Prophylactic Administration of Methylene Blue to Surgical Patients to Prevent Hypotension after Cardiopulmonary Bypass: An Educational Module for Anesthetic Practice

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ABSTRACT

Background: Millions of individuals are affected by cardiovascular disease (CVD). Many of these require surgical intervention; some of which undergo cardiopulmonary bypass (CPB). Unfortunately, refractory hypotension is a common occurrence when CPB is utilized; which leads to increased morbidity and mortality.

Aim: The traditional treatment for post-CPB vasoplegia is high doses of vasopressors, but this treatment option has been proven to be associated with tissue ischemia. The purpose of this scholarly project is to determine if prophylactic administration of Methylene Blue (MB) is a viable treatment option for post-CPB vasoplegia, as MB can prevent smooth muscle vasodilation while avoiding the adverse effects of vasopressors at high doses.

Results: MB appears to be a promising treatment option for the refractory hypotension that can follow the post-CPB period due to its ability to disrupt the Nitric Oxide pathway.

Discussion: Methylene Blue has proven to be an effective treatment for refractory hypotension after the discontinuation of CPB on various cases, and it has a wide margin of safety. However, most of its use is limited to last-line rescue therapy rather than prophylaxis.

Educational Project: An educational module was created to challenge conventional clinical thinking. An informative PowerPoint presentation was disseminated to anesthesia providers along with a Pre-Test to assess baseline knowledge, and a Post-Test to determine if learning had occurred. Clinicians were also asked about their likelihood to incorporate MB into their practice.

Conclusion: Methylene Blue is an old drug with great new potential. However, the number of studies that focus on prophylaxis is limited. More research is necessary to establish new practice guidelines that could provide great benefit to a large patient population.

INTRODUCTION

Problem Description

Cardiovascular disease (CVD) is the leading cause of death worldwide. Approximately 31% of all mortality is attributed to CVD.[1] In the United States, heart failure afflicts over five million individuals and over sixty million have been diagnosed with hypertension (HTN).[1,2] It is estimated that a staggering $316,000,000,000 is spent on treatment for CVD annually.[1] Although the school of thought behind the management of disease states in America is to apply interventions from least intrusive to most invasive, lifestyle modifications and pharmacology do not suffice in every scenario. Indeed, many of these patients require surgery to improve quality of life, and in various instances, to survive.

Anesthesia providers, such as Certified Registered Nurse Anesthetists (CRNAs), provide healthcare services to patients with cardiovascular disease often because the risk factors are numerous and quite common. These factors include advanced age, HTN, obesity, dyslipidemia, poor socioeconomic status, unbalanced diets that are high in fats and sodium, sedentary lifestyle, and smoking.[3] A proficient CRNA must be aware of the clinical implications linked to CVD management as some patients require major surgery with the use of cardiopulmonary bypass (CPB); a treatment modality that is known to cause postoperative refractory hypotension in 5% - 25% of patients.[4]

Background

Cardiopulmonary bypass is a treatment modality in which a device temporarily takes over the function of the heart and lungs during surgery. CPB is a continuous circuit that diverts blood from the surgical field to provide optimal operational exposure and conditions whilst maintaining the patient at near-physiological hemodynamic balance.[1] This technique may be employed for surgical interventions of the heart, lungs, or major blood vessels. At a glance, the concept of cardiopulmonary bypass seems like a medical marvel, but it is not without setbacks and major

potential risks. A potentially devastating consequence of complex cardiovascular surgery is the development of vasoplegic syndrome after CPB is discontinued.

Vasoplegic syndrome (VS) "is characterized by significant arterial hypotension, normal or high cardiac output, low systemic vascular resistance, and increased requirements for intravenous volume and vasopressors."[5] VS is linked to the release of cytokines, arginine-vasopressin system impairment, endothelial dysfunction, decreased myogenic reactivity to catecholamines, and increased nitric oxide (NO) production; all of which lead to marked vascular smooth muscle relaxation.[6] Of note, CPB is associated with increased NO levels proportional to the total time on bypass.[4]

Due to the nature of cardiovascular disease, patients scheduled for surgery may also present with additional compounding factors that will make VS post-CBP more likely such as the use of preoperative beta-blockers (BB), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), low ejection fractions, and other comorbidities.[4] Furthermore, procedures that employ CBP require heparin administration and consequent protamine administration which may produce profound vasodilation that is refractory to vasopressors and fluid resusitation.[7,1]

Significance of the Problem

Vasoplegic syndrome after cardiopulmonary bypass places a great burden on the American healthcare system due to increased morbidity and mortality in the aforementioned patient population. "Mortality rates for patients experiencing persistent vasoplegia for 36 to 48 hours range from 25% to 28.6%."[7] Moreover, individuals experiencing VS require acute care with potent vasopressor therapy which comes with a hefty price tag. In 2010, the estimated daily cost of hospital stays in an intensive care unit (ICU) was $4,300.[8] Furthermore, the average ICU length of stay (LOS) in the United States is 3.8 days, and two of the top three leading causes of death in ICUs are cardiovascular failure and multiorgan failure.[8] Lastly, the traditional treatment for VS – phenylephrine and norepinephrine – have serious adverse effects at high doses including

organ hypoperfusion and ischemic extremities; both of which can lead to tissue necrosis, acute renal failure, and metabolic acidosis.[7]

PICO Question

Do surgical patients undergoing cardiopulmonary bypass experience less postoperative hypotension with prophylactic administration of Methylene Blue than patients that do not receive Methylene Blue prophylactically?

METHODOLOGY

Systematic Review Rationale

Three glaring knowledge gaps exist in the clinical community in regard to the treatment of VS, and they are as follows. The use of preoperative ACE inhibitors presents a challenge to the management of hypotension that typically follows the discontinuation of CPB. When ACE inhibitors are taken within 8 to 24 hours of general anesthesia, hypotension is probable.[2] However, there is no general consensus or guideline for continuing or withholding ACE inhibitors in the preoperative period, which makes patient management challenging.[2]

Secondly, the role of the endothelial glycocalyx after CPB is also poorly understood. It is proposed that elements of the glycocalyx regulate vascular tone, and that would present a new avenue for treatment of VS. Unfortunately, there are no available therapeutic interventions that target the endothelial glycocalyx.[4] Lastly, methylene blue (MB) has recently gained widespread attention as an adjunct for the treatment of VS post-CBP, but there are no set guidelines for the timing or dosage of its administration.[7]

Objective of Proposed Solution

Methylene Blue is well known as the treatment of choice for methemoglobinemia, but its use should not be limited to just one condition.[9] The author of this scholarly paper proposes that MB should be prophylactically administered preoperatively to patients scheduled for complex cardiovascular surgery to prevent vasoplegic syndrome after cardiopulmonary bypass. Methylene Blue's "proposed mechanism of action is prevention of smooth muscle vasodilation due to

blockade of nitric oxide synthase."[10] Furthermore, "MB is a competitive inhibitor of guanylate cyclase that decreases intracellular levels of cyclic CMP. It binds to the heme moiety of the enzyme and inhibits cyclic GMP production increasing vascular tone."[11] Additionally, it has catecholamine-sparing effects that prevents the adverse consequences that accompany vasopressors at high doses.[7]

Refractory hypotension that ensues after cardiopulmonary bypass can have a significant impact on the wellbeing of cardiovascular patients and on the healthcare system as a whole. The traditional treatment options of phenylephrine, norepinephrine, and fluid resuscitation are not always effective and come with great risks. Methylene Blue, with a wide therapeutic safety profile, has proven to be effective in the treatment of VS post-CBP by significantly increasing mean arterial pressure, and decreasing the need for vasopressors and fluid resuscitation.[7,11]

Search Strategy and Sources

In order to carry out a literature review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used for guidance.[12] The platforms in which the searches were conducted were the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed Central, and Embase. The keywords or terms utilized were as follows: methylene blue, cardiopulmonary bypass, CPB, hypotension, refractory hypotension, low blood pressure, vasoplegia, refractory vasoplegia, vasoplegic syndrome, prophylaxis, prophylactic methylene blue, prevention, preoperative methylene blue, post-CPB hypotension, and post-CPB vasoplegia. The Boolean operators employed were: (methylene blue) AND (cardiopulmonary bypass OR CPB), (methylene blue) AND (vasopleg*), and (methylene blue) AND (hypotension OR low blood pressure). This search strategy yielded 77 results on CINAHL, 481 results on PubMed Central, and 134 results on Embase; for a total of 692 articles.

