CME Methylene Blue: Magic Bullet for Vasoplegia?

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Methylene blue (MB) has received much attention in the perioperative and critical care literature because of its ability to antagonize the profound vasodilation seen in distributive (also referred to as vasodilatory or vasoplegic) shock states. This review will discuss the pharmacologic properties of MB and review the critical care, liver transplantation, and cardiac anesthesia literature with respect to the efficacy and safety of MB for the treatment of shock. Although improved blood pressure has consistently been demonstrated with the use of MB in small trials and case reports, better oxygen delivery or decreased mortality with MB use has not been demonstrated. Large randomized controlled trials are still necessary to identify the role of MB in hemodynamic resuscitation of the critically ill. (Anesth Analg 2016;122:194–201)

A primary goal of the cardiovascular system is to provide adequate systemic blood flow and perfusion pressure to maintain organ homeostasis. Achieving this goal requires that vasoconstrictor and vasodilator influences be carefully balanced. Under some pathologic conditions, a vasodilatory state predominates, potentially compromising end-organ perfusion.

Known as "distributive shock," this condition includes multiple different etiologies (e.g., septic, neurogenic, and anaphylactic) and ultimately results in uncontrolled vasodilation, otherwise termed "vasoplegia."[1] The pathophysiology of vasoplegia is multifactorial and includes activation of several intrinsic vasodilatory pathways and a pathologic insensitivity to vasopressors. In this state, the body is incapable of achieving adequate end-organ perfusion pressure because of a lack of vascular tone, despite adequate or even high cardiac output (CO).[1] Moreover, vasoplegic patients are minimally responsive to the use of multiple pharmacologic agents that selectively increase systemic vascular resistance (SVR).[1] Regardless of the etiology, mortality in patients with vasoplegia can be as high as 50%.[2–5] The choice of optimal treatment strategy for vasoplegia remains controversial, with concerns regarding restoration of macrocirculatory parameters through the administration of vasoconstrictors when the primary resuscitation goal should be in optimizing microcirculatory function.[6,7]

Methylene blue (MB) has received much attention in the perioperative and critical care literature because of its ability to antagonize the profound vasodilation seen in states of distributive shock.[8–12] This review will focus on the pharmacologic properties of MB and examine the literature in regard to efficacy and safety when MB is used to treat distributive shock.

PHARMACOLOGY/CLINICAL USE

MB is a heterocyclic aromatic molecule with the chemical formula $C_{16}H_{18}ClN_3S$. When dissolved in water, the odorless dark green powder turns into a blue solution. MB should not be confused with methyl blue or new MB commonly used for histologic stains or with methyl violets that are often used as pH indicators. MB is metabolized to leucomethylene blue by nicotinamide adenine dinucleotide phosphate and excreted primarily in urine, turning the urine a blue-green color.[13] A small portion of the drug is also excreted unchanged in the urine. MB should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency, because it can cause hemolytic anemia owing to a decreased ability to reduce MB into its metabolites.[14] The terminal half-life of MB is 5.25 hours.[15] MB is frequently used by physicians as a dye in various medical procedures, for example, during urological surgery to aid in identification of the ureters or parathyroid surgery to aid in identifying the gland. The vasoconstrictive effect of MB occurs only during cases of nitric oxide (NO) upregulation, and, thus, increases in blood pressure are not seen when NO is given as a dye during straightforward procedures in nonvasoplegic patients. MB has a long track record of safety as a dye and as a treatment of nitrate-induced methemoglobinemia. Although the blue color of MB can also interfere with the accuracy of pulse oximetry, most anesthesiologists are well aware of this interference.[16,17]

PROPOSED MECHANISM OF ACTION

Under physiologic conditions, vasoconstrictors, such as norepinephrine and angiotensin II, bind to and activate receptors on the surface of vascular smooth muscle cells. These receptors then activate a G-protein–based signaling mechanism that, in turn, opens membrane-bound calcium channels and increases intracellular calcium concentrations. A calcium and calmodulin complex then forms within the cytosol, which activates the phosphorylation of myosin light chains. This phosphorylation then allows myosin to interact with actin, ultimately leading to muscle contraction. In contrast, endogenous vasodilators, such as atrial natriuretic peptide and NO, lead to the dephosphorylation of myosin.[18] NO competitively binds to and activates the enzyme-soluble guanylate cyclase (sGC). Activation of this heterodimeric enzyme causes the formation of cyclic guanosine monophosphate (cGMP), which, in turn, activates protein kinase G, stimulating reuptake of Ca^{2+}, myosin dephosphorylation, and smooth muscle relaxation[19,20] (Fig. 1).

