Original article

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Earlier methylene blue administration in vasoplegic shock does not improve hemodynamics: A case series

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Abstract

***Objective*: Vasoplegic shock, sometimes referred to as distributive shock, is a life-threatening clinical syndrome involving systemic vasodilation and is associated with significant morbidity and mortality in intensive care unit (ICU) patients. The most common etiology is sepsis; others include post-cardiac bypass vasoplegia and various toxidromes. Key components of management include fluid resuscitation and vasopressors to restore vascular tone. Methylene blue selectively targets inducible nitric oxide synthase, a key component of early vasodilation in response to inflammation. We investigated whether the timing of administration of methylene blue influences clinical response, as measured by subsequent vasopressor requirements, fluid resuscitation, organ system function, and mortality.**

***Design*: This study was a retrospective case series including 33 cases. Data were collected for each case, including timing of administration, vasopressor and fluid requirements, Sequential Organ Failure Assessment (SOFA) scores, and in-hospital mortality. A Spearman's rank correlation was performed to assess the correlation between the timing of administration of methylene blue and improvement in relevant clinical parameters.**

***Setting*: A large metropolitan Intensive Care Unit (47 beds).**

***Patients and participants*: Included in this study were adult patients who received methylene blue in the participating ICU between 2020 and 2022 for managing vasoplegic shock.**

***Interventions*: Administration of intravenous methylene blue.**

***Measurements and results*: No correlation between the timing of administration and reduction in vasopressor requirements was observed. Administration of methylene blue within 8 hours of the onset of shock refractory to 5 mcg/min of noradrenaline was found to weakly correlate with reduced total SOFA score on Day 1 (R_s=0.39, p=0.04), and patients who received methylene blue within eight hours had a lower mortality (60.0% vs 78.2%).**

***Conclusions*: These findings suggest that a prolonged period of vasoplegic shock before consideration of methylene blue should not discourage its use. A prospective randomized control study will be a valuable direction for future research.**

Key words: Methylene blue, vasoplegic shock, vasodilated shock, distributive shock, septic shock, vasoplegia, vasopressor.

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Introduction

Vasoplegic shock, otherwise referred to as distributive shock, is a life-threatening condition in which acute hypotension due to loss of peripheral vascular tone leads to inadequate perfusion of tissues relative to metabolic demands, resulting in potentially irreversible end-organ dysfunction. Sepsis as an etiology of vasoplegic shock is among the most common indications for Intensive Care Unit (ICU) admission globally. (1) Another important etiology is vasoplegic syndrome following cardiothoracic surgery, a

pathophysiologically complex entity associated with significant morbidity and mortality, the management of which is subject to ongoing research. (2) Timely resuscitation with crystalloid fluids, vasopressors, and targeted management as applicable are crucial aspects of shock management. However, these measures may not sufficiently restore tissue perfusion in the presence of ongoing endothelial dysregulation.

Methylene blue is a thiazine dye used in refractory vasoplegic shock as an adjunct to conventional vasopressors by selectively inhibiting inducible nitric oxide synthase (iNOS), a key mediator of inflammatory vasodilation. (3) Its use has been discussed largely in case reports and uncontrolled case series. Indications reported include septic shock, (4,5) vasoplegia following cardiopulmonary bypass, (6) vasoplegia during extracorporeal membrane oxygenation, (7) overdose of vasodilatory agents such as atenolol, amlodipine, and valsartan, (8) beta-blocker and calcium channel blocker overdose, (9) metformin/gliclazide overdose, (10) psychoactive polypharmacy overdose, (11) and anaphylaxis. (12) The few randomized controlled trials (RCTs) investigating the efficacy of methylene blue in vasoplegic shock have produced encouraging results. A systematic review (13) examining seven small RCTs identified a statistically significant improvement in hemodynamic parameters, decreased vasopressor requirements, and mortality (OR=0.54).

However, the overall mortality in these trials remained high (up to 70%), and the improvement in mortality and hemodynamic parameters were not reproduced uniformly across the literature. Many studies enrolled only patients with "refractory" shock following a failed trial of conventional vasopressor therapy, entailing a late administration of the drug. Some authors (14) suggested that the period of optimal efficacy for methylene blue was within eight hours of shock onset, as this was the timeframe during which nitric oxide synthase activity was maximal. (15) Whether the timing of methylene blue administration has any effect on the patient's hemodynamic response remains to be determined. Our study was an observational case series that investigated the influence of earlier administration on the effect of methylene blue on multiple clinical parameters, including average vasopressor requirements and markers of organ system function.

Methods

Ethical approval

Ethics approval for the use of patient information was granted by the Scientific Advisory Committee of the local Health District Human Research Ethics Committee.