Study Selection and Screening

With a grand total of 692 possible articles, the author of this scholarly paper began the selection process by reviewing titles and abstracts that were applicable to the original PICO

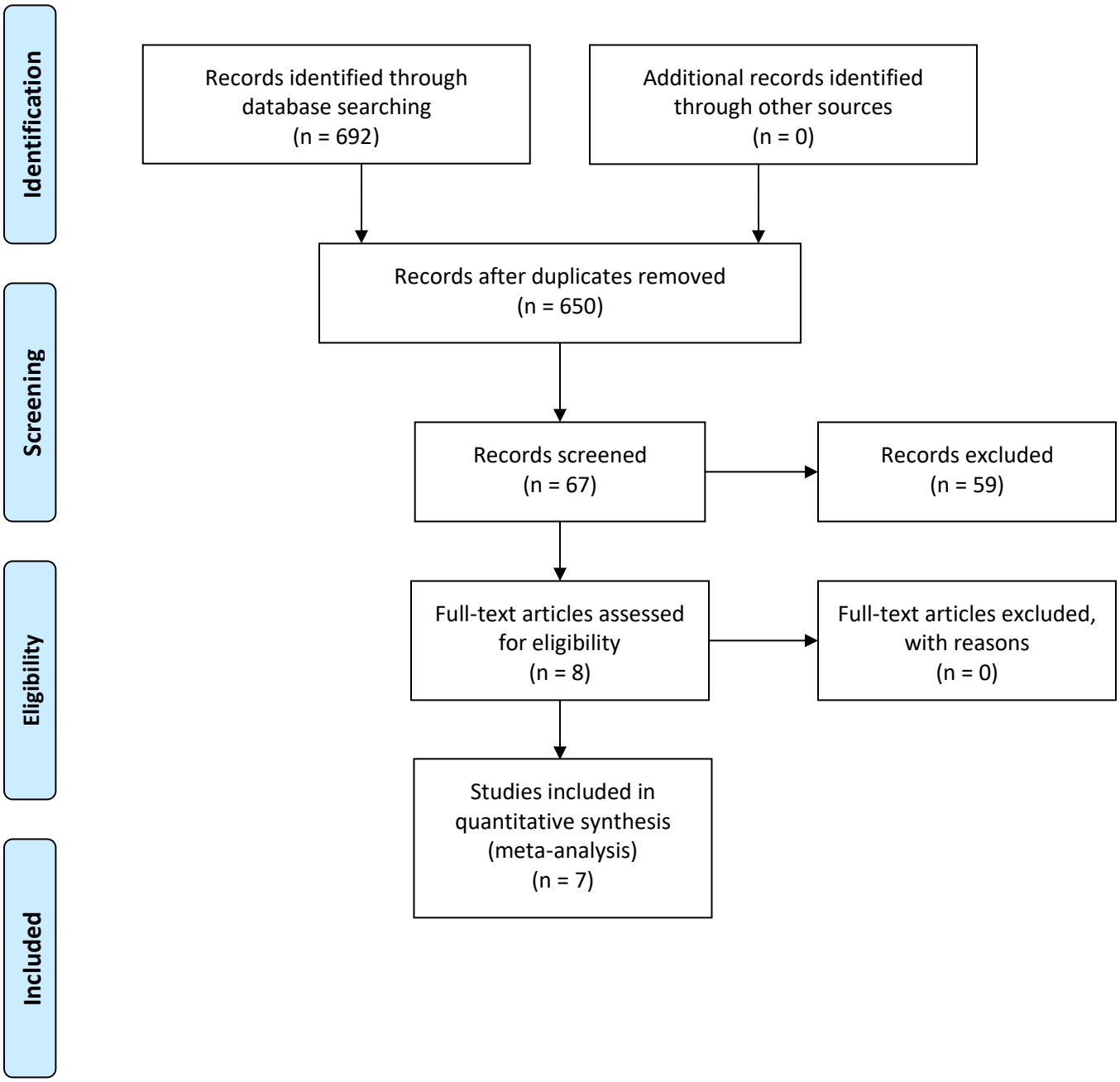
question. This process trimmed down the number of viable articles to 67. From that point inclusionary criteria helped further hone-in on the appropriate data: articles published between 1994 and 2020, articles published in English, adult test subjects, surgery that required cardiopulmonary bypass, cases in which refractory hypotension followed the post-operative period, and administration of Methylene Blue for the purpose of hemodynamic stability only. Exclusionary criteria included: articles in languages other than English, pediatrics, animal subjects, methylene blue administration for purposes other than hemodynamic stability, cardiac surgeries without the use of cardiopulmonary bypass, emergency procedures, and ASA classifications higher than 4.

The aforementioned criteria are displayed in tabular form below in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Population: • Adults • Cardiovascular patients • Patients with refractory hypotension after CPB Type of procedure: • Surgery with cardiopulmonary bypass Intervention: • Methylene Blue administration Outcomes: • Measurements of hemodynamic parameters post-CPB Type of study: • RCTS • Retrospective observational studies • Literature reviews • Publication dates from 1994 to 2020 • Articles published in English	Population: • Animals • Pediatrics • Parturients • ASA level above 4 Type of procedure: • Surgery without cardiopulmonary bypass • Emergency surgeries Intervention: • No administration of Methylene Blue • Administration of MB in combination with other pharmacologic agents Outcomes: • No hemodynamic measurements post-CPB Type of study: • Level IV articles • Level V articles

Figure 1. Prisma Flow Diagram



Data Analysis

The quality of the articles was evaluated with the Johns Hopkins Nursing Evidence-Based Practice evidence appraisal tool.[13] Strength of evidence falls under one of five different levels. Level I, the highest level of evidence is reserved for experimental studies, randomized controlled trials (RCTS), systematic review of RCTS, and explanatory mixed method designs that include only Level I quantitative studies.[13] Level II accommodates quasi-experimental studies; systematic review of RCTS and quasi-experimental studies, or quasi-experimental studies only; and explanatory mixed method designs that only include Level II quantitative studies.[13] Level III includes nonexperimental studies; systematic review of a combination of RCTs, quasi-experimental and nonexperimental studies, or nonexperimental studies only; qualitative studies or meta-synthesis; exploratory mixed-method studies; and explanatory mixed method designs that include only Level III quantitative studies.[13] Further down the line are levels that do not enjoy the strength of evidence of the aforementioned categories. Opinions of respected authorities and reports of nationally recognized committees make up Level IV.[13] Level V includes evidence obtained from literature reviews or case reports, and opinions of nationally recognized experts based on experience.[13]

Evaluation of Literature

The scholarly articles that were reviewed spanned from publications from 1994 through 2018. The final selection includes four Level I randomized controlled trials (RCTs), one Level III observational study without a control group, one Level III retrospective observational study without a control group, and one Level II literature review. After combing through the data, the following focal points arose.

Vasoplegia, or vasoplegic syndrome (VS), is a term that describes distinct clinical features that are associated with cardiopulmonary bypass: normal or high cardiac output (CO), hypotension, decreased systemic vascular resistance (SVR), and high requirements of vasopressors and fluid resuscitation. Its incidence lies between 5% to 25% after cardiac surgery.[7]

According to Leyh et al. “norepinephrine-refractory systemic vasoplegia is defined as a mean arterial blood pressure lower than 60 mm Hg, a cardiac output greater than 4.0 L/min, low SVR (<600 dyne) under intravenous norepinephrine infusion (≥0.5 mcg/kg/min).” [14]

The traditional treatments for the hypotension that usually follows the discontinuation of cardiopulmonary bypass (CPB) are phenylephrine and norepinephrine infusions. Prompt intervention is necessary because the mortality rates from VS that persists for up to 48 hours lie between the 25% and 28.6% range. [15] Unfortunately, high doses of vasopressors are often used to prevent mortality via VS and these medications are not without serious potential adverse effects. Both phenylephrine and norepinephrine can cause organ hypoperfusion and ischemic extremities at high doses. Additionally, these complications can lead to tissue necrosis, acute renal failure, and metabolic acidosis. [7]

The etiology of vasoplegia is multifactorial. Many cardiac surgical patients have different factors that place them at risk of developing VS, and CBP compounds the issue through increased production of nitric oxide. [7] “Nitric oxide is an important vasodilatory mediator that is synthesized from L-arginine by nitric oxide synthase (NOS) in endothelial cells. Nitric oxide synthase increases levels of NO, which then diffuses into the vascular smooth muscle and interacts with the enzyme guanylyl cyclase. This enzyme is important in the conversion of guanylyl triphosphate to cyclic guanylyl monophosphate (cGMP). Serving as a second messenger, cGMP activates protein kinases responsible for the phosphorylation of calcium ion ($Ca2^{+}$) channels, inhibiting influx of $Ca2^{+}$ into smooth muscle and promoting $Ca2^{+}$ sequestration into the sarcoplasmic reticulum. The result of this signaling pathway is a decrease in cytoplasmic calcium that prevents contraction of vascular smooth muscle.” [16] It is proposed that CPB propagates this response when blood comes in contact with the cardiopulmonary bypass circuit. [7]

RESULTS

Methylene Blue (MB) is traditionally used to treat methemoglobinemia, visualize ureters in urology procedures, and to identify specific endocrine tissue. [7] However, MB has gained recent

clinical interest as a treatment option for VS post-CPB due to its ability to disrupt the NO pathway. [14] All articles reviewed demonstrated promising patient outcomes with no adverse effects. In 2003, Leyh et al. assessed 54 patients that received 2mg/kg of intravenous MB to treat VS post-CPB. "Immediately after MB infusion, clinically significant increases in MAP and SVR combined with a significant decrease in NE dosage were seen in 92.4% of patients. [14] In an RCT in 2012, Cho et al. demonstrated that a single bolus of prophylactic MB yielded greater hemodynamic stability for the patient population in question. 21 patients (the experimental group) received 2mg/kg of IV MB before the initiation of CPB, and the entire experimental group required fewer colloid infusions than the control. [17]

In the 2005 RCT by Ozal et al. 50 patients (the experimental group) were preoperatively administered 2mg/kg of IV MB. The experimental group attained higher intraoperative SVR, reduced NE infusion requirements, lower incidence of required inotropic support, decreased need for fluid resuscitation, and reduced hospital length of stay. [18] Maslow's RCT of 2006 administered 3mg/kg of IV MB to its control group of 15 patients at the onset of cardiopulmonary bypass. The experimental group attained increased SVR and MAP when compared to the control. The control group also required greater amounts of NE. [15]

In an extensive literature review, Evora et al. reaffirmed that Methylene Blue is effective in cases of NO up-regulation and that it likely has a time-sensitive "window of opportunity" for its optimal effectiveness. [19] This time-sensitive window leads the author of this scholarly paper to propose that Methylene Blue be administered prophylactically for prevention of post-CPB hypotension rather than as a mere rescue alternative. The 2004 multicenter RCT by Levin et al. infused half of their cohort of 56 patients that were afflicted by VS with 1.5mg/kg IV MB. In this study, none of the participants from the experimental group perished and VS resolved within two hours. On the other hand, 8 subjects from the control group experienced VS for more than 48 hours and 6 of these individuals died. [20] Lastly, the retrospective observational study by Mehaffey et al. of 2017 assessed 118 subjects that received Methylene Blue after the onset of VS post-CPB.

