Methylene Blue as an Adjunct to Treat Vasoplegia in Patients Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass: A Literature Review

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The term vasoplegia describes hypotension refractory to vasopressor therapy, a common finding related to cardiac surgery requiring cardiopulmonary bypass. High doses of vasoactive agents are associated with adverse effects such as peripheral and mesenteric ischemia. Databases were systematically searched for literature on methylene blue as an adjunct therapy to treat vasoplegia. Fifteen articles were selected. The quality of the studies was evaluated using the US Preventive Services Task Force (USPSTF) grading tool, and a chart was created to present the components of each study. Preoperative, intraoperative, and postoperative administration of methylene blue has been shown to increase systemic vascular resistance and mean arterial pressure, with the period after surgery being the most common time for use of this therapy. Decreased vasopressor requirements have also been consistently demonstrated after methylene blue administration. This catecholamine-sparing effect prevents vasopressor-related injury. Its favorable safety profile as well as hemodynamic effects have made methylene blue a valuable adjunct in the setting of vasoplegia. Methylene blue is an effective treatment of refractory hypotension related to cardiac surgery requiring cardiopulmonary bypass. Larger, randomized controlled trials are needed to strengthen the state of the evidence and to define specific doses.

Keywords: Cardiac surgery, methylene blue, refractory hypotension, vasoplegia.

The term *vasoplegia* is used to describe a combination of clinical findings associated with cardiopulmonary bypass (CPB), including normal to high cardiac output, decreased systemic vascular resistance (SVR), hypotension, and increased vasopressor requirements.[1] There is no consensus on specific hemodynamic values that are associated with vasoplegia, but, in general, mean arterial pressure (MAP) less than 65 mm Hg, SVR less than 700 dynes · sec/cm^5, and cardiac index greater than 2.5 L/min/m^2 in the presence of high-dose vasopressor infusions characterize vasoplegia.[2] The incidence of vasoplegia after cardiac surgery ranges from 5% to 25%. Higher rates are noted in high-risk patient populations such as those receiving angiotensin-converting enzyme (ACE) inhibitors (44%), calcium channel blockers (47%), and heparin (55%).[3] Patients experiencing vasoplegic syndrome refractory to vasopressors have increased rates of morbidity and mortality. Mortality rates for patients experiencing persistent vasoplegia for 36 to 48 hours range from 25% to 28.6%.[4,5]

Traditional treatment of vasoplegia includes administration of fluids and vasopressor agents such as phenylephrine and norepinephrine.[3,6] These medications are usually enough to maintain hemodynamic stability,[4] but in some instances vascular tone can be refractory to conventional treatment. High doses of vasopressor therapy have serious adverse effects, including ischemia of the extremities and intestinal hypoperfusion, which could lead to tissue necrosis and metabolic acidosis.[4,7] Furthermore, norepinephrine has been shown to decrease pulmonary, cutaneous, renal, and splanchnic blood flow.[8] Patients who are dependent on vasopressor therapy show higher serum lactate and creatinine concentrations, have increased requirements for renal replacement therapies, and have prolonged intensive care unit stays.[9] These factors have led to a search for alternative therapies to restore hemodynamics and prevent negative outcomes associated with decreased perfusion and high-dose vasopressor therapy. Methylene blue (MB), a guanylyl cyclase inhibitor, is a novel agent that is gaining recognition as a useful adjunct in patients with vasoplegia.

The purpose of this review is to discuss the state of the evidence regarding the use of MB in adults experiencing vasoplegic shock related to cardiac surgery requiring CPB. Anesthetists are responsible for the initiation and management of hemodynamics in the perioperative period. It is therefore prudent to increase awareness of the potential benefit of MB administration.

