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The effect of hydroxocobalamin and methylene blue for vasoplegic syndromes: A systematic review

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ABSTRACT

Background: The role of methylene blue (MB) and hydroxocobalamin (B12) in treating patients with vasoplegic syndromes remains uncertain.

Objective: This systematic review aimed to assess the effects of MB and hydroxocobalamin on patients with vasoplegic syndromes following surgery.

Methods: A systematic search was conducted for articles reporting the use of MB and hydroxocobalamin in vasoplegic syndromes. The databases PubMed, ScienceDirect, Cochrane Library, Springer, Scopus, and medRxiv were systematically searched up to 9 June 2024. Clinical outcomes, hemodynamic outcomes, length of stay (LOS), mortality, and adverse events were extracted from each study.

Results: This review included five studies. The findings from these studies suggested that hydroxocobalamin, with or without MB, effectively reduced vasopressor requirements and improved MAP mainly at 1-hour post-administration. The LOS and mortality did not differ between the two groups. The most common reported side effects for MB include serotonin syndrome. Meanwhile, chromaturia affects the hydroxocobalamin group.

Conclusion: Hydroxocobalamin could lower the need for vasopressors and increase MAP better than MB only. Hydroxocobalamin can also cause temporary chromaturia, which resolves itself. Given the side effects, the choice between MB or hydroxocobalamin for treating vasoplegic syndrome should be based on the patient's condition. Further studies are required to confirm its findings.

Keywords: vasoplegic syndrome, health, hydroxocobalamin, methylene blue, surgery, systematic review

INTRODUCTION

Vasoplegic syndrome is an increasingly recognized condition that significantly contributes to morbidity and mortality in patients undergoing cardiac surgery [1]. The incidence of vasoplegic syndrome varies depending on the surgical procedure, ranging from 2.8% in off-pump coronary artery bypass grafting (CABG), to 6.9% in isolated on-pump CABG, 8.8% in general cardiac surgeries, and up to 19% in heart transplant recipients [2]. Vasoplegic syndrome is characterized by severe arterial hypotension, normal or elevated cardiac output, low systemic vascular resistance, and a heightened need for intravenous fluids and vasopressor support [3]. This syndrome has emerged as a critical cause of refractory perioperative hypotension, especially in cardiovascular and organ transplantation surgeries [4]. Refractory vasoplegic syndrome arises from uncontrolled vasodilation and vascular hypo-responsiveness to both fluid resuscitation and endogenous vasoconstrictors, resulting in the failure of the body's normal vasoregulatory mechanisms [5].

Methylene blue (MB) has emerged as a promising treatment for vasoplegic syndrome, a common complication following cardiac surgery characterized by hypotension and low systemic vascular resistance [6, 7]. Studies have shown that early administration of MB can improve survival and reduce major adverse events in patients with vasoplegic syndrome [8]. MB works by inhibiting nitric oxide (NO) synthase and guanylate cyclase, thereby improving refractory hypotension [6]. Recent research has compared MB to hydroxocobalamin, with mixed results. Some studies found no significant differences in vasopressor reduction between the two treatments [9], while others suggested potential advantages of combination therapy [10], or superiority of hydroxocobalamin in certain aspects [11].

Current studies indicates considerable variability in the clinical approach to managing perioperative vasoplegic syndrome, commonly involving intravenous fluid resuscitation

and vasopressor therapy [12, 13]. In cases of vasopressor-resistant vasoplegic syndrome, alternative treatments like MB and hydroxocobalamin are considered as rescue options. However, their impact on improving survival outcomes remains uncertain. Despite advances in therapeutic strategies, mortality rates remain high, ranging from 30% to 50%, primarily due to inadequate cellular oxygen utilization and the development of multi-organ failure, particularly acute kidney injury [14, 15]. This systematic review aims to comprehensively analyze the administration of MB and hydroxocobalamin as potential therapeutic interventions for vasoplegic syndromes.

METHODS

This PROSPERO-registered study (CRD42024521831) followed the preferred reporting items for systematic review and meta-analysis (PRISMA) 2020 guidelines.

