JCRMHS

Journal of Clinical Case Reports, Medical Images and Health Sciences

Volume 8 Issue 4, 2024

Article Information

Received date: 04/12/2024

Published date: 17/12/2024

*Corresponding author

*Paul Henning, MD, MS, Department of Emergency Medicine, University of South Alabama, Mobile, Alabama.

*Key Words:

Methylene Blue, Return of Spontaneous Circulation, ROSC, Cardiopulmonary Resuscitation, CPR, Neuroprotection, Vasoplegia

*List of Abbreviation

MB: Methylene Blue

ROSC: Return of Spontaneous Circulation

IHCA: In-Hospital Cardiac Arrest

OHCA: Out of Hospital Cardiac Arrest

VIS: Vasoactive Inotropic Score

CPR: Cardiopulmonary Resuscitation

MICC: Minimally Interrupted Chest Compressions

VF: Ventricular Fibrillation

MAP: Mean Arterial Pressure

LAD:Left Anterior Descending

Case Report

The effects of Methylene Blue administered during and after cardiac arrest: A case series of three patients who achieved ROSC

Paul Henning[1]*, MD, MS; Larry B. Mellick[2], MD, MS

[1]*Department of Emergency Medicine, University of South Alabama, Mobile, Alabama.*

[2]*Department of Emergency Medicine, Augusta University, Augusta, Georgia.*

Abstract

Background: While there is significant evidence that methylene blue (MB) administered intravenously has neuroprotective properties and provides benefit in treating refractory shock, there is no human evidence of benefit in rate of return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation or increased survival. In a limited number of animal studies evidence of methylene blue's benefit in ROSC and survival has been reported.

Case Presentations: We present a case series of 3 emergency department patients treated with methylene blue during cardiopulmonary resuscitation who achieved ROSC and were later discharged from the hospital with minimal to moderate neurologic sequelae. This reporting of ROSC after the off-label administration of methylene blue for these 3 patients describes an association which serves as an introduction to our review and discussion of animal studies showing ROSC benefit following methylene blue administration as well as to highlight methylene blue's triad of potential benefits to patients undergoing cardiopulmonary resuscitation.

Conclusions: Besides proven benefit in the management of methemoglobinemia there is growing evidence of methylene blue's neuroprotective and vasoplegic properties. When used properly, methylene blue has a good safety profile. Animal studies report mixed results but provide limited evidence of an improved rate of return of spontaneous circulation and prolonged survival. Our case series undergirded by a review of animal resuscitation studies and methylene blue's known neuroprotective and vasoplegic benefits may be sufficient and foundational evidence for multicenter clinical trials of methylene blue in advanced cardiac life support.

Background

There have been no significant advancements in therapeutic drugs for cardiopulmonary resuscitation in recent decades. Despite their limited impact on outcomes and neurological function, the only drugs currently recommended for cardiac arrest are lidocaine, amiodarone, and epinephrine.1–5 In advanced cardiac life support (ACLS) the ideal drug would increase the rate of return of spontaneous circulation, prolong survival, provide neuroprotection, and offer blood pressure support. While currently approved ACLS drugs provide one or more of these benefits, none of them provide neuroprotection. In our case series the three adult males with ventricular fibrillation (VF) cardiac arrest were administered methylene blue and had ensuing ROSC, apparent blood pressure benefit, prolonged survival, as well as an overall good neurologic outcome. The goal of this case series and focused literature review is to provide foundational evidence for multicenter research of methylene blue's potential benefit for ROSC in cardiopulmonary resuscitation.

Currently methylene blue has accepted medical applications for refractory shock or vasoplegia,6–9 hypotension post-cardiac bypass surgery,10,11

methemoglobinemia,12 and as a surgical dye.13 Despite growing evidence of methylene blue's neuroprotective properties and benefit in treating vasopressor resistant hypotension, cardiopulmonary resuscitation research is limited to a small number of animal studies.

