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Review

Vasoplegic syndrome—the role of methylene blue

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Summary

Vasoplegic syndrome is a recognized complication following cardiac surgery using cardiopulmonary bypass and is associated with increased morbidity and mortality. In several patients profound post-operative vasodilatation does not respond to conventional vasoconstrictor therapy. Methylene blue has been advocated as an adjunct to conventional vasoconstrictors in such situations. There is limited data pertaining to the use of methylene blue and a number of reports have been anecdotal observations. This article reviews the incidence and problems associated with the vasoplegic syndrome, the mechanism of action of methylene blue, its effects and adverse reactions and the literature supporting its intra-operative and post-operative use.

In cases where first-line therapy fails, the use of methylene blue seems to be a potent approach to refractory vasoplegia. The early use of methylene blue may halt the progression of low systemic vascular resistance even in patients responsive to norepinephrine and mitigate the need for prolonged vasoconstrictor use. However, dosing regimens and protocols need to be clearly defined before widespread routine use. Whether methylene blue should be the first line of therapy in patients with vasoplegia is a matter of debate, and there is inadequate evidence to support its use as a first line drug. More scientific evidence is needed to define the role of MB in the treatment of catecholamine refractory vasoplegia.

Keywords: Vasoplegic syndrome; Cardiopulmonary bypass; Methylene blue

1. Introduction

Cardiopulmonary bypass (CPB) can be complicated by a systemic inflammatory response characterized by profound vasodilation. Some patients exhibit a clinical state characterized by significant hypotension, low systemic vascular resistance (SVR) and increased requirements for fluids and vasopressors during or after CPB.

2. Definition and incidence

Vasoplegic syndrome [VS] is generally defined as an arterial pressure $<$50 mmHg, cardiac index $>$2.5 L min^{-1} m^{-2}, right atrial pressure $<$5 mmHg, left atrial pressure $<$10 mmHg, and low SVR ($<$800 dyne s^{-1} cm^{-5}) during intravenous norepinephrine infusion ($\geqq$0.5 μg kg^{-1} min^{-1}) [1].

The incidence of VS following cardiac surgery ranges from 8.8 to 10% [2–5]. Argenziano et al. [4] reported VS in 42% of patients undergoing LVAD insertion for end-stage heart failure during a 1-year period.

3. Risk factors for vasoplegic syndrome

Recent studies have established pre-operative intravenous heparin, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers as independent risk factors for post-operative VS [3,6,7]. The incidence of VS associated with the pre-operative use of these three agents has been as high as 55.6, 44.4, and 47.2%, respectively [6], in one study. The incidence of VS varies in different series' depending on the authors' definition of the syndrome, and hence the actual incidence of VS may not be this high in other studies. It is important however to recognize these drugs as potential risk factors for VS.

The long-term use of long acting ACE inhibitors leads to tissue accumulation, contributing to a decrease in SVR post-operatively. The renin-angiotensin system plays an important role in post-operative vascular tone changes [8]. ACE inhibitors decrease angiotensin II levels and increase the plasma levels of the vasodilator bradykinin. The increase in bradykinin is consequent to the fact that the lungs, which are the major site of bradykinin catabolism are excluded during CPB [9].

Mekontso-Dessap and co-workers [6] postulated that conditions like unstable angina and myocardial infarction are associated with a marked stress response leading to increased catecholamines levels, which are however

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depleted during CPB, thereby leading to diminished vascular tone and reactivity.

Argenziano et al. [4] reported low left ventricular EF (less than 0.35) and pre-operative heart failure as risk factors for vasodilatory shock following cardiac surgery. However, VS can also occur in patients with adequate ventricular function. Additional risk factors that have been identified include the use of alcuronium, the presence of diabetes, and the use of protamine [10].

4. The problem

Vasoplegic syndrome is associated with a poor prognosis. Norepinephrine-refractory vasoplegia is associated with a higher post-operative morbidity and mortality [6,11,12]. Mortality after cardiac surgery was 24% in a series reported by Levin and colleagues [3] and 25% in a series reported by Gomes and colleagues [12], in which post-operative VS persisted for longer than 36–48 h. The duration of norepinephrine-refractory vasoplegia significantly influences outcome. In patients with coagulation disorders, VS can cause oozing and diffuse bleeding that requires treatment with blood transfusions [12]. Thus, an aggressive management of post-operative VS is required to reduce post-operative morbidity and mortality.

The conventional treatment for intra-operative or post-operative vasoplegia has been hemodynamic support with vasopressors like phenylephrine, norepinephrine or vasopressin. Although norepinephrine is sufficient in most instances to restore adequate SVR and support systemic pressures, vasoplegia is refractory to norepinephrine in many instances. The efficacy of vasoconstrictors is limited by catecholamine resistance [4] and by significant toxic effects at high doses.

