Journal of Cardiothoracic and Vascular Anesthesia 38 (2024) 268–274

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Review Article

Methylene Blue Reduces Mortality in Critically Ill and Perioperative Patients: A Meta-Analysis of Randomized Trials

Alessandro Pruna, MD*, Alessandra Bonaccorso, MD*, Alessandro Belletti, MD*, Stefano Turi, MD*, Ambra Licia Di Prima, MD*, Filippo D'amico, MD*, Alberto Zangrillo, MD*,†, Yuki Kotani, MD*,†,‡, Giovanni Landoni, MD*,†,[1]

*Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
†School of Medicine, Vita-Salute San Raffaele University, Milan, Italy
‡Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Japan

Vasodilatory hypotension is common in critically ill and perioperative patients, and is associated with adverse outcomes. As a nitric oxide production inhibitor, methylene blue (MB) exerts its vasoconstrictor property and is an adjuvant for catecholamine-refractory vasodilatory shock. However, the effects of MB on clinically relevant outcomes remain unclear. Therefore, the authors performed a meta-analysis of randomized trials on MB in critically ill and perioperative patients. The authors searched through databases for randomized trials on MB in critically ill and perioperative patients, which yielded 11 studies consisting of 556 patients. The primary outcome was mortality at the longest follow-up. Secondary outcomes included hemodynamic parameters and organ dysfunction (PROSPERO: CRD42023409243). Nine out of the 11 included randomized trials reported mortality, which was significantly lower in the MB group (risk ratio, 0.60 [95% CI 0.43-0.84] p = 0.003), with findings confirmed in septic shock and cardiac surgery subgroups. The authors found reduced lengths of stay in the intensive care unit (mean difference [MD], −0.9 days [95% CI −1.06 to −0.77] p < 0.001) and in the hospital (MD, −2.2 days [95% CI, −2.68 to −1.70] p < 0.001) in the MB group. MB was associated with increased mean arterial pressure (MD, 8.4 mmHg [95% CI 5.01-11.75] p < 0.001) and systemic vascular resistance (MD, 94.5 dyn/s/cm^5 [95% CI 17.73-171.15] p = 0.02), with no difference in cardiac output (standardized MD, 0.16 [95% CI, -0.25 to 0.57] p = 0.45). This meta-analysis showed that MB reverses vasodilation in critically ill and perioperative patients and might improve survival. Further adequately powered randomized trials are needed to confirm these findings.

Key Words: methylene blue; vasoconstrictor agents; vasoplegia; shock; intensive care; critical illness

IN CRITICALLY ILL and perioperative patients, vasodilatory hypotension is common and is associated with mortality and morbidities. Fluids and adrenergic vasopressors are considered the first-line therapy to maintain adequate organ perfusion.[1-3] However, patients with severe vasodilatory shock may not attain a target blood pressure, even with high-dose adrenergic vasopressors, and require additional agents with different mechanisms of action.[1,4]

In the last 2 decades, alternative molecular pathways were studied as potential therapy targets, such as vasopressin and methylene blue (MB).[5] Nitric oxide (NO) is an endogenous endothelial-derived vasodilatory agent, and its overproduction is a hallmark of cytokine-induced vasodilation that can account for hypotensive state.[6] Methylene blue counteracts NO overproduction by inhibiting soluble guanylate cyclase and restoring vascular tone.[7] Several studies showed that MB may reduce the requirement of catecholamines and increase

[1]*Address correspondence to* Giovanni Landoni, MD, Professor, Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy.
E-mail address: landoni.giovanni@hsr.it (G. Landoni).

https://doi.org/10.1053/j.jvca.2023.09.037
1053-0770/

mean arterial pressure (MAP) and systemic vascular resistance (SVR).[5,8] Moreover, previous meta-analyses suggested a beneficial effect on hemodynamic parameters[9] and organ function.[10] Given the uncertainty about the efficacy of MB on clinically relevant outcomes, and the recent publication of randomized trials[11] showing prolonged vasopressor-free days, the authors performed an updated meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of MB on survival in critically ill and perioperative patients.

Materials and Methods

This study updated 2 previous meta-analyses,[9,12] and was conducted according to the PICOS (population, intervention, comparison, outcome, study design) framework—critically ill and perioperative patients (P), MB (I), any comparator (C), mortality at the longest follow-up (O), RCTs (S).

