Methylene blue for the management of pediatric patients with vasoplegic syndrome

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Background
Vasoplegic syndrome is a form of vasodilatory shock that can occur after cardiopulmonary bypass. Although norepinephrine is sufficient in most cases to restore adequate systemic vascular resistance and support systemic pressures, vasoplegia refractory to norepinephrine has been reported and is associated with high morbidity and mortality, especially in pediatric patients. The guanylate cyclase inhibitor methylene blue infusion could be a promising therapy for such cases. We reported in this study the response of pediatric cardiac patients with norepinephrine-refractory vasoplegic syndrome to methylene blue infusion.
Patient and methods
A total of 20 pediatric patients mean age 21.60 ± 9.88 months and mean weight 11.70 ± 3.63 kg, with norepinephrine-refractory vasoplegia after cardiopulmonary bypass were treated with an intravenous infusion of methylene blue (1.5 mg/kg) over 20 min. The effects on hemodynamic parameters, cardiac index, systemic vascular resistance index, and norepinephrine dosage were assessed 1 h after infusion.
Results
The mean arterial pressure increased significantly, with a mean difference of 16.70 ± 4.88 mmHg; also, a significant increase in systemic vascular resistance ($P < 0.001$), normalization of cardiac output, and a significant decrease in norepinephrine dosage (from 0.57 ± 0.05 to 0.11 ± 0.13 μg/kg/min) were observed in all patients within 1 h. No adverse effects related to methylene blue infusion were observed.
Conclusion
A single-dose methylene blue infusion appears to be a promising treatment for norepinepherine-refractory vasoplegia after cardiopulmonary bypass during pediatric cardiac surgery.

Keywords:
metheylene blue, pediatric, vasoplegic syndrome

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Introduction

Vasoplegic syndrome (VS) (vasoplegia) is a well-described form of vasodilatory shock that can potentially occur after separation from cardiopulmonary bypass (CPB). It is a state of low systemic arterial pressure with markedly low systemic vascular resistance (SVR) despite high cardiac output (CO) and adequate fluid resuscitation [1]. The reported incidence ranges from 9 to 44% [2].

VS is generally defined as an arterial pressure less than 50 mmHg, cardiac index (CI) greater than 2.5 l/min/m^2, right atrial pressure less than 5 mmHg, left atrial pressure less than 10 mmHg, and low SVR (< 800 dyne s/cm^5) during intravenous norepinephrine infusion of at least 0.5 μg/kg/min [3].

Yet, the origin has not been completely elucidated. In adults, vasoplegia has been reported to be associated with the long-term use of certain drugs [e.g. angiotensin-converting enzyme inhibitors (ACEIs), calcium channel antagonists, amiodarone, and heparin] [4], as well as patient-specific risk factors such as left ventricular ejection fraction (EF) less than 35%, symptoms of congestive heart failure, and diabetes mellitus [5].

Post-CPB vasodilatory shock results from pathologic activation of several vasodilator mechanisms. Interleukin-1 and atrial natriuretic peptide (ANP) levels are increased after CPB and both promote vasodilation through increased levels of intracellular cyclic guanosine monophosphate [6].

However, VS because of a nonseptic mechanism can be considered a kind of systemic inflammatory response (SIRS). The physiological response to SIRS is mediated by different mediators that induce the synthesis of nitric oxide (NO) and prostacyclin. The dysregulation of NO synthesis and release and also vascular smooth muscle cell guanylate cyclase activation; upregulation of inducible NO; and increase in NO production led to the generation of cyclic guanisine 3′,5-monophosphate,

resulting in marked relaxation of the vascular smooth muscle [7].

VS has also been attributed to endothelial injury and impairment in the arginine–vasopressin system [8]. It has been suggested that refractory vasoplegia may reflect a dysregulation of NO synthesis and vascular smooth muscle cell guanylate cyclase activation [9].

Although the conventional treatment for intraoperative or postoperative vasoplegia includes hemodynamic support with vasopressors such as phenylephrine, norepinephrine, or vasopressin, vasoplegia is refractory to norepinephrine in many cases [5].

VS is associated with a poor prognosis. Generally, the mortality rate of VS is as high as 25% in cardiac surgery [10]. In particular, norepinephrine-refractory vasoplegia has been associated with increased morbidity and mortality [11].