Review of Literature

• ***Method of Literature Search.*** A comprehensive review of the literature was performed using the following

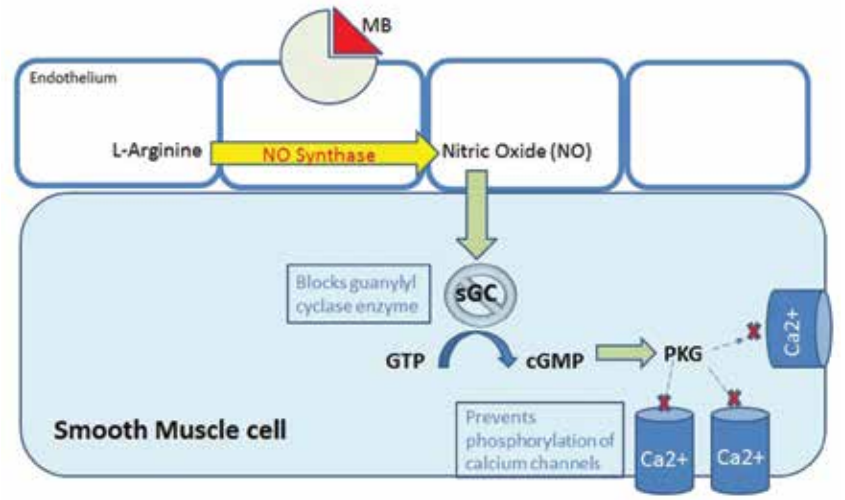

Figure. Mechanism of Action of Methylene Blue (MB)
Abbreviations: $Ca2^{+}$, calcium ion; cGMP, cyclic guanylyl monophosphate; GTP, guanylyl-triphosphate; PKG, protein kinase G.

databases: The Cochrane Library, PubMed, and Ovid MEDLINE. Google Scholar was also accessed to retrieve more articles. Medical Subject Heading (MeSH) terms were used to search for articles consistent with the subject focus, and the Boolean operator AND was used to narrow the search. The original search yielded 290 results using the MeSH terms *methylene blue* AND *vasoplegia*, and the second search yielded 230 results after addition of a third MeSH term *cardiac surgery* AND *vasoplegia*. No limitations were placed on the publication date. These results were broad, so individual databases were then used to focus on more pertinent information. The Cochrane Library was searched using the same 3 MeSH terms *methylene blue* AND *vasoplegia* AND *cardiac surgery*. This process displayed only 3 results, all of which were relevant to the topic of interest. PubMed yielded 35 results using the same search criteria, and MEDLINE displayed 23 results. A final method of article discovery involved a manual search of reference lists obtained from other articles.

After careful consideration of the results, only 15 articles were found to be consistent with the subject and were included in the literature review. Articles that only briefly mentioned MB or focused on pediatrics were excluded.

• ***Grading of Evidence.*** Of the included studies, 1 was a meta-analysis, 5 were randomized controlled trials, 2 were quasi-experimental studies, 1 was a retrospective nonexperimental study, and 6 were case reports. The compiled literature was graded based on the quality, quantity, and consistency of findings, using the US Preventive Services Task Force grading scheme. Each article was given a letter grade representing the strength of the recommendations found in that article. A grade A article is one in which the study methods and statistical analysis are strong, which gives a high level of certainty that the net benefit described in the article is substantial. A grade B article is missing variables such as effect size and confidence intervals that lend strength to articles but is strong enough that there is a high certainty that the benefit described is moderate or there is moderate certainty that the net benefit is moderate to substantial. The Table delineates each study and the corresponding grade it received, with the meta-analysis eliminated to prevent overlap of data.

All but one of the selected articles received either a grade A or B, showing that the literature provides fair to good evidence recommending the intervention. One article received a grade C, where the balance of benefits and harm was too close to justify a recommendation. After exclusion of that study, a matrix was developed, with similar studies grouped in chronological order (Table). The first study in the Table focused on preoperative administration of MB in patients who were deemed to be at high risk of development of vasoplegia (ie, those receiving ACE inhibitors, heparin, and calcium channel blockers). Four studies investigated the use of MB intraoperatively either right before CPB or added to the pump prime solution. Literature pertaining to the efficacy of postoperative MB administration comprised 8 studies. These studies combined represent the benefit of using MB during the entire perioperative period.