Physiologically, NO is continuously produced at low concentrations from the substrate L-arginine by the

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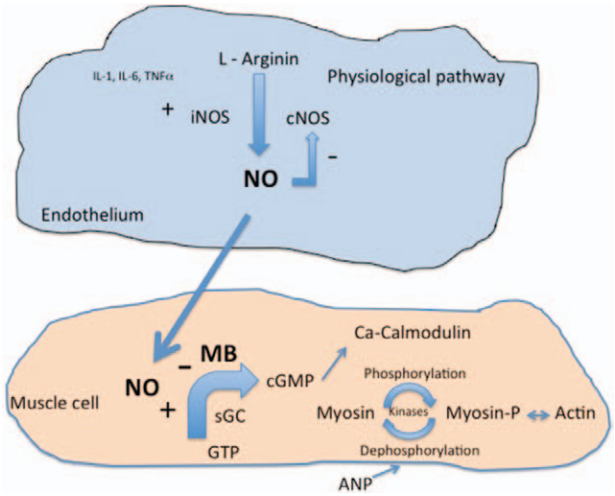

Figure 1. Nitric oxide–mediated vasodilation. ANP = atrial natriuretic peptide; cGMP = cyclic guanosine monophosphate; cNOS = constitutive nitric oxide synthase; GTP = guanosine-5′-triphosphate; IL-1 = interleukin-1; IL-6 = interleukin-6; iNOS = inducible nitric oxide synthase; MB = methylene blue; NO = nitric oxide; sGC = soluble guanylate cyclase; TNFα = tumor necrosis factor-α.

calcium-dependent enzyme nitric oxide synthase (NOS).[21] This enzyme plays an important role in the control of normal vascular tone. There are 2 forms of NOS: constitutive (cNOS), which has 2 isoforms, is constantly active and is found in neuronal and endothelial cells and inducible (iNOS), which is found in immunomodulatory cells, smooth muscle cells, and endothelium.[19,20,22–24] iNOS production is triggered by endotoxins and cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor-α, and interferon-γ.[25–28] Increased levels of these mediators are released in patients during cardiopulmonary bypass (CPB) and sepsis.[29] Although the activity of cNOS is regulated by a negative feedback mechanism, iNOS is not.[19,20,26] In states of severe inflammation, NO production is increased because of increased iNOS expression in the endothelium and vascular smooth muscle, leading to vasodilation. The amplified effects of iNOS are due to a 1000-fold greater ability to generate NO than cNOS. In addition, iNOS irreversibly binds to calmodulin, blocking its interaction with Ca^{2+} and preventing smooth muscle contraction.[30] Further mechanisms responsible for the loss of vascular tone include the activation of ATP-sensitive potassium channels (K_{ATP} channels) in the plasma membrane of vascular smooth muscle and deficiency of the hormone vasopressin.

MB directly inhibits NO synthase.[31,32] It also inhibits the enzyme sGC by binding to its iron heme moiety of sGC and preventing the accumulation of cGMP.[27,33–35] By competitively blocking the target enzyme of NO, MB reduces responsiveness of vessels to cGMP-dependent vasodilators and restores vascular tone (Fig. 1).