Eligibility Criteria

The authors screened the titles and abstracts of all retrieved studies based on the following eligibility criteria:

(1) vasoplegic syndromes patients in surgical patients,

(2) use MB or hydroxocobalamin as treatment,

(3) English language, and

(4) eligible studies should have reported at least one of our outcomes of interest.

Our endpoints included clinical outcomes, hemodynamic, length of stay (LOS), mortality and adverse events. Review articles, irrelevant studies, non-human studies, and duplicates were excluded.

Search Strategy and Selection of Studies

Two authors (DAPM and PO) conducted searches in the PubMed, ScienceDirect, Cochrane, Springer, Scopus, and medRxiv databases using the keywords "((Vasoplegic syndrome) AND ((Methylene blue) OR (Vitamin B12) OR (Hydroxocobalamin))" for article up to 9 June 2024, without language restrictions. Additionally, a manual search was performed to find further eligible articles. More details about the search strategy can be found in the supplementary materials. Titles and abstracts were individually reviewed to identify potentially eligible studies, and any disagreements between the two authors were resolved through discussion with all authors until a consensus was reached.

Data Extraction

Relevant data from each chosen study were extracted individually using a structured and standardized format by two authors (DAPM and DSB). The information extracted were: first author's name, year of publication, study design, country of origin, sample size, patient age, disease severity, dosage and administration of MB or hydroxocobalamin, and outcomes including clinical outcomes such as total dose of vasopressor, hemodynamic outcomes, LOS, mortality, and adverse events).

Quality Assessment

Two authors (DSB and PO) independently evaluated the risk of bias in each included studies using Newcastle-Ottawa scale (NOS) for cohort studies. The NOS consists of eight items across three domains: patient selection, comparability, and outcomes. Studies scoring 7-9 were classified as high quality, those scoring 4-6 as moderate quality, and those scoring 0-3 as low quality. Any differences in scoring were resolved through discussion until a consensus was reached.

Statistical Analysis

Due to significant differences in the comparisons made in each study and the various outcome measures used, we were unable to conduct a meta-analysis of the included studies and instead provided a narrative synthesis of the evidence.

RESULTS

Study Selection

The keywords search yielded 1,280 studies. After duplicate removal and screening the titles and abstracts, 101 articles were fully reviewed. After excluding 97 irrelevant studies, we finally included and extracted data from five studies (**Figure 1**).

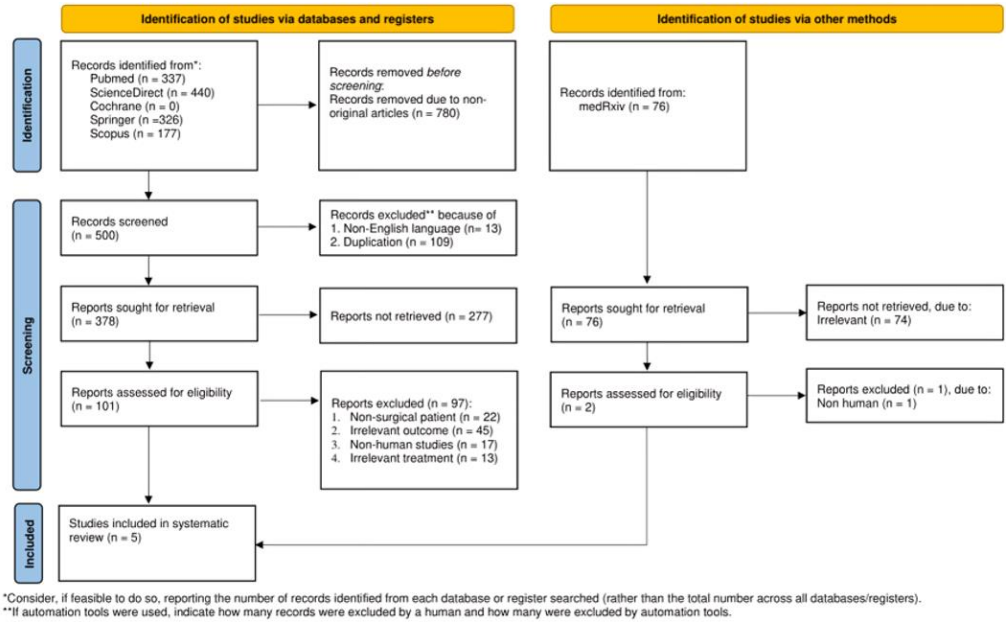

Figure 1. PRISMA flow diagram (Source: Authors' own elaboration)

