ORIGINAL ARTICLE

Effects of Early Use of Methylene Blue and Vasopressin on Noradrenaline Dose in Septic Shock: A Randomized Controlled Trial

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Abstract

Background: This study aimed to assess the influence of early administration of methylene blue (MB) and vasopressin on the dose of noradrenaline required to manage septic shock.

Materials and methods: This study was a parallel, randomized, controlled trial including 74 adult patients with septic shock admitted to the intensive care unit (ICU). Once the noradrenaline requirement exceeded 0.2 µg/kg/min, patients were randomly allotted to group M and group V. Group M received an intravenous 1 mg/kg bolus of MB over 30 minutes, then an infusion of 0.5 mg/kg over 6 hours. Group V received intravenous vasopressin at a rate of 0.04 units/min for 6 hours. The primary outcome of this research was the dose of noradrenaline required to reach the target mean arterial pressure (MAP) of ≥ 65 mm Hg at 6, 12, and 24 hours. Secondary outcomes included changes in lactate levels, urine output, and sequential organ failure assessment (SOFA) score.

Results: The M group required a higher dose of noradrenaline compared with the V group to maintain MAP above the target level at 12 and 24 hours. There had been no significant variation in lactate levels along with SOFA scores between the two groups at earlier time points. However, at 24 hours, the M group had higher lactate levels and SOFA scores than the V group. The V group also showed improvements in urine output at 24 hours compared with the M group.

Conclusion: Early administration of vasopressin compared with MB was associated with a reduced dose of noradrenaline required for maintaining target MAP in patients presenting with septic shock.

Keywords: Hemodynamic stability, Methylene blue, Noradrenaline, Septic shock, Vasopressin.

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Highlights

- The use of methylene blue as a potential adjunctive therapy for septic shock has been suggested.
- In this trial, 74 adult patients presented with septic shock in the ICU were given an intravenous infusion of either methylene blue or vasopressin after their noradrenaline dose exceeded 0.2 µg/kg/min.
- Early vasopressin infusion lowered noradrenaline dose to maintain target MAP in patients presenting with septic shock in contrast to methylene blue.

Introduction

Sepsis is a multifaceted condition characterized by an imbalanced and dysfunctional immune response to infection, resulting in impaired organ function and significant morbidity and mortality.[1] It must be identified and managed promptly to improve patient outcomes. The management of septic shock requires early antibiotics administration, fluid resuscitation, along with vasopressor therapy to maintain adequate blood pressure and organ perfusion.[2] However, the response to fluid resuscitation can be variable, and many patients require vasopressors to achieve hemodynamic stability.[3] Although norepinephrine has been commonly used as first-line vasopressor in septic shock, high doses of the drug may have negative side effects.[4] Therefore, reducing the duration of the norepinephrine requirement could potentially improve patient outcomes.

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There is growing interest in exploring alternative therapies to optimize hemodynamic management and reduce the reliance on high-dose norepinephrine.[5] The Surviving Sepsis Campaign guidelines advocate using vasopressin as a secondary vasopressor, which can be administered with norepinephrine.[6] Methylene blue (MB) has emerged as a potential adjunctive treatment for