Methylene blue (MB) inhibits NO synthase and guanylyl cyclase, and can also prevent NO-mediated vasodilatation by interfering with the NO-cyclic guanylate monophosphate pathway, inhibiting its effect on smooth muscle [12].

We hypothesized that pediatric patients who developed VS may have benefit from intravenous MB infusion. In this single-arm study, we reported our experience with the use of MB for the treatment of pediatric cases with norepinephrine-refractory VS, with a special focus on the potential risks and benefits of the drug in these cases.

Patient and methods

Between April 2012 and March 2013, 20 patients (2.7%), out of a total of 750 various elective pediatric corrective cardiac surgeries performed with CPB support at Atfal Misr Hospital, developed norepinephrine-refractory systemic VS.

Inclusion criteria were all patients who developed vasoplegia after CPB, which was defined as mean arterial pressure (MAP)≤50 mmHg, SVR <800 dyne s/cm^5 or indexed systemic vascular resistance (SVRI)≤1600 dyne s/cm^5/m^2, and CI ≥2.5 l/min/m^2, after 5 min of intravenous norepinephrine infusion (≥0.5 μg/kg/m) without improvement.

After the approval of the local ethics committee was obtained and informed written consent was taken from patients' parents, patients received the guanylate cyclase inhibitor MB (Methylene blue injection, USP 1%; American Regent Inc.) (1.5 mg/kg) infusion over 20 min in addition to norepinephrine for restoration of the mean systemic blood pressure and SVRI.

EF and the mean pulmonary arterial pressure (MPAP) were determined using transesophageal echocardiography. Left ventricular EF and MPAP were defined as normal when more than 50% and within 12–15 mmHg, respectively. Patients with a history of glucose-6-phosphate dehydrogenase deficiency, previous cardiac surgery, metabolic, renal or hepatic disorders, EF lower than 50%, with MPAP more than 15 mmHg, and patients who required other medications to control the condition such as vasopressin, phenylephrine hydrochloride, or corticosteroids were excluded. Also, patients with abnormal valve area and patients with more than mild aortic or mitral regurge were excluded because of (echo) measurement difficulties.

Anesthesia was induced using intravenous midazolam (0.05 mg/kg), propofol (1 mg/kg), and fentanyl (5 μg/kg). It was maintained with inhalational isoflurane in the lowest possible concentration necessary to maintain blood pressure and heart rate (HR) within the 20% limit of the patient's preoperative value. Additional fentanyl increments of 2 μg/kg were performed to supplement anesthesia. Pancuronium bromide was used for neuromuscular blockade. Ventilation was controlled to ensure normal blood gases using an inspired oxygen concentration of 50% (oxygen-air mixture) before CPB and 100% oxygen after separation from bypass. Before CBP, hypertension and hypotension were defined as an increase or a decrease in the MAP by at least 20% from the baseline, respectively. Hypertension was treated with additional increments of fentanyl. Hypotension was treated with an intravenous administration of lactated Ringer's solution (3–5 ml/kg). Ephedrine (3 mg bolus) could be used to maintain adequate MAP. Initial heparinization was carried out with 400 IU/kg and was supplemented as required to maintain an activated clotting time longer than 400 s. Initial ante-grade warm hyperkalemic blood cardioplegia (20 ml/kg) was used and (10 ml/kg) was repeated every 25 min.

All CPB was primed by colloids and carried out at a nonpulsatile, filtered arterial pump flow of 2.5–3.0 l/min/m^2 and gravity venous drainage. A hollow-fiber membrane oxygenator was used. The hematocrit was maintained at 25% and the pH was managed using an alpha-state strategy. MAP was maintained between 30 and 50 mmHg. Patients were cooled down to 28–30°C. Nitroglycerin infusion (1–3 μg/kg/min) was started during CPB and titrated according to need. Once CPB rewarming was started, dopamine (5–10 μg/kg/min), dobutamine infusion (5–10 μg/kg/min), and/or

an epinephrine infusion (0.05–0.1 μg/kg/min) were added according to the hemodynamic parameters.

For all patients, demographic data, medical and drug history, preoperative EF, type of surgical intervention, number of doses and total dose of cardioplegia, the aortic cross-clamp, and CPB times were recorded.

The direct invasive MAP, central venous pressure (CVP), HR, pulse oximetry (SpO_2), end tidal CO_2, and ECG were monitored.