The protocol of the authors' study was registered in the PROSPERO International Prospective Register of Systematic Reviews database (CRD42023409243). This study was performed in compliance with The Cochrane Collaboration[13] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

Search Strategy

Two trained investigators independently searched Medline, Embase, Clinicaltrials.gov, and the Cochrane Central Register of Clinical Trials for relevant studies on MB (updated up to 16 March 2023). Moreover, the authors employed backward snowballing and contacted international experts in the field for further studies. They did not impose any language restrictions. The full PubMed search strategy is available in the Supplemental material.

Study Outcomes

The primary outcome was mortality at the longest follow-up available. Secondary endpoints were MAP, SVR, and cardiac index or cardiac output (CO) 1 hour after the administration of the study drug or at the nearest timepoint available, red blood cell (RBC) transfusion, acute kidney injury, cerebrovascular events, and intensive care unit (ICU) and hospital lengths of stay.

Study Selection

Eligibility was assessed at the title and/or abstract level by 2 independent investigators according to the inclusion and exclusion criteria. All available randomized clinical trials comparing MB with any comparator in critically ill and perioperative patients were included. The exclusion criteria were duplicate publications, pediatric studies, nonhuman studies, administration routes of MB other than intravenous, and studies not reporting any outcome for this meta-analysis. All potentially relevant articles underwent a full-text evaluation, and 2 authors independently assessed compliance with the eligibility criteria and selected the studies for final analysis (Fig. 1). Disagreements during the cross-checking process

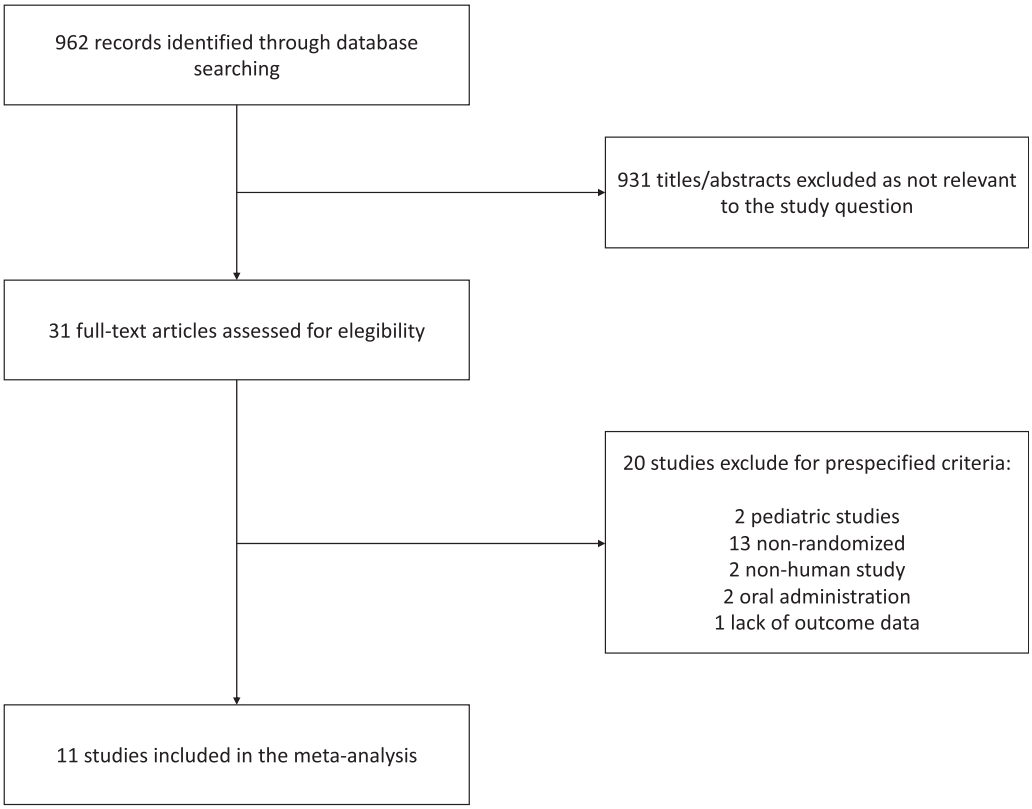

Fig 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart.

were discussed with a third experienced investigator and solved by consensus.

