The safety of methylene blue in the prevention of vasoplegic syndrome in cardiac surgery: a meta-analysis.

Alberto Ramírez-Saiz, RN, MSc. (A.R.S.) European University of Valencia. Department of Nursing and Nutrition, Faculty of Health Sciences
ORCID: https://orcid.org/0000-0002-7668-3173

Gisela Palma-Aguilar, RN, MSc. (G.P.A.) Master's Degree in Casualties, Emergencies and Critical Care from the European University of Valencia. Degree in Nursing from the Pontifical Catholic University of Ecuador.
ORCID: https://orcid.org/0009-0006-3795-6817

Correspondence: Alberto Ramírez. Av. Maestro Rodrigo 11-12º-2A, Valencia, España, 46015, ramirez_albsai@gva.es

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AUTHOR CONTRIBUTIONS

G.P.A. designed the data collection instruments, collected the data, conducted the initial analyses, assisted in the quantitative analysis and critically reviewed the manuscript.

A.R.S. conceptualised and designed the study, coordinated and supervised the data collection, conducted the quantitative analysis and critically reviewed the manuscript for academic content.

All the authors approved the final version of the manuscript as submitted and accept responsibility for all aspects of the study.

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ABSTRACT

Introduction and goals: Methylene blue (MB) is used in the treatment of refractory hypotension associated with vasoplegic syndrome during cardiac surgery. This study aims to assess adverse effects and mortality in patients treated with MA, as well as to analyse the length of hospital stay and perform a meta-analysis of safety in the context of cardiac surgery.

Material and methods: A systematic review was conducted following PRISMA guidelines. Randomised clinical trials with control group in patients aged 18 years and older treated with MB after cardiac surgery were included. The meta-analysis used a Bayesian methodology to assess adverse effects and morbidity and mortality events.

Results: Of the 29 studies identified, five met the inclusion criteria. The results showed that MB was associated with a significant reduction in postoperative bleeding and hospital stay. No significant differences were found in the incidence of renal failure, stroke or need for dialysis. However, one study that administered MB after diagnosis of vasoplegic syndrome reported a reduction in multi-organ failure and mortality. The meta-analysis showed inconclusive evidence on the overall safety of MB.

Conclusions: MB may be effective in reducing bleeding complications and mortality in patients with vasoplegic syndrome after cardiac surgery. However, the relative lack of studies and the variability in the doses used limit the generalisation of thee results, underlining the need for more high-quality research.

INTRODUCTION

Theoretical framework

Methylene blue (MB) is particularly well known for its use in the treatment of methaemoglobinaemia, a condition in which haemoglobin is oxidised to methaemoglobin, preventing efficient oxygen transport.[1] It acts by inhibiting endothelial nitric oxide synthase (eNOS), an enzyme that catalyses the production of nitric oxide (NO) in vascular endothelial cells from L-arginine, oxygen and NADPH.[2-5] NO is a crucial signalling molecule in several different physiological and pathological processes, including vasodilation, neurotransmission, and immune response.[6] NO is a gas that diffuses across cell membranes and binds to soluble guanylate cyclase (sGC).[7] sGC is an enzyme that transforms Guanosine Triphosphate (GTP) into cyclic Guanosine Monophosphate (cGMP), a signalling molecule that binds to potassium channels and promotes the extracellular outflow of potassium, thereby causing the hyperpolarisation of the muscle cell and hindering its contraction.[8] By inhibiting these pathways, MB can counteract excessive vasodilation and thus hypotension.[7]

Refractory hypotension refers to hypotension that does not respond appropriately to conventional treatment.[9] This situation frequently occurs in states of shock, where blood pressure remains dangerously low despite the administration of intravenous fluids and vasopressors.[10] Within the broad aetiopathogenic spectrum of shock, vasoplegic syndrome is noteworthy. It is a condition characterised by severe and persistent vasodilatation leading to refractory hypotension despite sufficient fluid resuscitation and the use of vasopressors. There are no standardised diagnostic criteria, but it is accepted that it is characterised by persistent, vasopressor-resistant hypotension, normal or elevated cardiac output and low systemic vascular resistance. [11] It is estimated that 5-50% of people undergoing cardiopulmonary bypass (CPB) may experience vasoplegic syndrome, and the prevalence is as high as 16% in patients undergoing cardiac surgery.[12,13]