The preoperative EF and MPAP were recorded. Using transesophageal echo calculation, CO, CI, SVR, and SVRI were assessed after CPB and 1 h after completion of infusion of MB, with recording of the dose of norepinephrine needed. Calculation of SVR was carried out by measurement of the time velocity integral (TVI) on the left ventricular outflow track (LVOT) in the deep transgastric four chamber view using pulsed wave Doppler. This was achieved using the following equations:

$$\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Cardiac output (CO)}},$$

Cardiac output (CO) = TVI × AVA × HR,

where TVI is the time velocity integral that represents the distance of the RBC crossed in a single heart beat; AVA is the aortic valve area through which blood flows to systemic circulation.

Assuming that LVOT is a cylinder, blood volume ejected in a single heart beat will equal the volume of a cylinder = base area×height or AVA × TVI = stroke volume (SV):

Stroke volume (SV) × HR = CO.

This method has been validated clinically by Abbas *et al.*[13], who concluded that 'Doppler echocardiography provides a reliable noninvasive assessment of SVR'.

Pressure gradient is the difference between the MAP and the CVP (MAP-CVP).

Thus, the final equation will be as follows:

SVR = 80 × (MAP–CVP/TVI × AVA × HE).

The SVRI will be calculated as follows:

$$\text{SVRI} = \frac{\text{SVR}}{\text{Body surface area}}.$$

Stroke volume index: 40–85 ml/m^2/beat.

SVRI: 1970–2390 dyne s/cm^5.

SVR: 900–1600 dyne s/cm^5.

Normal value of TVI LVOT: 16 ± 3 cm.

Normal value of TVI aortic valve: 22 ± 4 cm.

Aortic valve area index: 1.33 cm^2/m^2.

Statistical methods

Statistical analysis was carried out on a personal computer using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, New York, USA).

The sample size required was calculated using the G*Power version 3.1.3 software (Heinrich Heine Universität, Institut für Experimentelle Psychologie, Düsseldorf, Germany). The primary outcome measure was the difference between the SVR and the MAP before and after administration of MB. It was estimated that a sample size of 20 patients would achieve a power of 84% to detect a medium-to-large effect size (*dz*) of 0.7. The paired-samples Student *t*-test was used for sample size calculation and the type I error was set at a two-sided value of 0.05.

Normality of numerical data distribution was tested using the Kolmogorov–Smirnov goodness-of-fit test. Numerical data are presented as minimum, maximum, mean, SD, and quartiles. Categorical data are presented as number and percentage.

The paired-samples Student *t*-test was used to compare normally distributed paired numerical data.

A two-sided *P* less than 0.05 was considered statistically significant.

Results

Twenty children were enrolled in the study (12 males, eight females), mean age 21.60 ± 9.88 months and mean weight 11.70 ± 3.63 kg. Nine patients (45%) had a common A-V canal; six patients (30%) had a ventricular septal defect (VSD); one patient (5%) had a ventricular septal defect plus atrial septal defect; and four patients (20%) had fallot's tetralogy. A total of 30% of these patients (six patients) had Down's syndrome. Demographic data are presented in (Tables 1 and 2).

Sixteen patients (80%) were on an ACEI, 14 patients (70%) were on diuretics, and six patients (30%) were on -blockers. The mean preoperative hematocrit was 44.60% ± 10.50 (range 35.0–70.0%) (Table 2).