• ***Pathophysiology of Vasoplegia.*** The pathophysiology of vasoplegic syndrome is complex. The etiology is multifactorial, but literature shows that the inflammatory response initiated by CPB plays a major role in the development of refractory hypotension, primarily via increased endogenous nitric oxide (NO) production.[7,10,11] Nitric oxide is an important vasodilatory mediator that is synthesized from L-arginine by nitric oxide synthase (NOS) in endothelial cells. There are 2 forms of NOS, a constitutive form (cNOS) and an inducible form (iNOS).[2] The former is important for normal vascular tone control and the latter is upregulated after CPB. 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.[2] The result of this signaling pathway is a decrease in cytoplasmic calcium that prevents contraction of vascular smooth muscle.

The mechanism by which CPB is thought to propagate the inflammatory response that leads to NO-induced vasoplegia starts when blood contacts the CPB circuit. This results in platelet adhesion and activation of the complement and kallikrein-bradykinin systems.[12] Complement induces release of anaphylatoxins C3a and C5a, which stimulate production of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6.[12] These cytokines are known to increase the expression of iNOS that subsequently leads to the upregulation of NO production and the hemodynamic dysregulation characteristic of vasoplegic syndrome.[2] These same interleukins can also activate guanylyl cyclase independent of NO, leading to more pronounced vasodilation.[3] Activation of the kallikrein-bradykinin system by CPB increases circulating levels of bradykinin, which have been shown to be a guanylyl cyclase activating factor independent of nitric oxide.[13] Further increases in bradykinin occur because of lack of bradykinin lung metabolism due to cardiopulmonary bypass. Multiple pathways appear to contribute to the pathophysiology of vasoplegia, but the final common pathway involves guanylyl cyclase and increased levels of cGMP as prominent mediators of vasodilation. A guanylyl cyclase inhibitor, such as MB, attenuates this response (Figure).

• ***Methylene Blue.*** Historically, MB has been used to treat methemoglobinemia, prevent urinary tract infections in elderly patients, and intraoperatively to visualize the ureters, nerve tissue, or endocrine glands.[3] Its characteristic blue color makes it an excellent marker to visualize these structures. Recent literature has identified additional applications of MB, including vasoplegic syndrome after cardiac surgery requiring CPB and hypotension in septic shock and anaphylaxis.[14] The focus of the present literature review focuses on the use of MB in vasoplegia.

All 15 articles reviewed focused on patients undergoing cardiac surgery requiring CPB. The dosing and timing of MB administration varied between studies, with doses ranging from 0.5 to 2 mg/kg/h for 1- to 6-hour infusions or bolus doses of 2 to 3 mg/kg given preoperatively, intraoperatively, or postoperatively. Doses of 2 mg/kg over 20 to 30 minutes postoperatively was the most common approach. There was also variability in exclusion criteria, but the most commonly listed were endocarditis, off-pump cardiac procedures, aortic dissection, emergent procedures, and preexisting lung disease.

The most common adverse effect of MB administration is blue-green–tinged urine lasting up to 4 days.[5,15-20] Falsely low pulse oximeter readings are also common following MB administration because the blue dye interferes with the absorption of light. This effect can last about 60 minutes after a single bolus or longer with a continuous infusion[21]; other methods, such as arterial blood gas sampling, may be needed to monitor oxygen saturation. Providers should be aware that higher doses of MB could cause methemoglobinemia,[22] which is an increased amount of oxidized hemoglobin levels in the blood leading to decreased oxygen-carrying capacity.[23] Cyanosis despite adequate blood oxygen content, hypoxemia, and metabolic acidosis is evidence of this adverse effect.[24] Because methemoglobin absorbs both red and near-infrared light equally, another common finding in patients with methemoglobinemia is pulse oximeter readings of 85%.[25]

Methylene blue has been associated with decreased cardiac output, renal and mesenteric blood flow, cardiac dysrhythmias, coronary artery vasoconstriction, and increases in pulmonary pressures leading to impaired gas exchange.[3,11,13,26] These events have been documented with doses exceeding 2 mg/kg.[13,15] Report of decreased Pao_2 to fraction of inspired oxygen after CPB[27] cannot be attributed solely to MB administration but could result from pulmonary edema, a consequence of the inflammatory response due to CPB that causes increased capillary membrane permeability and decreased oxygen diffusion capacity.[28] The possibility of pulmonary hypertension[29] indicates that patients with underlying pulmonary vasculature dysfunction are not ideal candidates for this therapy. However, most of the literature shows that pulmonary pressures are unchanged after MB administration.[15,16,20]

