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Review

The role of methylene blue in the management of vasoplegic syndrome: a narrative review

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Abstract

Vasoplegic syndrome is an important clinical entity characterized by profound arterial hypotension refractory to vasopressor therapy. The underlying pathophysiology is characterized by a complex and multifactorial dysregulation of both vasodilatory and vasoconstrictive mechanisms. During the last decades, there is growing interest in using methylene blue as an adjunct therapy to treat vasodilatory shock. The present review evaluates the safety and efficacy of methylene blue in cardiac and transplant surgery, severe sepsis and septic shock, severe burn injury, paediatric intensive care, and intoxications. Although most of the currently available evidence reports a benefit in haemodynamic parameters and a decrease in vasopressor requirements following the administration of methylene blue, study designs are heterogeneous, and the overall level of evidence is low. Moreover, a clear and consistent benefit in morbidity and mortality is lacking. Large prospective randomized controlled trials are needed to evaluate the exact role and timing of methylene blue in the treatment of vasopressor refractory vasoplegia.

Keywords: **Methylene blue, vasoplegia , vasoplegic syndrome.**

Introduction

Maintenance of adequate tissue perfusion and oxygen delivery is the primary goal of the cardiovascular system. This requires an adequate balance between cardiac output (CO), systemic vascular resistance (SVR) and intravascular volume. A significant disturbance between these factors leads to inadequate tissue perfusion. Vasoplegic syndrome (VS) is a clinical entity characterized by a profound pathologic vasodilatory shock state[1]. VS is marked by profound arterial hypotension, normal or high CO and low SVR[2]. Most patients require vasopressors and intravascular volume expansion to preserve end-organ perfusion[1,3]. The pathophysiology of VS is multifactorial and comprises the activation of different interacting dynamic pathways, leading to profound hypotension. As a result, patients show a remarkable resistance to vasopressors such as norepinephrine (NE). Moreover, high doses of these vasoactive drugs may induce significant adverse effects, including pulmonary, splanchnic and renal hypoperfusion, potentially leading to ischaemia and tissue necrosis[1,3,4].

Despite some controversy, the following criteria are mostly used to define VS: 1/ severe hypotension with mean arterial pressure (MAP) < 50 mmHg (some authors use a cut off for MAP < 65 mmHg); 2/ low SVR (< 800 dynes sec cm^{-5}); 3/ normal or high CO (cardiac index > 2.2-2.5 L $min^{-1}m^{-2}$) and 4/ substantial vasopressor dependence (norepinephrine > 0.5 µg $kg^{-1}min^{-1}$)[2,5,6]. There are some considerable limitations to this definition. First, not all patients have (invasive) haemodynamic monitoring to reliably gather all previously mentioned parameters. Second, these criteria are non-specific and present in different distributive shock states.

During the last decades, there has been increasing interest in novel treatment options to counteract VS. Methylene blue (MB) is a guanylyl

cyclase inhibitor that blocks the effects of nitric oxide (NO) and other nitrovasodilators[7]. Therefore, MB could be an effective addition to the treatment armamentarium of VS. The aim of this critical literature review is to evaluate the indications, efficacy and safety of MB for the treatment of VS in critically ill patients.

Evidence acquisition

An elaborate review of the literature was done using the following three databases: PubMed, The Cochrane Library and Embase. The literature search included reports up to December 31st, 2020. The Medical Subject Heading (MeSH) terms were used for the search in PubMed and the Cochrane database. The search string included keywords "methylene blue" and "vasoplegia", along with derivative and related terms. In the Embase database, we used the Emtree tool. References cited in the retrieved articles were subsequently manually searched to identify additional manuscripts of interest that were not found by the initial search to ensure completeness. Following deduplication, the Rayyan QCRI Tool (Rayyan Systems Inc, Cambridge, MA) was utilised to list our results after the preliminary search. This tool was also used to conduct title and abstract screening and eventually full-text reading.

The present work represents a critical review of the current state of evidence regarding the use of MB for treatment of VS. The search strategy was kept broad to screen a maximum of articles describing the use of MB as potential adjuvant therapy in treatment of VS. There were no restrictions on the age of patients or the publication date.

While screening the records obtained from the three databases, the following exclusion criteria were used: 1/ animal or in vitro studies; 2/ comment, editorial or letter to the editor; 3/ language other than English, French, German or Dutch; 4/ no use of MB or just briefly mentioned; 5/ abstract or poster only, no full text available; 6/ use of MB in a different clinical setting (not related to treatment of VS).

Results

Although this is a narrative review, the authors systematically searched the literature and Figure 1 shows a detailed flowchart study selection according to the the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. The Scale of