Table 1 Patient characteristics and CPB details: Numerical variables

Variable	N	Mean	SD	Minimum	Maximum	1st quart.	2nd quart.	3rd quart.
Age, months	20	21.60	9.88	7.00	40.00	14.25	19.00	29.50
Weight, kg	20	11.70	3.63	6.00	18.00	10.00	11.50	14.75
Height, cm	20	99.65	15.13	70.00	125.00	91.75	100.50	109.75
BSA, m^2	20	0.57	0.13	0.34	0.79	0.50	0.57	0.67
Preoperative hematocrit, %	20	44.60	10.50	35.00	70.00	38.25	40.00	43.75
Diameter of aortic valve annulus, mm	20	9.62	1.23	7.60	12.00	8.50	9.70	10.58
Aortic valve area, mm^2	20	0.74	0.19	0.46	1.13	0.56	0.74	0.87
Aortic valve area index, cm^2/m^2	20	1.31	0.12	1.10	1.50	1.20	1.30	1.40
Preoperative EF	20	0.68	0.06	0.55	0.78	0.65	0.68	0.73
Temperature on CPB, °C	20	28.60	0.94	28.00	30.00	28.00	28.00	30.00
Volume of cardioplegic solution, ml	20	385.50	119.89	180.00	560.00	300.00	400.00	500.00
Duration of CPB, min	20	96.45	5.69	85.00	105.00	91.25	97.00	100.00
Duration of AoX, min	20	68.50	11.40	52.00	90.00	58.25	68.50	78.75
SaO_2, %	20	98.30	1.45	95.00	100.00	97.25	99.00	99.00
Dose of nitroglycerin, μg/kg/min	20	2.00	0.43	1.00	2.50	1.63	2.00	2.50

AoX, aortic cross-clamping; BSA, body surface area; G6PD, glucose-6-phosphate dehydrogenase; CPB, cardiopulmonary bypass; EF, ejection fraction; quart., quartile.

Table 2 Patient characteristics and CPB details: Categorical variables

Variable	Number	Percent
Gender		
Male	12	60.0
Female	8	40.0
Diagnosis		
Common A-V canal	9	45.0
VSD	6	30.0
VSD plus ASD	1	5.0
Fallot's tetralogy	4	20.0
Down's syndrome	6	30.0
Preoperative ACEI	16	80.0
Preoperative diuretic	14	70.0
Preoperative beta-blocker	6	30.0
Number of cardioplegia doses		
2 doses	14	70.0
3 doses	6	30.0

For all cases, the preoperative EF was assessed. Also, the diameter of aortic valve annulus (mm), aortic valve area (mm^2), and aortic valve area index (cm^2/m^2) were recorded (Table 1) to add the calculation.

For operative data, the mean value of the duration of aortic cross clamp was 68.50 ± 11.40 min, with a minimum and a maximum value of 52.00 and 90.00 min, respectively. The duration of CPB was 96.45 ± 5.69 min, with moderate hypothermia 28.60 ± 0.94°C. The mean value of the volume of the cardioplegic solution needed for patients was 385.50 ± 119.89 ml, with a minimum volume of 180.00 ml and a maximum volume of 560 ml (Table 1). The cardioplegic solution was perfused in two divided doses in 14 cases (70%) and in three divided doses in six patients (30%). The mean dose of nitroglycerin required by the 20 patients was 2.00 ± 0.43 μg/kg/min, with a minimum and a maximum dose of 1.00 and 2.50 μg/kg/min, respectively (Table 2).

Immediately after MB infusion, clinically significant increases in MAP and SVR were observed. Hemodynamic measures after 1 h were recorded in (Table 3) compared with the value of pre-MB infusion.

The MAP increased significantly, $P < 0.001$, from 40.60 ± 8.31 to 57.30 ± 10.45 mmHg, with a mean difference of 16.70 ± 4.88 mmHg (Fig. 1). This was accompanied by a significant decrease in HR by 12.75 ± 5.98 b/m, but, we did not detect a change in the rhythm after MB infusion (none of the patients showed major or prolonged dysrhythmia that required DC shock or pacing).

There was a concomitant significant decrease in CO from 3.90 ± 0.55 to 3.44 ± 0.38 l/min, with a concomitant significant decrease in CI, with a mean difference of 0.80 ± 0.44 l/min/m^2 ($P < 0.001$) (Fig 2).

In addition, there was an increase in CVP, with a mean difference of 2.75 ± 1.21 mmHg, that was statistically significant ($P < 0.001$) (Fig 1).

The SVR and SVRI showed a statistically significant increase, with a P value of 0.001. The SVRI increased from 1307.95 ± 150.16 to 2098.05 ± 241.02 dyne s/cm^5/m^2, with a mean increase of 790.10 ± 165.43 dyne s/cm^5/m^2 (Fig 3).

Although there was a marked and significant decrease in the dose of norepinephrine required (from 0.57 ± 0.05 to 0.11 ± 0.13 μg/kg/min), $P < 0.001$ (Fig 4), the MPAP showed a statistically significant increase, with a mean difference of 2.95 ± 1.73 mmHg after MB infusion (Fig 1).