Cautious use of MB is warranted in patients with a deficiency of glucose-6-phosphate dehydrogenase, a molecule responsible for the generation of nicotinamide adenine dinucleotide phosphate that is important in the conversion of MB into its metabolites.[30] Hemolytic anemia may result from accumulation of MB because of the inability of these patients to reduce the medication into leucomethylene.[3,7,11]

Discussion

Administration of MB 1 hour preoperatively to patients at high risk of development of vasoplegia (ie, those receiving ACE inhibitors, calcium channel blockers, and heparin) raises SVR during the surgical period and lowers norepinephrine requirements.[15] This maintenance of hemodynamic parameters after MB administration prevents vasoplegia postoperatively compared with individuals who do not receive MB (0% vs 26%). Crystalloid administration is also lower in those who receive MB preopera-

Study	Sample size	Patient exclusion criteria	Dose of MB used	Measurements	Results	USPSTF grade
Preoperative MB administration						
Ozal et al,[15] 2005	N = 100: n = 50 in control group; n = 50 in experimental group	Cardiogenic shock, EF < 35%	2 mg/kg administered over 30 min, 1 h before surgery	SVR, CO, MAP, CVP (measured every 5 min during surgery and every 30 min after surgery), norepinephrine requirements	• SVR significantly higher in experimental group during surgical period ($P < .001$). • Norepinephrine was required by significantly fewer patients in experimental group ($P < .001$). • MB group required less administration of crystalloid ($P = .024$), colloid ($P = .027$), and RBCs ($P = .001$). • Clinical signs of vasoplegia were seen significantly more often in control group (13/50 vs 0/50 in MB group). • Mean ICU/hospital stay was longer in control group (2.1 ± 1.2 days vs 1.2 ± 0.5 days in MB; $P < .001$).	A
Intraoperative MB administration						
Grayling & Deakin,[27] 2003	N = 1: 72-year-old man undergoing valve surgery for infective endocarditis	NA	2 mg/kg via pump prime followed by infusion of 1 mg/kg/h, which was then decreased to 0.5 mg/kg/h after CPB was weaned. Infusion was turned off 30 min later.	SVR, vasopressor requirements	• After MB therapy was initiated, no further phenylephrine or norepinephrine was needed. • SVR increased.	B
Ribeiro et al,[16] 2004	N = 60: n = 30 in control group; n = 30 in experimental group	None noted	2 mg/kg before CPB over 6 h independent of surgical time	Cytokine/NO level, hemodynamic parameters	• SVR and MAP increased in MB group ($P < .05$). • SVR was higher in MB group at all timeframes, especially 6 h after CPB. • NO levels were significantly higher in control group ($P < .05$). • No significant difference occurred between PAPs and PVR. • Measurement of interleukins did not show significant differences between the 2 groups, but TNF-α was significantly lower in MB group.	B

