegia requires patients to maintain a high cardiac output state. There were no objective measurements of cardiac output that could be identified retrospectively, thus our study relied on clinician estimation of high cardiac output. In nearly thirty percent of the methylene blue cohort, methylene blue was used as treatment for hypotension that was related to low cardiac output or cardiogenic shock, not vasoplegia. The adult studies that showed a difference in mean arterial blood pressures were examining methylene blue treatment of hypotension secondary to vasoplegic syndrome specifically. Additional prospective studies in pediatric patients are needed to evaluate the effectiveness of methylene blue in treating vasoplegic syndrome.

Conclusion:

Methylene blue may be a safe and effective treatment for vasoplegia in pediatric patients with congenital heart disease. Methylene blue use was associated with a decreased need for vasoactive-inotropic support when compared to the control cohort and may correlate with an increase in mean arterial blood pressure over time, specifically in those patients who are less than or equal to one year of age. There was a statistically significant decrease in ventilator days between the methylene blue cohort and the control cohort, but the methylene blue group had an increased incidence of reintubation. There was no difference in survival estimates between those patients who received methylene blue versus controls.

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Figure Legends:

Figure 1: Univariate linear regression of mean arterial blood pressure versus time for twelve hours post methylene blue treatment (β= 0.61, p< 0.001).

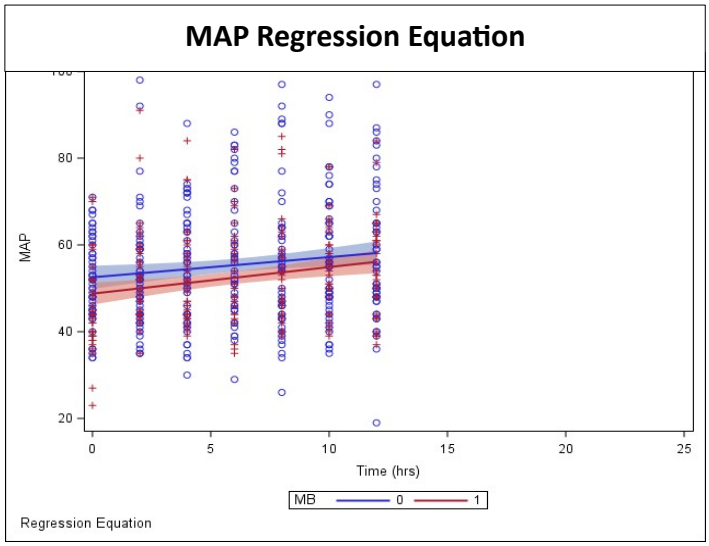

Figure 2: Linear regression modeling of vasoactive-inotropic scores demonstrating the statistically significant decrease of VIS versus time in the methylene blue cohort (β= -0.65, p< 0.001) compared to controls (β= -0.13, p= 0.001). The two linear regressions are statistically different (p=0.001).

Figure 3: Kaplan- Meier survival curves comparing mortality between the methylene blue cohort and controls. Log-rank test for equality between the two groups showed no significant survival difference ($X^2(1)$= 0.46, p= 0.5).

Figure 3: Kaplan- Meier survival curves comparing mortality between the methylene blue cohort and controls. Log-rank test for equality between the two groups showed no significant survival difference ($X^2(1)= 0.46$, $p= 0.5$).