Data Extraction

Baseline, procedural, and outcomes data were extracted independently by 2 trained investigators, with divergences discussed with a third experienced investigator and resolved by consensus. The authors assessed sources of potential clinical heterogeneity. They abstracted study design, sample size, clinical setting, MB administration modality, control treatment, and follow-up duration, as well as primary and secondary study endpoints. The authors contacted the manuscript corresponding authors via e-mail in case of missing data. For the primary outcome, they abstracted the longest follow-up available data for each of the included studies to be the most inclusive possible, considering that pooling different follow-up time points did not influence pooled point estimates of the effects on mortality.[15-18]

Data Analysis and Synthesis

Statistical analysis was performed with RevMan 5.4 by the Cochrane Collaboration and Stata version 16.1 (StataCorp, LLC). Statistical heterogeneity was tested by means of the Cochran Q test, with statistical significance set at the 2-tailed 0.10 level, whereas the extent of statistical consistency was measured with Higgins and Thompson's I^2. Dichotomous outcomes were analyzed to compute individual and pooled risk ratio (RR) with corresponding 95% CI using the Mantel-Haenszel method. The authors expressed continuous outcomes as individual and pooled mean difference (MD) or standardized MD, along with 95% CI using the inverse variance method. They used a fixed-effect model in case of low statistical inconsistency ($I^2 \leq 25\%$) or a random-effect model in case of high statistical inconsistency ($I^2 > 25\%$). If only a median and IQR were available, Wan's method was used to estimate the mean and SD.[19]

Statistical significance was set at the 2-sided 0.05 level for hypothesis testing. Unadjusted p values are reported throughout. The authors performed sensitivity analyses—first, they analyzed pooled data of low-risk bias studies and, secondly, used a random-effect model for the primary outcome, even if Higgins $I^2 \leq 25\%$.

A trial sequential analysis (TSA) was performed for the primary outcome, with a diversity-adjusted information size calculated using a 2-sided alpha of 0.05 and a power of 80%. The authors anticipated a relative risk reduction of 20%, and derived the incidence of the control arm from the included studies. The TSA Viewer software was used (Version 0.9.5.10 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research).

Risk of Bias Assessment

The risk of bias in included trials was assessed independently by 2 review authors using the RoB 2 tool according to Cochrane Collaboration methods,[20] with divergences solved by a third expert investigator. Publication bias was assessed by an analytical approach based on Begg's adjusted-rank correlation test[21] and Egger's linear regression test[22]; a 2-tailed p value < 0.10 was considered significant.

Results

A systematic database and literature search yielded 141 records, and the authors identified 11[11,23-32] eligible studies with 556 patients. Studies were published in the period between 2002 and 2023, and all but one were placebo-controlled (Table 1). A single slow bolus was the most common way of administration, and the most frequently administered dose was 2 mg/kg.

Primary Outcome

This meta-analysis showed significantly lower mortality in the MB group (15%) compared to the control group (25%) (RR 0.60 [95% CI, 0.43-0.84]; p = 0.003, $I^2 = 0\%$; Fig 2), with findings confirmed when a random-effect model was applied (Supplementary Figure S1) in septic shock (5 studies included) and cardiac surgery subgroups (Fig 2). Timepoint subgroup analysis revealed lower mortality in MB both in the 28-to-30 days subgroup (RR 0.68 [95% CI, 0.48-0.96]; p = 0.03, $I^2 = 0\%$; Supplementary Figure S2) and in the fewer than 28 days timepoint subgroup (RR 0.11 [95% CI, 0.01-0.85]; p = 0.03, $I^2 = 0\%$; Supplementary Figure S2). Sensitivity analyses were summarized in Supplementary Table S1. No small study effect bias was identified with Begg's rank correlation test[21] (p = 0.90) and Egger's linear regression test[22] (p = 0.49).

The result of TSA was inconclusive because the Z curve did not cross either O'Brien-Fleming alpha-spending boundary (Supplementary Figure S3); accordingly, the currently existing evidence was insufficient to conclude the MB benefits on survival.