Maslow et al,[5] 2006	N = 30: n = 15 in control group; n = 15 in experimental group	Emergency surgeries, patients receiving vasopressors before heart surgery, renal insufficiency, hepatic disease, or evidence of acid-base abnormalities preoperatively. Also pregnancy, history of sensitivity to MB, and known G6PD deficiency.	3 mg/kg after initiation of CPB	MAP, SVR, PAP, RAP, PAOP, CO (all values obtained before MB administration, and 10, 20, 40, and 60 min after MB administration), PaO_2, lactate level, vasopressor requirements	• Immediately after administration of MB, MAP increased significantly from predrug levels ($P < .001$) and was greater than in control group ($P < .05$). • Use of phenylephrine was reduced in MB group at all time periods, and fewer patients receiving MB required norepinephrine to maintain MAP after CPB ($P < .05$). - Lower lactate levels suggested that MB increases vascular tone without compromising global tissue perfusion. - Increased afterload. - PaO_2 was not significantly different between groups.	A
Cho et al,[17] 2012	N = 42: n = 21 in control group; n = 21 in experimental group	Positive blood culture results or signs of active inflammation, ASA class > 4, preexisting lung disease, severe hepatic or renal disease, cerebrovascular disease or coronary artery disease requiring revascularization	2 mg/kg over 20 min before CPB	Norepinephrine infusion rates, MAP, mean PAP, PAOP, cardiac index, and SVR obtained before MB, 20 min after CPB, after CPB was weaned, at sternum closure, immediately postoperatively, and 12 h postoperatively; transfusion requirements	• No significant difference occurred in vasopressor requirements in control vs experimental group. • Interestingly, 2 patients in the control group received MB postoperatively, and their blood pressure was restored (data omitted from the statistics). • MB decreased transfusion requirements. • Authors stated that subsequent infusion of MB may have yielded different results because MB declines after 40 min and in addition to CPB, an infective process is an additional stimulus potentially causing vasodilation that a single dose could not overcome.	A
Postoperative MB administration						
Yiu et al,[34] 1999	N = 1:72-year-old man after CABG	NA	2 mg/kg over 20 min	SVR, rate of vasopressor infusion	• SVR improved from 550 dynes to > 1,000. • Vasopressor requirements were decreased. Initially, patient required 45 µg/min of norepinephrine, but infusion was able to be turned off 1 h after MB; epinephrine therapy was weaned afterward.	B
Pagni & Austin,[32] 2000	N = 1: 20-year-old man after AVR	NA	2 mg/kg of MB over 30 min postoperatively; a second dose was given 22 h later	SVR, rate of vasopressor infusion	• SVR improved from 538 dynes to 842 dynes within first hour after first dose. SVR increased from 586 dynes to 1,058 dynes within 1 h after second dose. • Vasopressor requirements were decreased; norepinephrine therapy was discontinued 20 min after MB infusion; epinephrine therapy was slowly weaned.	B

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Kofidis et al,[18] 2001	N = 1: 55-year-old man after heart transplant	NA	2 mg/kg over 30 min	SVR, rate of vasopressor infusion	• Blood pressure immediately rose after MB administration. • Norepinephrine requirements decreased from 1 µg/kg/min to 0.22 µg/kg/min 1 h after MB administration, and norepinephrine therapy was discontinued after 6 h.	B
Leyh et al,[13] 2003	N = 54	Active endocarditis	2 mg/kg over 20 min	MAP, SVR, PAP, lactate, norepinephrine requirements, PaO_2/FIO_2	• Clinically significant increase in MAP/SVR and decrease in norepinephrine occurred 1, 6, and 12 h after MB administration ($P < .001$). • MB led to decreased lactate concentrations ($P < .001$). • MB decreased vasopressor requirements. • No significant change in mean PAP or PaO_2/FIO_2 was noted. • No adverse effects related to MB were noted.	A
Levin et al,[19] 2004	N = 56: n = 28 in control group; n = 28 in experimental group	Off-pump cardiac procedures, bacterial endocarditis, aortic dissection, emergent procedures	1.5 mg/kg over 1 h	Vasopressor requirements, morbidity and mortality, time to resolution of vasoplegia	• Mortality and morbidity was lower in MB group compared with vasopressors alone ($P = .01$); 6 patients died in the placebo group (21%) vs 0 patients in the MB group (0%). • After 3 h, vasopressor requirements were decreased in MB group ($P < .999$). • Resolution of vasoplegia took up to 48 h in placebo group vs intervention group ($P = .002$), in which resolution occurred 2-3 h after MB administration. • Incidence of renal failure, respiratory failure, sepsis, multiorgan dysfunction, and supraventricular arrhythmia was significantly lower in MB group. • No adverse effects related to MB were noted.	B
Raikhelkar et al,[33] 2012	N = 1: 74-year-old man after TAVR	NA	2 mg/kg MB over 30 min followed by an infusion of 0.5 mg/kg/h for 6 h	MAP, vasopressor requirements	• Norepinephrine and vasopressin infusions were able to be discontinued during MB infusion; over next few hours, epinephrine therapy was weaned off. • MB decreased lactate levels. • Hemodynamic stability occurred with MB administration.	B
Heim et al,[29] 2013	N = 200: 83 patients were treated with MB	None noted	An undefined dose was given IV over 20 min	Vasopressor requirements, survival rate	• SVR differences were not statistically significant. • Significant decreases in norepinephrine doses were noted. • Overall survival rates were similar for patients treated with MB and controls; however, survival rates 30 d postoperatively were better for MB-treated patients.	B
Manghelli et al,[20] 2015	N = 1: 75-year-old man after AVR/TAVR	NA	50 mg	SVR, vasopressor requirements	• Norepinephrine infusion dosage was decreased from 0.4 µg/kg/min to 0.24 µg/kg/min, and epinephrine dosage was tapered down from 0.2 µg/kg/min to 0.08 µg/kg/min, and patient remained normotensive. • PAPs were not affected. • MAP and SVR increased over next 3 h after MB administration.	B