5. The role of vasopressin

Argenziano et al. [4] described the association between vasodilatory shock after CPB and vasopressin [AVP] deficiency. In several patients undergoing LVAD implantation and transplantation, they used AVP in the setting of post-CPB vasodilatation. Vasopressin caused significant increases in mean arterial pressure and systemic vascular resistance, and resulted in a marked reduction in norepinephrine doses, with no appreciable change in cardiac index [4].

Although patients undergoing coronary surgery usually exhibit large increases in AVP levels during and after bypass [13], some authors have documented cases of post-CPB AVP deficiency manifesting as VS. Hyponatremia [14], activation of atrial stretch receptors [15], atrial natriuretic peptide (ANP) [16], and autonomic dysfunction [17] have been implicated as causative agents that inhibit the release of AVP.

The precise mechanism of action of vasopressin is unclear. Whereas both catecholamines and vasopressin effect vasoconstriction by increasing intracellular calcium levels in vascular smooth muscle through activation of voltage-gated calcium channels, AVP additionally inhibits the production of cyclic guanosine monophosphate, and the adenosine triphosphate-activated potassium channels of vascular smooth muscle [18]. Thus, the efficacy of vasopressin in clinical scenarios in which catecholamines are ineffective may reflect its ability to counteract specific vasodilatory mechanisms.

The discovery of nitric oxide as a mediator in the systemic inflammatory response after CPB, suggested that post-operative vasoplegia might be limited or prevented by inhibiting nitric oxide.

This was based on the knowledge of the role played by nitric oxide in guanylate cyclase enzyme activation, cyclic guanosine monophosphate production, and smooth vascular muscle relaxation. Several cases have been described in which the guanylate cyclase inhibitor methylene blue (MB) was administered intravenously to reverse norepinephrine-resistant vasoplegia after CPB [19–22]. However, the available data has been largely based on anecdotal observations and the effect of MB has not been examined in larger cohorts.

6. Pathophysiology and mechanisms

Post-CPB vasodilatory shock results from pathologic activation of several vasodilator mechanisms. Interleukin-1 levels are elevated in inflammatory states, while ANP is increased after CPB and both promote vasodilation through increased levels of intracellular cyclic guanosine monophosphate. VS has also been attributed to endothelial injury [23], arginine-vasopressin system impairment, and the release of vasodilatory inflammatory mediators [24].

It has been suggested that refractory vasoplegia may reflect a dysregulation of nitric oxide synthesis and vascular smooth muscle cell guanylate cyclase activation. Nitric oxide is produced by two types of nitric oxide synthase, a constitutive type and an inducible type. The inducible synthase is produced in vascular smooth-muscle cells [25,26], cardiac myocytes [27], and by inflammatory mediators such as tumor necrosis factor alpha [28] and interferon gamma [29].

Nitric oxide activates soluble guanylate cyclase to produce cyclic guanosine 3′,5′monophosphate (cGMP). In vascular smooth-muscle cells cyclic guanosine monophosphate causes vasodilation [29] and in myocytes may decrease contractility [27].

However, recent studies have failed to demonstrate increased levels of nitric oxide following CPB. Myles and associates [30] failed to identify an increase in nitric oxide release following CPB on the basis of the serum and urine nitrite/nitrate levels. Furthermore, Beasley and McGuiggin [31] and Schmidt [32] showed that interleukin-1 and oxygen free radicals can activate guanylate cyclase leading to vascular hyporeactivity in the absence of nitric oxide. Because cytokines and free radicals are produced during CPB, a nitric oxide-independent activation of the guanylate cyclase could be an initiator of refractory vasoplegia after CPB.

Hence, non-nitric cGMP-dependent pathways may be crucial to the development of VS [33]. It is likely that the CPB-triggered release of proinflammatory mediators acts

through the induction of the final common pathway, which is the activation of the guanylate cyclase, leading to vasodilation [34].

Hence it appears that the soluble intracellular enzyme guanylate cyclase (GC) is activated to produce cyclic guanosine monophosphate (cGMP) [3,7] presumably under the influence of several mediators, including nitric oxide (NO). Increases in the intracellular concentration of cGMP are followed by relaxation of myocardial and vascular smooth muscle [12,35].

Methylene blue is believed to act through competition with nitric oxide, in binding to the iron heme-moiety of soluble guanylate cyclase resulting in enzyme activation [36,37]. This inhibits the increases in the levels of cGMP, and thereby precludes its vasorelaxant effect in vascular smooth muscle [4]. Hence methylene blue counteracts the effects of nitric oxide and other nitrovasodilators in endothelium and vascular smooth muscle [33].