Two groups were specified: patients that received MB at the onset of VS (intraoperatively) and patients that received treatment once admitted into an intensive care unit (ICU). The "early" group had significantly lower rates of iatrogenic complications and mortality.[21]

DISCUSSION

"Administration of MB 1 hour preoperatively to patients at high risk of development of vasoplegia raises SVR during the surgical period and lowers norepinephrine requirements." [18] Maintenance of hemodynamic stability with Methylene Blue is statistically significant. Approximately 0% of patients experience postoperative vasoplegia, while approximately 26% of all patients without MB treatment experience the complication. [7] Through the years, Methylene Blue has proven to be an effective treatment for refractory vasoplegia after the discontinuation of cardiopulmonary bypass and it has a wide margin of safety. However, most of its use is limited to last-line rescue therapy rather than prophylaxis. In fact, the number of studies in which the pharmacological agent is used prophylactically is scarce.

Limitations for Research and Application

Further research about Methylene Blue for hypotension prophylaxis could be limited by its potential adverse effects. Possibly the most infamous undesired effect of MB administration is false low readings of pulse oximetry (SPO_2). The blue dye of MB interferes with light absorption and false SPO_2 readings can last approximately 60 minutes after just one bolus. [7] This could deter clinicians from adopting its widespread use because one would require arterial blood gas sampling to verify true level of oxygenation in a patient, which could become tedious and time-consuming. Another consideration that could limit future studies is that high doses of MB can cause methemoglobinemia. [7] Additionally, MB has been linked to cardiac arrhythmias, coronary vasoconstriction, decreased CO, decreased mesenteric and renal perfusion, and increased pulmonary pressure. [14, 19] Lastly, administration of Methylene Blue to a patient with undiagnosed glucose-6-phosphate dehydrogenase deficiency could be deleterious. In this patient population,

hemolytic anemia can occur because of the body's inability to metabolize MB into leucomethylene. [22]

CONCLUSION OF LITERATURE REVIEW

Methylene Blue is an old drug with great new potential. The pharmacological agent has proven to be effective in the treatment of refractory hypotension after the discontinuation of cardiopulmonary bypass, and it has a wide safety margin. Unfortunately, the number of studies with a focus on prophylaxis are few. This is understandable as the patient populations that could benefit from the treatment modality are at high risk for additional morbidity and mortality; securing consent for experimental treatment for this demographic is challenging. Further testing, however, should be carried on. 31% of all mortality in the world is attributed to cardiovascular disease, yet MB is not a prominent agent of treatment. [1] As stated by Evora et al. after analyzing decades' worth of data on the matter, there is no standard when it comes to the dosage and timing of administration of Methylene Blue, but the medical field could benefit greatly from the development of practice guidelines. [19]

IMPLEMENTATION of an EDUCATIONAL PROJECT

Goal

Various studies have proven that MB is effective at treating post-CPB VS and it is the goal of this scholarly paper's author to make clinicians consider MB as a prophylactic measure more often, rather than just as a last resort. This objective lead to a new clinical question: can anesthesia providers be influenced by an educational module to incorporate an unconventional treatment modality, and administer prophylactic Methylene Blue to patients undergoing cardiopulmonary bypass with the purpose of avoiding postoperative hypotension? The participation of anesthesia providers was solicited for the purpose of answering this query.

Setting, Participants and Recruitment

The educational project was conducted virtually in its entirety. A PowerPoint Presentation (PPT) was created which included the research findings from the literature reviewed.

This presentation was uploaded and distributed via an online platform to members of a Floridian anesthesia association; a clinical group comprised of CRNAs and Anesthesiologists that provide anesthesia services to a hospital in Miami-Dade County. The roster was contacted via email and participation was completely voluntary. The total number of participants was nine.

Description and Execution of the Project

The educational project was carried out through the web-based platform Qualtrics® XM. It consisted of a recruitment letter that specified expectations and details, a survey for the collection of demographic data, a Pre-Test for the purpose of establishing baseline knowledge of each clinician regarding Methylene Blue, the aforementioned PPT, and a Post-Test to determine if any learning had taken place. The Post-Test also asked about the likelihood of each clinician to incorporate MB into their own anesthetic practice.

Protection of Human Subjects

All anesthesia providers that accepted the invitation did so voluntarily and their participation remained anonymous. Anonymity was ensured through randomized, unique identification coding. Additionally, no personal identifiers were obtained at any point. All data were secured on a password-protected laptop computer with malware and spyware protection. No experimentation on any live human subjects was conducted on this undertaking. There was no perceived risk for the participants and the estimated total time to complete the task was 20 minutes or less.

Data Management

The investigator for this clinical education endeavor is the Doctor of Nursing Practice (DNP) candidate and author of this scholarly paper. The investigator is responsible for producing the survey, tests, PPT, acquiring participants, protecting anonymity, analyzing data, and ensuring the fidelity of the research. Statistical analysis is meant to evaluate baseline knowledge regarding MB, determine whether learning occurred during the presentation, and ascertain if an educational module can influence anesthetic practice.

RESULTS from IMPLEMENTATION

Participant Demographics

Out of all participants, 5 (55.6%) were female and 4 (44.4%) were male. Ethnic background resulted as follows: 1 (11.1%) Asian, 2 (22.2%) Caucasians, 5 (55.6%) Hispanics, and 1 (11.1%) Other. Most clinicians had attained a Doctorate Degree – 7 (77.8%) – and they had varying years of experience in anesthetic practice. 4 (44.4%) had one to two years of experience, 1 (11.1%) had three to five years, 1 (11.1%) had six to ten years, and 3 (33.3%) had over ten years of experience.

Participant demographics are displayed below in **Table 2**.

Total Participants	9
Gender	
Male	4 (44.4%)
Female	5 (55.6%)
Age	
20 – 29	3 (33.3%)
30 – 39	2 (22.2%)
40 – 49	1 (11.1%)
50 – 59	0 (0%)
60+	3 (33.3%)
Ethnicity	
African American	0 (0%)
Asian	1 (11.1%)
Caucasian	2 (22.2%)
Hispanic	5 (55.6%)
Other	1(11.1%)
Level of Education	
ASN	0 (100%)
BSN	0 (100%)
MSN	2 (22.2%)
Doctorate	7 (77.8%)
Years of Experience	
1 – 2	4 (44.4%)
3 – 5	1 (11.1%)
6 – 10	1 (11.1%)
10+	3 (33.3%)

Pre-Test: Assessment of Baseline Knowledge

The Pre-Test for the purpose of determining each clinician's baseline knowledge was delivered prior to the PowerPoint Presentation and it was identical to the Post-Test at the conclusion of the project. The format was a multiple choice-type questionnaire, and the questions were as follows:

1. Approximately what percentage of all mortality is attributed to cardiovascular disease?
2. The incidence of refractory hypotension after cardiopulmonary bypass ranges from:
3. Vasoplegic syndrome is characterized by:
4. Which factors increase the likelihood of refractory hypotension after cardiopulmonary bypass?
5. Mortality rates for patients experiencing persistent vasoplegia for __ to __ hours range from 25% to 28.6%:
6. Uses for Methylene Blue include:
7. How does Methylene Blue raise blood pressure?
8. Traditional treatment options for refractory hypotension that can occur after separation of cardiopulmonary bypass include:
9. What is the recommended dosage of Methylene Blue for the treatment of hypotension?
10. Methylene Blue can interfere with light absorption and result in false low readings on pulse oximetry. How long can this effect last after just one bolus?
11. In what type of patient condition is Methylene Blue contraindicated?
12. How likely are you to use Methylene Blue prophylactically when providing anesthesia services for patients undergoing cardiopulmonary bypass?

Regarding the twelfth question, 3 (33.3%) answered "unlikely", 4 (44.4%) answered "likely", and 2 (22.2%) answered "highly likely".

Pre-Test results are displayed below in **Table 3**.

Participant #	Correct Answers	Score
#1	6/11	54.5%
#2	8/11	72.7%
#3	3/11	27.3%
#4	7/11	63.6%
#5	8/11	72.7%
#6	5/11	45.5%
#7	1/11	9.1%
#8	6/11	54.5%
#9	6/11	54.5%

Post-Test: Assessment of Learning

The Post-Test was presented after the PPT, and it was meant to determine if any learning had occurred and if clinicians would be more open to incorporating Methylene Blue into their own anesthetic practice. All participants attained a higher score when compared to their performance on the Pre-Test. Furthermore, 6 (66.7%) of clinicians claimed that they would be "likely" to add prophylactic MB to their repertoire in the context of post-CPB VS and 3 (33.3%) stated that they would be "highly likely" to do so.

Post-Test results are displayed below in **Table 4**.