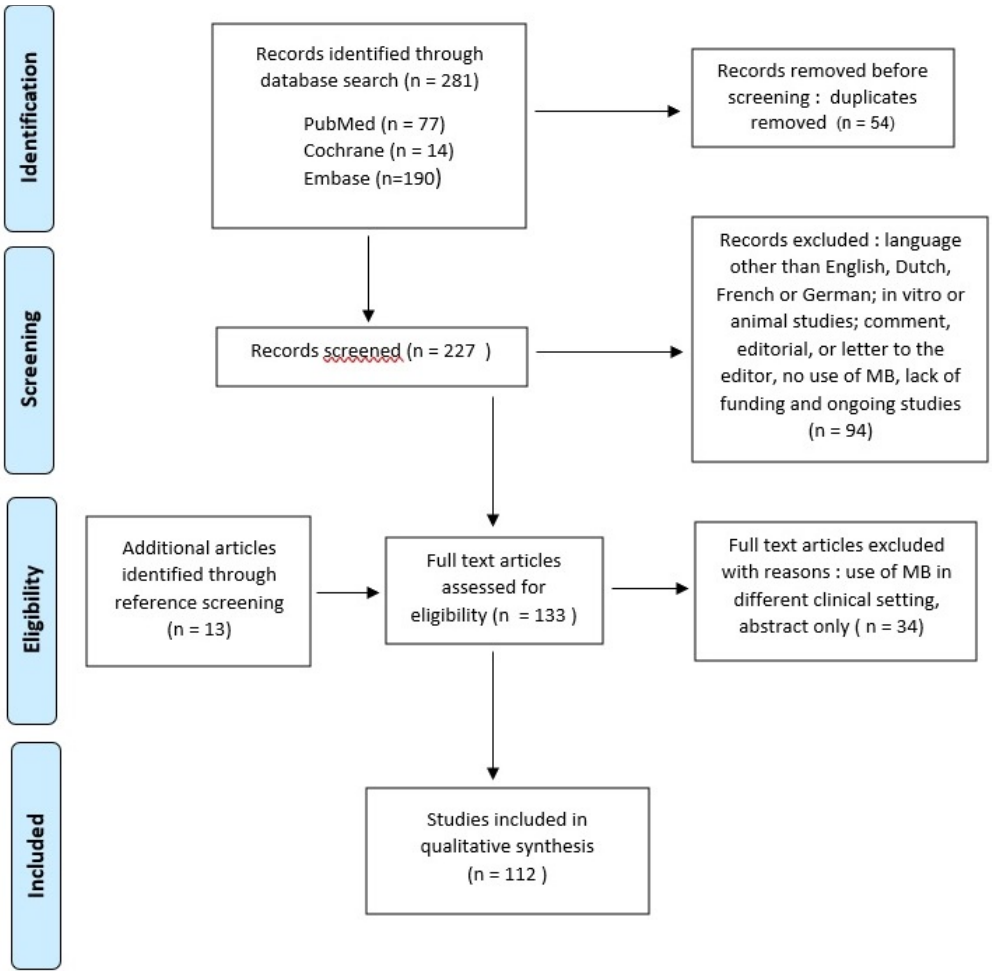

Fig. 1 — study flow chart according to the the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.

Narrative Review Articles (SANRA) was used as a tool to improve the quality of this work[8]. With consensus of the authors, a score of 10/12 was obtained (Figure 2).

Evidence synthesis

Pathophysiology of vasoplegic syndrome

Under normal physiological conditions, vascular tone is preserved by catecholamines (via α1 receptors), angiotensin II (via angiotensin type I receptors) and arginine vasopressin (via vasopressin I receptors). These endogenous hormones raise intracellular calcium levels via the activation of G-protein-coupled receptors (GPCR). Subsequently, an intracellular signalling cascade leads to the formation of a calmodulin complex, which enhances the phosphorylation of myosin forming myosin-actin cross-links and vasoconstriction[4,9,10].

Critically ill patients frequently display vascular hyporesponsiveness to catecholamines due to the excessive production of endogenous vasodilators such as nitric oxide (NO). NO is a competitive agonist at the enzyme soluble guanylate cyclase (sGC). This enzyme produces cyclic guanosine monophosphate (cGMP) out of guanosine-5'-triphosphate (GTP). cGMP leads to the inhibition of Ca^{2+} influx and stimulates Ca^{2+} reuptake and the activation of protein kinases, leading to dephosphorylation of myosin and vascular smooth muscle cell (VSMC) relaxation. NO further activates calcium- and ATP- sensitive potassium channels, leading to hyperpolarization and inhibition of the normal pathway for vasoconstriction mediated by GPCR. Second, GPCRs are prone to desensitization mediated by GPCR kinases. Both mechanisms explain why these patients are vasoplegic despite a high dose of frequently used vasopressors like

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

1) Justification of the article's importance for the readership

The importance is not justified.	0	
The importance is alluded to, but not explicitly justified.	1	2
The importance is explicitly justified.	2	

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated.	0	
Aims are formulated generally but not concretely or in terms of clear questions.	1	2
One or more concrete aims or questions are formulated.	2	

3) Description of the literature search

The search strategy is not presented.	0	
The literature search is described briefly.	1	2
The literature search is described in detail, including search terms and inclusion criteria.	2	

4) Referencing

Key statements are not supported by references.	0	
The referencing of key statements is inconsistent.	1	2
Key statements are supported by references.	2	

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

The article's point is not based on appropriate arguments.	0	
Appropriate evidence is introduced selectively.	1	1
Appropriate evidence is generally present.	2	

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately.	0	
Data are often not presented in the most appropriate way.	1	1
Relevant outcome data are generally presented appropriately.	2	

Sumscore 10

Fig. 2 — SANRA scale : 'explanations and instructions', filled in by the authors..