7. Dosage

Methylene blue is available as a solution (10 mg/mL). A single dose of IV MB (2 mg/kg, 20-min infusion time), as used by Leyh and co-workers [7], has been used as rescue treatment. Continuous MB infusion could be an option for patients not responding to a single dose of MB. Subcutaneous injection has been reported to cause necrotic abscesses.

8. Pharmacokinetics

The onset of the hemodynamic effects of methylene blue is relatively rapid. Oral absorption ranges from 53 to 97%. Methylene blue is reduced to leukomethylene blue, and is eliminated in bile, feces, and urine as leukomethylene blue [38].

9. Evidence in post-operative use

Methylene blue has predominantly been used to reverse vasoplegia in a post-operative setting.

Several groups have shown that the post-operative administration of a single dose of MB in VS can restore SVR [2,3,6,7,10]. Kofidis et al. [19] successfully used in MB for vasoplegia in a post-transplant patient.

Levin and colleagues [3] randomized 56 patients with vasoplegia to receive IV MB (1.5 mg/kg over 1-h) or placebo. There were no deaths in the MB group and six deaths (21.4%) in the placebo group. Methylene blue reversed vasoplegia in about 2 h, while in those treated with vasopressors (28.6%) only, vasoplegia persisted for more than 48 h. Leyh et al. [7] reported on the use of MB (2 mg/kg over 20 min) in 54 patients with norepinephrine-refractory vasoplegia with similar results.

Most studies have used single doses (1.5—2 mg/kg) of MB to treat post-operative vasoplegia. It is not uncommon in such circumstances for the effects to be transient, and some authors have administered repeat doses [35,39]. IV boluses may however constitute only a rescue measure, and it may be necessary to maintain a continuous infusion [21].

10. Intra-operative use

VS can occur during CPB and a few authors have reported the use of MB intra-operatively to treat profound vasodilatation. Grayling and Deakin [35] added MB to the pump prime as treatment for septic endocarditis during a valve operation, and followed this up with a post-operative infusion. Sparicio et al. [40] reported the peri-operative management of two patients who self-assumed lithium and had refractory hypotension during beating heart surgery. Both patients had a dramatic hemodynamic improvement after receiving methylene blue. Evora and colleagues [21], reported a patient in whom CPB had to be re-instituted, following a severe protamine reaction. During CPB, they were unable to increase arterial pressures even with norepinephrine and had to use an infusion of MB to generate adequate pressures.

11. Pre-operative use

Ozal and associates [1] identified 100 patients for coronary surgery who were at high risk for vasoplegia (pre-operative ACE inhibitors, calcium blockers, and heparin) and randomized these patients to receive methylene blue (2 mg/kg over 30 min) or placebo pre-operatively.

The prophylactic infusion of MB in these patients was associated with a higher SVR during surgery (compared to placebo) and a lower requirement for norepinephrine, inotropic support, fluid and blood transfusions. While prophylactic MB prevented VS in every patient in whom it was administered, 26% [13/50] of the patients in the placebo group had VS. In six patients, VS was refractory to norepinephrine. VS resolved later in four patients, while two showed no resolution and died of multiorgan failure. Although MB was administered to these two patients, it had no beneficial effect because it was administered after the development of multiorgan failure. This suggests that in those patients in whom MB is indicated, its early use could pre-empt the development of multiorgan failure and adverse consequences. Conversely, inordinate delays may not yield the same degree of benefit following the administration of methylene blue. Leyh et al. [7] reported four patients with heart failure who had an LVAD in situ, where MB failed to reverse vasoplegia. A persistent release of proinflammatory mediators following placement of the LVAD device was believed to have caused this phenomenon.

In clinical practice, intra-aortic balloon pumps are perhaps more commonly used than LVAD's, and a number of these patients manifest systemic vasodilatation and require moderate to large doses of vasoconstrictors. The development of mesenteric ischemia and peripheral ischemia of the upper and lower extremities, in such patients is a dreaded complication. The early use of MB, in these patients may potentially reverse the vasodilatory state in these patients and reduce the dose and duration of vasoconstrictors in these patients.

12. Effects

Methylene blue was initially used in desperate situations during the operative and post-operative period. Several groups have now shown that intravenous MB is effective in the treatment of norepinephrine-refractory vasoplegia after CPB, with no relevant side effects.