Table. Study and Sample Size

Abbreviations: AVR, aortic valve replacement; CPB, cardiopulmonary bypass; CVP, central venous pressure; EF, ejection fraction FIO_2, fraction of inspired oxygen; G6PD, glucose-6-phosphate dehydrogenase; ICU, intensive care unit; IV, intravenously; MAP, mean arterial pressure; MB, methylene blue; NA, not available; NO, nitric oxide; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; RBCs, red blood cells; SVR, systemic vascular resistance; TAVR, transcatheter aortic valve replacement; TNF, tumor necrosis factor; USPSTF, US Preventive Services Task Force.

tively, secondary to a stable MAP and SVR.[15]

Intraoperative administration of MB increases MAP and SVR, leading to decreases in phenylephrine and norepinephrine requirements during and after CPB.[5,16,27] Methylene blue should be given before CPB is initiated, or it may be added to the pump prime solution. Contrary to these findings, patients with infective endocarditis who receive a single intraoperative bolus of MB show no statistical difference in vasopressor requirements or hemodynamic values compared with a control group.[17] Infective endocarditis may serve as an additional pathway for NO upregulation via endotoxin induced NOS, which overwhelms the system during CPB,[31] and these patients may benefit from a subsequent infusion of MB after the bolus dose.[27]

The most common time for MB administration for the treatment of vasoplegia is the postoperative period, when marked improvement in hemodynamic parameters and decreased pressor requirements are seen.[13,18-20,29,32-34] Mortality among patients with vasoplegia is lower when MB is administered compared with vasopressor therapy alone, which does not resolve vasoplegia until 48 hours postoperatively.[19] Differences in mortality are likely secondary to lower incidence of renal failure, respiratory failure, sepsis, multiorgan dysfunction, and supraventricular arrhythmia in patients administered MB.[19] Findings of the current review study showed that of 28 patients treated with MB, none died; however, in the control group, 6 (21%) of 28 patients died.[13,33] Methylene blue administration postoperatively lowers lactate concentrations,[13,33] suggesting that MB increases vascular tone without compromising global tissue perfusion. Average intensive care unit and hospital stays are longer in vasoplegic patients who do not receive MB than in those who do.[15] This could have an impact on hospital costs, but studies are needed to support this idea. Methylene blue administration also decreases blood transfusion requirements,[15,17] decreasing the risk of transfusion-related consequences such as transfusion-related acute lung injury and transfusion-associated circulatory overload.

The effect of MB on morbidity after cardiac surgery is inconclusive. Results of a retrospective analysis indicate that MB use may be predictive of morbidity.[35] These findings are limited by unavailability of hemodynamic parameters, identification of vasoplegia based only on the need for vasopressor infusions, and the potential confounder that MB was given only to the sickest patients at the discretion of the anesthesia providers. However, substantial morbidity is possible in pregnant patients who receive MB, as teratogenic effects have been reported.[3] There is also a greater risk of hypoxia in the fetus due to inhibition of NO production.[2] For these reasons, MB is contraindicated in pregnancy.