Table 1. Characteristics of the included studies

R	Study design	Country	Surgery	Sample size		Age (year) M ± SD or median (IQR)		Dosage & administration	Comparison
				Intervention	Control	Intervention	Control		
[9]	Retrospective cohort	UK	Cardiothoracic surgery with CPB	B12: 22	MB only: 66	50 (38, 68)	55 (41, 66)	MB: 1.20 (0.9-1.9) mg/kg	MB: 1.2 (0.9-1.9) mg/kg hydroxocalamin: 5,000 mg
[10]	Retrospective cohort	USA	Cardiac surgery	MB and B12: 6	MB only: 14	67.0 ± 13.0	63.0 ± 13.0	MB: 1.35 (0.9-1.7) mm/kg	MB: 0.5 (0.5-0.7) mg/kg hydroxocalamin: 5,000 mg over 15 minutes
[16]	Retrospective cohort	USA	Cardiothoracic surgery	B12: 19	MB only: 16	56.5 ± 16.4	59.9 ± 8.6	MB: 123.00 ± 75.80 mg bolus, 25-minute infusion, or bolus followed by infusion	5 ± 0 g intravenously as a single 5 g dose over 15 minutes
[17]	Retrospective cohort	USA	Cardiothoracic surgery with CPB	B12: 77	MB only: 43	62.8 ± 12.0	60.7 ± 12.3	MB bolus dose (mg/kg): 1.2 (1-1.5) MB continuous infusion (mg/kg/h): 0.25 (0.25-0.5)	Hydroxocobalamin dose 5 g IV bolus over 15 minutes
[18]	Retrospective cohort	USA	Liver transplant	MB and B12: 68	MB only: 33	58.3 ± 10.9	54.2 ± 12.4	MB: 1.5-2.0 mg/kg	MB: 1.5-2.0 mg/kg, infused over 10 min hydroxocobalamin 5 g/200 ml infused over over 15 minutes

Note. R: Reference & M: Mean

Five cohort studies were assessed using the NOS assessment tool and considered to be of high quality.

Study Characteristics

Table 1 and **Table 2** summarize the characteristics of the included studies. The total number of patients in the intervention group (MB and/or B12) was 192, compared to 172 in the control group. All of these studies are retrospective cohort designs. Most studies are from the United States (USA), and one study is from the United Kingdom (UK). Four studies were cardiothoracic, and one was on liver transplant patients. All of the control groups received only MB. In the intervention group, three studies use MB and B12 as treatments for vasoplegic syndrome. The two other studies only used B12 for treatment. The control group received the MB dosage either as a bolus dose or as a continuous infusion. The intervention group receives a single 5-gram infusion of B12 over a period of 15 minutes.

