Annals of Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iann20

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To cite this article: Mohamed Elbayomi, Oliver Dewald, Presheet Pathare, Markus Kondruweit, Rene Tandler, Michael Weyand & Christian Heim (2025) The mystery of methylene blue and its role in managing post-cardiac surgery vasoplegic shock, Annals of Medicine, 57:1, 2460770, DOI: 10.1080/07853890.2025.2460770

To link to this article: https://doi.org/10.1080/07853890.2025.2460770

Published online: 04 Feb 2025.

Elevate Series

ANNALS OF MEDICINE
2025, VOL. 57, NO. 1, 2460770
https://doi.org/10.1080/07853890.2025.2460770

RESEARCH ARTICLE

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The mystery of methylene blue and its role in managing post-cardiac surgery vasoplegic shock

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ABSTRACT

Background: Vasoplegic syndrome is associated with high mortality. Methylene blue (MB) is a guanylate cyclase inhibitor that ameliorates this re-distributive type of shock. This study aims to investigate the outcome in patients who received MB early postoperatively.

Methods: 2753 patients who underwent cardiac surgery utilizing cardiopulmonary bypass at our institution in a time interval of two years were identified. The incidence of vasoplegic syndrome was 7.2% ($n=200$). Pharmacy records identified 84 patients (group 1, MB group) who received methylene blue and 116 patients (group 2, Control group) who didn't receive the drug. This single-center retrospective cohort study's primary outcome was in-hospital mortality. Secondary outcomes were postoperative hemodialysis, serum lactate levels at 24 h postoperatively, and intensive care unit stay length in days.

Results: MB patients have a shorter ICU stay as compared to the control group (9 ± 8 days vs. 16 ± 6.9; p-value <.001). In the control group, postoperative hemodialysis was higher (20% in the MB group and 40% in the control group; p-value <.05). At 24 h post-op, the methylene blue group had reduced serum lactate levels (1.8 ± 1.2 vs. 4 ± 1.8 in the control group; p-value <.001). The methylene blue group had a decreased 24-hour norepinephrine dose (1.5 ± 1.2 vs. 2.8 ± 2 in the control group; p-value <.05). In-hospital mortality was not significantly different between the two groups (38% in the MB group vs. 43% in the control group).

Conclusion: Early postoperative administration of methylene blue in patients with vasoplegic syndrome shortens intensive care unit stay and contributes to less end-organ damage.

ARTICLE HISTORY
Received 27 July 2024
Revised 15 January 2025
Accepted 16 January 2025

KEYWORDS
Cardiopulmonary bypass; vasoplegic syndrome; methylene blue

Introduction

The heart-lung machine is a milestone in the development of modern cardiac surgery. Since its introduction in medical practice over half a century ago, it has opened new horizons in caring for cardiac patients and treating complex heart diseases. Yet, it is associated with a systemic inflammatory response [1–3].

The systemic inflammatory response provoked by cardiac surgery using cardiopulmonary bypass (CPB) is complex and mainly triggered by blood contact activation by artificial surfaces of the extracorporeal circuit. Although it often remains subclinical and resolves spontaneously, in its extreme, it can progress to a systemic inflammatory response syndrome (SIRS), which can frequently lead to major organ dysfunction (MOD) and death [4].

Vasoplegic syndrome (VS) is a re-distributive form of shock caused by a significant drop in vascular resistance after CPB. Its incidence varies from 5% to 44% and is associated with higher mortality and worse operative outcomes [5,6]. This incidence will likely increase as the complexity of cardiac surgery cases rises.

Refractory hypotension associated with VS requires catecholamines like norepinephrine, vasopressin, and phenylephrine, which restore hemodynamic functions in most patients. However, high doses of these agents can cause serious side effects, such as peripheral or mesenteric ischemia [7].

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Methylene blue (MB) inhibits soluble guanylate cyclase and can restore vascular tone in vasoplegic scenarios. It is on the World Health Organization's List of Essential Medicines. It is a substance used during surgical procedures for its ability to dye certain tissues. As a medication, it is widely known in the treatment of methemoglobinemia by chemically reducing iron from a ferric to a ferrous state in hemoglobin [8]. In cardiac surgery, the drug has an 'off-label' use; it inhibits guanylate cyclase and the production of cyclic guanosine monophosphate, which is known to increase vascular smooth muscle relaxation by dephosphorylation of the myosin light chain. Through this pathway, MB can restore vascular tone in vasoplegic scenarios (Figure 1) [4,9,10].