Secondary Endpoints

Among hemodynamic parameters, the authors found a significant MAP increase in the MB group compared to the control group, with an MD of 5.79 mmHg (95% CI, 3.64-7.95, $p < 0.001$, $I^2 = 15\%$; Fig 3). Systemic vascular resistance was significantly increased in the MB group, with an MD of 94.5 dyn/s/cm^5 (95% CI, 17.73-171.15, p = 0.02, $I^2 = 0\%$; Supplementary Figure S4), whereas no effect was observed on cardiac index and CO (SMD, 0.46 [95% CI, −0.13 to 1.06]; p = 0.13, $I^2 = 69\%$; Supplementary Figure S5). Along with improved hemodynamics, MB was associated with a trend toward a lower number amount of packed RBCs transfusion compared to control (MD, −0.55 units (95% CI, −1.16 to 0.05; p = 0.07, $I^2 = 86\%$; Supplementary Figure S6).

Moreover, the authors found a reduced length of stay both in the ICU (MD, −0.9 days [95% CI, −1.06 to −0.77], $p < 0.00001$, $I^2 = 2\%$; Supplementary Figure S7) and in the hospital (MD, −2.2 days [95% CI, −2.68 to −1.70]; $p < 0.00001$,

Table 1
Characteristics of the 11 Randomized Trials that Studied Methylene Blue in Critically Ill and Perioperative Patients.

Author	Setting	Number of Patients Included	Comparator	MB Slow Bolus	MB Infusion	Follow-up	Adverse Events
Koelzow H et al 2002[32]	Surgery (liver transplant)	38	Placebo	1.5 mg/kg	No	30 d	NR
Memis D et al 2002[24]	Surgery (Septic shock)	30	Placebo	No	0.5 mg/kg/h for 6 h	28 d	None
Kirov MY et al 2003[23]	ICU (septic shock)	20	Placebo	2 mg/kg	0.25-2 mg/kg/h for 4 h	28 d	Urine and skin discoloration
Levin RL et al 2004[28]	Cardiac surgery	56	Placebo	No	1.5 mg/kg for 1 h	4 d	Green-blue discoloration of urine
Özal E et al 2005[29]	Cardiac surgery	100	Placebo	2 mg/kg	No	Hospital discharge	NR
Maslow AD et al 2006[31]	Cardiac surgery	30	Placebo	3 mg/kg	No	Discharge from operating theatre	Transient reduction of SpO_2 at the monitor
Cho JS et al 2012[27]	Cardiac surgery	40	Placebo	2 mg/kg	No	ICU discharge	NR
Senthilnathan M et al 2017[30]	Surgery (acute peritonitis)	30	Placebo	2 mg/kg	No	7 d	NR
Lu YP et al 2019[26]	ICU (septic shock)	54	Placebo	2 mg/kg	2 mg/Kg/h	28 d	NR
Li QS et al 2021[25]	ICU (septic shock)	66	Standard of care	2 mg/kg	No	28 d	NR
Ibarra-Estrada M et al 2023[11]	ICU (septic shock)	92	Placebo	No	100 mg in 6 h for 3 d	28 d	Green-blue discoloration of urine Increased maximum methemoglobin saturation

Abbreviations: ICU, intensive care unit; MB, methylene blue; NR, not reported.