Overall, MB is effective in treating vasoplegia related to CPB. Improvements in MAP and SVR are noted along with a decreased need for vasopressor therapy. Maintenance of hemodynamic parameters prevents the possible malperfusion associated with hypotension refractory to catecholamines. During the early postoperative period, it is important to maintain an adequate blood pressure to ensure sufficient organ perfusion.[18] Methylene blue has a catecholamine-sparing effect that is beneficial because it prevents adverse effects associated with high-dose vasopressor infusions such as ischemia and vasoconstriction of the coronary arteries.[19]

A meta-analysis on the use of MB as a vasopressor supports the idea that MB significantly raises MAP in patients with hypotension without a negative effect on survival.[36] It could not be determined whether a dose-dependent effect on hemodynamics occurs; however, MB has proved its ability to restore the physiological response to catecholamines in vasoplegia as well as other settings such as septic shock and anaphylaxis. Because of the small population sizes and variability in the literature, large randomized trials are still needed to strengthen the state of the evidence. However, this is difficult to accomplish in high-acuity patients presenting with vasoplegia because these critical situations involve the risk of death.[26]

Current literature suggests that MB is a safe and effective adjunct in treating vasoplegia associated with cardiac surgery and CPB that is refractory to catecholamines. The following recommendations are of moderate strength because larger studies are needed to provide sufficient statistical power to confirm the findings. Methylene blue can be administered preoperatively, intraoperatively, or more commonly postoperatively. Because dosing regimens and protocols have not been defined, careful evaluation of each patient is warranted by the anesthetist to determine the timeframe when MB would be most useful. Contraindications and possible side effects of this drug also must be considered.

Patients who are at increased risk of vasoplegia, such as those receiving ACE inhibitors, calcium channel blockers, or heparin, could benefit from preoperative or intraoperative use (ie, at the start of CPB). This would prophylactically inhibit guanylyl cyclase activation by NO and inflammatory cytokines. Methylene blue is most useful in the postoperative period when MAP and SVR are low despite high vasopressor infusions. In these cases in which first-line therapies have failed, MB is a safe and effective adjunct in the treatment of vasoplegia refractory to norepinephrine. Early administration of MB may halt the progression of hypoperfusion associated with low SVR and may prevent the need for prolonged vasopressor infusions.[10] A dose of 2 mg/kg of 10 mg/mL (1%) MB over 20 minutes is recommended upon recognition of vasoplegia before the shock is irreversible in the presence of metabolic acidosis and high lactate levels. A continuous infusion of 0.5 to 2 mg/kg/h can be initiated, with no

more than 7 mg/kg daily in patients who do not respond to a single bolus.[11,20,37] Methylene blue should not be relegated to a rescue drug, but rather considered an adjuvant therapy to be used after a thorough risk-benefit analysis.[26] The literature clearly indicates that the benefits of MB use far outweigh the risks for most patients.

Despite its safety profile in recommended doses, MB should not be administered to patients with known sensitivity to the drug or to those receiving serotonin reuptake inhibitors because the combination of medications could result in serotonin syndrome. Methylene blue is a monoamine oxidase inhibitor that, when interacting with other drugs that inhibit serotonin reuptake, can result in accumulation of serotonin, leading to symptoms such as mental status changes, autonomic hyperactivity, and hyperreflexia.[38] There are conflicting reports about the effect of MB on the pulmonary vasculature, so extra caution should be exercised if one is using MB in someone who has an underlying pulmonary condition such as pulmonary hypertension. This medication should be withheld from individuals with glucose-6-phosphate dehydrogenase deficiency and from those who are pregnant. Although it is clear that certain patients may not be candidates for MB therapy, most of the CPB population could benefit from the hemodynamic effects obtained from its off-label use without incurring significant risk.

Conclusion

Methylene blue is an effective treatment of refractory hypotension related to cardiac surgery requiring CPB. This medication can be administered preoperatively, intraoperatively, or most commonly, postoperatively. Methylene blue has a favorable safety profile; however, each patient should be assessed to identify any contraindications to administration. It should not be used as a last resort, but considered an adjunct medication to restore normal hemodynamic parameters. Larger, randomized controlled trials are needed to strengthen the state of the evidence and to define specific doses of this medication.

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