This research endeavor aims to ascertain the prevalence of vasoplegia syndrome induced by CPB and provide a detailed description of the current implementation of MB at an academic cardiac surgery center. It hypothesized that administering MB to vasoplegic patients after a CPB would reduce the risk of mortality and morbidity.

Patients and methods

Study design and patient population

Over two years, a total of 2753 various cardiac operations with CPB support were performed. In 7.2% of these cases ($n = 200/2753$), norepinephrine-refractory systemic vasoplegia developed. Norepinephrine-refractory systemic vasoplegia was defined as mean arterial blood pressure lower than 60 mmHg, a cardiac index greater than or equal to 2,5 L/min/m^2, low filling pressures (central venous pressure less than 8 mmHg and pulmonary wedge pressure less than 10 mmHg), low SVR (<600 dyne.s.cm^{-5}] under norepinephrine infusion (≥0.5 µg/kg/min). Of the 200 patients, 84 received the guanylate cyclase inhibitor and norepinephrine to restore mean systemic blood pressure. All patients in the methylene blue group (group 1) received the drug within 24 h postoperatively. Patients with active endocarditis and those who developed major bleeding post-operative (overt blood loss with a hemoglobin decrease of greater than 3 g/dL; any hemoglobin decrease of greater than 4 g/dL; transfusion of 2 units