MB can be used in refractory shock to counteract excessive NO-mediated vasodilation. [14] It has been used as an adjuvant treatment to raise blood pressure in patients with septic shock. Several studies have shown that administration of MB can improve blood pressure and tissue perfusion in patients with septic shock. [15]

However, MB is not exempt from risk. Several different adverse effects have been reported, including chromaturia, methaemoglobinaemia and in high doses, intravascular haelolysis. Furthermore, it is contraindicated in patients with enzymatic deficiency of glucose-6-phosphate dehydrogenase. [16]

Reason for the study

Knowledge about the safety of MB in the context of vasoplegic syndrome during cardiac surgery is of vital importance, as it addresses a critical issue in clinical practice. This syndrome can significantly complicate surgical procedures, and the use of MB may provide a promising therapeutic alternative. For nurses, understanding the efficacy and safety of this treatment is essential in ensuring safe and evidence-based care. In addition, the findings of this study may contribute to improving perioperative management protocols, thereby optimising patient outcomes and reducing complications.

Goals

The present study aims to: (1) assess the adverse effects associated with the use of MB in cardiac surgery procedures involving cardiopulmonary bypass; (2) analyse mortality and the length of hospital stay in patients treated with MB; and (3) conduct a quantitative analysis, by means of a meta-analysis, of the adverse effects related to the use of MB in the context of cardiac surgery.

MATERIAL AND METHODS

Bibliographic search and sources of information

The study is designed as a systematic review of the scientific literature published on the safety of MB in refractory hypotension after cardiac surgery. The guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in order to meet their goals of transparency, reproducibility, quality and comparability. [17]

The literature search took place in February 2024 and the electronic databases PubMed, Scielo, Dialnet and TripDataBase were consulted. An individualised search strategy was designed for each database (Table 1).

Table 1: Search strategy in electronic databases

DATABASE	STRATEGY	FILTERS	RESULTS
PUBMED	Methylene blue AND (hypotension OR shock OR vasoplegia)	Clinical trials and randomized controlled trial from last 20 years in adults	8
SCIELO	Methylene blue AND (hypotension OR shock OR vasoplegia)	Studies published in the last 20 years. Articles in health journals.	12
DIALNET	Methylene blue AND (hypotension OR shock OR vasoplegia)	Journal article	2
TRIP DATA BASE	Methylene blue AND (hypotension OR shock OR vasoplegia)	Clinical trials from last 20 years	15

Selecting studies

The inclusion criteria were as follows: (1) Randomised Clinical Trials with control group; (2) studies with population older than 18 years; (3) studies with patients admitted to Intensive Care Units (ICU) after cardiac surgery; (4) studies using MB and (5) studies aiming at the prevention or reduction of vasoplegic syndrome.

Exclusion criteria were: (1) experimental animal studies; (2) studies dealing with other types of shock than vasoplegic syndrome; and (3) duplicate studies.

Data extraction

Two reviewers (GP and AR) independently assessed abstracts for potential inclusion. Potential studies were analysed in their full text between the two reviewers for final inclusion and discrepancies were resolved by consensus between the two reviewers.

Study information was collected in a pre-designed table containing the following sections: basic study characteristics, type of surgery, sample characteristics, type of intervention, objectives, main outcomes, study limitations and the time of data collection.

Assessment of bias risk

The Jadad scale, or Oxford quality scoring system, was used to assess the quality of Clinical Trials. It is a scale initially validated for pain, although it has been widely used in other clinical areas. [18] The questionnaire consists of 7 items with a score ranging from 0 (weak quality) and 5 points (good quality). [19]

Statistical analysis

All adverse effects and morbidity and mortality events were extracted from each study and presented in contingency tables. In studies where different time measurements were performed, the highest number of events was selected to obtain the total number of patients who at some time had such an event during the study.

