Case Report

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Case report: methylene blue for cardiogenic shock

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Abstract

***Background*: Cardiogenic shock after acute myocardial infarction is a cause of elevated morbidity and mortality in coronary intensive care units. The pathophysiology of cardiogenic shock involves both heart failure and increased afterload, but sometimes, not frequently may present as a vasodilatory state secondary to systemic inflammation, which requires treatment with high doses of inotropics and vasopressors.**

***Objective*: We present 3 cases of patients with myocardial infarction who developed cardiogenic shock resistant to vasopressors, who were treated with methylene blue and who showed improved clinical outcomes.**

***Data sources*: Several studies have demonstrated that methylene blue increases systemic vascular resistance reflected by an increase in mean arterial pressure, or from a reduction in vasopressors requirements in patients with septic shock. It also improves myocardial contractility and oxygen delivery, although this is controversial. There is evidence that an inflammatory response with activation of inducible nitric oxide synthase might be responsible for the deleterious effects and persistent vasodilation in patients with cardiogenic shock resistant to vasopressors.**

***Conclusions*: We review briefly the changing paradigm in the use of nitric oxide antagonists in treating patients suffering cardiogenic shock.**

Key words: cardiogenic shock; methylene blue; myocardial infarction; left ventricle; vasopressors; nitric oxide.

Introduction

Cardiogenic shock is the primary cause of death in hospitalized patients with acute myocardial infarction, particularly when left ventricle failure occurs. The best management of shock secondary to right or left ventricle failure is reestablishing blood flow in the infarct-related artery. (1) Despite quick treatment, cardiogenic shock causes 50% of deaths within the first 24 hour of the event. (2) A new paradigm for cardiogenic shock assumes that the pathophysiology of the disease includes the participation of guanylate cyclase, leading to the production of nitric oxide that contributes to the vasodilation and the poor response to vasopressors of some patients with this complication. (2) Methylene blue, a guanylate cyclase inhibitor, decreases the need for high doses of vasopressors in patients with septic and anaphylactic shock, with vasoplegic syndrome and exhibiting vasodilation caused by protamine. Here we present 3 cases of patients admitted to our coronary care unit with vasopressor-resistant cardiogenic shock who were treated with methylene blue, and briefly review the literature on the use of this drug.

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Case 1

An obese 63-year-old man with hypertension and paroxysmal atrial fibrillation arrived at our emergency room complaining of chest pain, dyspnea and diaphoresis. Two weeks earlier, he had been diagnosed with pneumonia and was treated with oral antibiotics. An electrocardiogram confirmed an inferior myocardial infarction that was treated with reteplase, achieving reperfusion criteria. Five hours later, the patient developed cardiogenic shock and required mechanical ventilation. He was brought to our hospital for further treatment. At his arrival, a medium arterial pressure of 50 mmHg that was nonresponsive to phenylephrine (105 μg/min), norepinephrine (80 μg/min) or vasopressin (5 U/h) was documented. A Swan-Ganz catheter showed a profile with a cardiac output of 3.3 L/min and systemic vascular resistance (SVR) of 796 dynes × sec/cm^5. A bolus of 2 mg/kg of methylene blue was administered followed by an infusion of 0.25 mg/h (**Figure 1**).

Case 2

A 54-year-old man was admitted to our emergency room with severe chest pain and diaphoresis. An EKG revealed an anterior myocardial infarction. Percutaneous coronary intervention (PCI) was performed with revascularization of the anterior descending artery. During the procedure, the patient developed ventricular extrasystoles and hypotension. An intra-aortic balloon pump (IABP) was then placed. Treatment with amiodarone, magnesium and norepinephrine was started with good response; mechanical ventilation was required. A few hours later, the patient presented hypotension, with a cardiac output of 3.1 L/min, cardiac index 2.1 L/min/m^2 and SVR of 730 dynes × sec/cm^5. Administration of vasopressin (8 U/h), norepinephrine (100 μg/min) and phenylephrine (60 μg/min) infusions was commenced without response. A bolus of 2 mg/kg of methylene blue was started with a further infusion of 0.25 mg/h (**Figure 2**).