Participant #	Correct Answers	Score
#1	9/11	81.8%
#2	11/11	100%
#3	5/11	45.5%
#4	11/11	100%
#5	9/11	81.8%
#6	11/11	100%
#7	11/11	100%
#8	11/11	100%
#9	11/11	100%

Table 5. Pre-Test vs Post-Test Scores

Participant #	Pre-Test Score	Post-Test Score	Difference
#1	54.5%	81.8%	+27.3%
#2	72.7%	100%	+27.3%
#3	27.3%	45.5%	+18.2%
#4	63.6%	100%	+36.4%
#5	72.7%	81.8%	+9.1%
#6	45.5%	100%	+54.5%
#7	9.1%	100%	+90.9%
#8	54.5%	100%	+45.5%
#9	54.5%	100%	+45.5%

IMPLEMENTATION DISCUSSION

The virtual project produced significant positive results. All participants attained higher scores on the post-test when compared to the pre-test. On average, outcomes improved by 39.4%. Also, the number of clinicians that would be "unlikely" to incorporate MB into their care of patients undergoing cardiopulmonary bypass decreased from 33.3% to 0%. Lastly, those "likely" to use MB prophylactically increased by 22.3% and those "highly likely" by 11.1%.

Limitations

The most glaring shortcoming of the process was its small sample size. The South Florida anesthesia association that participated in this educational project currently has 42 active anesthesia providers, yet only 9 clinicians took part from beginning to end. This anesthesia group provides services for a facility with a dedicated cardiac surgical team, so an opportunity was missed to potentially help influence future clinical practice. Another limitation was that all interaction was web-based. Not only can an email invitation be easily overlooked, but also there is no guarantee that partakers would complete the online module without distractions.

Implications for Future Anesthetic Practice

The extensive literature review has shown that Methylene Blue has great potential to prevent hypotension after the discontinuation of cardiopulmonary bypass. However, the use of MB is mostly reserved as a last-line rescue therapy. The pharmacological agent is seldom used prophylactically and there are no standardized guidelines for dosage and timing. [19]

The educational project carried out by the author of this scholarly paper demonstrated that anesthesia providers are willing to learn new ways to use an old drug. It also demonstrated that they are open to adjusting their clinical practice in pursuit of the best possible patient outcomes. It is worthwhile to conduct future research on Methylene Blue with a focus on prophylaxis. New standardized guidelines could help decrease the incidence of morbidity and mortality in the patient population in question, and decrease healthcare costs.

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Appendix A: Summary of Literature Review

Evaluation table 1

Citation	Leyh RG, Kofidis T, Strüber M, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? *The Journal of Thoracic and Cardiovascular Surgery*. 2003;125(6):1426-1431. doi:10.1016/s0022-5223(02)73284-4
Design/Method	This was an observational study with no control group. / 54 adult patients with vasoplegia that was refractory to norepinephrine after CPB were administered 2 mg/kg of intravenous Methylene Blue. MB was administered over 20 minutes and the effects on patient outcomes were then evaluated.
Sample/Setting	"Between October 2000 and October 2001, a total of 1,111 various operations with CPB support were performed. In 4.8% of these cases (n = 54/1,111), norepinephrine-refractory systemic vasoplegia developed." Out of the 54 subjects, 41 were male, and the average age was 56.7 years. / Hannover, Germany
Major Variables Studied and Their Definitions	"Norepinephrine-refractory systemic vasoplegia: MAP < 60 mm Hg, CO > 4.0 L/min, SVR < 600 dynes"; MAP: average pressure in arteries during one cardiac cycle; Mean pulmonary artery pressure; Mean right atrial pressure; Mean left atrial pressure; CO: (cardiac output) amount of blood the heart pumps through the circulatory system in a minute; SVR: (systemic vascular resistance) resistance to blood flow by the systemic vasculature, excluding the pulmonary vasculature, which the left ventricle has to overcome in order to perfuse the body
Measurement and Data Analysis	"Continuous variables are expressed as a mean ± SD unless otherwise indicated. The Friedman test was used for comparisons of means within the group. Intragroup comparisons of values at sequential time points at different times were done with the Wilcoxon test for nonnormally distributed data. Statistical calculations were performed with the SPSS software package for Windows (SPSS Inc, Chicago, Ill)."
Findings	**MAP** ➔ before MB: 68 ± 9, 1 h after MB: 72 ± 12, 6 h after MB: 71 ± 9, 12 h after MB: 73 ± 10. **MPAP** ➔ before MB: 23 ± 6, 1 h after: 24 ± 7, 6 h after: 25 ± 5, 12 h after: 24 ± 8 **MRAP** ➔ before MB: 14 ± 4, 1 h after: 14 ± 4, 6 h after: 15 ± 4, 12 h after: 15 ± 5 **MLAP** ➔ before MB: 11 ± 4, 1 h after: 10 ± 3, 6 h after: 12 ± 5, 12 h after: 10 ± 5 **CO** ➔ before MB: 7.6 ± 3.1, 1 h after: 6.5 ± 2.8, 6 h after: 6.1 ± 2.4, 12 h after: 5.8 ± 1.9 **SVR** ➔ before MB: 547 ± 108, 1 h after 766 ± 194, 6 h after: 796 ± 153, 12 h after: 876 ± 184 **NE dose** ➔ before MB: 0.5 mcg/kg/min, 1 h after: 0.32 mcg/kg/min, 6 h after: 0.2 mcg/kg/min, 12 h after: 0.15mcg/kg/min

Results	Methylene Blue was administered 136 minutes postoperatively and 51 minutes after the start of a norepinephrine infusion to attain hemodynamic stability. In every case, and infusion of Methylene Blue was initiated when a NE dosage of at least 0.5 mcg/kg was reached. "Immediately after MB infusion, clinically significant increases in MAP and SVR combined with a significant decrease in NE dosage were seen in 92.4% of patients." SVR increased while CO decreased, but MPAP, MRAP, and MLAP were unaffected. Of note, none of the patients experienced adverse effects related to MB administration.
Conclusions	"A single dose of methylene blue seems to be a potent approach to norepinephrine-refractory vasoplegia after cardiopulmonary bypass for most patients, with no obvious side effects. Guanylate cyclase inhibitors could be a novel class of agents for the treatment of norepinephrine-refractory vasoplegia after cardiopulmonary bypass." A controlled clinical trial is now needed to evaluate the role of methylene blue in this situation. "The favorable effect of MB demonstrated in this study suggests that refractory vasoplegia after CPB may reflect a dysregulation of nitric oxide synthesis and vascular smooth muscle cell guanylate cyclase activation." "The inhibition of the soluble guanylate cyclase elicited by nitric oxide or any endothelially soluble guanylate cyclase activating factor could be a novel approach in the treatment of norepinephrine-refractory vasoplegia after CPB."
Appraisal: Worth to Practice/Level	This observational study with no control group falls under the Level III category of evidence. The evidence itself is strong, with consistent and compelling results. / This study is worthwhile because it deals with cardiovascular disease, which is a major problem worldwide. Furthermore, positive and consistent results were attained. An RCT should be conducted to determine if MB should be designated as the drug of choice for post-CPB vasoplegia that is refractory to vasopressors.

Evaluation table 2

Citation	Cho JS, Song JW, Na S, Moon JH, Kwak YL. Effect of a single bolus of methylene blue prophylaxis on vasopressor and transfusion requirement in infective endocarditis patients undergoing cardiac surgery. *Korean Journal of Anesthesiology*. 2012;63(2):142-148. doi:10.4097/kjae.2012.63.2.142
Design/Method	This was a "prospective, randomized and controlled trial." / A total of 42 patients were assigned randomly to the control group or the Methylene Blue group; 21 subjects received 2 mg/kg of Methylene Blue 20 minutes prior to the initiation of cardiopulmonary bypass, and 21 subjects received saline 20 minutes prior to CPB. The outcomes set for evaluation were vasopressor and transfusion requirements, and hemodynamics.
Sample/Setting	A total of 42 adults with infective endocarditis that were scheduled for surgery under cardiopulmonary bypass were selected and consented. Exclusionary criteria consisted of active fever, leukocytosis, preexisting lung disease, severe liver or kidney disease, CAD requiring surgical revascularization, and an ASA classification greater than 4. The anesthesiologists and surgeons involved in the surgeries were also blinded to the groups throughout the duration of the study.

Major Variables Studied and Their Definitions	MBP: (mean arterial blood pressure) average pressure in the arteries during one cardiac cycle; HR: (heart rate) number of heart beats in one minute; MPAP: mean pulmonary artery pressure; CVP: (central venous pressure) blood pressure in the vena cava near the right atrium; PCWP: (pulmonary wedge pressure) pressure measured by wedging a pulmonary catheter with an inflated balloon into a pulmonary artery; CI: (cardiac index) cardiac output in relation to total body surface area; SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; vasopressor requirements after CPB; and transfusion requirements after CPB.
Measurement and Data Analysis	"All statistical analyses were performed using SPSS (SPSSFW, SPSS Inc., Chicago, IL, USA). The primary end point of this study was to evaluate the amount of infused norepinephrine during and after CPB. A difference of 0.1 mcg/kg/min in the norepinephrine infusion rate between the groups was taken as clinically significant. Based on the institutional results for IE patients who underwent VHS, the standard deviation of norepinephrine infusion was 0.1 μg/kg/min. This calculation generated an estimated 18 patients in each group with 80% power and an alpha level of 0.05. Considering the 10% of drop- out rate, 20 patients in each group were enrolled. All data were expressed as the number of patients or the mean ± SD. The normality of distribution was assessed using a q-q plot and the Shapiro-Wilk test. Between-group data was compared by the X^2 test, Fisher's exact test, independent t-test with post hoc comparison using the Bonferroni test or Mann-Whitney U test with same post hoc comparison as appropriate. Continuous variables were presented as mean ± SD or median [interquartile range], and dichotomous variables were presented as number. A P value < 0.05 was considered as significant."
Findings	**MBP control** ➔ 68.2 ± 12.5 (baseline), 67.8 ± 11.2 20 (20 mins after CPB weaning), 68.3 ± 7.6 (at sternum closure), 77.6 ± 13.7 (immediately after closure), 74.5 ± 8.1 (12 after arrival at ICU) **MBP MB** ➔ 72.4 ± 10.1 (baseline), 61.7 ± 10.8 (20 mins after CPB weaning), 64.3 ± 6.4 (at sternum closure), 78.6 ± 12.7 (immediately after closure), 76.1 ± 12.3 (12 into ICU stay) **HR control** ➔ 78.4 ± 14.1 (baseline), 91.2 ± 12.9 (20 mins after CPB weaning), 95.2 ± 12.5 (at sternum closure), 93.8 ± 11.5 (immediately after closure), 85.6 ± 12.4 (12 hours into ICU stay) **HR MB** ➔ 83.1 ± 19.2 (baseline), 89.0 ± 13.0 (20 mins after CPB weaning), 93.2 ± 15.2 (at sternum closure), 94.1 ± 15.6 (immediately after closure), 85.2 ± 12.8 (12 hours into ICU stay) **CVP control** ➔ 8.5 ± 3.8 (baseline), 8.5 ± 2.3 (20 mins after CPB weaning), 9.8 ± 3.2 (at sternum closure), 7.7 ± 3.0 (immediately after closure), 8.9 ± 2.1 (12 hours into ICU stay) **CVP MB** ➔ 9.3 ± 4.7 (baseline), 9.3 ± 1.7 (20 mins after CPB weaning), 10.5 ± 1.8 (at sternum closure), 9.1 ± 2.9 (immediately after closure), 8.5 ± 2.2 (12 hours into ICU stay)