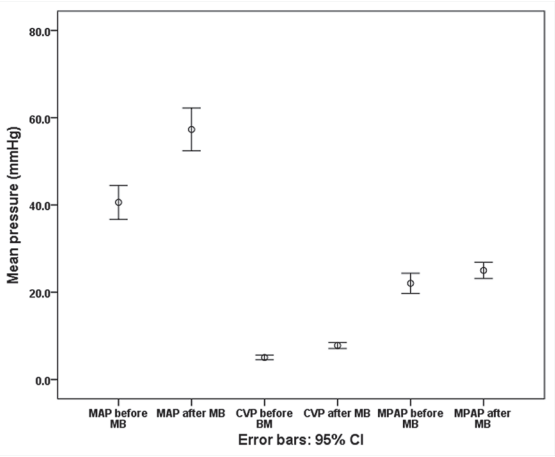
The mean reading of pulse oximetry after bypass was 98.30 ± 1.45%, with no change after MB infusion.

Table 3. Hemodynamic parameters and dose of norepinephrine before and after administration of methylene blue

		Mean	SD	SEM	$Mean_d$	SD_d	SEM_d	95% CI_d		P value
								Lower	Upper	
Norepi-nephrine, µg/kg/min	Before MB	0.57	0.05	0.01	0.46	0.12	0.03	0.40	0.51	<0.001
	After MB	0.11	0.13	0.03						
Heart rate, bpm	Before MB	165.30	6.10	1.36	12.75	5.98	1.34	9.95	15.55	<0.001
	After MB	152.55	5.70	1.27						
MAP, mmHg	Before MB	40.60	8.31	1.86	-16.70	4.88	1.09	-18.98	-14.42	<0.001
	After MB	57.30	10.45	2.34						
CVP, mmHg	Before MB	5.05	1.15	0.26	-2.75	1.21	0.27	-3.32	-2.18	<0.001
	After MB	7.80	1.47	0.33						
MPAP, mmHg	Before MB	22.05	4.91	1.10	-2.95	1.73	0.39	-3.76	-2.14	<0.001
	After MB	25.00	3.97	0.89						
CO, l/min	Before MB	3.90	0.55	0.12	0.45	0.28	0.06	0.32	0.59	<0.001
	After MB	3.44	0.38	0.08						
CI, l/min/m^2	Before MB	7.09	1.15	0.26	0.80	0.44	0.10	0.60	1.01	<0.001
	After MB	6.28	1.09	0.24						
SVR, dyn.s/cm^5	Before MB	719.45	98.40	22.00	-418.45	93.98	21.01	-462.43	-374.47	<0.001
	After MB	1137.90	150.16	33.58						
SVRI, dyn.s/cm^5/m^2	Before MB	1307.95	204.33	45.69	-790.10	165.43	36.99	-867.53	-712.67	<0.001
	After MB	2098.05	241.02	53.89						

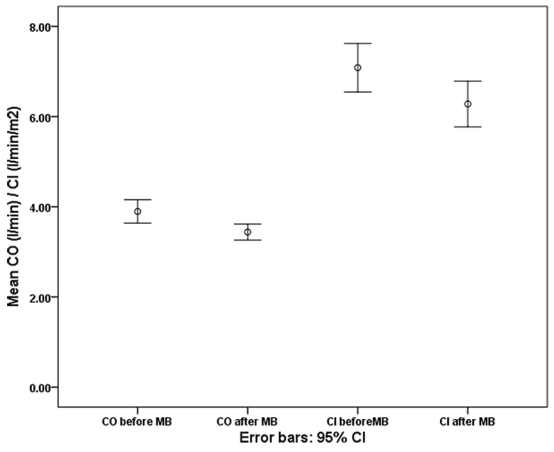
95% CI_d, 95% confidence interval for the mean difference; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; SD, standard deviation; SD_d, standard deviation of the mean difference; SEM, standard error of the mean, SEM_d, standard error of the mean difference; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

Figure 1



Mean arterial pressure (MAP), central venous pressure (CVP), and mean pulmonary artery pressure (MPAP) before and after administration of methylene blue (MB)

Figure 2



Cardiac output (CO) and cardiac index (CI) before and after administration of methylene blue (MB)