Case 3

A 58-year-old man with dyslipidemia and hypertension arrived at our emergency room complaining of severe chest pain, dyspnea and diaphoresis. EKG changes compatible with an anterior myocardial infarction were documented. PCI with revascularization of the anterior descending coronary artery was performed. During the procedure, the patient developed ventricular fibrillation that was treated with defibrillation and lidocaine. Norepinephrine-resistant cardiogenic shock refractory developed and an IABP was placed. At the coronary care unit, the patient continued to show hypotension, with a cardiac output of 3.2 L/min, a CI of 1.8 L/min/m^2 and SVR of 790 dynes × sec/cm^5 in spite of treatment with norepinephrine (15 μg/min), vasopressin (8 U/h) and phenylephrine (52 μg/min). Boluses of 2 mg/kg of methylene blue followed by a 0.25 mg/kg infusion were administered (**Figure 3**).

All patients showed clinical improvements; they were discharged from the unit to an intermediate care unit and later left the hospital.

Discussion

Paradigms to explain cardiogenic shock

It is generally accepted that the mechanism of disease of cardiogenic shock consists in profound depression of myocardial contractility resulting in a reduction of cardiac output, low blood pressure and further reductions in contractility and cardiac output. Compensatory systemic vasoconstriction with SVR occurs in response to the depression of the cardiac output. In patients with cardiogenic shock, the ability to constrict the vascular beds and thus reduce cardiac output is an important compensatory response. (2) Vasodilators, frequently administered in the management of cardiogenic shock, must be used with caution as they can produce hemodynamic instability, ischemia, renal failure and even shock. (3) A new paradigm to explain cardiogenic shock postulates that there is also an inflammatory response in these patients that leads to vasodilation. (2) Patients with large myocardial infarctions have an inflammatory response with cells producing nitric oxide at pathological levels in response to stress. Such expression leads to the production of cytotoxic nitric oxide-derived reactive nitrogen species, such as peroxynitrate formed by reaction with superoxide, and these induce vasodilation. (2)

Nitric oxide-derived reactive nitrogen species

Nitric oxide is an endogenous vasodilator produced from L-arginine by guanylate cyclase. There are 3 isoforms of

nitric oxide synthase (NOS): neuronal NOS, endothelial NOS (eNOS) and inducible NOS (iNOS). eNOS is a potent vasodilator, but it also has vasoprotective and antiatherosclerotic properties, inhibits platelet aggregation and adhesion to the vascular wall, and it may be beneficial in the microcirculation by preventing tissue damage. (4) iNOS is activated under the influence of endotoxins and cytokines secondary to an inflammatory response. (5) The effects of high level nitric oxide and nitric oxide-derived reactive nitrogen species are the direct inhibition of myocardial contractility and suppression of mitochondrial respiration in nonischemic myocardium. They also affect glucose metabolism, exert proinflammatory effects, cause reduced catecholamine responsivity and induce systemic vasodilation. (2) It has been hypothesized that high levels of iNOS in patients with myocardial infarctions exert detrimental effects on the left ventricle, produce myocardial stunning and may explain the observation of new or worsening hypotension after primary PCI in some patients. (2)

Methylene blue

Methylene blue is a chemical dye that easily crosses cell membranes, inhibits iNOS and is capable of inhibiting the guanylate cyclase enzyme in vascular myocytes. (4) Several studies have demonstrated that methylene blue increases SVR, reflected by an increase in mean arterial pressure or by a reduction in vasopressors requirements in patients with septic shock. (5) This drug also improves myocardial contractility and oxygen delivery, although evidence for these actions is controversial. Kirov et al (6) reported that the administration of a continuous infusion of methylene blue to patients with septic shock prevented deterioration in cardiovascular parameters such as the stroke volume index, the left ventricle cardiac work index and the mean arterial pressure; it also reduced the requirement for vasopressors. At present, there is no report of decreased mortality in such patients. On the other hand, the administration of the nitric oxide inhibitor N (G)-monomethyl L-arginine (L-NMMA) was associated with increased mortality. (5)