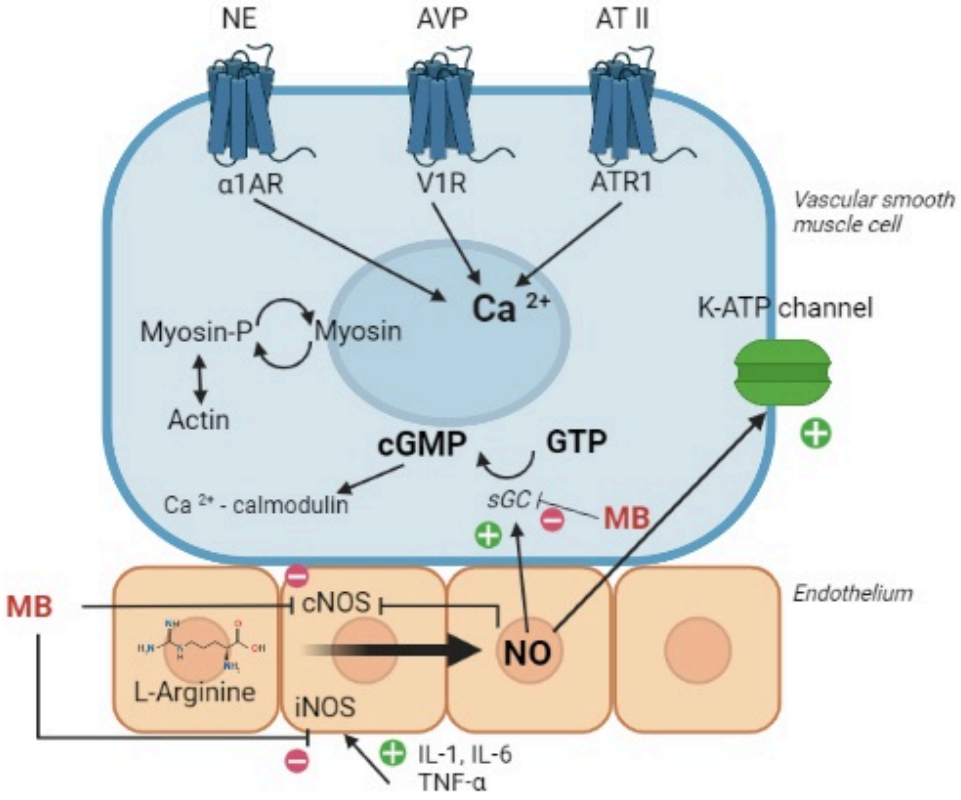

Fig. 3 — Schematic overview of the pathophysiology of VS and working mechanism of MB. The figure was made using Biorender.com with K.U. Leuven institutional access.
NE : norepinephrine, ADH : anti diuretic hormone, AT II : angiotensin II , α1AR : alpha-1 adrenoreceptor, V1R : vasopressin 1 receptor, ATR1 : angiotensin type I receptor, GTP : guanosine-5'-triphosphate , cGMP : cyclic guanosine monophosphate, sGC : soluble guanylate cyclase, NO : nitric oxide, cNOS : constitutive form nitric oxide synthase, iNOS : inducible form of nitric oxide synthase, IL-1 : interleukin 1, IL-6 : interleukin 6, TNF- α : tumor necrosis factor alpha.

NE and arginine vasopressin[1,4,9-13]. NO is produced from the amino acid L-arginine by nitric oxide synthetase (NOS). There are two different forms of NOS: a constitutive (cNOS) form being constantly active and producing a basal rate of NO that rapidly diffuses into the VSMC. NO can also be produced by an inducible form of NOS (iNOS). This enzyme is triggered by complement factors (C3a, C5a), proinflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) as well as other endotoxins[1,9,10,12,13].

As a result, iNOS expression in the endothelial cells and VSMC rises, and the production of NO can be increased to even a thousand-fold compared to the production of NO by cNOS. iNOS also interferes with VSMC contraction by binding calmodulin and blocking its binding to Ca^{2+}. Furthermore, the interleukins mentioned previously, and oxygen-free radicals also activate sGC resulting in vasodilatation[1,3,4].

The impact of MB on this cascade is twofold. First, it directly inhibits NOS and second, MB also blocks sGC and therefore prevents the accumulation of cGMP. The ability of MB to inhibit this rate-limiting enzyme explains why MB can restore vascular tone even if NO is not present[1,3,14]. MB should not be considered a vasoconstrictor but it facilitates the effects of classic vasoconstrictors such as catecholamines, by blocking the cCMP pathway[15]. Figure 3 shows a schematic overview of the pathophysiology of VS and working mechanism of MB.

Pharmacology of methylene blue

MB is an odourless, water-soluble powder and turns blue if mixed in a solution. Historically, it was first used to treat malaria or certain psychiatric diseases[11,16]. Currently, MB is used to treat methaemoglobinemia[17], as a dye to visualize certain anatomical structures such as endocrine glands (parathyroid), nerve tissue or ureters during surgery[4,11,18]. In order to treat VS, MB should be administered intravenously. The current evidence synthesis shows a great variability in dosing and timing of MB administration. The time required for the administration of a loading dose of MB varies between 10 minutes up to 6 hours[19,20]. In Belgium, the public price for 100 mg of MB (Metiblo®, Sterop, Belgium) is approximately

€30. MB is predominantly excreted in the urine, resulting in a characteristic blue-green colour. Of note, the administration of MB could interfere with the plethysmography of the pulse oximeter because of its blue colour and thus results in falsely low oxygen saturation readings[4]. Important contra-indications and adverse effects of MB are discussed in a separate topic below.

