Intraoperative vasoplegia: methylene blue to the rescue!

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Purpose of review
To evaluate the efficacy, dosing, and safety of methylene blue (MTB) in perioperative vasoplegic syndrome (VS).

Recent findings
Vasoplegic syndrome is a state of persistent hypotension with elevated cardiac output, low filling pressures, and low systemic vascular resistance (SVR). It occurs in up to 25% of patients undergoing cardiac surgery with cardiopulmonary bypass, can last up to 72 h, and is associated with a high mortality rate. MTB has been found to increase SVR and decrease vasopressor requirements in vasoplegic syndrome by inhibiting nitric oxide synthase, thus limiting the generation of nitric oxide, while inhibiting activation of soluble guanylyl cyclase and preventing vasodilation. MTB has been used in postgraft reperfusion during liver transplantation and anaphylaxis in a limited number of cases. Additionally, this medication has been used in septic shock with promising results, but similar to the cardiac surgical population, the effects of MTB administration on clinical outcomes has yet to be elucidated.

Summary
MTB should be considered during vasoplegic syndrome in cardiac surgery with cardiopulmonary bypass and usage may be more effective in an early critical window, prior to end-organ hypoperfusion. Other perioperative scenarios of MTB use show promise, but additional studies are required to develop formative conclusions.

Keywords
cardiac surgery, cardiopulmonary bypass, methylene blue, nitric oxide, vasoplegia

INTRODUCTION

Vasoplegic syndrome involves severe hypotension with normal or elevated cardiac output, tachycardia in patients who may reliably mount a compensatory response to hypotension, reduced cardiac filling pressures, and decreased systemic vascular resistance (SVR) [1]. Intravascular volume expansion does not typically improve the hemodynamic profile and aside from such clinical presentation, the exact definition of vasoplegic syndrome remains poorly defined. Proposed definitions encompass hypotension with mean arterial pressures (MAP) less than 50 mmHg, which is secondary to low SVR and normal or supranormal cardiac output. This prompts increased requirements for fluids and high-dose vasopressor therapy [2,3] but ultimately a state of vasodilatory shock remains with lack of adequate perfusion pressure because of extremely low vascular tone [4,5▪].

Several risk factors for vasoplegic syndrome have been identified, including preoperative intravenous heparin, angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, amiodarone, and use of protamine [3]. Other risk factors include low preoperative ejection fraction, higher additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) value [6], increased duration of cardiopulmonary bypass (CPB), and blood product administration [3,5▪].

Two distinct mechanisms are responsible for the loss of vascular tone and include: (1) activation of nitric oxide synthase (NOS) with dysregulation of

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KEY POINTS

- Methylene blue causes vasoconstriction by inhibiting inducible nitric oxide synthase and preventing subsequent activation of soluble guanylyl cyclase, in addition to directly inhibiting soluble guanylyl cyclase in smooth muscle cells.
- Most prospective and observational studies show that methylene blue causes an increase in systemic blood pressure and decrease in vasopressor requirements during vasoplegic syndrome after cardiac surgery, but improvement in morbidity and mortality have not been consistently demonstrated.
- Expansion of methylene blue into other perioperative uses, such as reperfusion after orthotopic liver transplantation and shock related to anaphylaxis or sepsis, show promise, but further investigation is warranted.

nitric oxide (NO) synthesis and activation of vascular smooth muscle cell-soluble guanylyl cyclase (sGC) activation (Fig. 1) [3]. The same Brazilian group that first reported perioperative vasoplegic syndrome, utilized methylene blue (MTB) as an inhibitor of NO synthesis and described their success in six patients [7]. In this letter to the editor, MTB was able to restore vascular tone, normalize MAP, and reduce vasopressor usage [7]. Subsequently, a few supportive randomized trials and retrospective observational studies were published, and MTB became recognized as a viable option for treating vasoplegic syndrome in patients undergoing cardiac surgery and quickly extending use to other surgical populations [8].

MECHANISM OF ACTION

MTB is an odorless, water soluble, dark blue-green crystalline powder, which turns blue whenever mixed in solution [9] and is often used as a dye in several medical procedures. As a vasopressor, MTB impacts the NO synthetic pathway by inhibiting inducible NOS and inhibiting the subsequent activation of sGC (Fig. 1) [10]. In addition, by binding to the iron heme moiety of sGC and causing enzyme inhibition, MTB blocks accumulation of cyclic GMP (cGMP), competing directly with NO in its ability to activate soluble guanylyl cyclase (Fig. 1) [10].