Study population and data collection

This study was a retrospective observational case series conducted at a 47-bed metropolitan ICU (Westmead Intensive Care Service, Westmead Hospital). Data collection involved a retrospective review of electronic medical records for all patients receiving methylene blue from 1 January 2020 to 31 December 2022. The records of all patients who received methylene blue within that period were retrieved, and all patients over eighteen years of age who received methylene blue for vasoplegic shock were included in the study (33 cases of methylene blue administration among 32 patients). Data collected included routine demographic information (patient age, sex, and weight), diagnosis at admission, Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score, timing of onset of shock and methylene blue administration, timing and cumulative doses of other vasopressors and resuscitation fluids, Sequential Organ Failure Assessment (SOFA) scores, and outcomes including survival to discharge from ICU. Cumulative vasopressor doses within a given timeframe were converted into noradrenaline-equivalent units per kg according to accepted formulae. (16) Timing of the onset of shock was defined as the point where the dose of noradrenaline exceeds 5 mcg/min, consistent with the thresholds in historical literature. (17,18) The definitions of "early" (eight hours following the onset of shock) and "late" administration were used to group patients for the descriptive presentation of their demographic data. The timing of methylene blue administration was according to the discretion of the attending intensivist.

Analysis

Spearman's rank correlation coefficients were calculated, and univariate regression was completed to assess the relationship between selected variables, including the noradrenaline-equivalent dose and the timing of methylene blue administration. No adjustment was made for multiple comparisons due to the small sample size.

Results

Thirty-three cases of methylene blue administration in 32 patients were included in the study. Demographic information and illness severity scores are presented in **Table 1**. Twenty-four patients (75%) were male; the average age was 60 (age range 24-88 years). On average, male patients received methylene blue within 10 hours of the onset of shock, and female patients within 18.9 hours. Average APACHE III and Day 0 SOFA scores were high for the entire cohort (99.8 and 15, respectively). The cohort consisted largely of patients with vasodilatory

shock due to sepsis (22 of the 32 patients had some underlying infectious etiology). Nine patients survived to discharge from ICU (mortality 72.7%).

The computed relationships between selected variables and the timing of methylene blue administration are presented in **Table 2**. No significant correlation was found between the timing of methylene blue administration and subsequent vasopressor dose requirements or in the change of SOFA scores over the next 48 hours. A weak positive statistically significant correlation was observed between the time until the administration of methylene blue and Day 1 total SOFA score (R_s=0.39, p=0.04) and fluid resuscitation requirements in the 24 hours following methylene blue administration (R_s=0.33, p=0.03), but not for the cardiovascular component of the Day 1 SOFA. There was a weak correlation between earlier methylene blue dose administration and higher cardiovascular system SOFA scores in the following 24 hours, which did not reach statistical significance.

Univariate regression was performed on the log-transformed noradrenaline equivalent doses. In this model, there was no association between the timing of methylene blue and the (log) noradrenaline equivalent dose (p=0.75).

To determine the confounding effect of cardiac surgery on the data, a sensitivity analysis was performed on the data set with those patients removed; this yielded similar summary statistics (Spearman coefficient =-0.17, 95% CI=-0.53, 0.26, and p=0.37; univariate regression model, p=0.64). Ranked coefficient values for other potential confounders (age, APACHE III score, sex, methylene blue total dose) were calculated and did not demonstrate a strong relationship, suggesting that the timing of methylene blue was not influenced by these factors (**Table 3**).

Discussion

The rationale for the early use of methylene blue in vasoplegic shock is based on the expectation that its pharmacological targets are maximally active within a narrow early "window of opportunity". (16) The elevation of regional microcirculatory nitric oxide levels due to activation of iNOS and soluble guanylate cyclase (sGC) is a key mechanism of vasodilation both in septic shock (19) and in post-cardiac bypass vasoplegic syndrome. (2) Animal data (15) suggest that the activity of these enzymes is maximal within the first eight hours following the onset of a systemic inflammatory response. Methylene blue directly inhibits iNOS and blocks sGC, the rate-limiting enzymatic step in the cascade, via which nitric oxide (NO) has its effect and additional significance in that other inflammatory mediators may also activate it. Methylene blue selectively antagonizes this pathway without affecting constitutive NO production (20) or hemodynamics under physiological conditions. (21) It may also restore vascular tone by acting as a monoamine oxidase inhibitor, increasing the circulating levels of endogenous catecholamines by inhibiting their degradation. (22) Peak concentrations occur at 30 mins from administration, with a half-life of 5-6 hours. (23)