Levin et al (7) reported the resolution of vasoplegic syndrome with an infusion of methylene blue and vasopressors after cardiac surgery in all patients studied, compared with 28% of those treated with vasopressors alone (p=0.01). Patients in the methylene blue treated group also showed lower mortality, but the syndrome was associated with the development of sepsis in 6 of the 28 patients in the control group. Several studies on animals have confirmed the action of methylene blue as an inhibitor of superoxide formation. It is believed that this mechanism reduces oxidative damage in the brain and the heart, thereby improving survival in patients with cardiac arrest receiving cardiopulmonary resuscitation. (8) The preoperative administration of a methylene blue infusion in patients at risk of developing vasoplegic syndrome after cardiac surgery stabilized the SVR, diminished the use of vasopressors and reduced the stay in an intensive care unit. (9) Similar beneficial effects of methylene blue have been seen in patients with vasodilation induced by protamine and with anaphylactic shock resistant to standard therapy. (10,11)

Cardiogenic shock and iNOS

As discussed above, there is evidence that an inflammatory response with the activation of iNOS may be responsible for the deleterious effects and persistent vasodilation in patients with cardiogenic shock resistant to vasopressors. For example, patients in the SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK) study had an average ejection fraction that was only moderately depressed (30%) and did not show elevated SVR despite treatment with vasopressors. (2) On the other hand, among patients with acute coronary syndromes (unstable angina, ST EKG segment elevation with myocardial infarction or with non-ST segment elevation with myocardial infarction), elevated leukocyte counts and C reactive protein levels were associated with a higher 6-month mortality. (12) This suggests that the vasodilation observed in these patients could have been caused by an acute inflammatory response syndrome. There are also experimental studies in knockout mice in which inhibition of NOS improved survival, coronary blood flow and had anti-stunning effects. (2) Therefore, it has been hypothesized that a NOS inhibitor (NOSi) would have beneficial effects on the treatment of patients with post myocardial infarction vasopressors-resistant cardiogenic shock. At least 2 studies have used a NOSi in the treatment of such patients. The first treated a small cohort of 11 patients with extensive myocardial infarction. (13) The results led the authors to treat a larger cohort of 30 post-PCI patients with left ventricular failure caused by myocardial infarction with the NOSi N (G)-nitro-L-arginine methyl ester (L-NAME). They infused high doses of the drug and measured hemodynamic parameters and

mortality rates over 1 month compared with a control group. They achieved a 1-month survival of 73% compared with 33% of the control group as well as statistically significant benefits in cardiac power index, SVR, mean arterial pressure, time with an IABP and time on mechanical ventilation without significant adverse effects. They concluded that L-NAME reduced mortality either by increasing myocardial contractility or by increasing SVR. (14) A subsequent phase II study compared the effects on mean arterial pressure among patients with myocardial infarction complicated with cardiogenic shock, treated with either 1 of 3 different doses of L-NMMA or placebo. This study obtained statistically significant results, but only in the first 15 min from the beginning of the infusion. (15) The TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable Myocardial Infarction Patients with Cardiogenic Shock) trial was a prospective, international, multicenter, randomized, double-blind, placebo-controlled trial. The aim was to evaluate survival rates in patients with cardiogenic shock complicating myocardial infarctions, after the administration of L-NMMA. Three hundred ninety eight patients were enrolled and treated with either L-NMMA or placebo. There were no improvements in 30-day or 6-month survival rates. There was a slight increase in blood pressure, but this was not clinically significant. (16) There is no clear explanation for the failure of NOSi in the treatment of post myocardial infarction cardiogenic shock resistant to vasopressors. Curiously, these drugs also failed to improve hemodynamic parameters in patients with septic shock and they even increased the mortality rate. (5) A possible explanation is that NOSi drugs are nonspecific and inhibit regulatory pathways that in the end are beneficial in patients suffering persistent shock.