Table 2. Outcomes of the individual studies

R	Clinical outcome M ± SD		Hemodynamic parameters M ± SD		LOS M ± SD		Mortality N (%)		Any adverse events N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
[9]	Norepinephrine equivalent (μg/kg/min): baseline: 0.35 (0.26-0.41) 30 min after: 0.3 (0.22-0.41) 1-h after: 0.32 (0.22-0.41) 2-h after: 0.28 (0.17-0.36) change in vasopressor requirement at 1-h: -0.023 ± 0.190	Norepinephrine equivalent (μg/kg/min): baseline: 0.3 (0.20-0.42) 30 min after: 0.28 (0.16-0.41) 1-h after: 0.28 (0.15-0.35) 2-h after: 0.24 (0.17-0.36) Change in vasopressor requirement at 1-h: -0.052 ± 0.230	MAP (mmHg): baseline: 75.5 (65.0-89.8) 30 min after: 74 (65.8-78.8) 1-h after: 72.5 (65.8-85.5) 2-h after: 74.5 (70.0-88.0) MAP change at 1-h: -2.79 ± 24.86	MAP (mmHg): baseline: 58 (48.8-70.3) 30 min after: 65 (58.8-73.3) 1-h after: 66 (59-76.3) 2-h after: 68.5 (62-76.3) MAP change at 1-h: 7.73 ± 20.87	ICU LOS (days): 18.8 [10.5-36.9] hospital LOS (days): 51.2 [26.3-85.7]	ICU LOS (days): 11.9 [3.8-22.2] hospital LOS (days): 27.9 [15.0-45.0]	6 (27.3%)	13 (19.7%)	Serotonin syndrome: 0	Serotonin syndrome: 1 (0.83%) 1/120
[10]	Norepinephrine equivalent (μg/kg/min) 1-h after: 0.25 (0.15-0.33) 6-h after: 0.2 (0.06-0.28) 12-h after: 0.22 (0.10-0.27) 24-h after: 0.03 (0-0.2) Change in vasopressor requirement at 1h: -0.073 ± 0.250	Norepinephrine equivalent (μg/kg/min) 1-h after: 0.28 (0.12-0.76) 6-h after: 0.21 (0.13-0.57) 12-h after: 0.16 (0.09-0.23) 24-h after: 0.14 (0.07-0.2) Change in vasopressor requirement at 1h: -0.003 ± 0.640	CI post-dose (L/min/m^2): 2.8 (2.2-4.6) CO post-dose (L/min): 6.8 (4.5-11.8) SVR before (dyn*sec/cm^5): 560 ± 238 SVR post-dose (dyn*sec/cm^5): 597 ± 246	CI post-dose (L/min/m^2): 2.7 (2.4-3.1) CO post-dose (L/min): 5.5 (4.7-6.7) SVR before (dyn*sec/cm^5): 666 ± 187 SVR post-dose (dyn*sec/cm^5): 687 ± 280	N/A	N/A	2 (33.3%)	7 (50.0%)	Serotonin syndrome: 0	Serotonin syndrome: 1 (7.14%)