NO is not the only substrate that can activate sGC.[28,36] Interleukins and oxygen-free radicals can also do so, causing vascular hyporeactivity even in the absence of NO.[37,38] Thus, the unique ability of MB to inhibit sGC, the rate-limiting enzyme in the enzymatic cascade, may explain its superior ability to restore vascular tone even in the absence of NO.[11]

Increases in intracellular cGMP concentration relax not only vascular smooth muscle but myocardial myocytes as well, explaining why uncontrolled activation of iNOS has been linked not only to vasoplegia but also to the development of myocardial depression commonly encountered in sepsis.[39–41] Cytokines, such as IL-2, IL-6, and tumor necrosis factor-α, produce a negative inotropic effect through an NO-dependent mechanism.[42] In addition to a reduction in vasopressor requirements, contractile function of the myocardium could theoretically improve after the administration of MB.[43] Experimental animal studies report that, in addition to a reduction in vasopressor requirements, inotropic support is reduced after the administration of MB, likely because of attenuation of the ischemia/reperfusion injury.[44]

MB IN CARDIAC SURGERY

Vasoplegic syndrome (VS) is a recognized and relatively common complication of CPB. First described by Gomes et al.[45] in 1994, VS occurs in 5% to 20% of patients during or after CPB and is characterized by hypotension, high or normal COs, a low SVR, and increased requirements for fluids and vasopressors.[45–48] Clinically, VS is generally defined as a mean arterial pressure (MAP) <50 mm Hg, cardiac index >2.5 $L \cdot min^{-1} \cdot m^{-2}$, right atrial pressure <5 mm Hg, left atrial pressure <10 mm Hg, and low SVR (<800 $dyne \cdot s^{-1} \cdot cm^{-5}$) in the absence of obvious infection and despite high doses of IV norepinephrine infusion (>0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[48] The etiology of VS remains unclear. Chronic preoperative use of angiotensin-converting enzyme inhibitors, β-blockers, calcium channel antagonists, amiodarone, and heparin has been implicated.[5,49–54] Patients with a left ventricular ejection fraction <35%, congestive heart failure, and diabetes mellitus also may carry a higher risk for developing this condition.[50]

Clinicians should recognize that vasoplegia resulting in systemic hypotension is not a hemodynamic nuisance, correctable with vasoconstrictor administration, but a distinct pathologic entity associated with an increased mortality and morbidity.[52,54] This distinction is especially true for norepinephrine-refractory VS, which can affect patient outcomes.[52] Gomes et al.[2] found that prolonged postoperative VS (>36–48 hours) was associated with an increased rate of multiorgan failure and a 25% mortality rate.

The conventional treatment for intraoperative or postoperative VS has been hemodynamic support with vasopressors, such as phenylephrine, norepinephrine, or vasopressin. An extensive literature review by Egi et al.[55] comparing the use of several vasopressor agents in post-CPB patients found no evidence that vasopressor infusions impaired organ perfusion or function in patients with vasodilatory shock nor could they find evidence of the superiority of any particular vasopressor. High-dose vasoconstrictor therapy can have serious side effects, however, which include peripheral ischemia of the upper and lower extremities or mesenteric ischemia because of decreased intestinal blood flow.[56–60] Subsequent reperfusion can cause damage at the cellular level that may progress to the development of mucosal injury, tissue necrosis, and metabolic acidosis. Therefore, alternative approaches to combat VS are needed.

To date, most literature regarding the postoperative use of MB has described it as a therapeutic intervention of last resort to reverse vasoplegia. The use of MB to treat VS associated with cardiac surgery was first reported by Evora et al.[61] in 1997 and was recently reviewed by Faber et al.[4] in 2005. Several groups have reported that the postoperative administration of a single dose of MB in VS can restore SVR.[4,46,48] The same studies showed that MB was able to reduce the dosage of vasopressors required to maintain not only stable hemodynamics, but also the duration of vasoconstrictor dependence. Current evidence also supports an outcome benefit to MB in VS. In a 2004 study of 638 cardiac surgical patients, 56 had VS and were randomly assigned to receive MB or placebo. Mortality was lower in patients receiving MB who fulfilled vasoplegia criteria (0% vs 21.4%).[4] An observational study of 54 patients published by Leyh et al.[12] also showed MB to be effective in treating vasoplegia after CPB, and the successful use of MB for vasoplegia after heart transplant has also been described.[62]