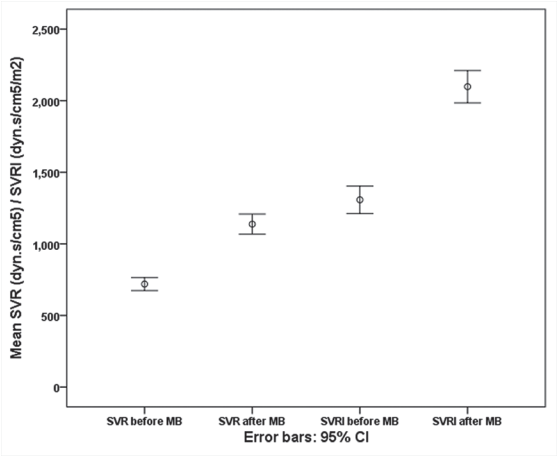
However, all 20 cases showed a change in the color of urine to greenish blue.

Discussion

Arteriolar tone is a major determinant of SVR, regulated by the neurohormonal system and endothelial function [14]. VS is a severe case of vasodilatory shock. Its manifestations are a recognized and relatively common complication of cardiac surgery with CPB [15]. The VS is a severe SIRS that is activated by CPB as well as nonspecific activation such as surgical trauma, blood transfusion, and hypothermia [16]. The physiological response to a SIRS is mediated by different mediators that induce a synthesis of NO and prostacyclin [7]. The dysregulation of NO synthase and release, and also vascular smooth muscle cell guanylate cyclase activation; upregulation of inducible NO; and increase in NO production led to the generation of cyclic guanisine 3¢,5¢-monophosphate, resulting in marked relaxation of the vascular smooth muscle [17].

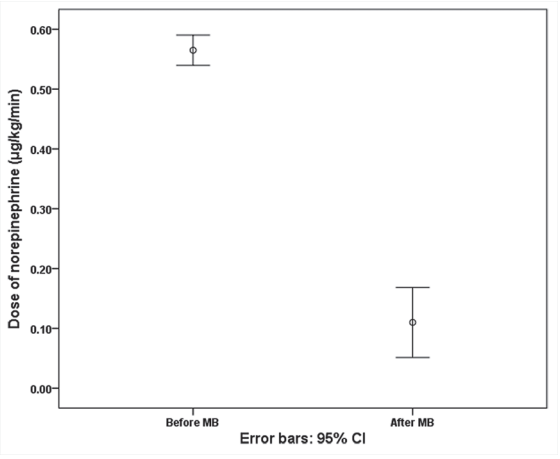
The management of vasoplegia is based on the vasoconstrictor effect of the drugs to support the

Figure 3



Systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) before and after administration of methylene blue (MB)

Figure 4



Dose of norepinephrine before and after administration of methylene blue (MB)

organ perfusion pressure. Unfortunately, the pressure catecholamines that are commonly administered have limited effectiveness as well as severe toxic effects at a high dosage [18].

The etiology of vasoplegia after CPB is multifactorial and depends on preoperative conditions as well as intraoperative events. In 2002, Viaro *et al*. [19] concluded that it is mainly because of exposure of the body to nonphysiological materials and the use of heparin/protamine that the inflammatory response syndrome is triggered.

Intraoperative risk factors of vasoplegia include hematocrit both at the start and at the end of CPB, prebypass median MAP, procedure type, bypass time in hours, use of antifibrinolytics or any vasopressors before CPB, lowest temperature measured during CPB, and the amount of vasopressor support required to separate from CPB [20].

Some data showed that preoperative β-blocker therapy provided protection against development of VS after on-pump surgery. Booth *et al*. [21] provided an explanation that β-blockers may attenuate acute β-adrenergic receptor desensitization (because of the effect of CPB) and maintain the sensitivity of myocardium to catecholamine after CPB. This was not in agreement with our results, where six patients (30%) under β-blocker treatment preoperatively developed VS.

Del Duca *et al*. [22] considered the use of MB, an inhibitor of NO, for the treatment of VS in patients who are refractory to vasopressor treatment. It is believed to act through competition with NO, in binding to the iron heme-moiety of soluble guanylate cyclase, resulting in enzyme activation [23,24]. This inhibits the increases in the levels of cGMP, and thereby precludes its vasorelaxant effect in vascular smooth muscle [5]. Hence, MB counteracts the effects of NO and other nitrovasodilators in endothelium and vascular smooth muscle [25].