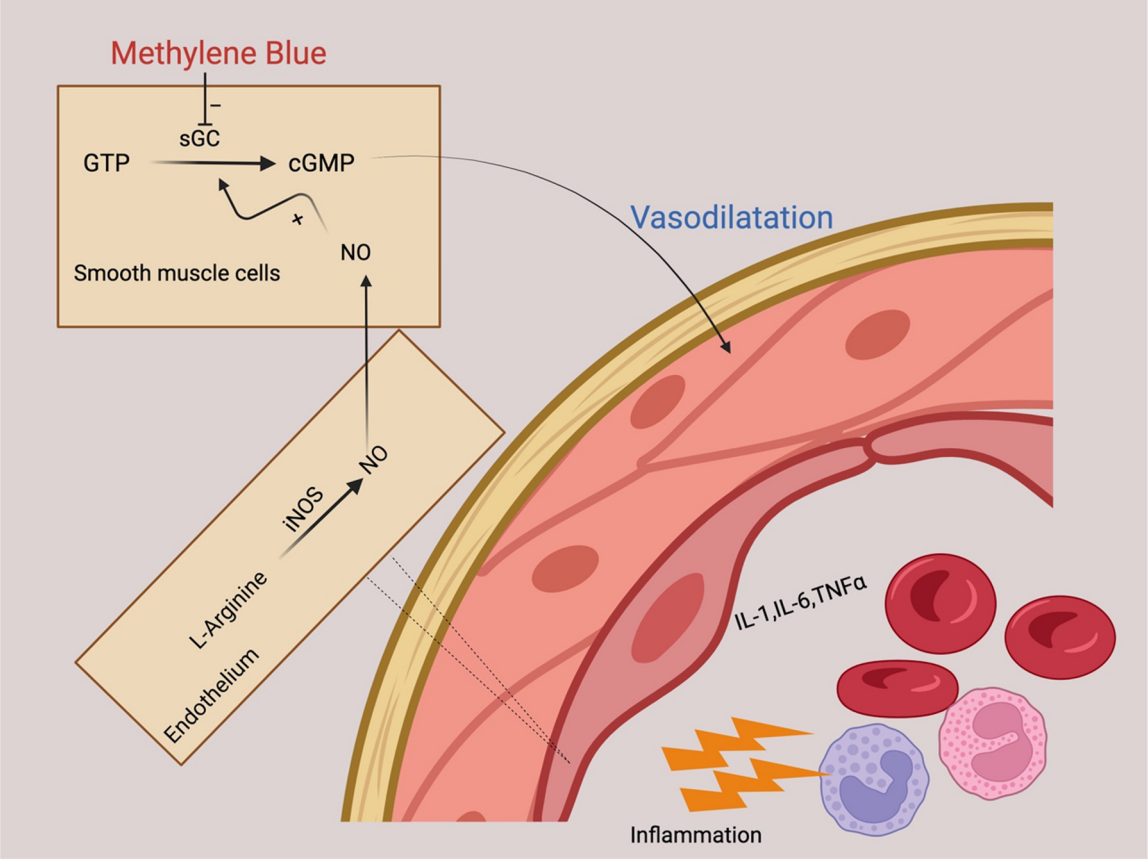

Figure 1. Schematic presentation of methylene blue in alleviating vasodilatation. Il-1: interleukin-1; IL-6: interleukin-6; TNFα: tumor necrosis factor alpha; NO: nitric oxide; iNOS: inducible nitric oxide synthase; GTP: guanosine triphosphate; sGC: soluble guanylyl cyclase; cGMP: cyclic guanosine monophosphate.

blood products or more) were excluded from this cohort to avoid misinterpreting the shock etiology. We used our institution's cardiothoracic database and electronic patient records for this single-center retrospective cohort study.

University of Erlangen MB protocol for post-CPB vasoplegia

Our institution's Division of Thoracic and Cardiovascular Surgery has utilized a consensus-based approach to managing post-CPB vasoplegic syndrome. Vasodilatation characterized by low systemic vascular resistance (SVR) and elevated cardiac index (CI) resulting in hypotension despite high doses of vasopressors on pump or postoperatively is included in the diagnosis of vasodilatation.

To counteract vasodilation, standard vasopressor support is administered with a preference for norepinephrine. Given the common hyperdynamic cardiac function associated with vasoplegic syndrome, with cardiac indices usually exceeding 2,5 L/min/m^2, epinephrine was cautiously administered.

Our protocol for administering MB to patients with refractory vasoplegic syndrome consisted of an intravenous bolus dose of 2 mg/kg, followed by 12 h of infusion at 0.5 mg/kg/hr. During the study period, this protocol was implemented for all patients. Absolute contraindications for the drug encompass pregnant patients, women of childbearing potential, patients with known Glucose 6-Phosphate Dehydrogenase (G6PD) deficiency, and patients with documented hypersensitivity to methylene blue or contrast dye.

The norepinephrine had a salt formulation of norepinephrine hydrochloride 'Arterenol® 1 mg/ml, Cheplapharm Arzeimittel GmbH, Mesekenhagen, Germany'.

Human participant protection

This retrospective investigation was conducted in accordance with the Helsinki Declaration (2000), and the analysis was endorsed by the local Ethics Committee (EC). (EC, No.24-50-Br) Based on retrospective data retrieval, the EC waived the need for written informed consent from patients.

Data collection and statistical analysis

The primary outcome was in-hospital mortality. Secondary outcomes were intensive care unit (days) and postoperative hemodialysis.

All patient-associated data were collected in an approved manner on a comprehensive spreadsheet. Continuous variables were expressed as mean ± SD. As applicable, comparisons were conducted using the chi-squared and student t-test. A *p*-value less than or equal to 0.05 was deemed to indicate statistical significance. The statistical analysis was conducted utilizing version 17.0 of the Stata/SE statistical software (StataCorp.; Texas, USA).

Results

The incidence of vasoplegic syndrome was 7.2% ($n = 200/2753$). Both study groups have similar CPB and aortic cross-clamp times. Patients in group 1 were statistically significantly younger, with a P-value of <.05; however, the logistic EuroSCORE between both groups showed no difference, as shown in Table 1.

The patients in the MB group ($n = 84$) have a lower intensive care unit stay duration in days (9 ± 8 days) vs. (16 ± 6.9) in the control group ($n = 116$).

The patients in the control group ($n = 116$) experienced more postoperative complications as the postoperative hemodialysis was higher in the control group (20% in the MB group ($n = 84$) and 40% in the control group). Serum lactate at 24 h postoperative was lower in the methylene blue group (1.8 ± 1.2 mmol/L in the MB group vs. 4 ± 1.8 mmol/L in the control group); this difference was statistically significant with a P-value <.001, as shown in Table 2.