In most studies, MB has been administered postoperatively as a single dose (1.5–2 mg/kg) to treat vasoplegia.[63] Other authors have reported using a maintenance infusion in addition to the initial dose.[64] In addition to postoperative use, limited existing literature supports the use of MB during the intraoperative period. Grayling and Deakin[65] describe the use of MB added to the pump prime as prophylaxis against the vasoplegia commonly encountered with valve surgery for septic endocarditis. Sparicio et al.[66] reported the perioperative use of MB in 2 patients who self-consumed lithium and developed refractory hypotension during beating heart surgery. Both patients improved dramatically after receiving MB. A severe protamine reaction led Evora[64] to administer MB to a patient in whom CPB had to be reinstituted. The authors were unable to maintain an adequate perfusion pressure with high-dose norepinephrine therapy but successfully restored normal hemodynamic parameters with MB administration.

Although initially used during the perioperative period only as a drug of "last resort," a few studies have argued for the benefit of the prophylactic use of MB. Ozal et al.[49] conducted a randomized controlled study of 100 patients undergoing coronary artery bypass surgery at high risk for VS because of preoperative angiotensin-converting enzyme inhibitors, calcium channel blockers, or heparin use. A preoperative MB infusion in the treatment group was associated with a higher SVR during surgery and lower requirements for norepinephrine, inotropic support, fluid, and blood transfusions. Moreover, prophylactic MB use prevented VS in every patient in the treatment group, whereas 26% (13/50) of the patients in the control group had VS. In 6 of these patients, VS was refractory to norepinephrine. Two of the 6 showed no resolution and eventually died of multiorgan failure. Interestingly, this study also noted that MB was ineffective if given after VS with multiorgan failure that had already developed, suggesting a greater benefit to early MB use.

In a 2006 randomized controlled trail, Maslow et al.[67] studied 30 patients who were at high risk of developing VS. They initiated MB administration after the onset of CPB and an initial period of stabilization and found improved patient hemodynamics and lower serum lactate levels than in patients not receiving MB. Critics were quick to question the timing of MB administration in this study, arguing that it was more logical to administer MB before initiating CPB to prevent the hypotensive insult of VS brought on by CPB.[68] Moreover, the study was insufficiently powered to evaluate the effects of MB on patient outcomes.

Not all published data support the generalized use of MB for treating vasoplegia. Grubb et al.[69] describe a potential interaction between MB and serotonin reuptake inhibitors (SSRIs) that led to the development of serotonin syndrome in a patient undergoing a heart transplant who received MB during CPB. Serotonin syndrome results when toxic levels of serotonergic agonism develop at central nervous system and peripheral serotonergic receptors.[69,70] The likely mechanism behind the interaction between MB and SSRI drugs includes MB inhibition of monoamine oxidase A. In 2011, the Food and Drug Administration released a warning detailing the increased likelihood of developing serious reactions when MB is administered to patients taking SSRIs, serotonin-norepinephrine reuptake inhibitors, or clomipramine, a tricyclic antidepressant. They recommended avoiding administering MB to patients chronically taking SSRIs and that SSRIs should be discontinued for at least 2 weeks before administering MB electively.[71]

Weiner et al.[72] reviewed the institutional experience with MB at Mount Sinai Hospital in New York in patients undergoing cardiac surgical procedures on CPB over a 2-year period. They identified 56 of 226 vasoplegic patients who had received MB and found that patients receiving MB had a significantly increased in-hospital mortality (odds ratio, 4.26; 95% confidence interval, 1.49–12.12) and a higher likelihood of experiencing a major morbidity (odds ratio, 4.80; 95% confidence interval, 1.85–12.43) compared with patients who were vasoplegic and had not received MB. After propensity score matching, however, only an association with morbidity (but not mortality) was identified. Issues regarding a possible "window of opportunity" for the use of MB and responders versus nonresponders to MB were expressed in letters to the editor critiquing the recommendations of Weiner et al. to use MB as a rescue agent only and not as first-line therapy.[73,74] They argued that MB should be used as a first-line agent for the right patient at the right time and called for randomized studies to better identify the use of MB under these circumstances. Until those studies are published, Weiner and Fischer[75] advocate for a conservative approach to the use of MB, as a rescue therapy for vasoplegia.