MB is available as a solution (10 mg/ml). A single dose of intravenous MB (2 mg/kg, 20 min infusion time), as used by Leyh and colleagues, has been used as a beneficial treatment. A continuous infusion of MB could be an option for patients not responding to a single dose of MB. A subcutaneous injection has been reported to cause necrotic abscesses. The onset of the hemodynamic effects of MB is relatively rapid. Oral absorption ranges from 53 to 97% [26]. MB is reduced in the erythrocyte to leukomethylene blue, and is excreted primarily in the urine, bile, and feces as leukomethylene blue and MB. Hemolytic anemia and hyperbilirubinemia have been reported after the administration of MB in doses exceeding 2 mg/kg [3].

Because of the low endogenous nicotinamide adenine dinucleotide phosphate concentration that is essential for leukomethylene blue production, MB should be used with caution in young patients with glucose-6-phosphate dehydrogenase deficiency [27].

MB is a safe drug when used in therapeutic doses (<2 mg/kg) [28]. Fortunately, Leyh and colleagues found cardiac arrhythmias; coronary vasoconstriction; decreases in CO, renal blood flow, and mesenteric blood flow; increases in pulmonary vascular pressure and resistance; and also deterioration in gas exchange to be some of the adverse effects of MB in the treatment of norepinephrine-refractory vasoplegia. They concluded that the majority of these side effects are dose dependent and do not occur when the dose of MB administered is 2 mg/kg or lower. Moreover,

they did not report any of the mentioned side effects in their 54 adult patients with norepinephrine-refractory systemic vasoplegia who received an intravenous infusion of MB (2 mg/kg) over 20 min [26].

We did not observe major side effects in our pediatric patients with dose (1.5 mg/kg), except the change in the color of the urine to greenish blue in all patients. However, we observed a significant increase in MPAP by 2.95 ± 1.73 mmHg (after MB infusion), which was more prominent in cases with VSD, atrial septal defect-ventricular septal defect (ASD-VSD), and common A-V canal. It remains a matter of debate whether this increase is related to the application of the MB or is an effect of closure of a septal defect and repair of the mitral valve in the previous cases. Moreover, we reported significant changes in hemodynamic parameters, a decrease in cardiac output (CO), and lower dose of norepinephrine requirement 1 h after MB infusion.

The interactions between MB and the cholinergic system may contribute toward the hemodynamic effects of MB. It has cholinesterase inhibitor effects, with additional, relevant affinity for muscarinic-binding sites at certain concentrations. The beneficial effects of MB in VS at the clinical concentrations (1–3 mg/kg) may be related to its modulatory effect on endothelial M_3 receptor (mediating cholinergic vasodilatation through NO release) by decreasing basal endothelial NO release. At the dose of 10 mg/kg, MB reduced cardiac function through the effect on M_2 receptors (abundant in cardiac tissue) [29].

Leyh and colleagues recorded an increase in MAP (from 68 to 72 mmHg) and decreased norepinephrine dose (from 0.50 to 0.35 μg/kg/min) 1 h after MB infusion. After 6 h, MAP was 71 mmHg and the norepinephrine requirement was 0.2 μg/kg/min. These changes were accompanied by a significant decrease in CO (from 7.6 to 6.5 l/min) and a significant decrease in the arterial serum lactate concentration within 24 h after MB infusion compared with the control group [26].

An open-label placebo-controlled randomized study was carried out by Levin *et al*. [30], who used MB (1.5 mg/kg over 1 h) in 28 adult patients with VS after CPB. In their study, 2 h after infusion of MB, vasoplegia resolved completely in all patients compared with none in the control group. Although no data were reported on changes in hemodynamic parameters, the patients in the MB group had significantly lower mortality and incidence of renal failure, respiratory failure, neuropathy, arrhythmias, sepsis, and multiorgan dysfunction.

Maslow *et al*. [31] randomized 30 patients who had received ACEIs to 3 mg/kg MB versus saline following CPB and cardioplegia. MB increased MAPs (with a statistically significant value at postdrug and 20–40 min of CPB time points, but not at 60 min of CPB or after CPB) and SVR (significantly increased up to 40 min); thus, the effects appeared to last only ~40 min. Administration of MB resulted in lower phenylephrine and norephrine requirements and in lower serum lactate levels. Although the MB group had higher CO after bypass (6.1 vs. 5.6 l/min), this did not reach statistical significance.