Cardiogenic shock and methylene blue

We have presented 3 cases of patients with myocardial infarction who developed cardiogenic shock resistant to vasopressors and were treated with methylene blue. Methylene blue is an iNOS specific inhibitor that has been useful in the treatment of patients with septic shock by decreasing vasopressors requirements and -although not proven- by increasing myocardial contractility and oxygen delivery. As cardiogenic shock following myocardial infarction is partly caused by an inflammatory response, and as there is evidence of beneficial effects of methylene blue in septic shock, we administered methylene blue to our patients with the aim of lowering their requirement for drugs and improve hemodynamic parameters. All patients in this series had persistent hypotension despite simultaneous treatment with 3 vasopressors (and placement of an IABP in two of them) at the time the methylene blue infusion was started. In **Table 1**, we present the patient´s hemodynamic parameters before and during the administration of methylene blue. The SVR changed for all 3 patients during the administration of the drug. **Figures 1-3** show the relationship between methylene blue infusion and the dosages of norepinephrine, vasopressin and phenylephrine, with a decrease in the infusion rate of the 3 vasopressors during the administration of the drug that continued for at least 24 h. It is important to note that one of the patients was admitted to our hospital with cardiogenic shock and septic shock caused by community-acquired pneumonia, which could have altered the results for this particular patient. All the patients showed clinical improvements; they were discharged from the unit to an intermediate care unit and later left the hospital.

Apparently, methylene blue decreased the need for vasopressors in these 3 patients. As expected, the SVR also improved with the administration of the drug. This may have been caused by inhibition of iNOS, which in pathological conditions can cause persistent vasodilation and increased demand for vasopressors. As in patients with septic shock, methylene blue may be an adjuvant for the treatment of cardiogenic shock by decreasing the need for vasopressors with deleterious effects. This action may give time to control the inflammatory response secondary to myocardial infarction and thereby prevent systemic organ failure. However, in the case of SVR and other hemodynamic parameters, the effect of the drug is controversial. At present, there is no other report of the use of methylene blue on the treatment of patients with postmyocardial infarction vasopressors-resistant cardiogenic shock. The current treatment for this complication does not include the use of any type of NOS inhibitor, specific or nonspecific. (17) Our results appear to justify the importance of starting a prospective study to test the benefit of methylene blue in treating this pathology.

Conclusions

Cardiogenic shock is the primary cause of mortality in patients with myocardial infarctions. A new paradigm

to explain this assumes that an inflammatory reaction is responsible for the persistent hypotension seen in these patients. Although NOSi drugs have not demonstrated any benefits for the treatment of this complication, methylene blue as a specific iNOS inhibitor might prove effective and further study on this drug is warranted.