MB IN LIVER TRANSPLANTATION

Patients with end-stage liver cirrhosis are characterized as having a hyperdynamic circulation with a high CO and low SVR, primarily because of splanchnic arterial vasodilation.[76] Although the cause of this state is unclear, one hypothesis is that low systemic pressures combined with elevated portal pressures induce shear forces in the vascular walls between the 2 circulations, which causes the NO release from the endothelium and increased cGMP production and leads to relaxation of smooth muscles, decreased systemic vascular tone, and vasodilation.[77,78]

This hemodynamic dysregulation becomes further complicated when these patients undergo liver transplantation as major hemodynamic changes, and blood loss, transfusion, and clamping/unclamping of major blood vessels are all common to this procedure. The preexisting derangements impair the normal physiologic response to hypovolemia and anesthetic-induced vasodilation. Thus, the use of vasoconstrictors to maintain hemodynamic stability is common. Clinically, these drugs have been used most often during the neohepatic phase after graft reperfusion.[79]

Postreperfusion syndrome manifests as severe cardiovascular dysfunction with bradyarrhythmias, decreased CO, decreased MAPs, decreased SVR, and increased pulmonary artery pressures (PAPs), left atrial pressures, and central venous pressures. This syndrome may be so profound that it precipitates intraoperative cardiac arrest.[80] The etiology of postreperfusion syndrome has been attributed to the washout of organ preservation fluid, causing acute acidosis, hyperkalemia, and hypothermia. Vasoactive substances released from the liver graft itself may also be involved. The incidence of refractory hypotension after liver reperfusion can range from 17% to 50% and often requires the use of high-dose vasopressors to maintain hemodynamic stability.[81–84] Current evidence suggests that vasopressor use during liver transplantation, as opposed to increased fluid administration to maintain hemodynamic stability, decreases the postoperative reintubation rate.[85]

Another vasoplegic condition associated with liver transplantation is the ischemia-reperfusion syndrome (IRS), which also occurs after graft reperfusion. IRS is distinct from postreperfusion syndrome and results from damage to the vascular endothelium that eventually leads to a systemic inflammatory response.[86,87]

A VS similar to that occurring post-CPB may be associated with either postreperfusion syndrome or IRS. It is characterized by hypotension that persists after treating or excluding other etiologies of hypotension, including hypovolemia, electrolyte abnormalities, severe anemia, or acidosis.[88] Urgent hemodynamic rescue is important as continued hypotension is associated with adverse graft function and survival.[89]

As described earlier, proposed mechanisms of VS in these patients include deficiency of the hormone vasopressin, massive oxidative stress triggering the release of proinflammatory mediators (including iNOS activation), and vascular smooth muscle ATP-sensitive potassium channels.[1,3,19] The role of NO as a mediator in this clinical scenario suggests that MB would be an effective intervention. Bezinover et al.[90] reported a case of VS in which the patient presented with increased preoperative levels of cGMP. They concluded that screening patients preoperatively for cGMP levels could potentially be used to risk-stratify for the development of VS.

Currently, only case reports have investigated the use of MB for the treatment of vasoplegia during liver transplantation. Fischer et al.[10] first reported the use of MB to treat vasopressor-refractory VS during liver transplantation and observed improved blood pressure with 2 mg/kg as a bolus followed by an infusion of 0.5 mg/kg for 6 hours. Further experience is limited to additional case reports using varying dosages with good success as a rescue therapy.[78,91]

A few small studies have explored the prophylactic use of MB to prevent vasoplegia during liver transplantation. In a 2002 study of 36 patients, Koelzow et al.[92] showed that the prophylactic MB administration (1.5 mg/kg) resulted in significantly higher MAP, a higher cardiac index, and less epinephrine requirement than placebo. Furthermore, despite the vasoconstrictor effects of MB, the treatment group had lower serum lactate levels than the placebo group. Another case report found that improvements in blood pressure were most pronounced 5 hours after administration.[93] In a rabbit model, the effect of MB lasted longer when used as treatment rather than prophylaxis.[94]