The mechanisms of septic shock are similar to those of post-CPB in that the peripheral vascular smooth muscle dilatation occurs mainly through the mediator NO. In 1996, a study was carried out on five neonates with presumed septic shock unresponsive to colloids, inotropic agents, and corticosteroids; MB was administered intravenously at a dose of 1 mg/kg/h. The average increase in blood pressure was 33 ± 20%. Three of five patients were weaned from inotropic support within 72 h. Three of five patients survived and were discharged home [32].

To our knowledge, this is one of the few studies with pediatric patients in whom severe vasoplegia after CPB was treated with MB. However, we found that many clinical studies showed increased production of NO in children as well as adults with various forms of shock. Also, the vessels isolated from animals in shock show a pronounced hyporeactivity to almost all vasoconstrictor agents tested (epinephrine, norepinephrine, phenylephrine, dopamine, endothelin, angiotensin, thromboxane, etc.). This hyporeactivity can be reversed by NO synthase inhibitors and specific inducible NO synthase inhibitors [33].

Another case study of a 22-month-old female with a history of Noonan's syndrome, biventricular hypertrophic cardiomyopathy with chronic positive pressure ventilation, developed septic shock that did not respond to conventional treatment. She was treated with intravenous MB. It was initiated with a loading dose of 1 mg/kg, followed by a continuous infusion at 0.25 mg/kg/h. With the initiation of MB, her systolic blood pressure increased 40% and diastolic blood pressure increased 46%. Also, there was an improvement in her physical examination and she could be weaned off all inotropes [34].

A similar result was found in the prognosis of a case study of a 5-year-old girl with a hypoplastic left ventricle and double outlet right ventricle who underwent a heart transplant following a failed Fontan conversion. She showed postoperative severe, progressive hypotension that was resistant to dopamine, dobutamine, milrinone,

bolus of epinephrine, epinephrine infusion, vasopressin, and also norepinephrine that was added. After demonstration of adequate cardiac function with the echocardiography, MB was administered as a bolus of 1 mg/kg over 5 min with an additional 1 mg/kg bolus at the bedside to be administered 1 h later. Over the next 10 min, the MAP increased by 30 to 60 mmHg. The epinephrine, norepinephrine and vasopressin infusions were weaned over the next 12 h [35].

The favorable effect of MB reported in these studies and documented in our study with a significant improvement in hemodynamic parameters, SVRI, and dose of norepinephrine suggest that refractory VS may reflect a dysregulation of NO synthase and vascular smooth muscle cell guanylate cyclase activation.

There is no intervention known to prevent VS; the physiopathologic findings suggest that VS may be limited or prevented early by inhibiting NO. Therefore, Levin *et al.* [30] reported that preoperative MB administration reduces the incidence and severity of VS in high-risk patients and also preoperative infusion of low-dose vasopressin contributes toward prevention of VS and reduces the doses of requirements of catecholamines.

Ozal and colleagues carried out a prospective randomized study to test the effect of the prophylactic MB (2 mg/kg over 30 min) 1 h before surgery in adult patients with predefined risks for vasoplegic shock. The two groups (n = 50 in each) showed a significant difference in the incidence of vasoplegic shock (0% in MB patients vs. 26% in controls; $P < 0.0001$) and ICU stay (1.2 days in MB patients vs. 2.1 days in controls; $P < 0.0001$) [3].

We have shown the intravenous application of MB to lead to an excellent response in the management of pediatric patients with norepinephrine-refractory vasoplegia after CPB, with no relevant side effects.

There has been no study focusing on the risk factors of vasoplegia in pediatric cardiac surgery; our results indicated that the type of pathology, Down's syndrome, and preoperative medications were independent risk factors for vasoplegia in post-CPB pediatric vasoplegia.

Despite the excellent response of the management of post-CPB vasoplegia with MB during this study, there are still limitations. This study did not follow the outcome of patients and their need for other doses. Also, this study did not compare MB with commonly used drugs such as vasopressin. In addition, this study did not include all pathological types of congenital heart diseases. Therefore, to generalize the results and prove the safety and efficacy of the drug, a prospective comparative controlled randomized study with more cases with different pathologies is desirable.

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Conflicts of interest

There are no conflicts of interest.

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