The rationale for adding methylene blue to other vasopressors is to reduce the potential for vasopressor toxicity. By decreasing the activity of iNOS and sGC, methylene blue may act as a "vasopressor sparing agent," reducing the dose of other vasopressor agents by having a synergistic effect on vasoconstriction. (23) Catecholamine vasopressors have substantial adverse effects, particularly at high doses. (24) The risk of relying solely on catecholamines may lead to what has been termed the loss of hemodynamic coherence, a phenomenon most often observed in early sepsis, where microcirculatory inadequacy and associated tissue hypoperfusion may be ongoing despite ostensibly satisfactory resuscitation as determined by cardiac output and mean arterial pressure. (23) These justifications also support the use of other catecholamine-sparing agents, such as vasopressin. (25)

Methylene blue is known to reduce vasopressor requirements. (18) A recent randomized controlled trial on its use in septic shock specifically (26) additionally demonstrated reduced duration of ICU and hospital stay and reduced fluid balance, which, in addition to being a marker of the hemodynamic response, may be regarded as an endpoint, given the demonstrated association between positive fluid balance and mortality in septic shock. (27,28) The hypothesis that the early introduction of methylene blue might maximize this effect is not supported by the observational data presented in this study. The lack of any observed change in the vasopressor-sparing effect of methylene blue can be explained by the hypothesis that some recovery of vascular reactivity may occur over the course of vasodilatory shock. Soluble guanylyl cyclase activity was observed to recover over twenty-four hours in an animal model, (15) and this may account for the ongoing efficacy of methylene blue even with late administration.

Methylene blue has been demonstrated in vitro (22) and in vivo to act as a monoamine oxidase inhibitor (MAOI), with the potential to produce a serotonergic toxidrome at doses exceeding 1 mg/kg. (29,30) Additionally, azure B (a metabolite of methylene blue) is an MAOI with six times more potency than the parent drug. (31) The MAO-A isoform of

the monoamine oxidase enzyme is additionally one of two main enzymes (the other being catechol-O-methyltransferase) responsible for the initial metabolic step in catecholamine degradation. (32) It is therefore possible that the observed persistence of the effect of methylene blue in late vasoplegic shock is related more to its inhibitory effect on catecholamine metabolism than to its effect on inducible nitric oxide synthase. The weak correlation between the timing of methylene blue and the improvement in the total SOFA score is difficult to attribute to the direct effects of methylene blue. Still, it could be related to an improvement in microcirculatory and vascular endothelial function that decreases the severity of acute respiratory distress syndrome, renal failure, disseminated intravascular coagulation, hepatic dysfunction, or septic encephalopathy, all of which would be reflected in SOFA measurements.

This study suffered from several limitations. A retrospective analysis of observational data could not establish causal relationships between the timing of methylene blue administration and the clinical effect on vasopressor requirements or organ system function. The completeness of the medical record was difficult to assess retrospectively, and the possibility of missing data could not be controlled for (e.g., undocumented changes in the infusion rates of vasoactive agents). The population of patients in this case series was heterogeneous, and the limited available documentation of comorbidities made it impossible to account for the presence of confounding factors in the statistical analysis. The small number of patients included in this study decreased the signal-to-noise ratio and increased the likelihood that the play of chance had influenced the findings.

The difficulty of determining the timing of the etiological insult is a limitation of this study and a challenge for any attempt to extrapolate clinical practice from laboratory research in this area. The hemodynamic significance of early iNOS upregulation is established in animal sepsis models. Retrospectively defining the starting point for a progressive pathophysiological process like sepsis occurring in a human who will likely have been unwell for some time before presenting to the hospital is far more difficult. Additionally, due to the status of methylene blue as a last-line agent, it would be unlikely for a patient to deteriorate from systemically well to unwell enough for it to be considered within eight hours. Post cardiac bypass vasoplegic syndrome, however, is a clinical scenario in which the time of inflammatory stimulus is more easily defined; indeed, in this context, there is evidence that administration of methylene blue immediately postoperatively improves outcomes, including survival, compared to the administration at any time in the next three days. (33) Identification of patients with other etiologies of vasoplegia who are likely to experience refractory shock - and for whom it may therefore be reasonable to consider methylene blue administration in response to early signs of deterioration than is currently conventional - would be both a challenge of any randomized controlled trial investigating this and a valuable direction of research in its own right.

Conclusion

No correlation was observed between the timing of methylene blue administration and vasopressor requirements in the subsequent 24-hour period. A weak correlation was found between the early administration of methylene blue and the total SOFA score after 48 hours, but not the cardiovascular component of the SOFA score. Though the late administration of methylene blue was associated with higher mortality (78.2% vs 60%), these observational data did not reveal any beneficial effect of the administration of methylene blue within eight hours of the onset of shock on the resolution of vasoplegia. A prospective randomized study comparing different timings of methylene blue administration is warranted to determine conclusively whether earlier use of methylene blue could influence the course of severe vasodilatory shock.

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