INTRAOPERATIVE USE OF METHYLENE BLUE

MTB may be used for hypotension refractory to high-dose vasopressors and intravascular volume administration during the perioperative setting and has been used extensively in the cardiac surgical population. It has also been used in liver transplantation for hypotension following graft reperfusion, anaphylaxis, carcinoid syndrome, and burn injuries. In a meta-analysis of five randomized controlled trials ($n = 174$), MTB was found to modestly increase arterial blood pressure [weighted mean difference, 6.93 mmHg; 95% confidence interval (CI) 1.67–12.18; $P = 0.01$] without an adverse effect on mortality [6% (14/88)] among MTB-treated patients and

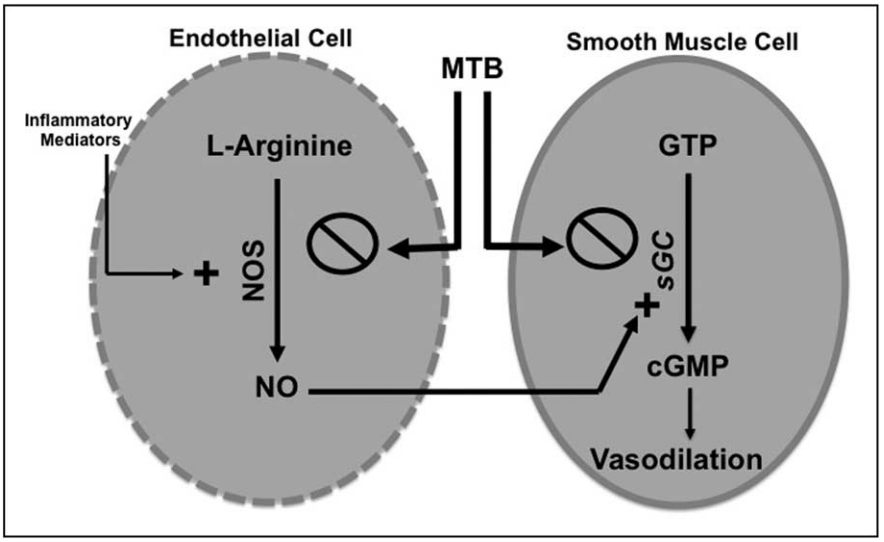

FIGURE 1. Mechanism of action of methylene blue. Methylene blue inhibits nitric oxide synthase and soluble guanylyl cyclase, preventing cGMP accumulation and vasodilation within smooth muscle. cGMP, cyclic guanosine monophosphate; GTP, guanosine 5′-triphosphate; MTB, methylene blue; NO, nitric oxide; NOS, nitric oxide synthase; sGC, soluble guanylyl cyclase.

23% (20/86) in the control group (OR 0.65; 95% CI, 0.21–2.08; $P = 0.5$) [11].

Cardiac surgery

Vasoplegic syndrome after cardiac surgery on CPB is thought to be largely the result of a severe inflammatory response [1,3]. During CPB, plasma proteins are absorbed by biomembranes, resulting in contact system activation of the extrinsic and intrinsic coagulation pathways, complement system activation, and fibrinolysis [3,12]. Activation of these pathways creates secretion of cytokines that activate endothelial cells and release vasoactive substances, including NO and prostacyclin [13]. Additional aspects that may contribute to the profound inflammatory response during cardiac surgery include reinfusion of hemolyzed cardiotomy blood that consists of other activated substrates, and removal of the aortic cross-clamp, which may cause an ischemia-reperfusion syndrome through neutrophil activation and release of reactive oxygen species [3,13]. Vasoplegic syndrome may occur in 5–25% of patients undergoing cardiac surgery using CPB, and the highest risk of vasoplegic syndrome has been associated with valve operations, orthotopic heart transplantation, and left ventricular-assist device implantation [3,5▪,14]. Although the duration of vasoplegic syndrome can last up to 72 h, vasoplegic syndrome lasting more than 36–48 h may lead to systemic complications and a mortality rate as high as 25% [14,15].