However, a large 2011 study of prophylactic use of MB to prevent reperfusion syndrome argued against the routine use of MB during orthotopic liver transplant. In a propensity-matched study of 105 patients who received MB and 610 controls, Fukazawa and Pretto[88] found that the administration of MB as a bolus (1.5 mg/kg) immediately before reperfusion did not prevent postreperfusion hypotension or decrease vasopressor usage or transfusion requirements. However, they also found no detrimental effect of MB on postoperative graft function. By inhibiting vasodilation, MB could diminish microcirculatory perfusion[92] and theoretically adversely affect post-transplant graft function.[81]

MB has also been used in the setting of liver failure in patients not undergoing liver transplantation. The hepatopulmonary syndrome is characterized by a triad of severe liver disease, arterial hypoxemia, and pulmonary edema due to capillary vasodilation. Among other effects, this vasodilation may increase flow to poorly ventilated areas of the lung, overcoming normal physiologic hypoxic vasoconstriction, and thereby contributing to shunting and hypoxemia. Studies performed on a rat model have indicated that the vasodilatory NO pathway plays a key role in this development.[95,96] Whether inhibiting this pathway with MB leads to improvement in intrapulmonary shunt and hypoxemia remains controversial. Almeida et al.[97] and Thomson et al.[98] describe cases where MB administration substantially improved vascular tone but did not reduce intrapulmonary shunting and hypoxemia, whereas Rolla et al.[99] and Roma et al.[100] report cases where both intrapulmonary shunting and hypoxemia improved. Schenk et al.[101] found improvements in arterial hypoxemia in a small study of 7 cirrhotic patients with severe hepatopulmonary syndrome. Patients in the case reports cited earlier received a single bolus of 3 mg/kg MB.

MB IN SEPTIC SHOCK

Sepsis is defined as an infection in the presence of systemic inflammation and is characterized by alterations in temperature, heart rate, respiratory rate, and white blood cell count.[102] Septic shock is defined as sepsis associated with arterial hypotension and a blunted response to vasopressors, despite adequate fluid resuscitation.[102] Myocardial contractility is impaired in septic shock, further exacerbating hypoperfusion. Prolonged hypotension and maldistribution of blood flow eventually lead to multiorgan failure and death. Despite advances in recognition and treatment, septic shock still has a high mortality rate, ranging from 20% to 50%.[3]

As previously described, septic shock is mediated by cytokine stimulation of iNOS, which results in increased NO production.[9,25–27] Unlike cNOS, iNOS is not controlled by a negative feedback mechanism.[19,20,26] Uncontrolled iNOS stimulation leads to vasodilation, myocardial depression, vascular hyporesponsiveness toward vasoconstrictors, and increased vascular permeability.[103,104]

Treatments targeting iNOS overexpression in septic shock, however, have not uniformly found benefit. L-Arginine analogs nonselectively inhibit NOS by preventing the binding of L-arginine to catalytic sites of NOS and blocking NO production. They improve SVR and also reduce CO, have detrimental effects on tissue oxygenation, and increase mortality in patients with septic shock.[105–109] Although most of these data were obtained in animal studies, a large 2004 trial randomly assigned 797 septic patients to receive the nonselective NOS inhibitor N^G-methyl-L-arginine hydrochloride or placebo.[109] In this phase III study, patients exposed to the NOS inhibitor showed an increased mortality. Although the mechanism linking iNOS inhibition with mortality is poorly understood, some have postulated that NO release during septic shock may increase blood flow to ischemic areas, improving microcirculatory flow, scavenging oxygen-free radicals, and exerting microbiocidal properties by increasing macrophage activity.[8,103] As a result, investigators have considered whether more downstream inhibition of NO or a selective iNOS inhibitor might provide greater benefit to patients by maintaining the protective effects of NO on the microcirculation, while at the same time blocking the pathologic actions.[103,110] Although MB inhibits both NOS and sGC, some evidence suggests that it selectively inhibits iNOS.[111] Animal data also imply that MB effects on sGC predominate, as demonstrated by a study of rabbits given MB for anaphylactic shock.[112] Although MB improved blood pressure, plasma nitrate (a marker of NO release) did not differ between groups that did and did not receive MB, suggesting that MB mediated its actions primarily via sGC inhibition over NOS inhibition.[112] It is still not clear why the effects of MB in sepsis differ from those of other NO inhibitors. It is possible that MB targets different mediators within the NO cascade, resulting in less global depression of NO and possibly thereby maintaining the beneficial effects of NO.

