



Efficacy of methylene blue for on vasoplegic syndrome

Mohsen Akhondi (MD)¹, Alireza Sabzevari (MD)¹, Shabnam Imannezhad (MD)^{*2}, Ali Rahdari (MD)¹

¹Department of Anesthesiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

²Department of Gynecology, School of Medicine, Mashhad University of Medical Science, Mashhad, Iran.

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ABSTRACT

Introduction: Administration of methylene blue has been proposed as a therapeutic strategy in the treatment of vasoplegic shock following cardiac surgery. Major aims of this systematic review were to evaluate the effect of methylene blue on mortality rate, duration of vasoplegic syndrome, and further complications of patients with vasoplegic syndrome following cardiac surgery.

Methods: PubMed was searched to obtain the most relevant articles. All the randomized control trials and cohort studies were included.

Result: A total of 54 articles were retrieved at the initial search. After studying the titles, abstracts, and full text of the articles, only five articles consisted of two randomized controlled trials (RCTs) and two observational studies were included.

Discussion: Based on included RCTs, the mortality rate and duration of the disease decreased in patients applied methylene blue in the treatment of vasoplegic syndrome compared with those did not receive this medication.

Conclusions: Based on included articles, application of methylene blue could be suggested as a treatment for vasoplegic syndrome, but further large multicenter RCTs are needed to certainly evaluate the efficacy of methylene blue.

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Introduction

Vasoplegic syndrome (VPS) is a relatively common and lethal complication following cardiopulmonary bypass (CPB) with the incidence rate of 5% to 25%. syndrome VPS can be characterized by severe and persistent hypotension, tachycardia, and normal to elevated cardiac output, diminished systemic vascular resistance (SVR), and high fluid intakes (1). Although VPS is a multifactorial condition, the exact pathophysiology is not clear; activation of vasodilators and resistance to vasopressors, all interfere in the occurrence of VPS in a form of vasodilatory shock and Low SVR (2). Patients-specific risk factors are possibly associated with the increased incidence rate of VPS, including the type and the duration of surgery,

preoperative hemodynamic instability, administration of angiotensin-converting enzyme (ACE) inhibitors or beta-blockers (2). The likelihood of developing postoperative vasoplegic syndrome (PVS) is reported to be higher following, valve procedures and surgery specifically intended for the management of heart failure while compared with coronary artery bypass grafting, aortic surgery, and reoperations. Based on the literatures, PVS is associated with poor prognosis, prolonged hospital stay, higher mortality, and morbidity risk (3). Vasoactive infusions like phenylephrine, norepinephrine, or vasopressin are known as the regular and conventional treatment strategy for intraoperative or postoperative VPS, however high

***Corresponding author:** Shabnam Imannezhad.

Department of Gynecology, School of Medicine, Mashhad University of Medical Science, Mashhad, Iran.

E-mail: imannezhadsh901@mums.ac.ir

Tel: 09155177449

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dosages of these medications might cause some serious side effects including peripheral and mesenteric ischemia, mucosal injury, tissue necrosis, and metabolic acidosis (4,5).

Despite methylene blue, a well-known dye, application as a medication for methemoglobinemia, it can bind to the iron heme moiety, can inhibit enzyme guanylate and can subsequently block the accumulation of cyclic guanosine monophosphate (cGMP). Therefore, methylene blue (MB) has been proposed as an alternative therapeutic strategy for vasopressor-resistant vasoplegia (6). Nowadays, the efficacy of post-CPB administration of methylene blue on the reversal of vasoplegia is under investigation. The main scope of this systematic review is to study the effect of methylene blue on mortality rate, duration of VPS, and the occurrence of further complications in patients with VPS following cardiac surgery.

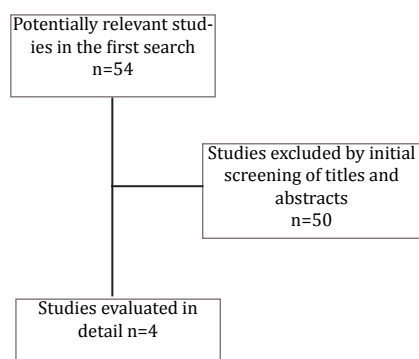
Methods

This systematic review was performed by literature search in PubMed from 1966 to 1st February 2015. Search strategy included "Methylene blue AND vasoplegic syndrome". Only cohort studies and human randomized controlled trials (RCT), which studied the efficacy of methylene blue on the prevention of VPS following cardiac surgery, were eligible to be included in the study.

Results

Literature search on therapeutic efficacy of methylene blue resulted in a total of 54 articles, which were directly related to the VPS in cardiac surgery. Titles, abstracts, and full text of the articles were studied for relevancy. Flow chart of the included articles is provided Figure 1.