The norepinephrine dose in mg/hour at 24 h was lower in the methylene blue group than in the control

Table 1. Baseline characteristics of the patient population.

	Methylene Blue Group ($n = 84$)	Control Group ($n = 116$)
Female sex- no. (%)	17 (20)	32 (27.5)
Age -yr	64.2 ± 12.6*	69.4 ± 12.1
Diabetes mellitus - no. (%)	39 (46.4)	38(32.8)
Reoperation- no. (%)	10 (11.9)	19 (16.4)
Log. EuroSCORE	20 ± 12.4	19.3 ± 16.6
EF Preoperative	36.7 ± 18	40 ± 19
CPB time-minutes	148.61 ± 135.51	128.37 ± 119.36
Cross-clamp time-minutes	152.82 ± 79.6	129.49 ± 74.7
APACHE II	22 ± 3	21.2 ± 2
Procedures - no. (%)		
CABG	23 (27)	40 (35)
Valve surgery	20 (24)	34 (29.2)
CABG+ Valve surgery	17 (20)	23 (20)
Typ A dissection	3 (4)	9 (8)
HTX	3 (4)	3 (2)
VAD	15 (17)**	6 (5)
Others	3 (4)	1 (0.8)

Plus-minus values are means ± SD.
*$p < .05$.
**$p < 0.01$: When compared with the control group.
CABG: coronary artery bypass surgery; APACHE II: acute physiology and chronic health evaluation II; EF: ejection fraction; EuroSCORE: European system for cardiac operative risk evaluation; HTX: heart transplantation; VAD: ventricular assist device. CPB: cardiopulmonary bypass.

group (1.5 ± 1.2 in the MB group vs. 2.8 ± 2 in the control group), with a P-value <.05.

The study's primary endpoint, In-hospital mortality, was insignificant between the two groups (38% in the MB group vs. 43% in the control group). The outcomes of the patients in the two groups are summarized in Table 2. The systemic vascular resistance has risen significantly in the MB group after receiving the medication compared to their peers in the control group; however, after 48 h, both groups eventually approached the same range of the SVR. At 48 h postoperatively, no difference in vascular resistance was noticed between the two groups, as shown in Figure 2.

One patient in the MB group experienced a side effect that is worth reporting; the patient has a mitral valve replacement with xenograft prostheses; postoperatively, she met the criteria of vasoplegic shock and was administered methylene blue in the dose mentioned in the protocol. Mean pulmonary artery pressure (PAP_m) before MB administration was normal by 12 mmHg; approximately 10 min after initiating the therapy, the mean pulmonary raised dramatically and approached the systemic arterial blood pressure; the PAP_m measured through the right heart catheter was about 50 mmHg. The perfusion of the MB was immediately stopped due to the evidence of an acute pulmonary hypertensive crisis. After the cessation of the drug, the PAP_m gradually decreased and reached the normal range after 48 h.

Table 2. Outcomes of patients receiving methylene blue versus the control group for vasoplegic syndrome.

	Methylene Blue Group (n = 84)	Control Group (n = 116)
ICU stay-days	9 ± 8**	16 ± 6.9
Postoperative hemodialysis- no. (%)	17 (20)*	46 (40)
Serum lactate in mmol/L after 24 hours	1.8 ± 1.2**	4 ± 1.8
Norepinephrine dose in mg/h after 24 hours	1.5 ± 1.2*	2.8 ± 2
In-hospital mortality- no. (%)	31 (38)	50 (43)

Plus-minus values are means ± SD.
*p < .05.
**p < 0.01: When compared with the control group.
ICU: intensive care unit; mg: milligram; mmol/L: millimole per liter.