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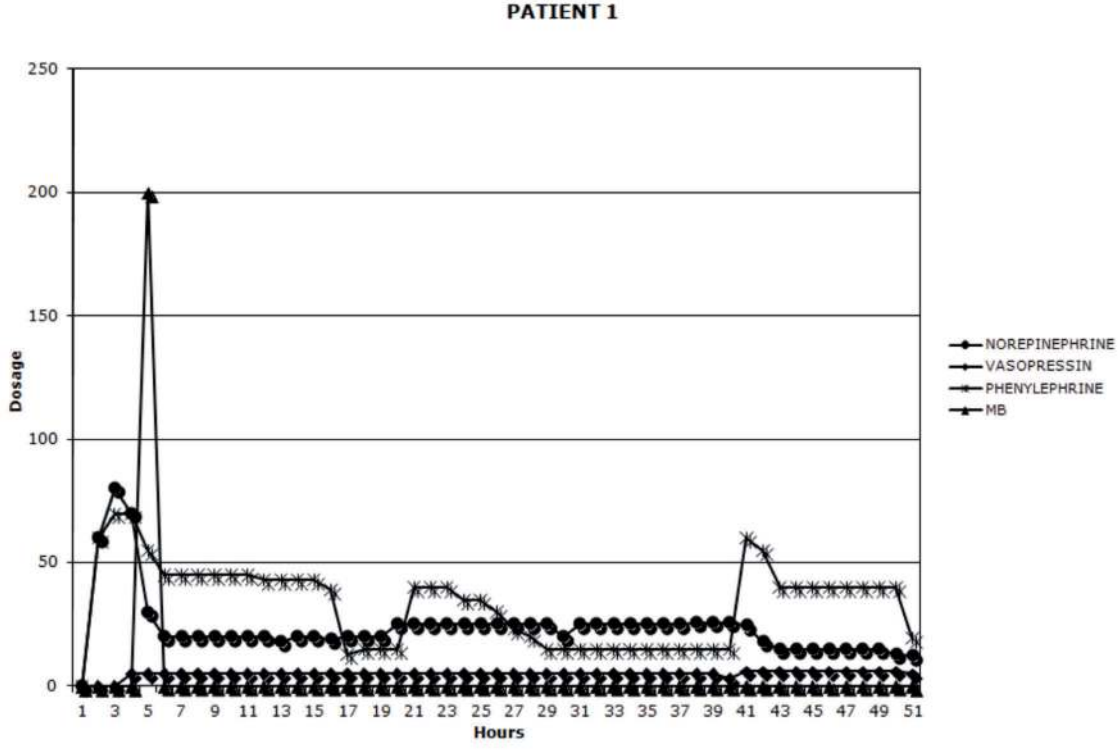
Table 1. Hemodynamic parameters in 3 patients before and during the administration of methylene blue (MB)

	Patient 1		Patient 2		Patient 3	
Hemodynamic parameters	Before MB	During MB	Before MB	During MB	Before MB	During MB
CI (L/min/m^2)	2.23	2.59	3.42	3.43	2.48	3
SVR (dynes x sec/cm^5)	796	991.96	760	996.2	840	983.02

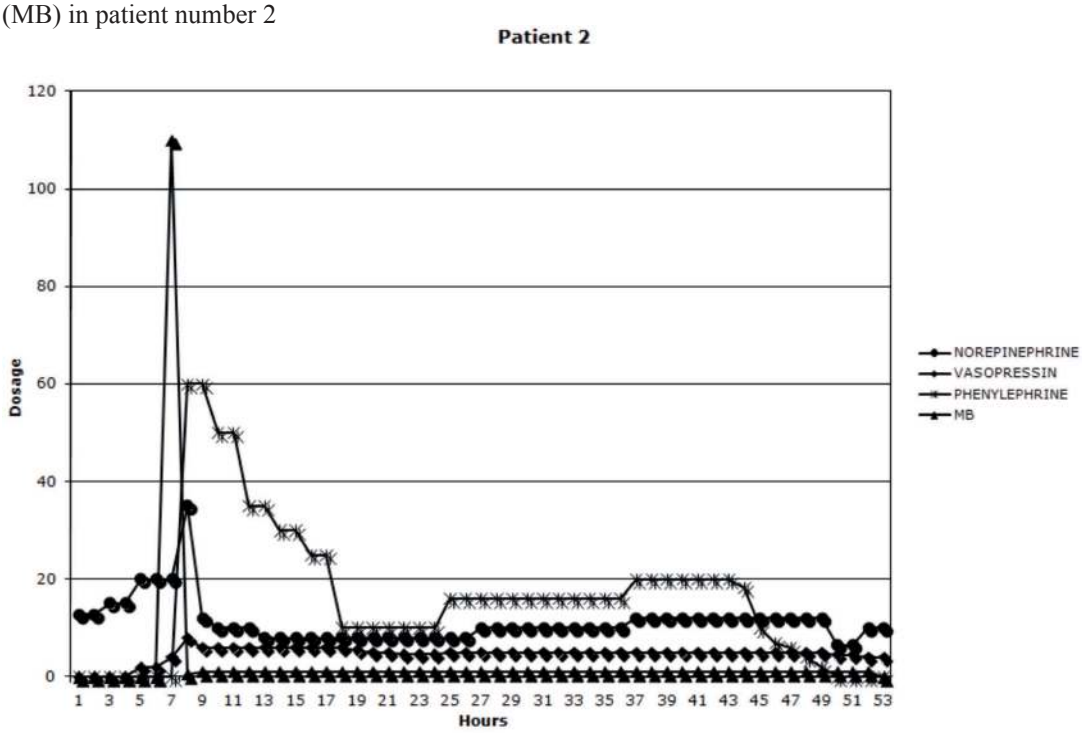
Legend: CI=cardiac index; SVR=systemic vascular resistance