The relative risk (RR) was calculated for each adverse event as follows: probability of negative events in the experimental group/probability of negative events in the control group. The natural logarithm of the RR was calculated before the arithmetic mean and standard deviation (SD) of all adverse events occurring in each study. The transformation of the RR to a logarithmic scale allows 0 to be the absence of differences in event probability between the two groups. In addition, negative values indicate that MB is a protective factor against morbidity and mortality events, while positive values indicate that MB is a risk factor against adverse events. RRs equal to 0 were discarded due to the impossibility of calculating their logarithm. Studies with less than two types of adverse events, after excluding those events where the RR is equal to 0, were excluded from the meta-analysis because they did not contain sufficient information.

A Bayesian meta-analysis was performed with the JASP tool v.0.17.3 (JASP Team 2023), which integrates the metaBMA package of R programming language. The advantage of Bayesian analysis is that it assesses the total effect and heterogeneity by comparing four possible models: (1) random effect model and H_0, (2) random effect model and H_1, (3) fixed effect model and H_0 and (4) fixed effect model and H_1. Bayesian meta-analysis analyses how each model predicts the actual a posteriori observations from prior a priori distributions. [20]

The Bayesian Factor (BF_{10}) is a ratio between the evidence for the alternative hypothesis and the evidence for the null hypothesis. The result has been interpreted as follows:[21] (<1/100) extreme evidence for H_0, (1/100 to <1/30) very strong evidence for H_0, (1/30 to <1/10) strong evidence for H_0, (1/10 to <1/3) moderate evidence for H_0, (1/3 to <1) inconclusive evidence for H_0, (>1 to 3) inconclusive evidence of H_1, (>3 to 10) moderate evidence of H_1, (>10 to 30) strong evidence of H_1, (>30 to 100) very strong evidence of H_1 and (>100) extreme evidence of H_1. BF_{rf} is a ratio between the evidence from the random-effect model and the fixed-effect model. The interpretation is similar to BF_{10}, described above. Values of BF_{rf} greater than 1 indicate evidence in favour of the random effect model, while values less than 1 indicate evidence in favour of the fixed effect model. We used $\mu \sim$ Cauchy (0, 0.707) [22] and $\tau \sim$ Inv-Gamma (1, 0.15)[23, 24] to set up the a priori distributions.

Conflicts of interests

The authors declare that they have no conflicts of interest.

RESULTS

Selecting studies

A total of 29 studies were obtained from the databases, eliminating 8 duplicates. Finally, five articles met the inclusion criteria and were included in the systematic review. The selection and screening process is described in the flow chart in Figure 1.