	MPAP control ➔ 24.9 ± 10.2 (baseline), 18.9 ± 4.1 (20 mins after CPB weaning), 19.1 ± 5.7 (at sternum closure), 18.1 ± 3.5 (immediately after closure), 17.4 ± 2.5 (12 hours into ICU stay) **MPAP MB** ➔ 30.4 ± 13.3 (baseline), 20.3 ± 4.4 (20 mins after CPB weaning), 20.9 ± 4.7 (at sternum closure), 20.3 ± 6.4 (immediately after closure), 18.0 ± 5.4 (12 hours into ICU stay) **PCWP control** ➔ 18.3 ± 7.7 (baseline), 13.7 ± 3.7 (20 mins after CPB weaning), 14.7 ± 3.4 (at sternum closure), 12.9 ± 2.7 (immediately after closure), 12.7 ± 2.1 (12 hours into ICU stay) **PCWP MB** ➔ 22.5 ± 11.2 (baseline), 14.7 ± 4.0 (20 mins after CPB weaning), 15.3 ± 4.4 (at sternum closure), 15.0 ± 5.1 (immediately after closure), 13.5 ± 4.8 (12 hours into ICU stay) **CI control** ➔ 2.7 ± 0.6 (baseline), 3.4 ± 0.6 (20 mins after CPB weaning), 3.4 ± 0.7 (at sternum closure), 3.8 ± 1.3 (immediately after closure), 3.3 ± 0.7 (12 hours into ICU stay) **CI MB** ➔ 2.8 ± 0.9 (baseline), 3.4 ± 0.6 (20 mins after CPB weaning), 3.5 ± 0.9 (at sternum closure), 3.5 ± 1.0 (immediately after closure), 2.9 ± 0.6 (12 hours into ICU stay) **SVR control** ➔ 1,175 ± 318 (baseline), 916 ± 268 (20 mins after CPB weaning), 948 ± 249 (at sternum closure), 960 ± 304 (immediately after closure), 1,071 ± 286 (12 hours into ICU stay) **SVR MB** ➔ 1,185 ± 376 (baseline), 843 ± 326 (20 mins after CPB weaning), 870 ± 343 (at sternum closure), 1,085 ± 540 (immediately after closure), 1,138 ± 330 (12 hours into ICU stay) **NorEpi control (mcg/kg/min)** ➔ 0.09 (immediately after CBP weaning), 0.06 (20 mins after CPB weaning), 0.07 (at sternum closure), 0.02 (immediately after closure), 0 (12 hours into ICU stay) **NorEpi MB (mcg/kg/min)** ➔ 0.06 (immediately after CPB weaning), 0.05 (20 mins after CPB weaning), 0 (at sternum closure), 0.02 (immediately after closure), 0 (12 hours into ICU stay) **PRBC units transfused control** ➔ 4.6 ± 2.9 **PRBC units transfused MB** ➔ 1.6 ± 0.5 **FFP units transfused control** ➔ 4.6 ± 4.0 **FFP units transfused MB** ➔ 2.0 ± 1.0 **PLT units transfused control** ➔ 6.2 ± 4.1 **PLT units transfused MB** ➔ 8
Results	Differences in vasopressor requirements between the 2 groups were statistically insignificant. The difference in transfusion requirement, however, was evident within 24 hours postoperatively. The MB group required less blood product transfusion than the control group.

Conclusions	In this particular study, prophylactic administration of Methylene Blue did not significantly reduce post-CPB vasopressor requirements. However, it did noticeably reduce requirements of blood product transfusions. The authors recognize that certain variables may have reduced the effectiveness of MB such as the pathophysiology of infective endocarditis, and patient medications such as ACE inhibitors perioperatively. Furthermore, there is no standardized protocol for prevention of post-CBP vasoplegia in regard to Methylene Blue, and the authors recommend that additional testing is called for.
Appraisal: Worth to Practice/Level	Randomized control trials fall under the Level I category of Evidence. This RCT has good quality because it had adequate forms of control, an adequate sample size, consistent results, fairly definitive conclusions, consistent recommendations, and it included references to other scientific evidence. / This study has merit because it pertains to cardiovascular disease, which is a major problem worldwide. Further studies could lead to significant change in clinical practice for a pharmacologic agent that has various proven benefits.

Evaluation table 3

Citation	Ozal E, Kuralay E, Yildirim V, et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg.* 2005;79(5):1615-1619.
Design/Method	"This was a prospective randomized comparative study in which one group received a single dose of MB in the preoperative period just before anesthesia and another group did not." The Methylene Blue group received an intravenous dose of 2mg/kg of MB over 30 minutes 1 hour before the surgical procedure. The control group was not subjected to such an intervention.
Sample/Setting	100 patients that were scheduled for CABG surgery on cardiopulmonary bypass and that had additional risk factors for the development of post-CPB vasoplegia were selected and consented. These risk factors were perioperative use of ACE inhibitors, heparin, and calcium channel blockers; all of which are known contributors to perioperative vasoplegia. Patients were assigned at random; 50 for the control group and 50 for the MB group.
Major Variables Studied and Their Definitions	"Vasoplegic syndrome was defined as severe and persistent hypotension (mean arterial pressure <50 mm Hg) occurring in the intraoperative period or in the early postoperative period within 6 hours after weaning from CPB." SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; CO: (cardiac output) amount of blood the heart pumps through the circulatory system in a minute; CI: (cardiac index) cardiac output in relation to total body surface area; MAP: (mean arterial pressure) average pressure in arteries during one cardiac cycle; CVP: (central venous pressure) blood pressure in the vena cava near the right atrium; PCWP: (pulmonary capillary wedge pressure) pressure measured by wedging a pulmonary catheter with an inflated balloon into a pulmonary artery; MPAP: mean pulmonary artery pressure

Measurement and Data Analysis	"All statistical analyses were performed using the SPSS 10.0 Statistical program for Windows (SPSS Inc, Chicago, IL). Continuous variables were expressed as the mean ± standard deviation. Differences between groups were tested for significance using the Student's t test or the Mann-Whitney U test. Categorical variables were ex- pressed as percentages and analyzed using the x^2 test or Fisher's exact test. Differences were considered significant when $p < 0.05$ was determined by the two-tailed test."
Findings	**Volume infusion (mL) control** ➔ 1,749.2 ± 414.3 **Volume infusion (mL) MB** ➔ 1,577.0 ± 329.4 **NE (≥ 0.5 mcg/kg/min) control** ➔ 13 subjects **NE (≥ 0.5 mcg/kg/min) MB** ➔ 0 subjects **Inotropy required during CPB weaning control** ➔ 24 subjects **Inotropy required during CPB weaning MB** ➔ 7 subjects **Incidence of vasoplegia control** ➔ 13 subjects **Incidence of vasoplegia MB** ➔ 0 subjects **Incidence on NE-refractory VS control** ➔ 6 subjects **Incidence of NE-refractory VS MB** ➔ 0 subjects **ICU stay control** ➔ 2.2 ± 1.2 days **ICU stay MB** ➔ 1.2 ± 0.5 **Hospital stay control** ➔ 8.4 ± 2.0 **Hospital stay MB** ➔ 6.1 ± 1.7 **Mortality control** ➔ 2 subjects **Mortality MB** ➔ 0 subjects
Results	When compared to the control group, the methylene blue group attained the following benefits: significantly higher intraoperative SVR, significantly reduced NE infusion requirements, lower incidence of required inotropic support, decreased need for crystalloid and colloid infusions, and reduced ICU and hospital length of stay.
Conclusions	The authors of this study achieved better hemodynamic stability and overall clinical outcomes for patients undergoing cardiac surgery under cardiopulmonary bypass with a single prophylactic dose of Methylene Blue (2 mg/kg of 1% MB). These results were obtained without any adverse effects related to MB, and despite multiple risk factors for VS in the patient population studied.
Appraisal: Worth to Practice/Level	Randomized control trials fall under the Level I category of Evidence. This RCT has a high quality because it had adequate forms of control, an appropriate study design and sample size, consistent results, definitive conclusions, recommendations that are consistent with the findings, and it included references to other scientific evidence. / This study has merit cardiovascular disease is a major problem worldwide, and the vasoplegic syndrome that often develops after CPB is associated with poor patient outcomes and prognosis. Furthermore, VS

	post-CPB leads to extended ICU and overall hospital length of stay. Further studies at a larger scale could lead to significant change in clinical practice.