Case Series

Case #1: Patient 1 is a 52-year-old male who presented to the emergency department with left-sided chest pain. He was found to be hemodynamically unstable and diagnosed with an ST elevation myocardial infarction (STEMI) in the anteroseptal leads. Within minutes of arrival, he deteriorated into ventricular fibrillation (VF). Minimally interrupted chest compressions (MICC) were performed using a Lucas device for 2 minutes, followed by a pulse check lasting less than 10 seconds. The patient received an initial bolus of 1 mg of 1:10,000 epinephrine and 300 mg (3 mg/kg) of methylene blue (MB) within 5 minutes of starting chest compressions. Defibrillation was performed with a biphasic defibrillator at 200 joules. High-flow oxygen was administered via a non-rebreather face mask. A second defibrillation of 200 joules was administered for sustained ventricular fibrillation (VF), followed by a second dose of epinephrine (1 mg) and 100 mg (1 mg/kg) of lidocaine. After the second shock, return of spontaneous circulation (ROSC) was achieved 9 minutes after the VF arrest. The patient was intubated, and due to a mean arterial pressure (MAP) of 31 mm Hg, a 500 mL bolus of lactated Ringer's was administered. Norepinephrine (1.0 mcg/kg/minute), dobutamine (1.0 mcg/kg/minute), and a methylene blue drip (0.25 mg/kg/hour) were initiated for hypotension. Serum lactate levels were monitored and decreased within six hours. Cardiac catheterization revealed an LAD lesion, which was stented. The patient was extubated after eighteen hours and discharged on day four. At discharge his Cerebral Performance Category (CPC) score14,15 was one. Figure 1 demonstrates a resuscitation timeline and sequence of events. Table 1 presents the patient's vasoactive inotropic score (VIS) over time.

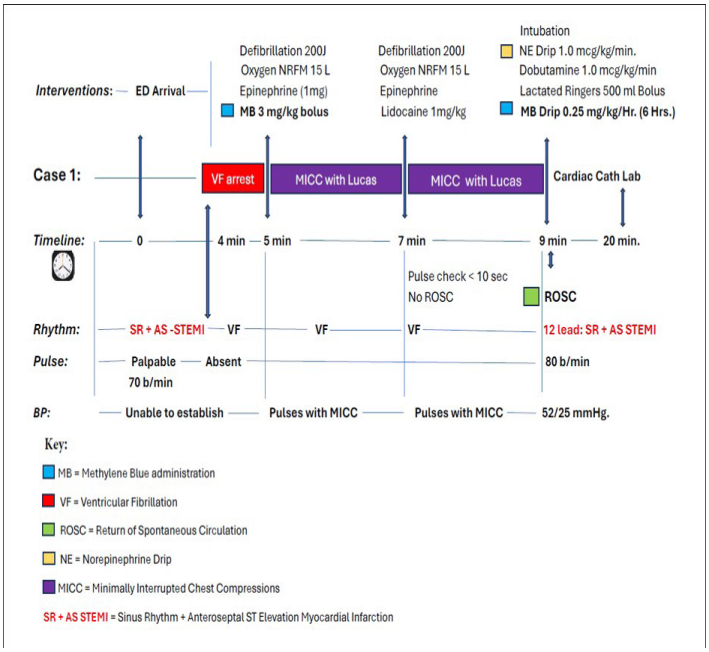


Figure 1: *Sequence of Events During Cardiac Arrest (Case #1)*

Case #2: Patient 2, a 60-year-old male, presented to the emergency department with palpitations. Within minutes (< 5 minutes), his rhythm deteriorated to pulseless ventricular fibrillation. MICC was initiated, followed by an initial shock of 200 J, but there was no return of spontaneous circulation. The patient received an intravenous bolus of 1 mg epinephrine (1:10,000), 300 mg of amiodarone, and 3 mg/kg of methylene blue. After the second 200-joule defibrillation, the patient converted to a pulseless idioventricular rhythm. Epinephrine was administered every 5 minutes during resuscitative efforts. At the 13-minute mark, an additional bolus of 2 mg/kg of methylene blue was given and was followed by the return of spontaneous circulation at the 15-minute mark. With a MAP of 34 mm Hg post-resuscitation, a 500 mL bolus of lactated Ringer's was administered. Norepinephrine (1.0 mcg/kg/minute) and methylene blue (0.25 mg/kg/hour) drips were started. The patient was intubated and a dobutamine infusion (2.0 mcg/kg/minute) was added. Both norepinephrine and methylene blue drips were continued, and serum lactate levels showed ongoing improvement.