Discussion

In May 1953, John Gibbon made medical history by performing the first open heart surgery on humans using a machine of his invention, the heart-lung machine. The path to success was not smooth; lethal setbacks took place, but the machine ultimately found its purpose and has since saved millions of lives. The machine, however, is a double-edged sword as it can provoke robust systemic inflammation [2]. This systemic inflammation can predispose a re-distributive form of shock due to a significant drop in the resistance in the vasculature. Heart failure with a low ejection fraction, renal failure, pre-operative use of angiotensin-converting enzyme inhibitors, and left ventricular assist device surgery are well-recognized independent risk factors for developing a vasoplegic shock after cardiac surgery [4,11]. Prolonged cross-clamp time was identified as a

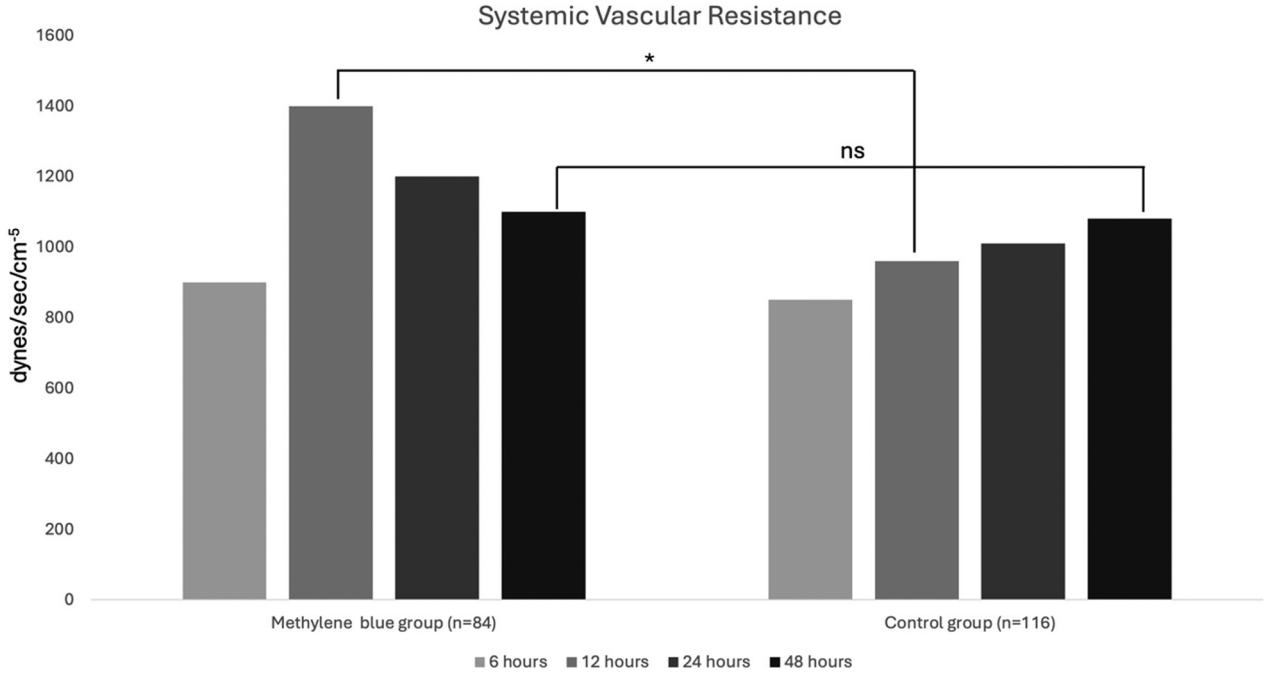

Figure 2. Systemic vascular resistance changes during the first 48 h; a t-test was used to compare the mean between the groups.

risk factor for vasoplegic syndrome following cardiovascular surgery [3] as well as an independent predictor of hospital mortality following aortic surgery [12]. The pathophysiology of VS following CPB is complex and multi-factorial. Surgical trauma, exposure to CPB circuit components, and ischemia-reperfusion induce a systemic inflammatory response by releasing vasodilatory cytokines (IL-1, IL-6, IL-8, and TNF-α) [3,9]. Oxygen-free radicals are capable of causing vascular hyporeactivity [10].

The mortality associated with VS usually is up to 10% [5,13]; for patients with persisted VS for more than 48 h, the mortality rate approaches 30% [14]. Thus, aggressive and prompt therapy for postoperative norepinephrine refractory vasoplegia is essential and highly desired. The inhibition of the soluble guanylate cyclase elicited by nitric oxide or any endothelially soluble guanylate cyclase activating factor (e.g. interleukin-1, bradykinin, oxygen-free radicals, etc.) could theoretically be a novel approach in the treatment of norepinephrine-refractory vasoplegia after CPB, as the only alternative for these patients is the increase of the catecholamine dosage with the known side effects such as arrhythmias, ischemia, and malperfusion of the visceral organs.