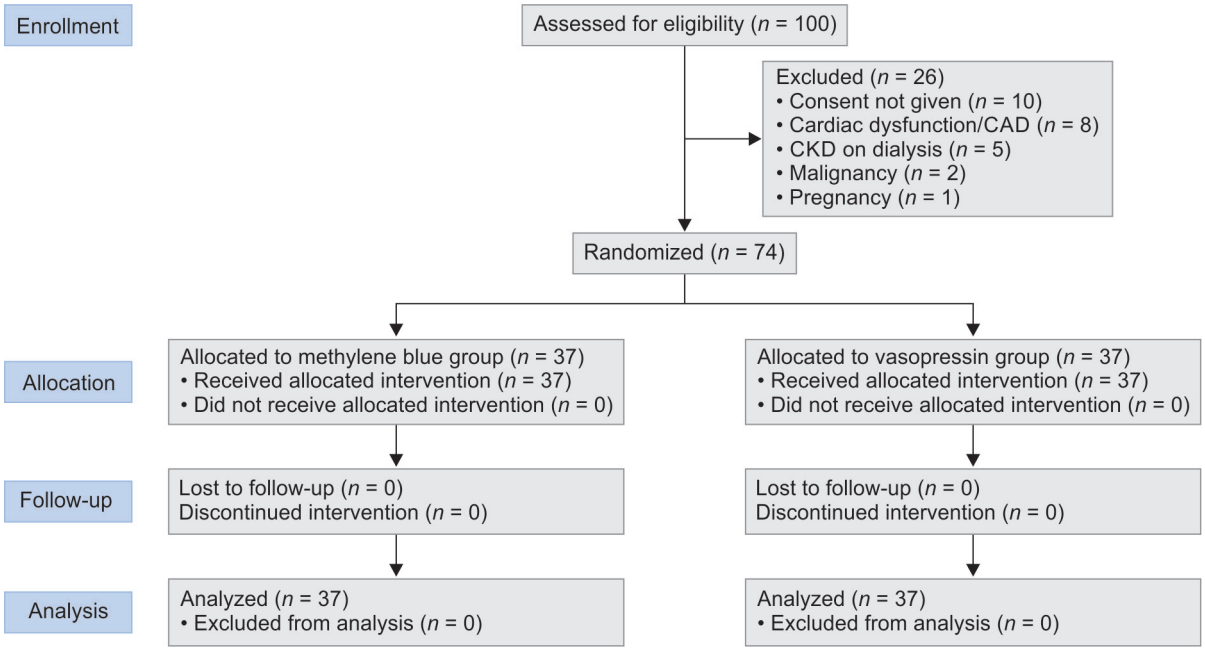

Fig. 1: Consort flow diagram

septic shock.[7,8] It acts as an inhibitor of nitric oxide (NO) synthesis and signaling, targeting vasodilation and endothelial dysfunction seen in septic shock.[9]

The purpose of this investigation was to evaluate the influence of early administration of MB and vasopressin on the dose of noradrenaline required to manage septic shock.

Materials and Methods

This prospective parallel-group randomized experiment was executed in the ICU at a tertiary care center from July 2021 to December 2022. The study protocol (AIIMS/IEC/2021/3673) was accepted by the institutional ethical committee according to the 1964 Declaration of Helsinki's ethical guidelines. Subsequently, the trial was recorded in the Clinical Trials Registry in India (Ref. No. CTRI/2021/12/038542).

The eligibility for inclusion in this trial was evaluated within 24 hours of the patient's stay in ICU if they were 18 years of age or older, satisfied the Sepsis-3 criteria for septic shock, and required noradrenaline to maintain a mean arterial pressure (MAP) of ≥65 mm Hg after appropriate fluid resuscitation.

Patients were excluded from the investigation if their relatives refused to provide consent, had underlying cardiac dysfunction (cardiac index < 2.2 L/min/m^2), or unstable coronary artery syndrome, stroke, chronic renal failure requiring dialysis, malignancy or irreversible illness with a high mortality risk, acute mesenteric ischemia, pregnancy, known hypersensitivity to norepinephrine or MB, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Following informed consent, patients were randomly allotted to group M and group V using an online randomization method (http://www.randomizer.org). The allocation concealment was attained through sealed opaque envelopes, opened immediately before the patient's enrollment in the study. Once their noradrenaline requirement exceeded 0.2 µg/kg/min, group M received intravenous (IV) MB 1 mg/kg bolus over 30 minutes, then by a 0.5 mg/kg infusion over 6 hours. Group V received an IV vasopressin infusion of 0.04 units/min for 6 hours.

The primary outcome of this trial was the dose of noradrenaline required to achieve target MAP (≥ 65mmHg) at 6, 12, and 24 hours after initiation of the study drug infusion. The secondary outcomes were changes in lactate levels, urine output, and sequential organ failure assessment (SOFA) scores simultaneously. All these data were collected by an independent observer who was not part of this study.