Table 2 (Continued). Outcomes of the individual studies

R	Clinical outcome M ± SD		Hemodynamic parameters M ± SD		LOS M ± SD		Mortality N (%)		Any adverse events N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
[16]	Norepinephrine equivalent (mg/kg/min): 1-h before: 0.326 ± 0.106 15 min after: 0.273 ± 0.141 30 min after: 0.375 ± 0.546 1-h after: 0.255 ± 0.129 2-h after: 0.258 ± 0.151 4-h after: 0.247 ± 0.180 6-h after: 0.233 ± 0.245 time free for mechanical ventilatition (days): 7.4 ± 6.5 change in vasopressor requirement at 1-h: -0.071 ± 0.170	Norepinephrine equivalent (mg/kg/min) 1-h before: 0.374 ± 0.133 15 min after: 0.447 ± 0.101 30 min after: 0.408 ± 0.124 1-h after: 0.409 ± 0.178 2-h after: 0.374 ± 0.153 4-h after: 0.367 ± 0.199 6-h after: 0.372 ± 0.195 time free for mechanical ventilatition (days): 6.4 ± 6.6 change in vasopressor requirement at 1-h: 0.035 ± 0.220	MAP (mmHg) 15 min before: 59.4 ± 14.8 15 min after: 72.5 ± 12.7 30 min after 70.9 ± 12.2 1-h after: 71.2 ± 13.2 2-h after: 68.3 ± 12.8 4-h after: 70.0 ± 9.6 6-h after: 67.8 ± 10.3 change in SVR after 1-h (dyn*sec/cm^5): 254 ± 247 MAP change at 1-h: 11.80 ± 19.83	MAP (mmHg) 15 min before: 52.2 ± 10.3 15 min after: 62.2 ± 13.2 30 min after: 66.0 ± 13.5 1-h after: 62.8 ± 9.2 2-h after: 72.2 ± 13.4 4-h after: 65.2 ± 9.0 6-h after: 65.1 ± 10.5 change in SVR after 1-h (dyn*sec/cm^5): 192 ± 230 MAP change at 1-h: 10.60 ± 13.81	ICU LoS (days): 4.9 ± 4.9	ICU LoS (days) 3.5 ± 4.5	7 (36.8%)	8 (50.0%)	0	0
[17]	Norepinephrine equivalent (µg/kg/min): baseline: 0.34 (0.28, 0.40) 1-h after: 0.27 (0.21, 0.33) 3-h after: 0.23 (0.16, 0.29) 6-h after: 0.20 (0.13, 0.26) 12-h after: 0.16 (0.09, 0.22) 24-h after: 0.12 (0.06, 0.18)	Norepinephrine equivalent (µg/kg/min): baseline: 0.59 (0.52, 0.66) 1-h after: 0.44 (0.38, 0.51) 3-h after: 0.35 (0.28, 0.41) 6-h after: 0.33 (0.26, 0.39) 12-h after: 0.29 (0.23, 0.36) 24-h after: 0.24 (0.18, 0.31)	MAP (mmHg): baseline: 64.7 (62.7, 66.8) 1-h after: 72.7 (70.7, 74.7) 3-h after: 74.3 (72.3, 76.3) 6-h after: 75.4 (73.3, 77.4) 12-h after: 74.4 (72.4, 76.4) 24-h after: 75.8 (73.8, 77.8) SVR (dyn*sec/cm^5): baseline: 648.4 (537.5, 759.4) 1-h after: 803.2 (680.2, 926.1) 3-h after: 807.1 (678.8, 935.4) 6-h after: 860.7 (754.1, 967.4) 12-h after: 853.7 (749.6, 957.7) 24-h after: 842.1 (735.8, 948.4)	MAP (mmHg): baseline: 56.5 (54.2, 58.9) 1-h after: 67.4 (65.0, 69.8) 3-h after: 71.1 (68.7, 73.5) 6-h after: 70.9 (68.5, 73.3) 12-h after: 71.5 (69.1, 73.9) 24-h after: 71.9 (69.5, 74.3) SVR (dyn*sec/cm^5): baseline: 606.5 (493.0, 720.0) 1-h after: 814.9 (698.0, 931.8) 3-h after: 852.5 (742.7, 962.3) 6-h after: 859.2 (751.3, 967.2) 12-h after: 851.5 (745.4, 957.7) 24-h after: 791.2 (683.1, 899.3)	ICU LOS (days): 16.0 (7.0, 33.0) Hospital LOS (days): 34.0 (22.0, 54.0)	ICU LOS (days): 19.0 (9.0, 36.0) Hospital LOS (days): 30.0 (20.0, 50.0)	9 (11.7%)	9 (20.9%)	N/A	N/A
[18]	Postop days on mechanical ventilation: 2.3 ± 6.9	Postop days on mechanical ventilation: 2.8 ± 5.4	SVR(dyn*sec/cm^5): baseline: 481.6 ± 163.6 15 min after: 574.6 ± 222.1 conclusion of surgery: 562.9 ± 294.3	SVR(dyn*sec/cm^5): baseline: 514.6 ± 220.5 15 min after: 524.3 ± 226.5 conclusion of surgery: 502.5 ± 207.2	ICU postop LOS (days): 4.4 ± 9.3 Hospital LOS (days): 15.7 ± 19.3	ICU postop LOS (days): 5.4 ± 9.7 Hospital LOS (days): 12.1 ± 11.5	0	0	Worsening AKI: 1 (1.4%) chromaturia: 67 (98.5%)	Worsening AKI: 0 chromaturia: 0

Note. R: Reference; M: Mean; Intervention: B12; & Control: MB

Clinical Outcomes

Three studies [9, 16, 17] revealed that using B12 has significantly reduced vasopressor requirements 1-hour post-administration. Furthermore, a significant reduction in vasopressor requirement was shown until 6-hour [16, 17] and 24-hour following B12 administration [17]. However, when B12 was administered with MB, it resulted in no significant reduction in vasopressor requirements compared with MB-only at 1-hour post-administration and thereafter [10].