The patient was extubated within thirty hours and had a hospital stay of eight days. During his stay, an Implantable Cardioverter-Defibrillator (ICD) was placed. Prognostically, the patient developed a foot drop but was otherwise neurologically intact. His Cerebral Performance

Table 1: *Vasoactive Inotropic Score. (Case #1).*

Post ROSC	30 minutes	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours
VIS Score	100	100	80.5	70.5	50.5	20.5	10.5	10
Norepinephrine Dose [mcg/kg/min]	1	1	0.8	0.7	0.5	0.2	0.1	0.1
Dobutamine Dose [mcg/kg/min]	1	0.5	0.5	0.5	0.5	0.5	d/c	d/c
Methylene Blue [mcg/kg/min]	0.25	0.25	0.25	0.25	0.25	0.25	d/c	d/c
MAP Range [mm Hg]	32	68	65	66	72	75	68	75

Legend: *VIS quantifies the degree of hemodynamic support. A higher score is a predictor of poor outcomes. The vasoactive inotropic score includes norepinephrine + dobutamine in the calculation. Based on Belletti et al, a correction factor of 20 could apply to the dose of MB in their 2020 updated VIS version.17 Methylene Blue infusion was constant at 0.25/mcg/kg/minute and continued for 6 hours.*

DOI: 10.55920/JCRMHS.2024.08.001361

Category (CPC) score14,15 at discharge was two. Figure 2 demonstrates a resuscitation timeline and sequence of events. Table 2 presents the patient's vasoactive inotropic score (VIS) over time.

Case #3: Patient 3, an obese 42-year-old male, had a witnessed syncopal event followed by unresponsiveness at a local shopping mall. Bystander CPR was initiated within three minutes. An Automatic External Defibrillator (AED) was located, attached to the patient, and used for defibrillation. The patient was pulseless and apneic prompting bystanders to continue chest compressions without ventilations. A 911 call was made, and a Basic Life Support (BLS) EMS unit from a nearby regional trauma center arrived at the scene within a few minutes. The patient was defibrillated a second time without ROSC. The EMS crew noted the patient was in fine ventricular fibrillation (VF). An oropharyngeal airway was inserted, and the patient was ventilated with a BVM. He was placed on a long spine board, and chest compressions continued. During transport, the patient was defibrillated for a third time without successful conversion. On arrival at the trauma center, ACLS resuscitative measures were continued. Total downtime with BLS transport was estimated to be fifteen minutes. A primary and secondary survey were conducted. There were no signs of any obvious external injuries. The patient was intubated and peripheral intravenous access including intraosseous access was established. A mid-line thoracic surgical scar consistent with a previous coronary artery bypass graft (CABG) was noted. The ECG demonstrated fine VF. The patient was defibrillated at 200 joules and received 300 mg of amiodarone, 1 mg of epinephrine (1:10,000), and 2 mg/kg of methylene blue intravenously. Four cycles of MICC were initiated with interruptions of less than ten seconds. At the 21-minute mark, an additional 150 mg of amiodarone, 1 mg of epinephrine, and 2 mg/kg bolus of methylene blue was administered. The patient underwent defibrillation four more times, with one defibrillation occurring after each 2-minute MICC cycle. Return of spontaneous circulation (ROSC) was attained 25 minutes post-arrest. The MB infusion continued at 0.25 mg/kg/hour. Due to a low MAP of 30 mm Hg, a norepinephrine infusion at 0.5 mcg/kg/minute and milrinone bolus (50 mcg/kg) and drip (0.75mcg/kg/min) were started. A 12-lead ECG demonstrated Q waves in the anterior, septal, and lateral