The release of inflammatory cytokines decreases the expression of alpha −1 adrenoreceptors at the molecular level by decreasing the gene transcription of the receptor [15]. This phenomenon of adrenoreceptor desensitization explains the vasoplegic shock refractory to adrenoreceptors' medicated drugs, as increasing the norepinephrine would not improve the patient's vital parameters. It also highlights the need for other drugs to restore the vasculature's tone using a different pathway, like methylene blue.

The lower incidence of new hemodialysis in the intensive care unit might be due to methylene blue contributing to the transient hemodynamic improvement and better end-organ perfusion with less acidemia in the critical 24 h postoperatively.

Methylene blue inhibits guanylate cyclase in the smooth muscle of the blood vessels, thus reducing cyclic guanosine monophosphate (cGMP), a potent vasodilator. Reducing the levels of (cGMP) in the smooth muscles of the blood vessels explains the rise in the systemic vascular resistance in the methylene blue group 6 h after medication administration [3].

Methylene blue triggers greenish blue-colored urine, observed in all patients in the methylene blue group (group 1). This colorization, however, was self-limiting and ceased to exist after a few days. Mild skin discoloration was also observed in most patients, but it resolved spontaneously. No documented permanent skin injury was observed due to MB at the dose specified in our protocol. No significant organ injury related to methylene blue in this cohort was noticed in the subjects with the dose previously described.

Methylene blue has been associated with hemolytic anemia in patients with glucose-6-phosphate deficiency (G6PD) [16]. Any clinical or laboratory clues of intravascular hemolytic anemia during or shortly after the infusion of methylene blue should raise suspicion about G6PD, followed by immediate medication stops. G6PD is the most common human enzyme deficiency, an X-linked recessive disorder. In the peripheral blood smear, Heinz bodies can be detected, which are denatured globin chains precipitating within the red blood cells (RBCs) due to oxidative stress and Bite cells, which result from the phagocytic removal of Heinz bodies by the splenic macrophages. No such event was recorded in patients included in this study.

MB has a monoaminoxidase inhibitor activity, which explains why it can sometimes lead to serotonin syndrome, especially when used with other teratogenic agents such as serotonin selective reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressant drugs. Symptoms of serotonin syndrome like diaphoresis, tremors, and flushing should warn the treating physician about possible interaction with the methylene blue and immediate cessation of the drug to prevent more dramatic symptoms like hyperthermia, seizures, rigidity, coma, or even death [17].

Methylene blue use might be limited in pediatric cardiac surgery as it has been associated with respiratory depression and hemolytic anemia [18]. This retrospective study can't confirm or decline these drug side effects as all the subjects were adults over 18. The need for cardiac surgery during pregnancy is an event of rare entity; it is important to mention that methylene blue is contraindicated in pregnancy and from the Federal Drug Administration (FDA) is assigned with a Class X rating and carries evidence of teratogenicity [19].

A pulmonary hypertensive crisis occurs when an abrupt rise in pulmonary arterial pressure results in a transient decrease in the pulmonary blood flow. Nitric oxide (NO) is produced in the vascular endothelium by the endothelial NO synthase (eNOS) from the precursor L-arginine. Once formed, NO diffuses into the adjacent smooth muscle cell and activates soluble guanylate cyclase (sGC), producing cyclic guanosine monophosphate (cGMP). cGMP results in smooth

muscle cell relaxation through protein kinase G (PKG). MB is helpful in vasoplegic shock as it inhibits this pathway [20]. Administering the drug through a central venous line can abolish the NO levels in the pulmonary circulation, leading to abruptly increased vascular resistance. This serious complication was observed in one of the patients (1 in 84) who received the methylene blue. She had a normal baseline mean pulmonary arterial pressure; however, after applying the medication, the mean pulmonary arterial pressure approached 50 mmHg. The pulmonary artery catheter provided real-time data and helped decide whether to stop the medication immediately. It is a serious complication yet non-fatal and reversible, as the patient was discharged two weeks later with no permanent co-morbidity in the pulmonary circulation.