Hemodynamic Parameters

On hemodynamic parameters, studies conducted comparing B12 and MB reported significant improvement of MAP at 1-hour post-administration (72.5 [inter-quartile range (IQR) 65.8 to 85.5] vs. 66 [IQR 59.0, 76.3]; p = 0.04) and (72.7 [IQR 70.7 to 74.7] vs. 67.4 [IQR 65.0 to 69.8]; p < 0.001), respectively [9, 17]. In addition, it was revealed in vasoplegic syndrome undergoing cardiac surgery at 1-hour post-administration, the MAP was 71.2 (standard deviation [SD] = 13.2) using B12, while 62.8 (SD = 9.2) using MB [16]. Using B12 plus MB resulted in no significant improvement in cardiac output compared with MB-only (p = 0.33) [16]. There were no differences between using B12 and MB to improve SVR at 1-hour post-administration. Furthermore, two studies using B12 plus MB also showed no significant improvement in SVR compared with MB-only.

Length of Stay

Four studies documented the LOS in the intensive care unit (ICU) [9, 16-18]. It was found that patients who received B12 had significantly longer lengths of stay in the ICU compared to those who did not receive B12 (p = 0.025). Nevertheless, the other studies failed to show significant differences in the LOS in the ICU between the group that received MB only and the group that received B12 (p > 0.05) [16-18]. Only one study (p = 0.001) reported a significantly longer hospital LOS in the B12 group [9]. The rest of the studies did not find any significant differences [17, 18].

Mortality

The mortality rates were identical between the group that received MB only and the group that received B12 [9, 10, 16-18]. However, in our study, the B12 group tends to have lower mortality than the MB only group. Only one study reported that the B12 group had higher mortality than the MB only group (27.3% vs. 19.7%) [9].

Adverse Events

Incidence of serotonin syndrome was observed solely in the control group that received MB monotherapy. However, the group that received MB and B12 did not experience any cases of serotonin syndrome [9, 10]. On the third day after the operation, a patient in the intervention group experienced a deterioration of the acute kidney injury and developed acute tubular necrosis. Before the operation, this patient had anuria. The worsening of acute renal injury is attributed to preoperative hypotension and postoperative supratherapeutic tacrolimus levels. All the remaining patients, who had no anuria, showed purple chromaturia. The chromaturia were resolved spontaneously after 2 weeks without associated complications [18]. Yet, it was not documented any adverse events among either of the groups [16].

DISCUSSION

Vasoplegic syndrome is a condition characterized by a high cardiac output state and low systemic vascular resistance [19]. In our systematic review, using hydroxocobalamin for vasoplegic syndrome significantly reduces vasopressor requirement and improves hemodynamics over MB, particularly the MAP. Furthermore, we found intriguing results that using B12 in combination with MB did not show a significant impact compared with MB-only. A retrospective study conducted on 33 patients who received hydroxocobalamin for refractory hypotension during or after cardiopulmonary bypass showed that 73% of patients had a pressor effect–although response was highly heterogeneous among individuals. Also, since such heterogeneity might be due partly to the mode of administration, Seelhammer et al. conducted a study to assess the impact of a continuous infusion of hydroxocobalamin (5 g over 6 hours) after surgery on 12 patients with severe vasoplegic shock. The results demonstrated that this treatment approach allowed for a significant reduction in vasopressors in all patients, with the effects lasting more than 10 hours [20]. The mechanism of B12 could improve MAP by inhibiting NO synthase enzymes and direct NO inactivation [21]. By contrast, although the mechanism of MB could improve MAP involves NO-dependent vasodilation; however, the primary mechanism of MB to improve MAP was through the inhibition of guanylyl cyclase [22]. Hence, we speculate that the difference was caused by the way B12 and MB influence hemodynamics.