Only 2 small randomized controlled trials in humans have examined the use of MB in sepsis. Kirov et al.[113] (20 patients) and Memis et al.[114] (30 patients) both demonstrated increased MAPs with MB administration in sepsis. However, Kirov et al.[113] found no effect of MB on oxygen delivery, and neither study found an effect on mortality, although they were both underpowered to measure this outcome. Memis et al.[114] also found no difference in cytokine levels in the group treated with MB.

In addition to the 2 trials mentioned above, several small observational studies have evaluated the use of MB in sepsis. Andresen et al.[115] prospectively studied 10 patients with severe septic shock in the intensive care unit. Patients receiving 1 mg/kg of MB had a significant increase in MAP, SVR, and PAP. Lactate levels also decreased, even though thermodilution CO found no effect on oxygen delivery. In a small prospective study, Donati et al.[104] assessed the hemodynamic effects of MB on 15 patients with septic shock. In all patients, MAP, SVR, and PAP increased but CO remained unchanged. Oxygen delivery was unaffected by MB. In a small prospective clinical trial with 14 patients, Preiser et al.[8] found an increase in MAP and SVR with MB administration but, again, no increase in CO or oxygen delivery.

The dosage of and timing of MB administration during sepsis have also been studied. Juffermans et al.[107] administered MB to 15 patients in septic shock and correlated hemodynamic changes with MB dose. They concluded that MB produced a transient and dose-dependent increase in MAP, CO, and SVR (even at a dose of 1 mg/kg), although high doses of MB (7 mg/kg) may compromise splanchnic perfusion.[107] Fernandes et al.[116] used a rat model of sepsis to examine the outcomes of using MB during different stages of sepsis. This study found that MB improved survival if administered in late but not early sepsis. The authors hypothesized that this finding was the result of increased sGC levels typically occurring in late sepsis.

A systematic review of the literature regarding the use of MB in sepsis by Kwok and Howes[117] concluded that, although the studies are mostly observational, MB increased SVR and MAP, but its effect on oxygen delivery and mortality is unknown.

RESULTS

In a recent meta-analysis of MB use in vasoplegia (cardiac, liver transplant, and sepsis), 5 randomized control trials met their inclusion criteria.[110] Four of the 5 studies demonstrated a statistically significant increase in MAP, with no adverse events noted except for blue/greenish discoloration of skin and urine. However, these findings should be interpreted with caution, because the study populations were varied, the number of studies few, the number of patients in each trial very small (all $n < 60$), and the goal of MB use heterogeneous (prophylactic versus therapeutic).

CONCLUSIONS

In summary, without outcome data from large, prospective, randomized controlled trials, the therapeutic and prophylactic use of MB in cardiac, hepatic, and septic patients, appropriate dosage, timing, and the duration of administration remain largely anectodal.[110,117] However, MB has been used safely for years in the treatment of methemoglobinemia and malaria. The dangers of global NO blockade have been observed in animal studies. Because MB inhibits iNOS and sGC, it may block the catastrophic hemodynamic effects of NO without blocking some of its protective actions. Although MB clearly improves blood pressure, improved oxygen delivery or decreased mortality with MB use has not yet been demonstrated. In the light of these incomplete data, we believe that MB is best used to treat vasoplegia unresponsive to traditional vasopressors, but it should not be a first-line agent until it has been further studied. Large, randomized controlled trials are urgently needed to determine whether the use of MB in VS is beneficial, inconsequential, or detrimental in regard to clinical outcomes.[74,75]

DISCLOSURES

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