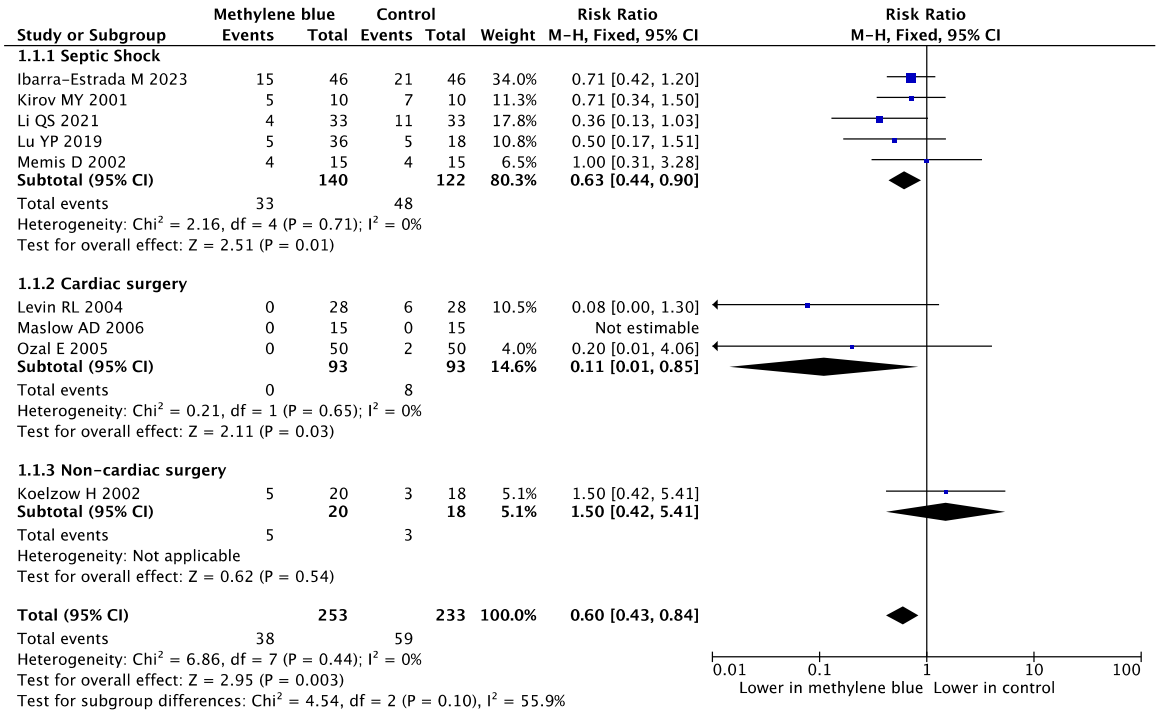

Fig 2. Forest plot for mortality.

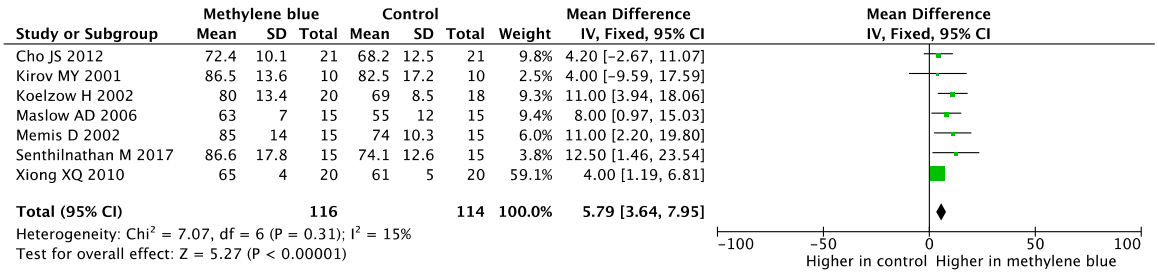

Fig 3. Forest plot for the effect of methylene blue on mean arterial pressure.

I^2 = 0%; Supplementary Figure S8). No differences in acute kidney injury (Supplementary Figure S9), cerebrovascular events (Supplementary Figure S10), de-novo start of renal replacement therapy (Supplementary Figure S11), and myocardial injury (no events in both groups) were detected (Table 2).

Discussion

Key Points

This meta-analysis of RCTs showed that MB may have a possible beneficial effect on survival, which was more evident in septic shock and cardiac surgery patients. This was the first meta-analysis of RCTs only to show a significant effect on survival in septic shock patients. Interestingly, in the cardiac surgery subgroup, the authors found 0 out of 93 fatal events in the MB group against 8 out of 93 events in the control group. A possible explanation for the absence of events in the MB group could be first because vasoplegic states in cardiac surgery could be deeply refractory even to high doses of norepinephrine, and MB-mediated NO inhibitions actively contribute to counteracting the leading local vasodilatory mediator; secondly, multimodal therapies are associated with fewer drug-related adverse events.[33] Although pooling mortality data at different time points may improve the precision of the pooled-effect estimates,[15-17] the authors performed subgroup analyses according to the follow-up time point (28-30 days and fewer than 28 days), which confirmed the statistical significance of the beneficial effect of MB. Furthermore, the authors' study showed that MB increased MAP and SVR without depressing CO. They also found reduced ICU and hospital stay durations in the MB group.