Figure 1. Flowchart of selection of studies



Majority of the extracted articles were case reports, which were omitted. Only four articles consisted of RCTs and cohort studies were included in this systematic review. The quality of the included RCTs is summarized in Table 1, based on oxford center for evidence based medicine chart.

The results of these articles are provided in Table 2.

Table 1. Quality control of the included randomized controlled trials

Author Year Reference	Type of study and surgery	Similarity of the groups at first/similarity of the treatment	Loss to follow-up	Results presentation
Levin 2004 (7)	RCT ¹ (randomization based on hospital admission number), elective cardiac surgery	Y/Y ²	NA ³	Odds ratio
Ozal 2005 (8)	RCT (randomization based on a table of random digits), Preoperative CPB ⁴	Y/Y	NA	Odds ratio

¹RCT: Randomized Controlled Trial; ²Y: Yes; ³NA: Not available; ⁴CPB: Cardiopulmonary bypass

One RCT was about the efficacy of preoperative administration of MB, and one RCT on its postoperative application (7,8). One observational study also studied the efficacy of MB on patients undergoing cardiac surgery with no control group. Another observational study compared the efficacy of MB with control group(9,10).

Mortality rate was reported in both RCTs relevant to our study. One RCT reported a reduction of mortality in VPS group treated with MB compared with VPS group treated with conventional treatment. Preoperative administration of MB reported no death following cardiac surgery compared with those without MB prophylaxis. The most recent observational study showed higher mortality rate in VPS patients administered MB compared to control group.

Regarding the duration of VPS, Levin et al. reported the clearance of VPS in < 2 hrs in patients treated with MB, and > 48 hrs in patients treated with conventional medications (7).

Based on the included RCTs, VPS was characterized based on various indices including hypotension, mean arterial pressure <50 mm Hg, low filling pressures, central venous pressure <5 mmHg, wedge capillary pressure < 10 mm Hg, normal or elevated cardiac index >2.5 L/min/m², peripheral resistance <800 dyn/s/cm⁵-, and need for vasopressor medications. However, cardiac output of 4 L/min, SVR600- dyne/s/cm⁵, and norepinephrine 0.5 mg/kg/min were regarded as the characterization of norepinephrine-resistant VPS (9). In a nonrandomized observational study performed by Weiner et al., vasoplegia was defined as the requirement of >200 ng/kg/min of norepinephrine plus >2 units/hour of vasopressin (10).

Table 2. Detailed information of the included studies

Author Year Reference	Patients	Intervention	Mortality: N ¹ (%)	Duration of VPS ²	Other complications MB ³ : placebo
Leyh 2003 (9)	VPS/total; 54/1111 (4.8%) 41(76%) male, mean age 56.7 ± 15.1 years	MB: 2 mg/kg IV ⁴ in 20 min, 136±48 min after the sur- gery in addition to norepinephrine	4/54 (2 pa- tients did not response to MB)		Hemodynamic data before: after MB:(1hr ⁵ :6hr:12hr) MAP ⁶ : 68±9: 72±12: 71±9: 73±10 CO ⁷ : 7.6±3: 6.5±2.8: 6.1±2: 5.8±2 SVR ⁸ : 547 ±108: 766±194: 796±153: 876±184
Levin 2004 (7)	Number: VPS/NVPS: 56/582:8.8% VPS+ MB: 28 VPS+ placebo: 28	MB group: 1.5 mg/kg IV over 1 hr.	VPS+placebo: 6 (21.4%) VPS+MB: 0 NVPS ⁹ : 21(3.6%) Odds ratio: 0.31; CI (0.11 to 0.91)	MB gr: all <2 hr Placebo gr: >48 hr: 8 (28.6%)	Renal failure: 0:4 Respiratory failure: 0:4 Myopathy: 0:4 SVT ¹⁰ ; 2:8 Sepsis,0:7 MSOF ¹¹ 0:7
Ozal 2005 (8)	Number: MB gr ¹² : 50 Control gr: 50	(preoperative MB (IV): 2 mg/kg for 30 min	MB: 0 Control: 2/50 Odds ratio: 0.1921 95 % CI: 0.0090 to 4.1043	Incidence of VPS: MB:0/50 Control:13/50 Progress of VPS: VPS refractory to Norepinephrine 6/50 -4 resolved with- in 8 hr -2 died of MSOF	SVR: significantly higher in MB vs control Norepinephrine requirement: MB: 2/50 control:41/50 Inotropic support: MB:2 control:24 Length of hospital stay (days): MB: 6.1±1.7 Control: 8.4±2.0
Weiner 2013 (10)	Number: MB:57 Control:169	MB group: 2 mg/kg IV for 6 hr.	MB: 26 (45.6%) Control: (26)15.4%		Lung morbidity: MB: 33.3% control:17.8% Renal failure: MB:35.1% con- trol:13% Sepsis:MB:26.3% control:15.4%

¹N: Number; ²VPS: Vasoplegic syndrome; ³MB: Methylene blue; ⁴IV: Intravenous; ⁵hr: Hour; ⁶MAP: Mean arterial pressure (mmHg); ⁷CO: Cardiac output (L/min); ⁸SVR: Systemic vascular resistance; ⁹NVPS: Nonvasoplegic syndrome; ¹⁰SVT: Supraventricular arrhythmia; ¹¹MSOF: Multiorgan dysfunction; ¹²gr: Group.