The perioperative use of MTB for vasoplegic syndrome was first described by Evora *et al.* [7] in the immediate postoperative period after cardiac operations with and without CPB, and MTB was subsequently implemented for vasoplegic syndrome following cardiac surgery by other early adopters [16,17]. There have been several case reports and case series demonstrating successful use in the early postoperative period, with improvement of MAP and decrease in vasopressor requirements [7,16–18]. Levin *et al.* illustrated a decrease in mortality (0 versus 21.4%, $P = 0.01$, $n = 56$) and duration of vasoplegic syndrome (2 versus 48 h; $P = 0.002$) for patients who were randomized to receive MTB versus placebo in patients experiencing vasoplegic syndrome in the postoperative period after cardiac surgery [2]. In a randomized controlled trial of 30 patients undergoing elective cardiac surgery, Maslow *et al.* [19] administered MTB or saline during CPB and demonstrated increased MAP (63 versus 55 mmHg, $P < 0.05$), lower norepinephrine requirements post-CPB (40 versus 73%, $P < 0.05$), and decreased lactate levels (0.84 versus 1.30, $P < 0.01$) in the group receiving MTB compared with placebo. In a randomized controlled trial of 100 patients, Ozal *et al.* [20] administered MTB at 1 h prior to cardiac surgery in patients with risk factors for vasoplegic syndrome, and found higher SVR ($P < 0.001$), less norepinephrine usage between groups (2/50 versus 41/50, $P < 0.001$), and reduced intravascular volume administration in patients who received MTB (1577 versus 1749 ml, $P = 0.024$).

Timing of MTB administration seems to effect the hemodynamic response in cardiac surgical patients. In a retrospective study of 88 vasoplegic patients, MTB administration resulted in higher MAP when compared with patients that did not receive MTB (OR 1.04, 95% CI 1.01–1.07, $P = 0.02$). In particular, patients that underwent deep hypothermic circulatory arrest for complex aortic repair experienced a greater hemodynamic improvement after receiving MTB (23.9%, $n = 21$; OR 4.48, 95% CI 1.54–13.06; $P = 0.006$). [21▪▪]. These findings suggest that the use of MTB as a last resort agent may not be an appropriate strategy for the treatment of vasoplegic syndrome and earlier use is recommended in at-risk patients.

Controversially, MTB has been suggested for the treatment of cardiopulmonary collapse associated with adverse protamine reactions as a result of systemic hypotension and potential for catastrophic pulmonary hypertension [22,23,24▪▪]. The major concern of administering MTB for this indication is the unknown impact MTB will have on further increasing pulmonary vascular resistance (PVR) following NO and sGC inhibition, potentially leading to right heart failure. It remains largely unknown whether there may be utility in delivering an inhaled pulmonary vasodilator, such as NO or prostanoids, in order to mitigate the increased PVR caused by MTB while avoiding further reduction in SVR by intravenous vasodilators.

Contrary to other studies supporting the administration of MTB during vasoplegic syndrome in cardiac surgery, a single institutional experience of 266 cardiac surgery patients with vasoplegic syndrome was evaluated and found a statistically significant mortality and morbidity difference between the cohort that received MTB ($n = 56$) and those that did not ($n = 210$; in-hospital mortality OR 4.26, CI 1.49–12.12, $P = 0.007$; morbidity OR 4,80, CI 1.85–12.43, $P = 0.001$). However, after propensity-matching was performed within the cohort, only MTB and major morbidity remained statistically important, suggesting that patients at risk for complications of vasoplegic syndrome were more likely to receive MTB [25].

Liver transplantation

Administration of MTB prior to graft reperfusion in order to limit hypotension upon vascular clamp

release during orthotopic liver transplantation was evaluated in a randomized controlled trial of 36 patients and led to increased MAP ($P = 0.035$), reduced epinephrine dosages ($P = 0.02$), higher cardiac indices ($P = 0.03$), and reduced serum lactate levels at 1 h after administration ($P = 0.03$), compared with the control group [26]. However, in a retrospective propensity-matched cohort, Fukazawa *et al.* [27] found that preemptive MTB administration did not prevent postreperfusion hypotension and did not decrease vasopressor usage. Nevertheless, several case reports and case series have affirmed improved hemodynamic profiles following MTB as a rescue agent for refractory hypotension after hepatic reperfusion during transplantation [28–30].

Anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death as a result of cardiovascular and pulmonary compromise but the presence of reduced blood pressure or shock is not necessarily required for the diagnosis [31]. It occurs secondary to release of histamine and other mediators in response to an antigenic trigger. Evora *et al.* [32] proposed that histamine activates G-proteins, which leads to a cascade of events resulting in the activation of endothelial NOS and production of NO from L-Arginine, ultimately resulting in vasodilation. Other mediators of anaphylaxis (tumor necrosis factor, leukotriene, platelet-activating factors) are thought to act along the same pathway and cause vasodilation [33].

The experience with the use of MTB in anaphylactic shock is limited to case reports [23,34,35] and it is unclear whether the reactions were anaphylaxis or anaphylactic shock, and immune-mediated or nonimmune-mediated. In addition, in some reports, MTB was given with or without epinephrine or administered after epinephrine. The largest of such reports contains 10 cases, which displayed an increase in MAP, SVR, and resolution of anaphylaxis [36].

Septic shock

Several studies and case reports exist in the literature describing the use of MTB in septic shock. Brown *et al.* [37] has reported the successful use of continuous MTB infusion over 44 h with sustained hemodynamic benefit and without toxicity in a septic patient. Preiser *et al.* [38] utilized an initial infusion of MTB in 14 septic shock patients, with re-dosing of MTB in 6 patients, in a prospective, observational study. The administration of MTB resulted in a transient and reproducible increase in arterial pressure and SVR, but did not increase cardiac output, oxygen delivery, or oxygen consumption. In addition, there was no sustained clinical improvement and 11 of 14 patients died. In a prospective observational study, Donati *et al.* [39] illustrated acute vasoconstrictive and positive inotropic effects of MTB during septic shock. The effects were not associated with changes in blood volume, myocardial diastolic function, or pulmonary vascular permeability assessed by extravascular lung water. In a recent meta-analysis including 20 randomized studies (10 during septic shock and 7 postcardiac surgery), Belleti *et al.* [40] found that the use of nonadrenergic vasopressors (including vasopressin, terlipressin, or MTB) was associated with a significant mortality reduction [34.3 (278/810) versus 38.7% (309/798), RR 0.88, CI 0.79–0.98, $P = 0.02$], but whenever the agents were considered separately, only a nonsignificant trend towards improved survival remained. Not surprisingly, MTB administration during refractory septic shock is associated with increased MAP and reduction in vasopressor requirements, whereas its effects on morbidity and mortality remain largely unknown [41].

DRUG ADMINISTRATION

Dosing

A therapeutic bolus of 1–2 mg/kg is commonly administered over 10–20 min, or up to 1 h, for vasodilatory shock. Intravenous administration typically has a terminal plasma half-life of 5–6 h, and continuous infusions may be beneficial after the initial bolus for up to 48–72 h [9]. Studies in septic shock have reported an initial intravenous bolus of 2 mg/kg, followed by continuous infusion of 0.25 mg/kg/h for up to 6 h [9]. In a dose-finding human study, bolus doses of 1 and 3 mg/kg showed favorable hemodynamic augmentation without deleterious effects to splanchnic perfusion, whereas a higher dose (7 mg/kg) showed decreased splanchnic perfusion [42]. Additionally, infusion rates of 1 mg/kg/h have shown favorable hemodynamic effects without compromise in splanchnic perfusion. In cardiac surgery, the most commonly used dosage from a literature review was found to be 2 mg/kg intravenous bolus, followed by a continuous infusion of 2 mg/kg/h [43].

Timing of administration

The timing of administration of MTB varies amongst studies, although early administration of MTB and at the time of a higher MAP is often advocated in

order to result in a more robust hemodynamic response [21▪▪]. Additionally, in a recent retrospective study of cardiac surgical patients, early MTB administration was associated with reduced renal failure and perioperative mortality compared with postoperative intensive care unit administration [44▪▪]. Early administration is also advocated as a result of increased NOS and sGC upregulation within the first 8 h, followed by down-regulation in the subsequent 8 h [43]. In the third 8-h window, there is upregulation of NOS and sGC again, but effective MTB administration may be too late because of the prolonged state of shock, metabolic acidosis, and circulatory failure.