Adverse effects of methylene blue

Using MB as an adjunct to treat VS has some possible adverse effects. First, a known glucose–6–phosphate dehydrogenase (G6PD) deficiency is a contra-indication for MB use. G6PD is a necessary molecule in the production of nicotinamide adenine dinucleotide phosphate (NADPH), which reduces MB into its urinary metabolite leucomethylene. Patients with a G6PD deficiency have low levels of NADPH, so these patients are prone to develop haemolytic anaemia[1,4,11,21].Other contra-indications are severe kidney injury and documented hypersensitivity to MB[7]. MB can provoke cardiac arrythmias, coronary- , renal- and splanchnic vasoconstriction, increase pulmonary vascular resistance and PAP and deteriorate gas exchange[6,22]. The risk of adverse effects significantly increases when higher doses of MB are administered (> 5 mg kg^{-1}). The recommended dose of 1.5–2 mg kg^{-1} is considered safe[7,16]. Second, MB is as a potent inhibitor of mono amino oxidase A (MAO-A) and can subsequently lead to serotonin and central nervous (CNS) toxicity, especially in patients under MAO inhibitors and selective serotonin inhibitors (SSRI). The diagnosis is made clinically and by using the Hunter Serotonin Toxicity criteria with an 84% sensitivity and 97% specificity[23,24].Typical symptomatology includes the triad of altered mental status, autonomic hyperreactivity and neuromuscular dysfunction. Treatment is solely supportive and includes cessation of all serotonergic medications, sedation (preferably with benzodiazepines), oxygen and IV fluid resuscitation. The syndrome usually lasts for 24 hours after discontinuation of the eliciting serotonergic drugs but can last longer in case of active metabolites or drugs with long half-lives[23,25]. Gilman et al. reported on 14 cases of CNS toxicity after the use of MB. Almost all cases (13/14) were serotonin toxicity that met the Hunter Criteria. Research showed that even a dose of 1 mg kg^{-1} in patients under SSRI can lead to serotonin toxicity. Patients taking other serotonergic medications like MAO-B inhibitors and some types of tricyclic antidepressants (TCA) are also at risk[23]. There are many case reports describing the development of a serotonin syndrome after treatment with MB to counter VS[26-30].

Methylene blue in cardiac surgery

During cardiopulmonary bypass (CPB), the exposure of blood to the surface of the extracorporeal circuit leads to platelet adhesion and activation of the complement and kallikrein – bradykinin system. Complement activation triggers the production of inflammatory mediators like IL-1, IL-6 and TNF- α, which mediate the expression of iNOS and subsequently the production of NO[7,9,11]. Higher levels of bradykinin also activate sGC independently of NO[22].

Reported incidences of VS after cardiac surgery vary between 5-25%[4,11,18,20]. There are some perioperative factors known to independently increase the risk of developing a VS following cardiac surgery. The reported incidence of VS is higher in case of the preoperative use of angiotensin converting enzyme (ACE-i) inhibitors (44%), calcium channel (CCBs) blockers (47%) and unfractionated heparin (55%). A preoperative low left ventricular ejection fraction <35% is also an independent risk factor[6,7,11]. Refractory and long-lasting states of vasoplegic syndrome (36-48h) are associated with a significant morbidity and mortality up to 25%[1,4,5,14].

Preoperative use

A randomized controlled trial (RCT) of 100 patients at high risk (ACE-i, CCBs or unfractionated heparin preoperative) for developing VS after coronary bypass grafting (CABG) with CPB were randomly allocated to either receive a preoperative bolus of MB (2 mg kg^{-1}) or saline[6]. The treatment group showed significantly higher SVR during surgery, lower need for NE and lower inotropic support. The treatment group also required fewer crystalloids, colloids and red blood cell transfusion to maintain the same haemodynamic goals. Last, the average duration of intensive care unit (ICU) and hospital stay was significantly lower in the treatment group[6].

Intraoperative use

The intraoperative use of MB was first evaluated by Ribeiro et al. They prospectively studied a cohort of 60 patients, who were randomized to receive either a 2 mg kg^{-1} infusion of MB over 6 hours just prior to the initiation of CPB or placebo. The MB group showed a significantly higher diastolic blood pressure and SVR at 3 and 6 hours postoperatively. The authors also reported lower TNF-α and NO levels in the treatment group[19]. A RCT with 30 patients taking ACE-I scheduled for elective cardiac surgery with CPB showed similar results. The intervention group had a significantly higher MAP, lower vasopressor requirement and

lower serum lactate levels. Unfortunately, the study was underpowered to evaluate the effects of MB on patient outcomes[14,31].

In contrast with previous results, Cho et al. conducted a RCT in patients with infective endocarditis undergoing cardiac surgery. In their study, the administration of 2 mg kg^{-1} of MB 20 minutes before start of CPB was not associated with any significant benefits in haemodynamic parameters or vasopressor doses, although it resulted in a significant reduction in transfusion requirements[32]. The authors noted, however, that the most of the patients included were either on ACE-i, CCBs or unfractionated heparin. The varying degree of success of MB administration to restore SVR depends on the activity of sGC[32]. The combination of a CPB circuit and infective endocarditis leads to an excessive activation of inflammatory pathways and NO production causing sGC depletion. Some authors suggest that there might be an optimal window of opportunity for MB administration during resynthesis of sGC[11,15,32].