Evaluation Table 4

Citation	Maslow AD, Stearns G, Batula P, Schwartz CS, Gough J, Singh AK. The hemodynamic effects of methylene blue when administered at the onset of cardiopulmonary bypass. *Anesthesia and Analgesia.* 2006;103(1):2-8.
Design/Method	This was an RCT in which 30 adult patients scheduled for surgery on cardiopulmonary bypass with the additional VS risk factor of perioperative use of ACE inhibitors were selected and consented. Out of this group, half of the subjects were randomly selected to receive 3 mg/kg of Methylene Blue intravenously at the onset of CPB, while the other half would only receive saline. The dose of MB or its equivalent volume if saline were administered after the initiation of cardiopulmonary bypass (given a 5-minute window for patient stabilization). Hemodynamic data was obtained at the cohort's baseline; after initiation of CPB, but before drug administration; 10 minutes after administration; 20 minutes after initial administration; 40 minutes after; 60 minutes after; and post-CPB.
Sample/Setting	The 30 patients selected used ACE inhibitors perioperatively and were scheduled for surgery under cardiopulmonary bypass. Exclusionary criteria included patients that required vasopressor support before surgery, emergency procedures, preexisting liver and renal disease, pH abnormalities, parturients, patients with a history of hypersensitivity to MB, and patients with a G6PD deficiency.
Major Variables Studied and Their Definitions	MAP: (mean arterial blood pressure) average pressure in the arteries during one cardiac cycle; HR: (heart rate) number of heart beats in one minute; MPAP: mean pulmonary artery pressure; Mean right atrial pressure; PCWP: (pulmonary wedge pressure) pressure measured by wedging a pulmonary catheter with an inflated balloon into a pulmonary artery; CO: (cardiac output) amount of blood the heart pumps through the circulatory system in a minute; SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; and vasopressor requirements after CPB
Measurement and Data Analysis	"Demographic variables are presented as number and percentage or mean, and SD. Hemodynamic data are presented as the mean values and SD or occurrence and percentage. Demographic, presurgical, surgical, and hemodynamic variables were compared using Student's *t*-tests, analysis of variance, or Fisher's exact tests for categorical and continuous data. Univariate analyses were performed to assess the impact of perioperative variables on hemodynamic changes. *P* values <0.05 was considered as statistically significant. SAS v.8.2 (SAS Institute Inc., Cary, NC) was used for the statistical analysis."
Findings	**MAP control** ➔ 80 (baseline), 60 (CPB pre-drug), 55 (CPB post-drug), 57 (CPB 20 mins), 57 (CPB 40 mins), 58 (CPB 60 mins), 71 (post-CPB) **MAP MB** ➔ 81 (baseline), 54 (CPB pre-drug), 63 (CPB post-drug), 60 (CPB 20 mins), 62 (CPB 40 min), 60 (CPB 60 mins), 72 (post-CPB

	HR control ➔ 69 (baseline), 89 (post-CPB) **HR MB** ➔ 70 (baseline), 88 (post-CPB) **SVR control** ➔ 1,399 (baseline), 975 (CPB pre-drug), 896 (CPB post-drug), 928 (CPB 20 mins), 922 (CPB 40 mins), 953 (CPB 60 mins), 916 (post-CPB) **SVR MB** ➔ 1,440 (baseline), 841 (CPB pre-drug)m 986 (CPB post-drug), 939 (CPB 20 mins), 952 (CPB 40 mins), 946 (CPB 60 mins), 901 (post-CPB) **Phenylephrine control (mL/patient)** ➔ 25.2 (21.0) ➔ 80% (post-drug), 73% (CPB 20 mins), 53% (CPB 40 min), 60% (CPB 60 mins) **Phenylephrine MB (mL/patient)** ➔ 1.8 (4.3) ➔ 0% (post-drug), 0% (CPB 20 mins), 7% (CPB 40 mins), 7% (CPB 60 mins)
Results	The Methylene Blue group displayed increased SVR and MAP when compared to the control group. The effect of the single bolus of MB had a duration of action of 40 minutes. On the other hand, the control group demonstrated less desirable hemodynamic values throughout CPB and beyond. This group required more frequent doses on phenylephrine while on pump and greater amounts of NE post-CPB.
Conclusions	The authors of this study managed maintain adequate SVR and MAP in patients undergoing cardiac surgery under cardiopulmonary bypass with a single administration of 3 mg/kg of intravenous Methylene Blue. In doing so, they managed to reduce the incidence and severity of VS post-CPB. The requirement for post-operative vasopressors was reduced, and patients in the MB group attained better clinical outcomes than the control group.
Appraisal: Worth to Practice/Level	Randomized control trials fall under the Level I category of Evidence. This RCT has good quality because it had adequate forms of control, an adequate sample size, consistent results, fairly definitive conclusions, consistent recommendations, and it included references to other scientific evidence. / This study has merit because it pertains to cardiovascular disease, which is a major problem worldwide, and promising results were attained. Further studies could lead to significant change in clinical practice for a pharmacologic agent that has various proven benefits.

Evaluation table 5

Citation	Evora, Paulo Roberto Barbosa, Alves Junior, Lafaiete, Ferreira, Cesar Augusto, Menardi, Antônio Carlos, Bassetto, Solange, Rodrigues, Alfredo José, Scorzoni Filho, Adilson, & Vicente, Walter Vilella de Andrade. (2015). Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. *Brazilian Journal of Cardiovascular Surgery*, *30*(1), 84 92. https://doi.org/10.5935/1678-9741.20140115
Design/Method	This particular study is a literature review that analyzes articles regarding the use of Methylene Blue in treatment of VS related to cardiac surgery. To retrieve the data, the authors utilized the following search platforms: ISI WEB of Science, SCOPUS, and Medline. Key words utilized in the search were: “Methylene blue and heart surgery” or “Methylene Blue and cardiac surgery.”

Sample/Setting	The articles reviewed span over 20 years of international publications. The authors retrieved 58 publications related to the aforementioned topic that were released between 1994 and 2009. Additionally, they retrieved 30 more articles published between 2010 and 2014.
Major Variables Studied and Their Definitions	Vasoplegic syndrome "is a constellation of signs and symptoms: hypotension, high cardiac index, low systemic vascular resistance, low filling pressures, diffuse bleeding tendency, and sustained hypotension despite the use of high doses of vasoconstrictor amines." SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; CO: (cardiac output) amount of blood the heart pumps through the circulatory system in a minute; CI: (cardiac index) cardiac output in relation to total body surface area; and MAP: (mean arterial pressure) average pressure in arteries during one cardiac cycle
Measurement and Data Analysis	N/A
Findings	The authors discovered that the interest in Methylene Blue as a treatment option for VS related to cardiac surgery has been steadily increasing over the past 5 years prior to their literature review.
Results	The authors reaffirmed the following concepts: the lethal dose of Methylene Blue is 40 mg/kg (the traditional dose of 2 mg/kg is safe); MB is effective in cases of up-regulation of Nitric Oxide; endothelial dysfunction is not caused by Methylene Blue; MB works by inhibiting the cGMP pathway (it is not a vasoconstrictor itself); after 40 minutes of a single bolus, MB plasma level decrease sharply; and it is possible that MB has a "window of opportunity" for its effectiveness.
Conclusions	The benefits of Methylene Blue have been well documented over the years, but there is no standard in regard to its dosage and timing of administration. It is possible that the overall effectiveness of MB is time-sensitive, and further studies are needed with the intention of developing a protocol.
Appraisal: Worth to Practice/Level	This literature review falls under the Level II category of evidence. The strength of evidence is good and consistent, which calls for further studies. / This article has merit because cardiovascular disease is a major problem worldwide, and the vasoplegic syndrome that often develops after CPB is associated with poor patient outcomes and prognosis. As the authors stated, there is no standard in regard to dosage and timing of administration for MB. There is need for the establishment prophylactic guidelines and determination of a therapeutic window.