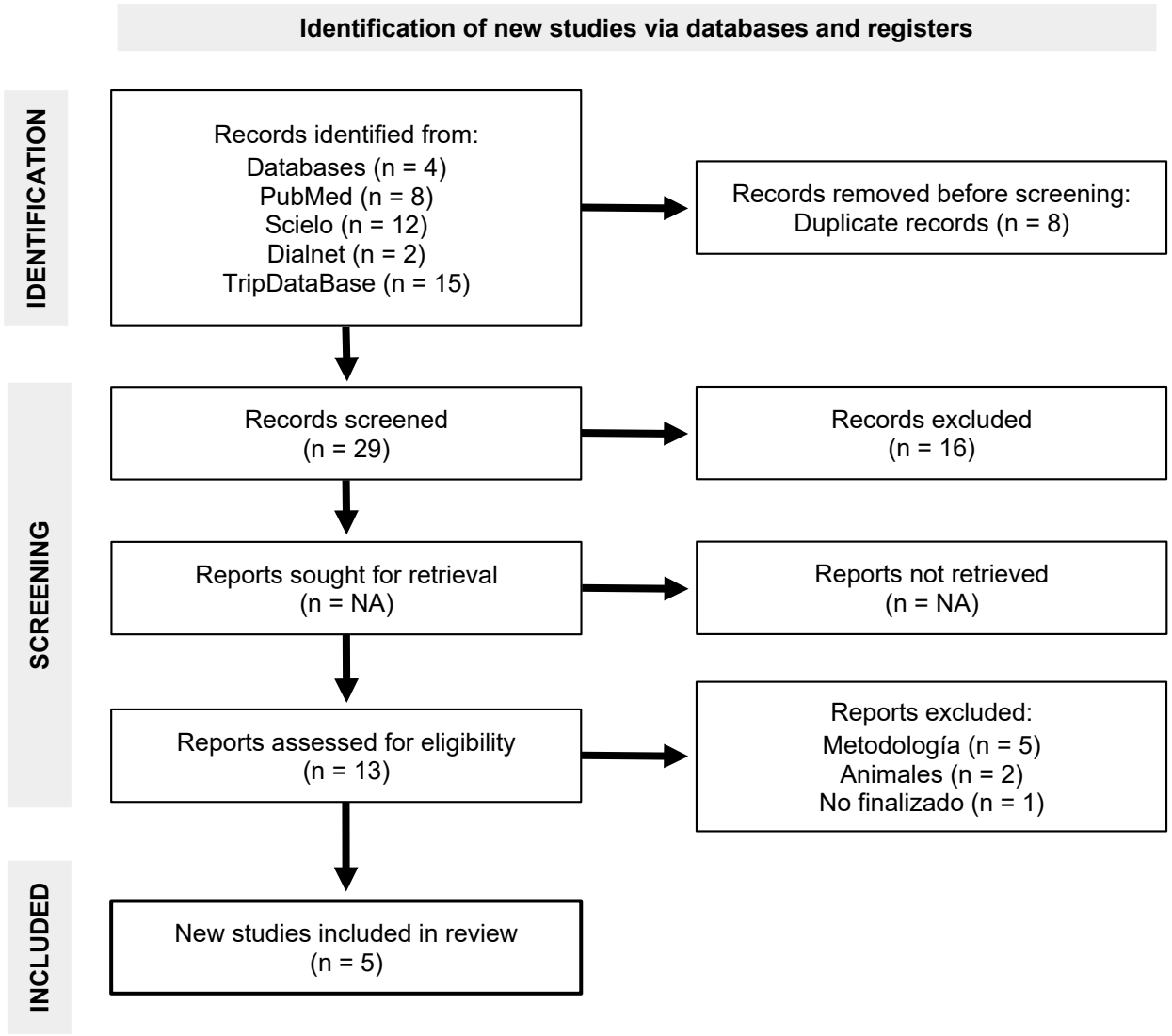

Figure 1: PRISMA item selection diagram [25]

Characteristics of the studies included

The studies included were published between 2004 and 2019. The mean methodological quality score, as measured by the Jadad scale, was 2.4±1.1. The individual Jadad scale scores are shown in Figure 2.