Postoperative use

Most of the literature describes the use of MB to treat VS after cardiac surgery in the postoperative period, considering MB as last resort therapy in the treatment of VS. Evora et al. were the first authors to report the administration of MB in a patient developing VS after cardiac surgery[1,15]. Leyh et al. reported an observational study in which 54 patients with NE refractory vasoplegia (NE > 0.5 μg kg^{-1} min^{-1} with MAP < 60 mmHg) after CPB were treated with a single bolus (2 mg kg^{-1}) of MB[22]. Most of the patients (51/54) showed an increase in SVR and a decreased need for NE 1 hour after surgery. Serum lactate levels 12 hours after infusion of MB were also lower, suggesting that MB predominantly restores vascular tone without compromising global tissue perfusion[22]. Their results were confirmed by a second retrospective analysis in 2017, showing that a single bolus of MB (1-2 mg kg^{-1}) after CPB is associated with a moderate increase in MAP and decrease in NE dose. Factors associated with a positive response to MB were a higher MAP at the time of drug administration and deep hypothermic arrest during surgery. However, a major limitation of this analysis is the lack of a control group[20].

The benefit of MB administration in terms of morbidity and mortality remains a matter of debate. Levin et al. evaluated the use of MB in a RCT in 638 patients scheduled for elective cardiac surgery requiring CPB[5]. A total of 56 patients developed VS and were subsequently randomized either to a 1.5 mg kg^{-1} MB bolus or placebo infusion. Overall mortality was 4.2%, with a significant difference between the vasoplegic and nonvasoplegic group (10.7% versus 3.6%, p =0.02). There were no deaths in the group treated with MB compared to 6 deaths (0% versus 21.4%, p=0.01) in the placebo group. The study also showed a benefit in terms of postoperative morbidity like respiratory and renal failure, supraventricular arrythmia, multiorgan dysfunction and sepsis in the treatment group[5]. This difference in morbidity can explain the difference in mortality between both groups[1,5].

In 2017, Mehaffey et al. retrospectively evaluated a large cohort of 3608 patients of which 118 were treated with MB to counteract CPB related VS[33]. First, this analysis showed that patients receiving MB for VS had a significantly higher rate of operative mortality (21.2% versus 3.2%, p<0.0001) compared to patients who did not require MB. Second, when stratified by early (in the operating theatre) versus late (on the ICU) MB administration, patients showed less renal failure (10.4% versus 28.6%, p<0.018) and 30-day mortality (10.4% versus 28.6%, p< 0.018)[33]. Similar results were obtained in a smaller retrospective observational patient-matched case control study[34]. Two groups of 28 patients were compared and showed that treatment of VS with MB is associated with a favourable evolution of haemodynamic parameters, need of vasopressors and hospital stay (both in hospital and ICU). The 30-day mortality (3.6% versus 21.4%, long rank P = 0.04) and new onset of renal failure (7.1% versus 32.1%, p=0.04) were significantly higher in the control group[34].

Conversely, Weiner et al. reported that the use of MB as treatment for VS after cardiac surgery with CPB was associated with poor outcomes[35]. Over a two-year period, 226 patients developed VS and 56 of them received MB. The administration of MB was an independent risk factor for in-hospital mortality (odds ratio 4.26, 95% confidence interval 1.49-12.12, p = 0.007), a compilation of morbidities (odds ratio 4.80, 95% confidence interval 1.85-12.43, p = 0.001), ICU length of stay and inotropic support. However, patients receiving MB had higher preoperative morbidity, reflected in higher EuroSCORE values, ASA classifications and preoperative renal failure. To reduce confounding, the authors performed 2 propensity-score-matched analyses. Thirty-one pairs of comparable patients were first balanced for preoperative covariates and indicators for attending anaesthesiologists to predict the propensity for receiving MB. A second analysis was performed adjusting for intraoperative variables. Both analyses confirmed MB as an independent predictor of morbidity, but there was no statistically significant difference in mortality[35].

Another retrospective cohort analysis evaluated the effect of MB administration on patients who underwent left ventricular assist device (LVAD) implantation. No improvements were observed in MAP up to 12 hours after infusion of MB[36].There was a decline in NE doses 2-3 hours after MB, similar to earlier reports[20,33]. Clinical outcomes, however, did not improve and were not affected by the timing of MB administration[36].

In conclusion, MB seems to be effective in treating VS during and after CPB. Current literature reports improvements in MAP and SVR and a decreased need for vasopressor therapy. However, the current evidence is mainly based on observational data and large prospective trials are needed to confirm these findings.

Transplantation Surgery

Orthotopic liver transplantation (OLTx)

Vasoplegia after OLTx is usually caused by ischaemia reperfusion injury. Post reperfusion cardiovascular dysfunction is characterized by a varying degree of cardiac arrythmias, a decrease in CO, MAP and SVR, elevated pulmonary arterial pressure (PAP) and central venous pressure (CVP). Ischaemia reperfusion syndrome results from damage to the vascular endothelium and leads to a systemic inflammatory response syndrome (SIRS). The incidence of severe hypotension after OLTx varies between 17-50%[1,37]. MB should be considered in patients with severe vasoplegia after reperfusion. On the other hand, cGMP and NO also play a role in microcirculation of the graft[37]. The use of MB blocks the synthesis of NO which is already diminished after reperfusion. Currently, there is no evidence available showing the merit of treating vasoplegia over possible deleterious effects to the liver graft[37].