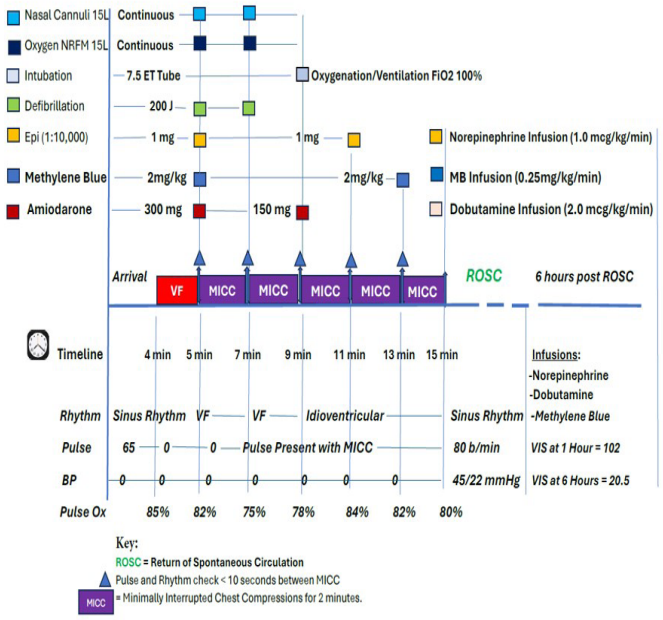


Figure 2: *Timeline and sequence of events during cardiac arrest (Case #2)*

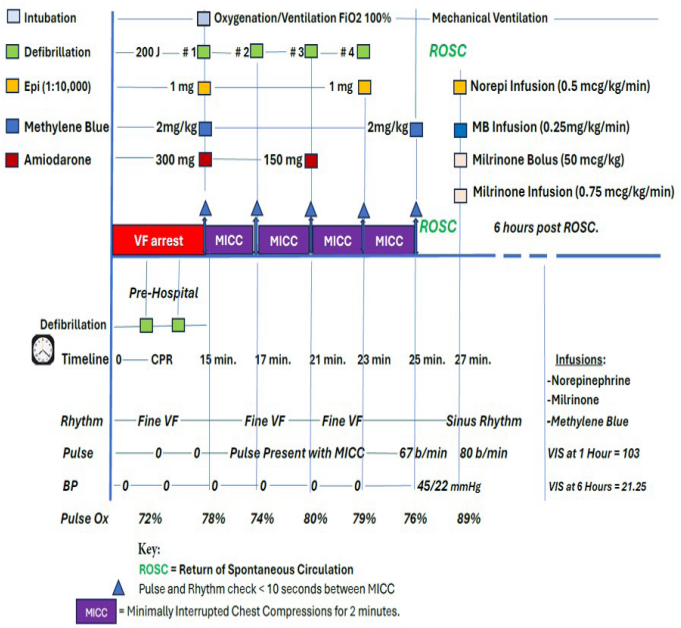


Figure 3: *Timeline and sequence of events during cardiac arrest (Case #3)*

Table 2: *Vasoactive Inotropic Score (Case #2).*

Post ROSC	30 minutes	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours
VIS Score	102	102	81	70.8	50.5	40.5	20.5	10.05
Norepinephrine Dose [mcg/kg/min]	1	1	0.8	0.7	0.5	0.4	0.2	0.1
Dobutamine Dose [mcg/kg/min]	2	2	1	0.8	0.5	0.5	0.5	0.5
Methylene Blue [mcg/kg/min]	0.25	0.25	0.25	0.25	0.25	0.25	0.25	d/c
MAP Range [mm Hg]	34	68	65	66	72	75	68	67

Legend*: VIS quantifies the degree of hemodynamic support. A higher score is a predictor of poor outcomes. The vasoactive inotropic score includes norepinephrine + dobutamine in the calculation. Based on Belletti et al, a correction factor of 20 could apply to the dose of MB in their 2020 updated VIS version.17 Methylene Blue infusion was constant at 0.25/mcg/kg/minute and continued for 6 hours.*

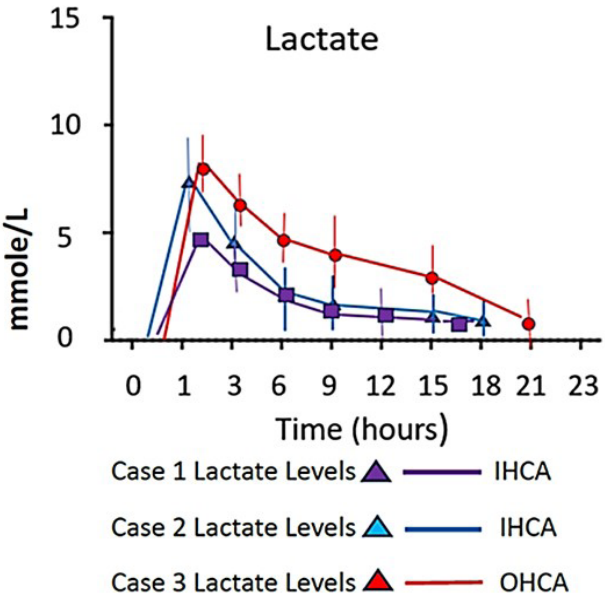
DOI: 10.55920/JCRMHS.2024.08.001361

Table 3: *Vasoactive Inotropic Score (Case #3)*

Post ROSC	30 minutes	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours
VIS Score	51	103	82.5	72	62	31	21.25	11.25
Norepinephrine Dose [mcg/kg/min]	0.5	1	0.8	0.7	0.6	0.3	0.12	0.1
Dobutamine Dose [mcg/kg/min]	0.125	0.3	0.25	0.25	0.2	0.125	0.125	0.125
Methylene Blue [mcg/kg/min]	0.25	0.25	0.25	0.25	0.25	0.25	0.25	d/c
MAP Range [mm Hg]	31	52	59	68	67	66	68	67