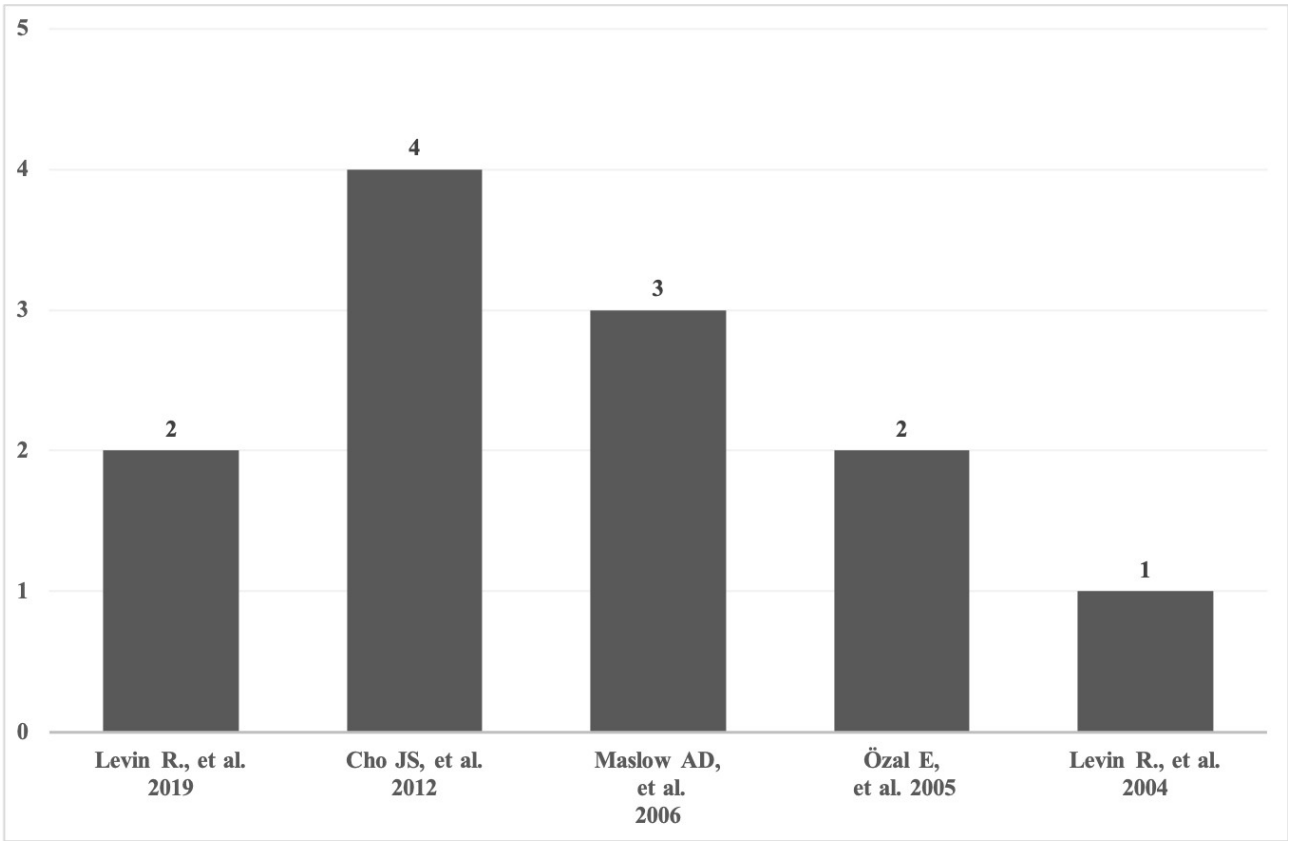

Figure 2: Individual Jadad scale scores

The study by Levin R et al.[14] used a sample of 56 patients undergoing coronary artery bypass surgery with cardiopulmonary bypass (CPB) who met vasoplegia criteria. 28 received methylene blue and 28 received placebo. The study by Ozal E et al.[26] collected a sample of 100 patients on heparin, angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium channel blockers, who were to undergo coronary artery bypass grafting with CPB. Half of them received the MB intervention and half received a placebo. The study by Maslow AD et al.[27] selected 30 patients on ACE inhibitors undergoing cardiac surgery, of whom 15 received MB and 15 received placebo with saline. The study by J.S. Cho et al.[28] included 42 patients with endocarditis undergoing cardiac surgery with CPB, 21 received MB and 19 received saline. Finally, the study by R. Levin et al.[29] included 64 patients undergoing left ventricular assist device (LVAD) implantation with CPB, 33 were given MB and 31 received saline as placebo.

Most studies initiated the intervention before surgery and before the onset of vasoplegic syndrome.[26-29] The study by R. Levin et al.[14] was the only one to initiate the administration of methylene blue after the diagnosis of vasoplegic syndrome.

The dose of MB used varies between studies: four of them used single doses of 1.5 mg/kg,[14] 2 mg/kg [26, 28] and 3 mg/kg;[27] while one of them used an initial dose of 1.5 mg/kg followed by perfusion of 0.5 mg/kg/h.[29]

Morbimortality of methylene blue

The number of patients with postoperative bleeding was significantly lower in the MB-treated group (45.4%) compared to the placebo group (70.9%).[29] One study found no difference between groups in haematocrit percentage or in the use of aprotinin and aminocaproic acid for bleeding control.[27] Another study found no difference in the mean number of units of packed red cells and fresh frozen plasma required between the two groups.[26], although the volume of crystalloid and colloid infused in this same study was significantly lower in the MB-treated group. Another study reported a lower need for units of packed red cells and fresh frozen plasma per patient in the group that received MB [28]