Using MB during OLTx is mainly based on anecdotical evidence[38-41]. Koelzow et al. randomized 36 patients to either receive a single dose of MB (1.5 mg kg^{-1}) or placebo before reperfusion of the graft liver. Patients treated prophylactically with MB had significantly higher MAP and CO, less epinephrine requirements and lower serum lactate levels[42]. In contrast, a large propensity score-matched cohort study showed that a single bolus of MB (1-1.5 mg kg^{-1}) prior to reperfusion did not prevent post-reperfusion hypotension. There was no significant difference in MAP or vasopressor requirement in patients treated with MB or placebo, and there was no difference in the incidence of acute rejection, graft survival, primary non-functioning or retransplantation between the two groups[43].

Kidney transplantation

It is rather uncommon to develop VS after kidney transplantation. Two case reports describe the successful use of MB in restoring haemodynamic parameters and reduction of vasopressor requirements after kidney transplantation[44,45].

Heart - or lung transplantation

The evidence concerning the use of MB in heart- or lung transplantation is very limited. One of the major concerns is the negative effect of MB on the pulmonary vascular resistance since NO is a well-known and frequently used selective pulmonary vasodilator. Kofidis et al. reported a catecholamine sparing effect after heart transplantation[46] and Carley et al. reported the use of MB to treat vasoplegia during a lung transplantation on cardiopulmonary bypass[47].

Methylene blue and septic shock

Sepsis probably represents the most frequent cause of vasodilatory shock. Septic shock is known to result in significant morbidity and mortality[1,3,48]

The severe inflammatory systemic response caused by pathogens triggers the production of proinflammatory cytokines, complement factors and numerous other inflammatory mediators. As previously described, these cytokines activate iNOS, leading to NO and cGMP accumulation. The excessive production of NO and cGMP and the activation of other vasodilatory pathways subsequently leads to profound vasodilation, hyporesponsiveness to vasopressors and myocardial depression[3,13,49].

Interestingly, there are only 2 small RCTs available evaluating the use of MB in septic shock patients[50,51]. Kirov et al. included 20 patients with septic shock who were randomly allocated (in a 1:1 ratio) to receive either isotonic saline or a single bolus of MB (2 mg kg^{-1}), followed 2 hours later by a continuous infusion of MB at increasing rates of 0.25, 0.5, 1 and 2 mg kg^{-1} h^{-1} for 1 hour each[50]. Patients who received MB showed higher MAP and SVR at 1, 6 and 24 hours after infusion compared to placebo. MB also preserved oxygen delivery, stroke volume and cardiac index, whereas it was decreased in the control group. Lastly, infusion of MB significantly reduced catecholamine requirements. The difference in 28-day-mortality between the intervention group and placebo (50% versus 30%) was not statistically significant ($p=0.65$)[50]. Notably, patients receiving corticosteroids were excluded in this trial.

The other RCT evaluated the effect of MB on plasma levels of cytokines in patients with severe sepsis[51]. In total 30 patients with severe

sepsis, with or without shock, were included and randomly allocated in a 1:1 ratio to receive either a continuous infusion of MB (0.5 mg kg^{-1} h^{-1}) for 6 hours or isotonic saline. Patients treated with MB showed higher MAPs after infusion but returned to baseline values at 24 and 48 hours after the infusion. MB treatment had no significant impact on the plasma levels of the investigated proinflammatory cytokines. Unfortunately, this trial was not designed to assess clinical outcomes[51].

During the last 2 decades, multiple reviews already evaluated the evidence on MB in septic shock. Also these reviews had to rely on the 2 RCT's described above in addition to multiple small observational prospective analyses or case reports[1,3,48,49].Notably, these studies only enrolled a limited number of patients with different inclusion criteria, severity of illness, dosing regimens and outcome parameters leading to important heterogeneity. Despite these important limitations, all these studies reported a variable increase in MAP and/or SVR in patients treated with MB and some of these studies also showed decreased vasopressor requirements. The effects on oxygen delivery, cardiac output and clinical end-points such as morbidity and mortality remain, however, largely unknown.

Methylene blue in burn patients

Severe burn wounds cause vascular hyperpermeability, intravascular volume depletion and vasoplegia, leading to a profound distributive shock state, with potential evolution to circulatory and respiratory failure. Experimental evidence suggests that thermal injuries are an important trigger for NO production and hence result in increased vascular permeability and development of VS[52].

Jaskille et al. were the first authors to report the use of MB to treat 2 severely burned patients who did not respond to conventional vasopressor treatment. Although both patients eventually deceased due to burn related complications, in both cases the use of MB resulted in dramatically reduced dosage of frequently used vasopressors like norepinephrine and vasopressin[53].

In 2015, 2 other case reports reported the use of MB in severe burn patients. A 52-year-old man successfully received MB for the treatment of VS but died 2 months later because of multi-organ failure[54]. The second case report describes the use of MB as adjunct therapy to acute septic cardiomyopathy. MB altered not only SVR, but the authors also suggest sensitization of the myocardium to catecholamines to improve contractility[55]. It is, however, very important to emphasize an adequate fluid resuscitation as primary therapy and therefore MB should not be used as a first line treatment in severely injured burn patients[54].