ElAdawy and Omran reported a dose of norepinephrine in the MB group (0.1 ± 0.1 µg/kg/min) as compared with the vasopressin group (0.26 ± 0.15 µg/kg/min) in patients with sepsis-induced vasoplegia.[10] To detect a 40% decrease in the dose of norepinephrine, we estimated a sample size of 37 subjects in each group at alpha of 0.05, power of 80, and 10% contingency.

Statistical Analysis

The patient data were examined utilizing IBM Statistical Package for the Social Sciences (SPSS) version 25. The Fisher's exact test or Chi-squared test was utilized to assess categorical data between groups. An independent sample *t*-test was utilized to compare the means of quantitative parameters with normal distributions among study groups. Mann–Whitney *U* test had been applied to quantitative parameters with non-normal distributions. *p*-values below 0.05 had been regarded as statistically significant.

Results

Primarily, 100 individuals were assessed for eligibility in the present investigation; among them, 26 were excluded for various reasons. Finally, 74 patients were included in the trial (37 in each group (Fig. 1). There was no difference in the baseline features of subjects in each group (Table 1).

There had been no significant variation between the two groups regarding baseline hemodynamics and dose of noradrenaline to maintain target MAP initially at 0 and 6 hours. However, a significant

Table 1: Characteristics of patients in the two group

	Group		
Characteristics	*M (N = 37)*	*V (N = 37)*	*p-value*
Age (years)	50.78 ± 14.49	55.11 ± 14.06	0.196
Sex (F/M)	20/17	15/22	0.244
Weight (kg)	48.57 ± 11.38	51.38 ± 10.91	0.398
Comorbidities			
CRD	13 (35.14%)	12 (32.43%)	0.806
DM	16 (43.24%)	23 (62.16%)	0.103
HTN	23 (62.16%)	21 (56.76%)	0.636
Source of sepsis			
Lung			
CAP	6 (16.22%)	8 (21.62%)	
VAP	5 (13.51%)	6 (16.22%)	
ARDS	3 (8.11%)	2 (5.40%)	
Lung abscess	0 (0.00%)	1 (2.70%)	
Abdomen			
Peritonitis	7 (18.91%)	7 (18.91%)	
Urinary tract infection	5 (13.51%)	6 (16.22%)	
Pancreatitis	2 (5.40%)	0 (0.00%)	
Liver abscess	1 (2.70%)	1 (2.70%)	
Blood			
Candidemia	1 (2.70%)	2 (5.41%)	
Brain/CNS			
Meningitis	2 (5.40%)	3 (8.10%)	
Pots spine	1 (2.70%)	0 (0.00%)	
Encephalitis	1 (2.70%)	0 (0.00%)	
Skin and soft tissue			
Soft tissue	1 (2.70%)	0 (0.00%)	
Gluteal abscess	1 (2.70%)	0 (0.00%)	
Necrotizing fasciitis	1 (2.70%)	0 (0.00%)	
Pectoral abscess	0 (0.00%)	1 (2.70%)	

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; CRD, chronic respiratory disease; DM, diabetes mellitus; F, female; Group M, methylene blue group; Group V, vasopressin group, HTN, hypertension; M, male; VAP, ventilator-associated pneumonia; SD, standard deviation. Values are given in either mean ± SD or number (percentage)

variation was recorded in the dose of noradrenaline at 12 hours (1.54 ± 0.59 µg/kg/min in M group and 1.27 ± 0.56 µg/kg/min in V group ($p = 0.042$) and 24 hours (1.55 ± 0.8 µg/kg/min in the M group and 1.06 ± 0.79 µg/kg/min in the V group ($p = 0.009$) (Table 2).

There had been no significant variation in serum lactate level between both groups at 0 hour, 6 hours, and 12 hours. A significant difference was observed in serum lactate level among both groups at 24 hours (6.50 ± 3.28 mmol/L in M group and 3.80 ± 2.99 mmol/L in V group, $p = 0.048$) (Table 3).