Legend: *VIS quantifies the degree of hemodynamic support. A higher score is a predictor of poor outcomes. The vasoactive inotropic score includes norepinephrine + dobutamine in the calculation. Based on Belletti et al, a correction factor of 20 could apply to the dose of MB in their 2020 updated VIS version.17 Methylene Blue infusion was constant at 0.25/mcg/kg/minute and continued for 6 hours.*

Figure 4: *Lactate levels post ROSC for the 3 Cases.*



leads. The patient was admitted to the medical intensive care unit. His vasoactive inotropic scores (VIS) including serum lactate levels were trended with improvement. The patient remained intubated for approximately forty-eight hours. During the patient's 6-day hospital course an ICD was placed by cardiology. At hospital discharge, the patient exhibited signs of neurologic sequelae, including mild ataxia and memory impairment, with a CPC score of two. Figure 3 demonstrates a resuscitation timeline and sequence of events. Table 3 presents the patient's vasoactive inotropic score over time.

Clinical Findings

Our resuscitation parameters included Cerebral Performance Category (CPC) outcomes at discharge, a 5-category scale for measuring neurologic status after cardiac arrest,14–16 lactate levels, Figure 4, and a Vasoactive Inotropic Score (VIS).17,18 See Tables 1, 2, and 3.

Case 1 had a CPC score of one and Cases 2 and 3 had a CPC score of two. Good cerebral performance or CPC 1 is defined as conscious, alert, and able to work but with the possibility of a mild neurologic or psychologic deficit. CPC 2, moderate cerebral disability, is defined as sufficient cerebral function for independent activities of daily life and able to work in a sheltered environment.15

Lactate levels were also trended. See Figure 4. Case 1, who achieved ROSC after nine minutes, had the lowest lactate levels compared with Case 2 with ROSC in thirteen minutes. Case 3, the out of hospital VF arrest, had the most prolonged downtime (25 minutes) and consequently the highest lactate levels and longest time to resolution.

Vasoactive Inotropic Score (VIS) can be used to objectively quantify the degree of hemodynamic support. A higher VIS score is a predictor of poor outcomes.17–19 In these cases, vasoactive substances used were inotropes, dobutamine and milrinone, and vasopressors with norepinephrine being considered the first-line treatment option.20 The VIS incorporates inotropes and vasoconstrictors in a single unitless composite score and is calculated using the following formula:18

VIS = Dopamine (mcg/kg/minute) + Dobutamine (mcg/kg/minute)

+ (100 x Epinephrine (mcg/kg/minute)

+ (100) x Norepinephrine (mcg/kg/minute)

+ (10,000 x Vasopressin (U/kg/minute)

+ (10 x Milrinone (mcg/kg/minute)

In all three cases, a MB bolus followed by an MB infusion post-ROSC appeared to reduce requirements for vasoactive substances post-resuscitation. At the 6-hour interval all 3 cases had improved from an extremely high VIS (>100) to a score of 10.5, 20.5, and 21.5 respectfully. See Tables 1, 2, and 3.

Spurious reduction in arterial oxygen saturation as measured by pulse oximetry was reported in all three cases.21 This is because MB has an absorption peak of 668 NM, and therefore absorbs most of the 660 nm pulse oximeter light emission. This is interpreted by the pulse oximeter to indicate the presence of reduced hemoglobin, and hence a decrease in oxygen saturation is indicated.

Citation: *Paul Henning. The effects of Methylene Blue administered during and after cardiac arrest: A case series of three patients who achieved ROSC. Jour of Clin Cas Rep, Med Imag and Heal Sci 8(5)-2024.

DOI: 10.55920/JCRMHS.2024.08.001361

Methemoglobin capillary saturation was continuously monitored by pulse co-oximetry.

An additional side effect and clinical finding noted was the green-blue discoloration of urine which follows administration of methylene blue.22

Discussion

These three case presentations describe an association of ROSC after the off-label administration of methylene blue as well as provide an in-depth description of their clinical course. Two cases involved hospital cardiac arrests (IHCA), for whom methylene blue boluses were administered early during resuscitation. Both patients achieved successful ROSC (MAP > 30 mm Hg lasting > 5 minutes) with minimal to moderate neurologic sequelae. The third case was an out-of-hospital cardiac arrest (OHCA) due to a witnessed VF arrest, with a downtime of fifteen minutes before hospital arrival. Early minimally interrupted chest compressions (MICC) were performed, and the patient was defibrillated twice before arrival. In addition to aggressive ACLS the patient received two boluses of MB in the emergency department and upon achieving ROSC a methylene blue drip along with two vasopressors.