Between the B12 and MB groups, there are no differences in lengths of stay [9, 16-18]. LOS in cardiac surgery is influenced by several factors, including age; low LVEF; nonelective surgery; comorbidities such as COPD, renal failure; and inotrope support [23]. B12 groups had a lower ejection fraction, resulting in a LOS [9]. Infection incidence also affects the LOS in cardiac surgery. The development of an infection was an independent risk factor that could increase hospital stay duration by more than nine days, with an odds ratio of approximately 19 [24]. Meanwhile, in liver transplant, LOS was associated with BMI, surgical duration, and bacterial infection [25]. A high-scale study involving more than 70,000 adults concluded that the most significant causes of prolonged hospital stays were ICU admission, previous transplant, hospital admission, and ventilator dependence [26].

Likewise, mortality rates in both groups are not statistically significant [9, 10, 16-18]. A meta-analysis comparing B12 with MB for vasoplegic syndrome revealed similar findings (odds ratio [OR] = 0.92, 95% confidence interval = 0.42-2.0) [11]. However, in our study, the B12 group tended to have lower mortality. These may be related to the adverse effects of MB administration, which cause serotonin syndrome. Serotonin syndrome is a life-threatening condition associated with increased serotonergic activity in the central nerve system [27]. MB is a potent inhibitor of monoamine oxidase (MAO) A and also MAO B in higher concentrations. Combining a significant MAO inhibitor with a selective serotonin reuptake inhibitor increases the risk of serotonin syndrome [1, 28]. Serotonin toxicity, commonly referred to as serotonin syndrome, is characterized by a clinical presentation that includes altered mental status, autonomic stimulation, and neuromuscular excitation. These may appear as rapid onset, hyperreflexia, tremors, and either inducible or spontaneous ocular clonus, which are more frequent in the lower limbs [27]. Another unfavorable effect of MB is that it may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, which is crucial for the drug's metabolism [1, 29]. MB could worsen arterial oxygenation, impair alveolar capillary gas exchange in the lungs, induce mesenteric vasoconstriction, and reduce renal blood flow at doses exceeding 2 mg/kg [29, 30]. Additional significant side effects include interference with co-oximetry, which may result in a false reduction of apparent oxygen saturation owing to the blue dye's inhibition of light transmission [1].

Chromaturia, or dark orange or red urine, is the most common side effect of B12 and usually resolves spontaneously within 2 weeks [18, 31]. One patient in the B12 group experienced worsening AKI [18]. Hydroxocobalamin may have potential renal toxicity because of its association with calcium oxalate nephropathy, which leads to AKI [32].

Hydroxocobalamin may affect laboratory results, unintentionally trigger the blood leak alarm during dialysis, and cause transient hypokalemia in patients with megaloblastic anemia due to vitamin B12 deficiency. Laboratory values affected by B12 include hemoglobin, basophils, creatinine, glucose, alkaline phosphatase, bilirubin, aPTT, PT, and INR within a certain period of time [31].

This systematic review has several limitations. The number of included studies and sample population is relatively small, which limits the generalizability of the findings. The small sample size reduces the statistical power and may introduce bias. Moreover, the included studies exhibited significant heterogeneity in terms of study design, population characteristics, and interventions. This variability made it challenging to perform a meaningful meta-analysis, as pooling the data would not yield reliable or valid results.

CONCLUSION

Hydroxocobalamin is able to reduce vasopressor requirements and improve MAP compared to MB. No significant differences were observed in LOS or mortality between the two groups. MB could induce vasoplegic syndrome in a specific population, which may be life-threatening. While hydroxocobalamin causes chromaturia that resolves spontaneously. Considering the side effects, the selection of MB or B12 for vasoplegic syndrome should be tailored to the patient's specific condition.

Author contributions: WM, DAPM, PO, & DSB: draft manuscript; **WM, DAPM, DSB, & CECZM:** extensive research on topic & critical revisions; **WM, DAPM, DSB, & CDKW:** methodology, literature search, study screening, data acquisition, & risk of bias assessment; **CECZM & CDKW:** project conceptualization; & **CDKW:** formal statistical analysis, result interpretation, & project supervision. All authors have agreed with the results and conclusions.

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Ethical statement: The authors stated that the study does not require any ethical approval, because it is a secondary study, and data are obtained directly from published records.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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