Methylene blue in a paediatric population

During the last decade, there is emerging evidence to support the use of MB to treat vasoplegia in a paediatric patient population. The successful use of MB for infants was first described in a case series of 5 neonates with vasoplegia due to septic shock.[56].

The only RCT conducted in a paediatric patient population was published by Abdelazim et al. in 2016. This study included 40 patients between 2-8 years old. The patients developed VS after weaning from cardiopulmonary bypass. They were randomly assigned to receive MB as adjunct to NE or NE alone. The intervention group received 1.5 mg kg^{-1} over 20 minutes if NE infusion was > 0.5 µg $kg^{-1}min^{-1}$ for at least 5 minutes. Administration of MB did significantly increase MAP, CVP and SVR and lowered CO and HR. MB also decreased the dose of NE with no adverse effects[57].

Bitterman et al. reported a retrospective analysis of 7 patients who received MB as rescue therapy in VS. Their age varied between newborn to 4.5 years old. The dose administered was a bolus of 1 mg kg^{-1} followed by a continuous infusion of 0.25 mg $kg^{-1}h^{-1}$. Six out of 7 patients showed a favourable response, with elevated MAP and lower vasopressor requirements. No adverse events were registered in all 7 patients[58]. Two other case reports describe the successful use of MB after an orthotopic heart transplantation[59] or in a 22-month-old girl with Noonan syndrome, biventricular hypertrophic cardiopathy and chronic respiratory failure who developed a severe septic shock[60]. Up to date, there is no universal dosing regimen for MB in children. Similar to an adult population, a maximum dose of 2 mg kg^{-1} seems to be safe[60].

Methylene blue vs. hydroxocobalamin

Hydroxocobalamin (HCB) is primarily used in the treatment of cyanide intoxication but also raises blood pressure. Although the exact mechanism is still unknown, HCB acts like MB, inhibiting NOS and also directly blocking NO. Some authors claim that HCB also interacts with other endogenous vasodilators like carbon monoxide and innate hydrogen sulphide[9,61]. A recent case series of 2 patients suggests HCB could play a role in the stabilisation of capillary membranes, whereas MB cannot do so. This can explain some synergistic effects of HCB and MB in treatment of vasopressor resistant VS[61]. Furnish et al. conducted a retrospective cohort study in which they evaluated the effect of MB compared to HCB in the treatment

of VS during and after cardiac surgery[62]. Both therapies were associated with a similar increase in MAP and SVR but did not significantly change the time-averaged NE equivalent requirements in the first hour after rescue therapy. Clinical outcomes such as mortality, the number of days free of ICU and mechanical ventilation were equal in both groups. The patient group receiving MB as rescue therapy appeared to be more critically ill at the time of administration (reflected by significantly higher APACHE II scores and a trend towards higher EuroSCORE II values) and hence comparisons between both groups are challenging[62].

A second retrospective analysis comparing MB monotherapy versus a combination therapy of MB and HCB in a cohort of cardiac surgery patients showed a similar increase in MAP 1 hour after administration. The analysis showed no statistical difference between the mono – and the combination therapy, with both groups showing a reduction in vasopressor requirement at 6,12 and 24 hours after administration[63].

Methylene blue in the treatment of intoxications

There is anecdotal evidence to use MB in the treatment of severe intoxications with β-blockers, CCB or metformin[64,65]. Metformin causes peripheral vasodilation, and recent evidence suggests increased levels of cNOS associated with metformin intoxication[66].