Evaluation table 6

Citation	Levin RL, Degrange MA, Bruno GF, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Annals of Thoracic Surgery.* 2004;77(2):496-499.
Design/Method	This was a multicenter RCT in which patients undergoing cardiac surgery with cardiopulmonary bypass were selected and consented. The subjects with VS were

	randomly assigned to one of two groups; one group received 1.5 mg/kg of intravenous Methylene Blue, and the other was the control group.
Sample/Setting	638 patients were initially included in the study, but only 56 of them met the criteria of VS post-CPB. All subjects were scheduled for elective cardiac surgery between 2001 and 2002.
Major Variables Studied and Their Definitions	"Vasoplegic syndrome was defined using the following criteria: hypotension, mean arterial pressure less than 50 mm Hg, low filling pressures, central venous pressure less than 10 mm Hg, normal or elevated cardiac index more than 2.5 $L/m/m^2$, low peripheral resistance, less than 800 $dyne/s/cm^{-5}$, and vasopressor drug requirements." MAP: (mean arterial pressure) average pressure in the arteries during one cardiac cycle; CVP: (central venous pressure) blood pressure in the vena cava near the right atrium; PCWP: (pulmonary wedge pressure) pressure measured by wedging a pulmonary catheter with an inflated balloon into a pulmonary artery; CI: (cardiac index) cardiac output in relation to total body surface area; SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; and vasopressor requirements.
Measurement and Data Analysis	"The differences between populations with and without VS (control group) were analyzed as were those treated with MB and the placebo using the x^2 test and Fischer's exact test for those categorical variables and the Student's t test for continuous variables. The relationship among variables is shown as odds ratio (OR) of 95%. A p value lower than 0.05 was considered significant."
Findings	**Mortality control** ➔ 6 (21.4%) **Mortality MB** ➔ 0 **Renal failure control** ➔ 4 (14.3%) **Renal failure MB** ➔ 0 **Dialysis control** ➔ 2 (7.1%) **Dialysis MB** ➔ 0 **Respiratory failure control** ➔ 4 (14.3%) **Respiratory failure MB** ➔ 0 **Liver failure control** ➔ 3 (10.7%) **Liver failure MB** ➔ 0 **CVA control** ➔ 1 (3.6%) **CVA MB** ➔ 0 **Neumopathy control** ➔ 4 (14.3%) **Neumopathy MB** ➔ 0 **SVT arrhythmia control** ➔ 8 (28.6%) **SVT arrhythmia MB** ➔ 2 (7.1%) **Ventricular arrhythmia control** ➔ 3 (10.7%)

	Ventricular arrhythmia MB ➔ 0 **Sepsis control** ➔ 7 (25%) **Sepsis MB** ➔ 0 **Multi-organ dysfunction control** ➔ 7 (25%) **Multi-organ dysfunction MB** ➔ 0
Results	None of the patients in the MB group perished. Additionally, vasoplegia resolved within 2 hours for all subjects in this group. On the other hand, 8 out of 28 patients in the control group remained vasoplegic beyond the 48-hour mark and 6 of those perished.
Conclusions	Out of the original 638 patients selected, only 56 met the criteria of post-CPB VS. The control group demonstrated higher incidence of morbidity and mortality, while the MB group reduced postop complications in this high-risk population.
Appraisal: Worth to Practice/Level	This randomized control trial falls under the Level I category of Evidence. This RCT has good quality because it had adequate forms of control, an adequate sample size, consistent results, fairly definitive conclusions, consistent recommendations, and it included references to other scientific evidence. / This study has merit because it pertains to cardiovascular disease, which is a major problem worldwide. The mortality rate in the MB group was 0% and postoperative complications were minimal. This study calls for further studies; particularly for studies that target prevention rather than rescue therapy.

Evaluation table 7

Citation	Mehaffey JH, Johnston LE, Hawkins RB, et al. Methylene Blue for Vasoplegic Syndrome After Cardiac Operation: Early Administration Improves Survival. *Annals of Thoracic Surgery*. 2017;104(1):36-41.
Design/Method	This was a retrospective observational study with no control group. "All patients that underwent cardiopulmonary bypass at our institution (Jan 1, 2011 to Jun 30, 2016) were identified through our Society of Thoracic Surgery database. Pharmacy records identified patients receiving MB within 72 hours of cardiopulmonary bypass. Multivariate logistic regression identified predictors of major adverse events among patients receiving MB."
Sample/Setting	Out of the 3,608 patients that underwent surgery under CPB in the aforementioned time frame, only 118 subjects received MB treatment for VS post-CPB.
Major Variables Studied and Their Definitions	The diagnosis of post-CPB vasoplegia "includes vasodilation characterized by low SVR with elevated cardiac index (CI) resulting in hypotension despite high doses of vasopressors on pump or postoperatively." SVR: (systemic vascular resistance) resistance in the systemic circulatory system which the left ventricle has to overcome in order to perfuse the body; CO: (cardiac output) amount of blood the heart pumps through the circulatory system in a minute; CI: (cardiac index) cardiac output in relation to total body surface area; MAP: (mean arterial pressure) average pressure in arteries during one cardiac cycle; MAE: major adverse events; Early administration: intraoperatively; Late administration: in the ICU setting; and vasopressor requirements.

Measurement and Data Analysis	"The primary outcome was major adverse event (MAE) after administration of MB for vasoplegic syndrome. MAEs included the STS major morbidities (permanent stroke, renal failure, reoperation, deep sternal wound infection, and prolonged ventilation) as well as operative mortality (in-hospital or 30-day). Standard STS definitions were used for all variables, including new onset renal failure and prolonged ventilation (>24 hours). In addition, preoperative and intraoperative variables associated with MB treatment for vasoplegic syndrome were assessed. Early administration was defined as operating room, and patients not receiving MB until reaching the postoperative intensive care unit were classified as late administration. Univariate analysis was performed using x^2 and Mann-Whitney U tests for categorical and continuous variables, respectively. Multivariable logistic regression was used to identify risk-adjusted predictors of MAEs in patients receiving MB for vasoplegic syndrome. SAS version 9.4 (SAS Institute, Cary, NC) statistical soft- ware was used for analysis with a statistical threshold for significance set at 0.05."
Findings	**Postop A Fib control** ➔ 725 **Postop A Fib MB** ➔ 27 **Stroke control** ➔ **71** **Stroke MB** ➔ 6 **Renal failure control** ➔ 151 **Renal failure MB** ➔ 25 **Deep sternal wound infection control** ➔ 2 **Deep sternal wound infection MB** ➔ 1 **Reoperation control** ➔ 222 **Reoperation MB** ➔ 31 **Prolonged ventilation control** ➔ 232 **Prolonged ventilation MB** ➔ 27 **Operative mortality control** ➔ 112 **Operative mortality MB** ➔ 55 **Major adverse event composite control** ➔ 516 **Major adverse events composite MB** ➔ 55 <u>Outcomes of MB administration for VS (early vs late)</u> **Postop adverse event (early)** ➔ 34 **Postop adverse event (late)** ➔ 53 **Blood transfusion (early)** ➔ 44 **Blood transfusion (late)** ➔ 58 **Length of stay (days) (early)** ➔ 12 **Length of stay (days) (late)** ➔ 12

	Postop A Fib (early) ➔ 14 **Postop A Fib (late)** ➔ 13 **Postop cardiac arrest (early)** ➔ 5 **Postop cardiac arrest (late)** ➔ 8 **Stroke (early)** ➔ 2 **Stroke (late)** ➔ 4 **Renal failure (early)** ➔ 5 **Renal failure (late)** ➔ 20 **Reoperation (early)** ➔ 10 **Reoperation (late)** ➔ 21 **Deep sternal wound infection (early)** ➔ 1 **Deep sternal wound infection (late)** ➔ 0 **Prolonged ventilation (early)** ➔ 11 **Prolonged ventilation (late)** ➔ 16 **STS major morbidity (early)** ➔ 17 **STS major morbidity (late)** ➔ 37 **30-day mortality (early)** ➔ 5 **30-day mortality (late)** ➔ 20
Results	The group that was administered Methylene Blue intraoperatively at the onset of VS had significantly lower rates of major adverse effects and eventual mortality. The group that received treatment late (once admitted into the ICU) demonstrated suboptimal results when compared to the early group.
Conclusions	The rate of morbidity and mortality in patients that experience VS post-CPB is high. Methylene Blue has proven to ameliorate VS, and this study reinforced postulations from other clinicians that MB has a "window of opportunity" in regard to its maximum efficiency. In this study, early treatment with Methylene Blue reduced the incidence of postop complications and improved that chance of survival.
Appraisal: Worth to Practice/Level	This retrospective observational study falls under the Level III category of evidence. The evidence itself seem promising, with consistent and compelling results. / This study is worthwhile because it deals with cardiovascular disease, which is a major problem worldwide. Furthermore, positive and consistent results were attained. A prospective RCT should be the next step to definitively ascertain the relationship between timing of administration and efficacy of Methylene blue for refractory hypotension that often follows the period after cardiopulmonary bypass.

Appendix B: IRB Exemption Letter

Office of Research Integrity
Research Compliance, MARC 414

MEMORANDUM

To: Dr. Vicente Gonzalez

CC: Cesar Lopez

From: Elizabeth Juhasz, Ph.D., IRB Coordinator EJ

Date: June 17, 2021

Protocol Title: "Prophylactic Administration of Methylene Blue to Surgical Patients to Prevent Hypotension after Cardiopulmonary Bypass: An Educational Module for Anesthetic Practice"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-21-0248 **IRB Exemption Date:** 06/17/21

TOPAZ Reference #: 110237

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.

2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.

3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

APPENDIX C: Recruitment Letter

Mount Sinai
MEDICAL CENTER

March 1, 2021

Vicente Gonzalez, DNP, CRNA, APRN
Clinical Education Coordinator
Department of Nurse Anesthesiology Practice
Florida International University

Dr. Gonzalez
Thank you for inviting Mount Sinai Medical Center to participate in Doctor of Nursing Practice (DNP) project conducted by Cesar Lopez entitled "Prophylactic Administration of Methylene Blue to Surgical Patients to Prevent Hypotension after Cardiopulmonary Bypass: An Educational Module" in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthetist Practice at Florida International University. I have warranted his permission to conduct the project using our providers.

This project intends to evaluate if a structured education targeting providers will increase knowledge on the use of Methylene Blue to prevent hypotension after cardio-pulmonary bypass. Prior to the implementation of this educational project, the Florida International University Institutional Review Board will evaluate and approve the procedures to conduct this project.

We understand the educational intervention will be via Qualtrics, with pretest and posttest questionnaire, any data collected by Cesar Lopez is confidential and will be stored in a locked filing cabinet at our office. We expect that Cesar Lopez will not interfere with normal hospital performance, behaving in a professional manner and following standards of care.

We support the participation of our provides and staff in this project and look forward to working with you.