Relation to Previous Studies

The present study was an update of 2 previously published meta-analyses on MB.[9,12] In 2013, the authors' group pooled 5 RCTs with 174 patients, and found an increased MAP in hypotensive patients, but was underpowered to detect an effect of MB on survival.[9] In the present study, the authors

Table 2
Summary of Study Results

	No. of Studies	MB, n/N (%)	Control, n/N (%)	RR (95% CI)	p Value	I^2, (%)
Mortality						
Overall	9	38/253 (15)	59/233 (25)	0.60 (0.43-0.84)	0.003	0
Cardiac surgery	3	0/93 (−)	8/93 (8)	0.11 (0.01-0.85)	0.03	0
Septic shock	5	33/140 (24)	48/122 (39)	0.63 (0.44-0.90)	0.01	0
Non-cardiac surgery	1	5/20 (25)	3/18 (17)	1.50 (0.42-5.41)	0.54	–
Secondary outcomes						
Organ dysfunction outcomes						
Acute kidney injury	3	8/95 (8)	14/95 (15)	0.59 (0.26-1.30)	0.19	0
Cerebrovascular events	4	0/145 (-)	3/154 (2)	0.33 (0.01-7.99)	0.24	0
Renal replacement therapy	2	2/74 (3)	3/74 (4)	0.76 (0.08-7.20)	0.81	30
Myocardial injury	2	0/61 (−)	0/61 (−)	–	–	–
		N	N	MD/sMD (95% CI)		
Hemodynamic end points						
Mean arterial pressure, mmHg	6	96	94	8.4 (5.01-11.75)	< 0.001	0
Systemic vascular resistance, dyn/s/cm^5	4	61	61	94.5 (17.73-171.15)	0.02	0
CI/CO*	4	79	79	0.46 (−0.13 to 1.06)	0.13	69
pRBC, unit	4	132	132	−0.55 (−1.16 to 0.05)	0.07	86
Other secondary end points						
Length of stay in ICU, d	5	142	142	−0.92 (−1.06 to −0.77)	< 0.001	2
Length of stay in hospital, d	5	160	169	−2.2 (−2.68 to −1.70)	< 0.001	0

Abbreviations: AKI, acute kidney injury; CI/CO, cardiac index/cardiac output; CVE, cerebrovascular events; n, number of events; N, total number of cases; MB, methylene blue; MD, mean difference; sMD, standardized mean difference; pRBC, packed red blood cells; SVR, systemic vascular resistance.

* The effect of this outcome was evaluated with sMD.

tripled the number of patients, which allowed them to detect a statistically significant mortality reduction in the MB group. In addition to increased MAP, they assessed other hemodynamic variables, and showed that MB significantly increased SVR with no differences in cardiac index and CO between the groups. In another meta-analysis, Zhao et al.[12] identified reduced mortality in patients with vasodilatory shock, but the majority of the included studies were not randomized, and they did not include 4 RCTs, which were included in this meta-analysis. Belletti et al.[5] previously had suggested a beneficial effect of non-adrenergic vasoconstrictors on survival, but their meta-analysis on RCTs also included vasopressin and terlipressin, and only 5 RCTs on MB were included.

Significance of Study Findings

The authors' meta-analysis showed an overall improved survival, which is the most relevant outcome for critically ill patients, and improved hemodynamics with MAP and SVR increases. Considering that cytokine-mediated NO overproduction characterizes inflammatory states, such as sepsis and cardiac surgery (especially with cardiopulmonary bypass), NO actively contributes to systemic vasodilation and the instances of refractory hypotension and shock.[34] MB increases MAP and SVR by inhibiting soluble guanylate cyclase, and opposes NO overproduction.[7] In contrast to nonselective NO synthase inhibitors, which increased mortality in septic shock,[35] the authors' study showed that MB improved hemodynamics and survival. Interestingly, they showed that the addition of MB to standard treatment did not decrease cardiac index and CO. There may be a concern about the possibility that a deep SVR rise could lead to left ventricular impairment due to an afterload increase. The authors' counterintuitive findings on CO might be attributed to an improved right ventricular function associated with the increased blood pressure. However, they cannot exclude the possible direct effect of MB on cardiac performance.

The hemodynamic improvement due to MB administration was probably the main explanation for patients' improved survival. An increase in blood pressure might improve perfusion in the kidneys and brain, as suggested by Perdhana et al.,[10] in cardiac surgery, a setting where vasoplegia is frequent,[36] and might impair organ perfusion.[37] An improved MAP also might be associated with reduced infusion of fluids and packed RBCs and their related side effects.[38] The catecholamine-sparing effect identified by Zhao et al.[12] also can explain, at least in part, the beneficial effect of MB on survival.[1] Catecholamine-sparing strategies may reduce catecholamine-related adverse events (eg, arrhythmia), and improve patients' outcomes.[39] In addition, catecholamines may compromise regional perfusion and may lead to splanchnic hypoperfusion, with a consequent increase in blood lactic acid levels.[40] In contrast, MB increases MAP without compromising splanchnic perfusion,[41] which might make MB a promising agent for a multimodal vasopressor strategy.