Discussion

Vasoplegic syndrome is a type of low systemic vascular resistance syndrome which activates an inflammatory response and leads to postoperative complications following cardiac surgery. According to the previous studies, incidence of VPS will change the clinical outcomes and results in poor overall prognosis. To prevent the possible side effect of conventional treatments of VPS such as arrhythmias or ischemia, efficacy of new medications is under investigation. MB has been proposed as an inhibitory drug over nitric oxide (NO, activates guanylate-cyclase enzyme, induces cGMP production, and leads to the relaxation of smooth vascular muscle) (11,12). According to the Leyh et al., over 90% of patients with norepinephrine-resistant VPS responded to the treatment with postoperative MB (9). Based on one RCT, MB prophylaxis in patients at higher risk of VPS has significant power to avoid the incidence of intraoperative and postoperative VPS in preoperative MB-treated patients (8).

Mortality rate

According to the RCT performed by Levin et al., mortality rate will be significantly reduced following intravenous (IV) application of MB in the treatment of postcardiac surgery VPS. In the observational study of Leyh et al., performing without any control group, the mortality rate was reported to be in 4 out of 54 patients and only two patients did not response to MB (9). Ozal et al. reported no mortality in patients with higher risk of VPS who applied preoperative MB compared with control group. In two cases of the control group, MB was applied after the occurrence of VPS and multiorgan failure, which could not treat the VPS or inhibit the death of patients. (8). In contrast to the mentioned studies, Weiner et al. research was the first study that revealed higher mortality and morbidity following MB administration as a result of vasoplegic shock in patients under cardiac surgery (10); this study is a nonrandomized observational study and is hardly sufficient to disapprove the prognostic value of MB.

They have also suggested that an increased mortality rate might be due to the beneficial physiological effects of NO, which were inhibited by applying MB.

Duration of the PVS

Duration is an important factor which is associated with poor prognosis. Therefore, aggressive treatment of postoperative refractory vasoplegia is essential to inhibit the consequences. PVS was considerably lower (<2 hrs) in patients treated with MB compared with those applied vasopressin following cardiac surgery (>48 hrs) and no adverse effect has been reported due to infusion of MB (7). The lower duration of PVS during the application of MB is due to the NO blockade and the consequent inhibition or limitation of the inflammatory response; this event has high prognostic value during postoperative inflammatory response. Continuance of the PVS for more than 48 hrs, is associated with worse prognosis, and increases the likelihood of further morbidities or even death (13). Levin et al. reported higher incidence of renal and respiratory failures, sepsis, myopathy, and supraventricular arrhythmia in those with PVS more than 48 hrs, and no incidence of mentioned diseases in PVS patients treated with MB application and nitric oxide blockade in 2 hrs (7).

Hospital stay

Only one RCT evaluated the efficacy of administering MB on hospital stay which revealed a longer hospital stay following preoperative application of MB in patients at higher risk of VPS compared with those that applied MB after the surgery and incidence of VPS (8).

Adverse effect

Experimental studies and some previous studies which are not included in these study, proposed several adverse effects of administering MB in the treatment of norepinephrine-refractory vasoplegia, such as cardiac arrhythmias, coronary vasoconstriction, reduced cardiac output, renal blood flow and mesenteric blood flow, and elevated pulmonary vascular pressure and resistance (14-16). According to the RCT of Levin et al., green or blue coloration of urine is the only reported symptoms following MB administration in PVS group. This was also observed by preoperative administration of MB in patients at higher risk of PVS; the green color of urine was disappeared spontaneously after 3 days (8). In the observational study of Leyh et al., no adverse effect was observed in patients following administration of MB (9). It seems that possible side effects are dose dependent and might occur following the administration MB at dosage greater than 2 mg/kg.

Conclusion

Based on our knowledge, only 2 RCTS has studied the efficacy of MB on the prevention of VPS following cardiac surgery. MB prophylaxis can be effective in inhibiting the incidence of VPS, shortening the hospital stay, maintaining adequate SVR following cardiac surgery in high risk patients. Eventually, further studies are needed to certainly illustrate the efficacy of MB on the treatment of VPS.

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Conflict of Interest

The authors declare no conflict of interest.

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