In a retrospective study involving 54 patients, MB was used postoperatively in the settings of norepinephrine refractory vasoplegia after cardiac surgery with CPB; there was a clinically relevant and statistically significant drop in the norepinephrine dosage and increase in the SVR after administration of the MB. However, that was an observational study with no control group [21].

In a randomized clinical trial (RCT) of 100 patients at high risk for vasoplegic syndrome, methylene blue (1% solution) was administered 1 h before the surgery in 50 patients vs. 50 patients in the control group. The MB group had a shorter intensive care unit and hospital stay. Moreover, in those high-risk patients who received the MB, the systemic vascular resistance during the surgery was higher compared to the control group; the required norepinephrine and inotropic agents through the cardiac surgery were fewer in the methylene blue group. However, the drug failed to show again a mortality benefit. The two groups statistically differed in the incidence of VS (0% in the MB group vs. 26 in the control group; P-value < .001) [22]. In this RCT, the preoperative use empirically of MB in high-risk patients, MB could effectively reduce the incidence of VS.

Retrospectively, a multivariate logistic regression demonstrated that early administration of MB independently reduces the risk of major adverse events (permanent stroke, renal failure, reoperation, deep sternal wound infection, and prolonged ventilation) with (OR 0.35, p=.035) [23].

Smoking tobacco can impair the vascular endothelium's proper function through reduced nitric oxide synthesis [24]. In a cohort of patients with vasoplegic shock, smoking tobacco was independently associated with reduced rates of major adverse events [23]. This supports the theory of nitric oxide's role in the pathophysiology of vasoplegic shock. The adjunctive administration of methylene blue for the refractory post-CPB vasoplegic syndrome was recently reviewed by Michael Zhu et al. The review, which included 7 studies (4 randomized clinical trials and 3 observational studies), suggested that the drug is safe and may provide benefits in the form of improved hemodynamic stability, reduced vasopressor requirements, and reduced mortality [25].

Our results are consistent with prior research on this subject [21,22]. Methylene blue did not reduce the risk of mortality in patients who developed catecholamine-resistant vasoplegic shock following cardiac surgery. Nevertheless, it did reduce their duration of stay in the intensive care unit (ICU). This might be seen as reducing the postoperative burden on patients as well as reducing costs. Additionally, the MB's contribution to reduced end-organ injury is indicated by a lower serum lactate and a lower frequency of hemodialysis, although this did not result in a significant benefit. This single-center study carries multiple limitations that might compromise the study's internal validity; some might be associated with the retrospective nature of the analysis. However, this retrospective analysis might suggest the possible benefits of the drug in case of vasoplegia. A multicenter randomized trial is needed to address the effectiveness and safety profile of methylene blue on a broader scale of the patient population. Randomization of patients for the drug will also eliminate the possibility of exciting confounding variables. The results of this analysis can only apply to patients with vasoplegia shock after cardiac surgery. The results of this study apply only to vasoplegia after cardiopulmonary bypass.

Conclusions

The analysis of this retrospective dataset showed that early postoperative administration of methylene blue in patients with vasoplegic syndrome shortens intensive care unit stay and contributes to less end-organ damage. However, no mortality benefits could be observed.

Acknowledgements

The authors would like to thank the Institute of Medical Informatics, Biometry and Epidemiology (IMBE) (Erlangen, Germany) for support in statistical analysis.

Authors contributions

M.E. and C.H. conceived the presented idea. C.H. developed the theory and performed the computations. P.P. contributed

to sample preparation and designed the figures. C.H. and M.K. verified the analytical methods. C.H. supervised the findings of this work. M.E. took the lead in writing the manuscript. O.D. provided a critical review of the manuscript. M.W. and R.T. aided in interpreting the results. All the authors have read and approved the final manuscript.

Authorship

All the authors meet the criteria of authorship formulated by the International Committee of Medical Journal Editors.

Ethics approval and consent to participate

This retrospective study complied with the Helsinki Declaration (2000), and the local Ethics Committee at the University of Erlangen-Nuremberg approved this analysis (EC, No.24-50-Br) based on retrospective data retrieval. For this reason, the EC waived the need for written patients' informed consent.

Disclosure statement

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The authors received no financial support for this article's research, authorship, and publication.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [M. E], upon reasonable request.

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