The re-operation rate was lower in the MB-treated group although it did not reach significance. [28, 29] Several studies reported shorter hospital and ICU length of stay in the MB group versus the placebo group;[14, 26] although one of them was not significant.[28] Mortality in the MB group was 16.9% lower than in the placebo group in the study by R. Levin et al.[29], with a significance level of 0.05. Another study found no significant difference in mortality between the two groups. [26]

Studies that administered methylene blue before surgery detected no significant differences between groups in either the incidence of renal failure,[28, 29] stroke[26, 28, 29] and multi-organ failure,[26] or the need for dialysis.[29] There was also no difference in the need for mechanical ventilation greater than 48 hours.[28] Cardiac events, such as arrhythmias and ischaemia, were similar in both groups.[27] On the other hand, the study administering MB after the onset of vasoplegic syndrome[14] showed a significant reduction in renal failure, respiratory failure, multi-organ failure, supraventricular arrhythmias and sepsis in the group of patients with vasoplegic syndrome treated with MB compared to the placebo group. The same study found no difference in the need for dialysis or in the incidence of liver failure, stroke or ventricular arrhythmias.

Other adverse events, such as nausea, vomiting and dizziness, were similar in both groups [27]. Methaemoglobinaemia levels, measured during CPB, were significantly higher in the group receiving MB (0.65 ± 0.12) in comparison to the placebo group (0.52 ± 0.18).

Meta-analysis

Three studies measured two or more adverse events and were ultimately included in the meta-analysis. The studies by R. Levin et al.[29], J.S. Cho et al.[28] and A.D. Maslow et al.[27] had an RR log for morbidity and mortality of -0.34 [-0.41, -0.27], -0.33 [-0.67, 0.01] and -0.07 [-0.20, 0.07], respectively. Figure 3 shows the differences in effect size with the fixed effect model -0.28 [-0.35, -0.22], the random effect model -0.23 [-0.48, 0.02] and a weighted mean model of both -0.23 [-0.47, 0.01].

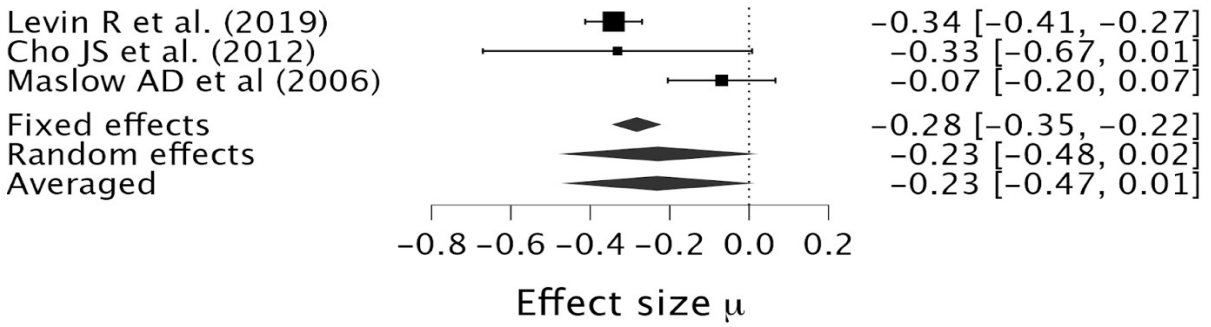

Figure 3: Forest plot of total adverse events.

The value of BF_{rf} is 48.23, indicating strong evidence in favour of using the random effect model. On the other hand, the value of BF_{10} for the random model is 1 and 1.04 for the weighted mean model. Both results indicate inconclusive or anecdotal evidence for the alternative hypothesis and do not therefore allow us to discard the null hypothesis. The rest of the results are summarised in Table 2.

Table 2: Estimates a posteriori by model

				95% Confidence Interval		
		Mean	**SD**	**Higher**	**Lower**	**BF_{10}**
Fixed effect	μ	-0283	0032	-0347	-0220	$7.784\times10^{+15}$
Random effect	μ	-0230	0120	-0481	0023	0999
	τ	0190	0132	0056	0518	24.106 *
Mean effect	μ	-0232	0118	-0474	0015	1041
	τ					48229

NB. μ and τ are the size of the group effect and the standard deviation, respectively. Effect size is measured in RR log.
* Bayesian factor of the random model in H_1 in the fixed model in H_1.