There had been no significant variation in SOFA score among both groups at 0 hour, 6, and 12 hours. There was a significant difference observed in SOFA score between both groups at 24 hours [14.00 (10.0–16.0) in the M group and 10.00 (6.0–14.0) in the V group, $p = 0.022$] (Table 4). Similarly, there had been no significant variance in urine output among both groups at 0 hour, 6, and 12 hours. However, a significant variation was recorded in urine output among both groups at 24 hours (28.40 ± 6.11 mL/hour in the M group and 33.40 ± 5.99 mL/hour in the V group, $p = 0.017$) (Table 5). In M group, 36 subjects out of 37 had green urine.

Table 2: Comparison of the dose of noradrenaline required to achieve the target mean arterial pressure (MAP) ≥ 65 mm Hg at different time intervals

	Dose of noradrenaline (mcg/kg/min) (Mean ± SD)		
Time	*Group M (N = 37)*	*Group V (N = 37)*	*p-value*
0 hour	1.47 ± 0.49	1.35 ± 0.70	0.391
6 hours	1.50 ± 0.53	1.41 ± 0.51	0.431
12 hours	1.54 ± 0.59	1.27 ± 0.56	0.042*
24 hours	1.55 ± 0.8	1.06 ± 0.79	0.009*

Group M, methylene blue group; Group V, vasopressin group; SD, standard deviation; *Statistically significant *p*-value

Table 3: Comparison of serum lactate levels at different time intervals

	Serum lactate level (mmol/L) (Mean ± SD)		
Time	*Group M (N = 37)*	*Group V (N = 37)*	*p-value*
0 hour	5.20 ± 2.21	5.10 ± 2.01	0.439
6 hours	5.63 ± 2.38	5.26 ± 1.94	0.459
12 hours	5.50 ± 3.11	4.40 ± 2.87	0.246
24 hours	6.50 ± 3.28	3.80 ± 2.99	0.048*

Group M, methylene blue group; Group V, vasopressin group; SD, standard deviation; *Statistically significant *p*-value

Table 4: Comparison of SOFA Score between the groups at different time intervals

	SOFA score Median (IQR)		
Time	*Group M (N = 37)*	*Group V (N = 37)*	*p-value*
0 hour	12.00 (12.0–14.0)	14.00 (10.0–15.0)	0.400
6 hours	12.00 (12.0–14.0)	14.00 (10.0–15.0)	0.274
12 hours	13.00 (10.0–15.0)	12.00 (8.0–14.0)	0.065
24 hours	14.00 (10.0–16.0)	10.00 (6.0–14.0)	0.022*

Group M, methylene blue group; Group V, vasopressin group; SD, standard deviation; *Statistically significant *p*-value

Discussion

Methylene blue infusion inhibits guanylate cyclase by decreasing nitric oxide generation and enhancing vasoconstriction. Therefore, we planned this study to explore the early role of MB on noradrenaline dose in patients presenting with septic shock. However, in the present investigation, vasopressin was more effective than MB in maintaining hemodynamic stability, improving lactate clearance, and maintaining urine output in the initial stage of septic shock.

Table 5: Comparison of urine output (mL/hour) between the groups at different time intervals

	Urine output (mL/hour) Mean ± SD		
Time	*Group M (N = 37)*	*Group V (N = 37)*	*p-value*
0 hour	30.00 ± 4.08	31.41 ± 3.96	0.199
6 hours	31.21 ± 5.06	32.77 ± 5.43	0.205
12 hours	30.15 ± 5.69	32.01 ± 5.01	0.140
24 hours	28.40 ± 6.11	33.40 ± 5.99	0.017*

Group M, methylene blue group; Group V, vasopressin group; SD, standard deviation; *Statistically significant *p*-value