Patient population	Author	Study design and sample size	Dose of MB used	Summary of results
Cardiac surgery				
Preoperative	Ozal et al.[6]	RCT, N = 100	2 mg kg^{-1}	MB group: ↑SVR, ↓NE & inotropic support. ↓Administration of crystalloid, colloid and RBC transfusion. ↓Mean ICU & hospital length of stay
Intraoperative				MB group: ↑SVR and MAP, ↓TNF- α & NO levels
	Ribeiro et al.[30]	RCT, N = 60	2 mg kg^{-1}	MB group: ↑MAP, vasopressor requirement & lactate levels
	Maslow et al.[31]	RCT, N = 30	3 mg kg^{-1}	No significant difference SVR, MAP and vasopressor requirement.
	Cho et al.[32]	RCT, N = 40	2 mg kg^{-1}	MB group: ↓transfusion requirement
Postoperative				MB group: ↑SVR, ↓NE dose & lactate levels
	Leyh et al.[20]	Observational cohort , N = 54	2 mg kg^{-1}	MB group: ↑MAP, ↓NE dose
	Mazzeffi et al.[29]	Retrospective analysis, N = 88	1 – 2 mg kg^{-1}	MB group: ↓morbidity and mortality, ↓vasopressor requirement
	Levin et al.[5]	RCT, N = 56	1.5 mg kg^{-1}	Patients treated with MB: ↑operative mortality. Early administration of MB: ↓30-day mortality & renal failure
	Mehaffey et al.[33]	Retrospective analysis, N = 118	2 mg kg^{-1}, 12 h infusion 0.5 mg kg^{-1} h^{-1}	Patients treated with MB: ↑MAP & SVR, ↓vasopressor dose, mean hospital stay, ↓30-day mortality and new onset of renal failure
	Habib et al.[34]	Retrospective analysis N= 56	2 mg kg^{-1} +/- infusion 0.5-1 mg $kg^{-1}h^{-1}$	Patients treated with MB↑: risk of in-hospital mortality, morbidity, mean ICU length of stay & inotropy. After PSMA : MB = independent predictor of morbidity
	Weiner et al.[35]	Retrospective analysis N = 226	2 mg kg^{-1}, 6 h infusion 0.5 mg kg^{-1} h^{-1}	Patients treated with MB: ↓NE requirement , no difference in MAP or clinical outcomes
	Saha et al.[36]	Observational cohort, N = 27	1-2 mg kg^{-1}	
Transplantation surgery				
OLTx	Koelzow et al.[42]	RCT N = 36	1.5 mg kg^{-1}	MB group: ↑MAP & CO, ↓epinephrine dose & lactate levels
	Fukazawa et al. [43]	Retrospective cohort N = 106	1-1.5 mg kg^{-1}	No significant difference in MAP, vasopressor requirement, acute graft rejection and graft survival.
	Denny et al. [45]			
RTx	Herschmann et al.[44]	case report N =1	1.5 mg kg^{-1}	↑SVR & MAP, ↓vasopressor dose
		case report N = 1	1 mg kg^{-1}	↑MAP, ↓vasopressor dose
	Kofidis et al. [46]			
HTx	Carley et al.[47]	case report N=1	2 mg kg^{-1}	MAP, ↓vasopressor dose
DLTx		case report N=1	2 mg kg^{-1}	MAP, ↓vasopressor dose, ↑urine output
Septic shock	Kirov et al.[50]	RCT, N = 20	2 mg kg^{-1} , infusion 0.5-2 mg kg^{-1}	MB group: ↑MAP, SVR, SV & CI , ↓catecholamine dose. No difference in mortality
	Memis et al.[51]	RCT, N = 30	Infusion 0.5 mg kg^{-1} h^{-1}	MB group: ↑MAP
Burn patients				
	Jaskille et al. [53]	case report N = 2	2 mg kg^{-1}	↑MAP, ↓vasopressor dose
	Church et al.[54]	case report N = 1	2 mg kg^{-1}	↑MAP, ↓epinephrine dose
	Schlesinger et al.[55]	case report N = 1	2 mg kg^{-1}	↑CO, SVR, ↓vasopressor dose
Paediatric population				
	Abdelazim et al.[57]	RCT, N = 40	1.5 mg kg^{-1}	↑MAP, SVR, CVP , ↓CO, HR & NE dose
	Bitterman et al.[58]	Retrospective analysis N = 7	1 mg kg^{-1} , infusion 0.5 mg kg^{-1} h^{-1}	6/7 patients: ↑MAP, ↓vasopressor dose

RCT: randomized controlled trial, LOS: length of stay, MB: methylene blue, SVR: systemic vascular resistance, NE: norepinephrine, ICU: intensive care unit, TNF- α: tumor necrosis factor alpha, NO: nitric oxide, MAP: mean arterial pressure, PSMA: propensity score matching analysis, OLTx: orthotopic liver transplantation, RTx: renal transplantation, HTx: heart transplantation, DLTx: double lung transplanation SV: stroke volume, CI: cardiac index, CVP: central venous pressure, HR: heart rate.

Fig. 4 — Use of MB in the different patient populations discussed in this review.

Discussion

This review presents a comprehensive overview of the current literature on the management of VS with MB. The search strategy used in the three databases was intentionally unrestricted to evaluate the use of MB in different clinical settings and patient populations. The absence of standard guidelines for non-systematic reviews poses a question mark on the validity of this narrative review. The SANRA tool, and in particular the 'explanations and instructions' (Figure 2) document was used as a guide to improve the quality of the current review. The lack of a universal definition for VS, multiple comorbidities in critically ill patients suffering from vasoplegia and different dosing protocols lead to a large variability between patient groups and small sample sizes. Some authors suggest an optimal window of opportunity to treat patients with MB[3,11,15,32], subsequently leading to different times of MB administration. Despite these limitations, this review suggests that MB therapy is effective in treating vasoplegia with a favourable impact on haemodynamic parameters and response to catecholamines. Lower vasopressor requirement may prevent well-known adverse effects like mesenteric ischaemia or tissue necrosis. Most of the up-to-date evidence is, however, based on retrospective cohort studies and case reports. The effect of MB on clinical outcome parameters such as morbidity and mortality and optimal timing of administration is inconclusive and large randomized controlled trials are necessary to further examine the potential benefits and risks of adverse effects of MB in treatment of vasoplegic shock states. Figure 4 summarizes the available evidence in treating VS with MB in the different patient populations described above.

Conclusion

We present a critical overview of the current literature concerning the use of MB for the treatment of VS. Most of the available evidence is based on retrospective studies or case reports. MB can be used in different patient populations and has an acceptable safety profile, but should be avoided in patients with a known hypersensitivity or G6PD deficiency and carefully titrated in patients taking drugs interfering with the metabolism of serotonin. While most reports show that MB has a favourable impact on haemodynamic parameters and vasopressor requirement, the effect on morbidity and mortality are less clear. As such, there is no high-level evidence for the use of MB as a first-line drug to treat vasoplegia. Large randomized controlled trials are needed to further evaluate the indications, safety profile, optimal doses and timing of administration as well as the effects on clinical outcomes.

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