DISCUSSION

The safety of methylene blue in cardiac surgery

MB is a drug used for several conditions such as methaemoglobinaemia and refractory hypotension in septic shock. A meta-analysis highlighted that MB does not increase the risk of adverse events in patients with septic shock. [30] Despite its proven safety in intravenous administration, the use of MB remains controversial due to the paucity of clinical trials and discrepancies in efficacy between articles. [31].

The literature found in this review was sparse and only five RCTs met the criteria for inclusion. In addition, the characteristics of the articles make comparisons between studies difficult. The dose of MB administered is highly variable and there is no consensus on the appropriate dose or schedule of administration. The study by A.D. Maslow et al.[27], which used a dose of 3 mg/kg, had a worse mean score in the quantitative analysis of risk of adverse events compared to the studies by R. Levin et al.[29] and J.S. Cho et al.[28], with doses of 1.5 and 2 mg/kg respectively. It is possible that a higher dose of MB may lead to an increase in adverse effects, based on the trend of the quantitative analysis. However, the low methodological quality and the paucity of RCTs do not allow the assurance of such a correlation.

Haemorrhagic events after cardiac surgery appear to be reduced with the administration of MB. The number of red cell concentrates and fresh frozen plasma was significantly lower in the intervention group, as was the volume of crystalloids infused. Several studies have described the role of MB in reducing reactive species produced during inflammatory and infectious processes, and in regulating the immune system, extending fibroblast life and promoting tissue repair. [32, 33]

Mortality in the group treated with MB was significantly lower, as was ICU stay and hospital stay. Other studies cannot conclude significant results, although the trend is favourable for the MB group. There was no significant difference in the incidence of organ failure in the studies that administered MB prior to surgery, although a significant reduction in organ failure was reported in the study by R. Levin et al.[14]

Methaemoglobin levels were, paradoxically, higher in the MB-treated group in the study by A.D. Maslow et al.[27] These results, non-pathological in either group, remain contrary to the literature published to date and to the physiological mechanism of MB.

Limitations

The limited literature published on the use of MB in cardiac surgery makes it difficult to generalise the results and requires a cautious interpretation thereof. Furthermore, the randomised clinical trials (RCTs) included scored moderate-low on the JADAD scale of methodological quality.

The variability in results can also be attributed to the different methods used in the administration of MB. There is no consensus on the most appropriate dose for the prevention of vasoplegic syndrome and the optimal mode of administration; some studies favour a single bolus, while others prefer an initial bolus followed by continuous infusion.

The meta-analysis was limited by the low incidence of some adverse effects and the lack of information on adverse effects in the studies included. The variability in the dose of MB administered may have influenced the results.

Possible lines of research

Further high-quality clinical trials with a sufficiently large sample size are essential to accurately quantify adverse effects and morbidity and mortality events associated with the use of MB in cardiac surgery. These additional studies should be carefully designed to overcome the methodological limitations observed in previous research and ensure more robust and generalised results.

In addition, future research should focus on establishing a clear relationship between the MB dose and safety. This includes determining the optimal dose that maximises therapeutic benefits while minimising risks. It is crucial for studies to compare different administration regimens, such as the use of a single bolus versus an initial bolus followed by a continuous infusion, to identify the most effective and safe approach. Standardisation of these protocols will contribute significantly to improving clinical practice and providing evidence-based guidelines for the use of MB in cardiac surgery.

Long-term follow-up of patients is also essential to assess the long-term effects of MB, both in terms of clinical benefits and potential complications. Detailed analysis of morbidity and mortality data will identify subgroups of patients who may benefit most from treatment and those who may be at increased risk of adverse effects.

CONCLUSIONS

- Methylene blue (MB) has been shown to be a safe drug in patients undergoing cardiac surgery, contributing to the reduction of associated morbidity and mortality events.
- Patients treated with MB had a shorter hospital and ICU stay, as well as a lower mortality rate compared to the group that did not receive MB.
- The meta-analysis identifies MB as a protective factor against various morbidity and mortality events related to cardiac surgery. However, the results obtained do not allow us to completely rule out the possibility that there are no significant differences between the groups treated and not treated with MB.

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