The present meta-analysis found that MB significantly reduced ICU and hospital lengths of stay. This finding was surprising because survivors treated with medications able to improve survival generally had a prolonged length of stay. Unfortunately, none of the 11 RCTs included in this meta-analysis had a follow-up longer than 30 days, and none of them investigated quality of life. Therefore, the authors can only speculate that MB might be associated with reduced post-intensive care syndrome and improved postdischarge quality of life.

Because none of the included studies reported severe adverse events related to MB administration, MB might be considered a safe drug. The most mentioned adverse reaction was a gray-blue discoloration of urine. To note, only 1 author reported several cases of a transient drop of pulse oximetry value,[31] which is a constant finding with MB administration. Ibarra-Estrada et al. showed a mildly increased methemoglobinemia saturation.[11] Nonetheless, in a previous report, the authors documented 3 cases of serotoninergic syndrome with "blue coma" in patients on chronic selective serotonin reuptake inhibitors drugs. These patients did not show any brain injury at diagnostic examinations, and the coma state regressed within a few days.[42] However, the authors' meta-analysis here did not show an increase in adverse cerebral events associated with MB administration.

Strengths and Limitation

The main limitation of this study was the low number of RCTs available. The included studies were performed in heterogeneous clinical settings (ie, cardiac surgery, septic shock, and noncardiac surgery), and mostly were single-center trials with small sample sizes. Moreover, secondary endpoints of this meta-analysis were not available for all studies, and given the promising effects on hemodynamic status, it would be reasonable to assess the efficacy of MB on mortality. Despite the heterogeneous study settings, these studies had vasodilation as the common pathophysiologic characteristic, which made MB administration a possible therapeutic option. Additionally, the authors included only RCTs to minimize biases. They are aware that meta-analytical findings are hypothesis-generating rather than confirmative. These findings should promote future adequately powered multicenter RCTs to assess the effects of MB clinically relevant outcomes.

Conclusions

This meta-analysis showed that MB may improve survival in critically ill and perioperative patients, with reductions in ICU and hospital lengths of stay. Methylene blue also significantly improves MAP and increases SVR without detrimental effects on cardiac index and CO. Current evidence supports the beneficial effect of MB and suggests it as a possible adjunctive agent in a multimodal vasopressor approach. Large-scale international, pragmatic RCTs are needed to confirm the authors' findings.

Declaration of Competing Interest

None.

Acknowledgments

The authors really appreciated the support of Dr. Miguel Ibarra-Estrada, who shared adjunctive data on secondary outcomes, and Dr. Gui-Jun Zhu, who provided us with some hard-to-find studies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2023.09.037.