MB infusion is generally initiated when a norepinephrine dosage of at least 0.5 $\mu g\ kg^{-1}\ min^{-11}$ is reached. Most studies have reported a clinically relevant increase in SVR and a decrease in norepinephrine dosage shortly after the MB infusion. Mean pulmonary arterial, right and left atrial pressures did not change following MB infusion. Several studies have also found a significant decrease in serum lactate concentrations within 24 h after MB infusion, underlining the restoration of normal peripheral blood flow.

13. Side effects

Adverse effects of MB include cardiac arrhythmias (transient nodal rhythm and ventricular ectopy) [41], coronary vasoconstriction, angina [21], decreases in cardiac output, renal blood flow and mesenteric blood flow, increases in pulmonary vascular pressure and resistance and deterioration in gas exchange [1]. Arrhythmias and angina have usually been transient and self-limiting. Most side effects however, are dose dependent and do not occur with doses <2 mg/kg [42,43]. Most studies have reported normal renal function and pulmonary gas exchange (expressed as the ratio of PaO_2 to inspired oxygen fraction). Other side effects include precordial pain, confusion, headache, fever, nausea, vomiting, abdominal pain and diaphoresis.

MB is reduced in the erythrocyte to leukomethylene blue, and is excreted primarily in the urine as leukomethylene blue and MB [44]. Hemolytic anemia, Heinz body anemia, and hyperbilirubinemia have been reported after MB administration in doses exceeding 2 mg/kg [45].

Transient and self-limiting increases in serum aspartate aminotransferase and alanine aminotransferase have been reported in some studies [1]. It is not known whether the increased enzyme levels were related to the methylene blue, the associated norepinephrine, or both.

14. Discolouration of skin and urine

Methylene blue is also well known to turn the urine greenish-blue [1,46]. This discoloration can be quite alarming to patients and their relatives who should be advised about this side effect. However, the discolouration is usually self-limiting and disappears spontaneously after a few days after discontinuing the drug. Mild skin discoloration can also be observed in most patients, but it usually self-limiting. Skin discoloration can be treated with topical administration of dilute hypochlorite solution [38]. No permanent skin damage has been reported [1].

Pulse oximetry is not reliable as an oxygen-monitoring device in that methylene blue interferes with the pulse oximeter's light emission (at a wavelength of approximately 660 nm), resulting in falsely depressed oxygen saturation readings [47].

15. Contra-indications

Contra-indications to methylene blue include severe renal insufficiency and hypersensitivity to methylene blue. Methylene blue should be used with caution in young patients with G6PD deficiency (due to low endogenous NADPH concentrations, which is essential to leukomethylene blue production). This group of patients can develop a hemolytic anemia characterized by formation of Heinz bodies [48].

16. Drug interactions

Methylene blue can exacerbate dapsone-induced hemolytic anemia because of the formation of the dapsone reactive metabolite hydroxylamine, which oxidizes hemoglobin [49,50]. Barring this no other major drug interactions have been reported with methylene blue.

17. Conclusions

Vasoplegic syndrome occurs in 8–10% of patients following cardiac surgery and is associated with increased morbidity and mortality. In a subset of patients with profound vasodilatation, VS does not response to fluids and conventional vasoconstrictors.

In patients who do not respond to noradrenaline, the early use of vasopressin is beneficial and in some centers vasopressin is rapidly replacing noradrenaline as the first line treatment for vasoplegic syndrome.

The inhibition of guanylate cyclase elicited by nitric oxide or any endothelially soluble guanylate cyclase-activating factor (e.g. interleukin-1, atrial natriuretic peptide, and bradykinin) could be a novel approach in the treatment of norepinephrine-refractory vasoplegia after CPB, and forms the basis for the use of methylene blue.

In cases in which first-line therapy has failed, methylene blue seems to be a potent approach to norepinephrine-refractory vasoplegia with no major side effects. The early use of methylene blue may halt the progression of low SVR even in patients responsive to norepinephrine and mitigate the need for a prolonged vasoconstrictor use. However, dosing regimens and protocols need to be clearly defined before widespread routine use.

Risk factors for the development of VS include pre-operative ACE inhibition, IV heparin and calcium channel blockers. Preliminary results suggest that pre-operative methylene blue reduces the incidence and severity of vasoplegic syndrome in such high-risk patients, thus ensuring adequate SVR intra and post-operatively. Whether methylene blue should be the first line of therapy in patients with VS is a matter of debate. There is inadequate evidence to support its use as a first line drug, and on the basis of the current evidence methylene blue does not appear to be the 'magic bullet' for the management of vasoplegic syndrome.

More scientific evidence is needed to define the role of MB in the treatment of catecholamine refractory vasoplegia. There appears to be sufficient prima facie evidence for a randomized clinical trial to define the indications, dosing regimens and contra-indications to the use of MB in the treatment of vasoplegic syndrome.

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