We found that both the MB and vasopressin groups could maintain MAP above the target level of 65 mm Hg at all time points. However, the MB group required a higher dose of noradrenaline to achieve the target MAP at 12 and 24 hours than the vasopressin group. Hence, vasopressin in our study was effective in maintaining the MAP with a minimum dose of norepinephrine. Luis-Silva et al.,[11] in their study on 42 patients with septic shock, discovered that administering a loading dose of IV MB (3 mg/kg) then by a maintenance dose (0.5 mg/kg/h) for 48 hours, when commenced concurrently with vasopressin as a secondary vasopressor, resulted in an immediate decrease in noradrenaline dosage and a more rapid reduction in vasopressin dosage relative to the control group. Ibarra-Estrada et al.[12] investigated the effects of MB on 91 patients presenting with septic shock. In their study, for the overall three doses, the MB group was given an intravenous infusion of 100 mg in 500 mL of 0.9% sodium chloride solution once daily for 6 hours. They observed that MB group had a shorter duration of vasopressor withdrawal (69 h [IQR 59-83] *vs* 94 h [IQR 74-141]; $p < 0.001$) and 1 additional day of the vasopressor-free day on day 28 compared with the control group. The disparity between these results and our study is that we administered MB and vasopressin separately only when the noradrenaline dose exceeded 0.2 µg/kg/min. This discrepancy may also be attributable to the fact that in our trial, MB was administered only for 6 hours.

In their study, Ibarra-Estrada et al.[12] found similar lactate levels within the first 3 days in the MB and control groups. Similarly, in our study, the M group had similar lactate levels at baseline, 6 and 12 hours. However, there were significantly higher lactate levels in the M group at 24 hours in contrast to the V group. In our study, analysis of the SOFA scores exhibited no significant variation among the two groups at 0, 6, and 12 hours. However, at 24 hours, the M group had higher SOFA scores than the V group. Typically, the SOFA score is calculated upon admission to the ICU and at 24-hour intervals. However, in this current investigation, we tried to explore the effects of early utilization of MB and vasopressin on noradrenaline dose in septic shock (till 24 hours and at intervals of 6, 12, and 24 hours). Therefore, we measured the SOFA score initially and at 6, 12, and 24 hours for this study.[13] Sequential organ failure assessment score consists of six parameters; out of these four parameters (partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspiratory oxygen concentration (FiO_2) (mmHg), Glasgow Coma Scale (after cessation of sedative medication), MAP or vasopressors required, and urine output) were noted at 6, 12, and 24 hours. Additionally, serum bilirubin, creatinine, and platelet count values were repeated at 6,12, and 24 hours for the purpose of this study. These values were available at the time of initiation of the investigation. We discovered that V group had a significantly greater urine output at 24 hours than the M group. These findings are consistent with previous research highlighting the beneficial effects of vasopressin on urine output in patients suffering from septic shock.[14,15]

Methylene blue has been used as a catecholamine-sparing drug to manage patients with refractory septic shock.[16] Rajbanshi et al., in their study on patients suffering from refractory septic shock, noticed that IV methylene blue, as an adjunctive therapy, increased MAP and reduced the need for vasopressor drugs.[17] A few systematic reviews or else meta-analyses of MB investigation in shock have been published, indicating favorable hemodynamics; nevertheless, they relied on very limited data.[18,19] However, the dosage of MB, the time and duration of administration, and the concurrent use of other vasopressors have all been highly inconsistent in the included investigation. In the current investigation, we noted that the earlier administration of vasopressin, compared with MB, decreased the requirement for noradrenaline to sustain target MAP in patients presenting with septic shock.

Limitations

This investigation had certain limitations. It was conducted in a single tertiary care facility with a limited sample size. The blue color of the investigational drug precluded the blinding in this trial. The long-term effects, including mortality, hospitalization, and ICU stays were not evaluated. The study medications were administered for a single day for 6 hours. The use of MB or vasopressin as one of the salvage management strategies in a sepsis-induced refractory vasoplegic situation has shown promising results, though the practice of its routine utilization has been yet to be recognized as well as requires further research and larger-scale studies, and whether it should be used as an alternative to, or in conjunction with, other vasopressors remains an open question.

Conclusion

Earlier vasopressin administration was associated with a lower dosage of noradrenaline to maintain target MAP compared with MB in patients with septic shock.

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