References

1 Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181–247.
2 LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000;28:2729–32.
3 Belletti A, Azzolini ML, Baldetti L, et al. Inotropes and vasopressors use in critical care and perioperative medicine: Evidence-based approach. Gen Reanimatol 2022;18:60–77.
4 Guarracino F, Habicher M, Treskatsch S, et al. Vasopressor therapy in cardiac surgery-An experts' consensus statement. J Cardiothorac Vasc Anesth 2021;35:1018–29.
5 Belletti A, Musu M, Silvetti S, et al. Non-adrenergic vasopressors in patients with or at risk for vasodilatory shock. A systematic review and meta-analysis of randomized trials. PLoS One 2015;10:e0142605.
6 Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588–95.
7 Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. Biochem Pharmacol 1993;45:367–74.
8 Hosseinian L, Weiner M, Levin MA, et al. Methylene blue: Magic bullet for vasoplegia? Anesth Analg 2016;122:194–201.
9 Pasin L, Umbrello M, Greco T, et al. Methylene blue as a vasopressor: A meta-analysis of randomised trials. Crit Care Resusc 2013;15:42–8.
10 Perdhana F, Kloping NA, Witarto AP, et al. Methylene blue for vasoplegic syndrome in cardiopulmonary bypass surgery: A systematic review and meta-analysis. Asian Cardiovasc Thorac Ann 2021;29:717–28.
11 Ibarra-Estrada M, Kattan E, Aguilera-González P, et al. Early adjunctive methylene blue in patients with septic shock: A randomized controlled trial. Crit Care 2023;27:110.
12 Zhao CC, Zhai YJ, Hu ZJ, et al. Efficacy and safety of methylene blue in patients with vasodilatory shock: A systematic review and meta-analysis. Front Med 2022;9:950596.
13 Higgins JPT, Thomas J, Li T, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022.
14 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
15 Kotani Y, Pruna A, Lee TC, et al. Authors' reply to Hansel's letter to the editor. Crit Care 2023;27:223.
16 Kotani Y, Pruna A, Lee TC, et al. Authors' reply to the comment from Benavides-Zora et al. Crit Care 2023;27:255.
17 Kotani Y, Pruna A, Lee TC, et al. Comment to: "Propofol and survival: An updated meta-analysis of randomized clinical trials": Authors' reply. Crit Care 2023;27:237.
18 Roth D, Heidinger B, Havel C, et al. Different mortality time points in critical care trials: Current practice and influence on effect estimates in meta-analyses. Crit Care Med 2016;44:e737–41.
19 Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
20 Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
22 Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
23 Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: A pilot, randomized, controlled study. Crit Care Med 2001;29:1860–7.
24 Memis D, Karamanlioglu B, Yuksel M, et al. The influence of methylene blue infusion on cytokine levels during severe sepsis. Anaesth Intensive Care 2002;30:755–62.
25 Li QS. Application of methylene blue in septic shock. Diet Health 2021;9:79.
26 Lu YP, Yu HJ, Liu QY, et al. Efficacy of continuous intravenous infusion of methylene blue in patients with septic shock. Nat Med J China 2019;99:4.
27 Cho JS, Song JW, Na S, et al. Effect of a single bolus of methylene blue prophylaxis on vasopressor and transfusion requirement in infective endocarditis patients undergoing cardiac surgery. Korean J Anesthesiol 2012;63:142–8.
28 Levin RL, Degrange MA, Bruno GF, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg 2004;77:496–9.
29 Özal E, Kuralay E, Yildirim V, et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. Ann Thorac Surg 2005;79:1615–9.
30 Senthilnathan M, Cherian A, Balachander H, et al. Role of methylene blue in the maintenance of postinduction hemodynamic status in patients with perforation peritonitis: A pilot study. Anesth Essays Res 2017;11:665–9.
31 Maslow AD, Stearns G, Butala P, et al. The hemodynamic effects of methylene blue when administered at the onset of cardiopulmonary bypass. Anesth Analg 2006;103:2–8;table of contents.
32 Koelzow H, Gedney JA, Baumann J, et al. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. Anesth Analg 2002;94:824–9.
33 Leone M, Einav S, Antonucci E, et al. Multimodal strategy to counteract vasodilation in septic shock. Anaesth Crit Care Pain Med 2023;42:101193.
34 Kilbourn RG, Griffith OW. Overproduction of nitric oxide in cytokine-mediated and septic shock. J Natl Cancer Inst 1992;84:827–31.
35 López A, Lorente JA, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. Crit Care Med 2004;32:21–30.
36 Liu H, Yu L, Yang L, et al. Vasoplegic syndrome: An update on perioperative considerations. J Clin Anesth 2017;40:63–71.
37 Monaco F, Di Prima AL, Kim JH, et al. Management of challenging cardiopulmonary bypass separation. J Cardiothorac Vasc Anesth 2020;34:1622–35.
38 Blet A, McNeil JB, Josse J, et al. Association between in-ICU red blood cells transfusion and 1-year mortality in ICU survivors. Crit Care 2022;26:307.
39 De Backer D, Foulon P. Minimizing catecholamines and optimizing perfusion. Crit Car 2019;23:149.
40 Beale RJ, Hollenberg SM, Vincent JL, et al. Vasopressor and inotropic support in septic shock: An evidence-based review. Crit Care Med 2004;3:S455–65.
41 Juffermans NP, Vervloet MG, Daemen-Gubbels CRG, et al. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide 2010;22:275–80.
42 Martino EA, Winterton D, Nardelli P, et al. The blue coma: The role of methylene blue in unexplained coma after cardiac surgery. J Cardiothorac Vasc Anesth 2016;30:423–7.