ADVERSE EFFECTS

In small studies of patients in septic shock, MTB was found to lead to worsening arterial oxygenation and reduced arterial oxygen tension:fraction of inspired oxygen (*P*/*F*) ratios because of inhibition of hypoxic pulmonary vasoconstriction and impaired alveolocapillary gas exchange in the lung [45,46]. MTB may also lead to mesenteric vasoconstriction and compromised blood flow [42]. Continuous peripheral infusion of MTB for prolonged duration may lead to local cutaneous necrosis [47] and administration (bolus and infusion or just infusion) can also cause artificially low pulse oximetry readings because of the blue coloration [48].

Toxic manifestations of MTB (≥7 mg/kg) include hemolysis, methemoglobinemia, nausea and vomiting, chest pain, and hypertension [9]. At high doses (≥20 mg/kg), MTB can cause severe intravascular hemolysis, hyperbilirubinemia, and death [49]. MTB is a treatment modality for methemoglobinemia by reducing the hemoglobin molecule to the oxygen-carrying state. At higher doses, however, MTB becomes an oxidizing agent and prevents hemoglobin–oxygen transport.

CONTRAINDICATIONS

MTB inhibits monoamine oxidase A, which is an enzyme responsible for breaking down serotonin in the brain. There have been reports of patients developing serotonin syndrome after administration of MTB in patients taking certain antidepressant medications (Table 1) [50,51]. Serotonin syndrome is a life-threatening condition that causes altered mental status, altered neuromuscular excitability, and autonomic instability. As such, the Food and Drug Administration (FDA) issued a warning in 2011 against concomitant use of MTB and serotonergic drugs [52]. In a nonurgent setting, serotonergic medications should be discontinued for 2 weeks prior to administration of MTB and may be resumed 24 h after administration [49]. Other serotonergic medications may also cause serotonin syndrome after concomitant use with MTB, but reports are lacking (Table 1).

Table 1. Medications that may interact with methylene blue to cause serotonin syndrome

Categories	Medications
Selective serotonin reuptake inhibitors	Paroxetine
	Fluvoxamine
	Fluoxetine
	Sertraline
	Citalopram
	Escitalopram
	Vilazodone
Serotonin norepinephrine reuptake inhibitors	Venlafaxine
	Desvenlafaxine
	Duloxetine
Tricyclic antidepressants	Clomipramine
	Amitriptyline
	Desipramine
	Imipramine
	Nortriptyline
	Protriptyline
	Doxepin
	Trimipramine
Monoamine oxidase inhibitors	Isocarboxazid
	Phenylzine
	Transdermal selegeline
	Tranylcypromine
Other psychiatric medications	Amoxapine
	Maprotiline
	Nefazodone
	Trazadone
	Bupropion
	Buspirone
	Mirtazapine
Antibiotics	Linezolid

In addition, MTB inhibits cytochrome P450 (CYP) isozymes and may affect hepatic medication metabolism (Table 2). Typically, medications with a narrow therapeutic index will be most affected. MTB is metabolized by the liver and excreted by the kidneys and patients with hepatic or renal dysfunction are at risk of toxicities and potential drug interactions [49].

The use of MTB is contraindicated during pregnancy because of the increased expression of NO in the placenta and subsequent risk of fetal hypoxia following MTB administration [9]. MTB has been

Table 2. Medications that may accumulate with methylene blue

CYP isoenzyme metabolism	Digoxin
	Warfarin
	Phenytoin
	Alfentanil
	Fentanyl
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Pimozide
	Quinidine
	Sirolimus, Tacrolimus

CYP, cytochrome P450.

used previously in neonates, but caution is warranted because of the risk of hemolytic anemia and hyperbilirubinemia [9]. MTB is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, and may cause hemolytic anemia owing to a decreased ability to reduce MTB into its metabolites [9].

CONCLUSION

MTB is a reasonable and recommended treatment for vasoplegic syndrome in critically ill cardiac surgical patients. Early use is advocated, as there may be a critical window of efficacy before the development of refractory shock. Though there is an improvement in the hemodynamic profile after MTB in patients undergoing cardiac surgery using CPB, the effect of MTB use on clinical outcomes has not been established. MTB may be used in septic shock whenever refractory hypotension is encountered; although administration is not currently supported by the Surviving Sepsis Guidelines [53]. Routine use in anaphylaxis and liver graft reperfusion during transplantation cannot be supported at this time because of the paucity of data and randomized controlled trials are warranted in these critically ill populations.

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Conflicts of interest

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