Figure 1. Relationship between the dosages of norepinephrine (NE), vasopressin (V) and phenylephrine (PP) and the administration of an infusion of methylene blue (MB) in patient number 1



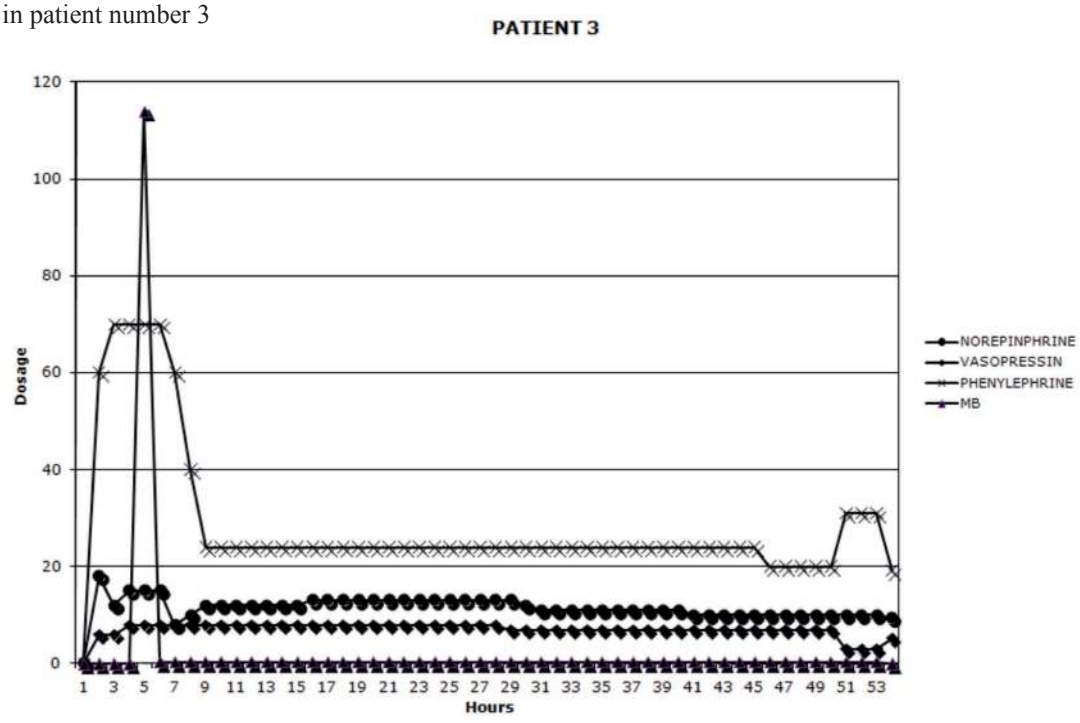
Legend: dosages are in µg/min for NE, U/h for V, µg/min for PP and mg/h for MB

Figure 2. Relationship between the dosages of norepinephrine (NE), vasopressin (V) and phenylephrine (PP) and the administration of an infusion of methylene blue (MB) in patient number 2



Legend: dosages are in µg/min for NE, U/h for V, µg/min for PP and mg/h for MB

Figure 3. Relationship between the dosages of norepinephrine (NE), vasopressin (V) and phenylephrine (PP) and the administration of an infusion of methylene blue (MB) in patient number 3



Legend: dosages are in µg/min for NE, U/h for V, µg/min for PP and mg/h for MB

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