Jampierre Mato, DNP, CRNA

Date: March 1, 2021

Executive CRNA Director

Miami Beach Anesthesiology Assoc.

Student Supervisor

FIU Dept. of Nurse Anesthetist Practice

APPENDIX D: Educational Module Questionnaire

Pretest and Post-Test Questionnaire:

Prophylactic Administration of Methylene Blue to Surgical Patient to Prevent Hypotension after Cardiopulmonary Bypass: An Educational Module for Anesthetic Practice

INTRODUCTION

The primary aim of this educational project is to improve the knowledge of anesthesia providers pertaining to the role of Methylene Blue for patients that undergo cardiopulmonary bypass. Please answer the questions below to the best of your ability. The questions either in multiple choice or true/false format and are meant to measure knowledge and perceptions on the use of Methylene Blue for refractory hypotension.

PERSONAL INFORMATION

1. **Gender:** Male Female Other
2. **Age:** 20 – 29 30 – 39 40 – 49 50 – 59 60+
3. **Ethnicity:** African American Asian Caucasian Hispanic Other
4. **Level of Education:** Associates Bachelors Masters Doctorate
5. **How many years have you been an anesthesia provider?**

   1 – 2 years 3 – 5 years 6 – 9 years 10+ years

QUESTIONNAIRE

1. **Approximately what percentage of all mortality is attributed to cardiovascular disease?**
   - **a.** 11%
   - **b.** 21%
   - **c.** 31%
   - **d.** 41%

2. **The incidence of refractory hypotension after cardiopulmonary bypass ranges from:**
    - **a.** 3% – 13%
    - **b.** 5% – 25%
    - **c.** 12% – 32%
    - **d.** 2% – 4%
3. **Vasoplegic syndrome is characterized by:**
    - **a.** Significant arterial hypotension, normal or high cardiac output, low systemic resistance, increased vasopressor requirements, and increased requirement for intravenous volume.
    - **b.** Significant arterial hypotension, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, temperature > 38 C or < 36 C, increased vasopressor requirements.
    - **c.** Significant arterial hypotension, low cardiac output, low systemic vascular resistance, increased nitric oxide production, decreased requirement for intravenous volume.
    - **d.** Significant arterial hypertension, heart rate < 60 beats/min, irregular respiratory pattern.
4. **Which factors increase the likelihood of refractory hypotension after cardiopulmonary bypass?**
    - **a.** Perioperative use of beta-blockers
    - **b.** Preoperative use of angiotensin-converting enzyme inhibitors
    - **c.** Preoperative use of calcium channel blockers
    - **d.** Low ejection fractions
    - **e.** A, B, C
    - **f.** All of the above
5. **Mortality rates for patients experiencing persistent vasoplegia for ___ to ___ hours range from 25% to 28.6%:**

a. 12 – 18

b. 24 – 36

c. 36 – 48

d. 72 – 96

6. **Uses for Methylene Blue include:**

a. Treatment of Methemoglobinemia

b. Surgical marker during urology procedures

c. Treatment of hypotension refractory to vasopressors

d. Identification of specific endocrine tissue

e. A, B

f. All of the above

7. **How does Methylene Blue raise blood pressure?**

a. Direct alpha-adrenergic stimulation

b. Direct alpha-adrenergic and beta-adrenergic stimulation, and indirect release of endogenous catecholamines

c. Prevention of smooth muscle vasodilation due to blockade of nitric oxide synthase

d. Potentiation of guanylate cyclase that increases intracellular levels of cyclic CMP

8. **Traditional treatment options for refractory hypotension that can occur after separation of cardiopulmonary bypass include:**

a. Phenylephrine infusion

b. Norepinephrine infusion

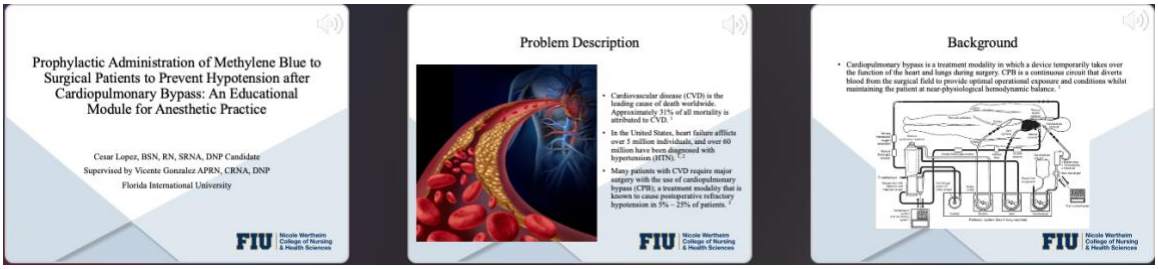
c. Crystalloid infusion

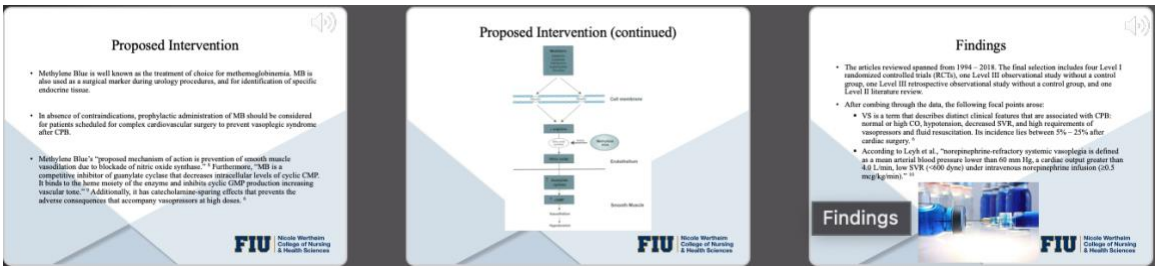
d. All of the above

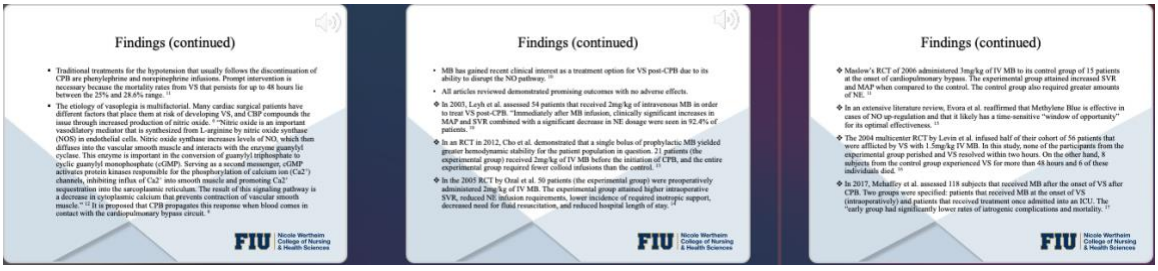
e. None of the above

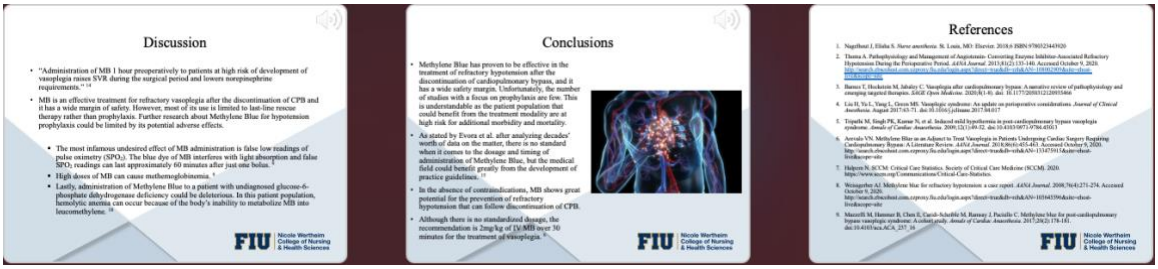
9. **What is the recommended dosage of Methylene Blue for the treatment of hypotension?**
    - **a.** 1mg/kg
    - **b.** 2mg/kg
    - **c.** 4mg/kg
    - **d.** 8mg/kg
10. **Methylene Blue can interfere with light absorption and result in false low readings on pulse oximetry. How long can this effect last after just one bolus?**
    - **a.** 15 minutes
    - **b.** 30 minutes
    - **c.** 45 minutes
    - **d.** 60 minutes
    - **e.** 90 minutes
11. **In which type of patient condition is Methylene Blue contraindicated?**
    - **a.** Glucose-6-phosphate dehydrogenase deficiency
    - **b.** Pseudocholinesterase deficiency
    - **c.** Multiple Endocrine Neoplasia Type 1
    - **d.** Sepsis
12. **How likely are you to use prophylactic Methylene Blue when providing anesthesia services for patients undergoing cardiopulmonary bypass?**
    - **a.** Highly likely
    - **b.** Likely
    - **c.** Unlikely
    - **d.** Highly unlikely

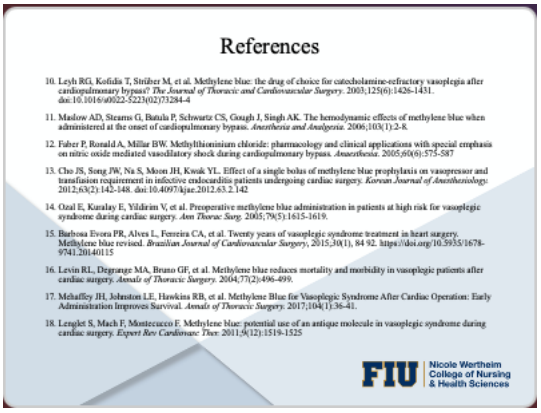
APPENDIX E: Educational Module











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