Methylene blue has the pharmacological potential to provide both neuroprotection23–27 and blood pressure support to patients in cardiac arrest.7–9 In the absence of serious contraindications each of these benefits alone could theoretically justify trials of methylene blue in resuscitation. Methylene blue's potential to improve the rate of ROSC has never been reported or studied in humans. Our three cases are the first reports of methylene blue administration during early ventricular fibrillation arrest and with an associated successful return of spontaneous circulation. Animal studies of methylene blue administration during cardiac arrest are limited and show mixed results. In the majority of animal studies methylene blue was administered after prolonged periods of untreated cardiac arrest (most commonly 12 minutes) and MB and the other study solutions were administered 1 minute after CPR started. The prolonged untreated cardiac arrest used in animal studies may be a confounding variable weakening any evidence of potential benefit. Nevertheless, a systematic review of the literature found seven relevant animal studies28–34 of which three reported no evidence of benefit.28,32,33 Other studies reported evidence of improved rate of ROSC,29 improved survival29,31 and improved markers.30 A hemorrhagic shock study of Wistar rats reported increased survival rates among other benefits when methylene blue was added to the resuscitation treatments.34

Dose, Dosing, and Delivery

The evidence suggests that dosing and timing of methylene blue administration in septic vasoplegia significantly impact the early discontinuation of vasopressors, the number of vasopressor-free days, shorter ICU stays and in some studies increased survival.35–39

Methylene blue (MB) increases systemic vascular resistance and mean arterial pressure (MAP) by augmenting aortic diastolic pressures. This effect is achieved through the inhibition of nitric oxide synthase and the inactivation of soluble guanylate cyclase, which prevents vasodilation and promotes vasoconstriction.40–42 These mechanisms collectively enhance vascular tone and improve blood pressure, which is beneficial in septic shock and cardiopulmonary resuscitation (CPR).

In case 1, the first IHCA, MB (3 mg/kg intravenously) was administered within five minutes of VF arrest and shortly after epinephrine and amiodarone administration. Nine minutes after ROSC a MB infusion (0.25 mg/kg/hour) started and maintained for six hours. See Figure 1. Case 2 received a bolus of MB (2mg/kg) 5 minutes after epinephrine and amiodarone administration. This was followed by a 2nd bolus of MB at thirteen minutes, after which ROSC was achieved. This was followed by an infusion of 0.25 mg/kg/hour of MB which was maintained for six hours. See Figure 2. Case 3 also received a total of 4 mg/kg (MB 2 mg/kg + MB 2 mg/kg) followed by an infusion of 0.25 mg/kg/hour. See Figure 3. It is unclear if more frequent dosing of MB might be associated with increased survival of both IHCA and OHCA. Juffersman et al. tested the effects of MB at different dosages in septic patients and concluded that although 7mg/kg of MB infused over 20 minutes increased MAP, the dosage may compromise splanchnic blood flow.43

The methylene blue dosing strategies used in these cardiac arrest patients were consistent with the study by Sari-Yavuz et al.,36 which administered a 2 mg/kg bolus followed by a continuous infusion of 0.25 mg/kg/hour in critically ill adult patients with shock. There was an observed reduction in mortality among patients with shock who received a bolus of methylene blue followed by a continuous infusion. Additionally, all groups showed a decreased need for vasopressors.36 In our patients the greatest need for cardiovascular support was observed during the first hour after resuscitation, which justified the decision to continue with an infusion post-ROSC.

Finally, the timely administration of methylene blue within five minutes of IHCA, compared to thirteen minutes in porcine studies,29–31 along with maintaining an MB infusion, highlights a theoretical potential to increase the rate of ROSC and improve neurologic outcomes.

Conclusion

We report three patients who had successful outcomes associated with off-label administration of methylene blue during cardiopulmonary resuscitation. The reporting of

DOI: 10.55920/JCRMHS.2024.08.001361

these cases is intended to herald animal studies showing improved ROSC and survival rates after methylene blue administration during CPR. We feel that these reports along with the known neuroprotective and vasoplegic benefits of methylene blue may be sufficient evidence to support clinical trials of methylene blue administration during advanced cardiac life support.

Declarations

Ethics approval and consent to participate: This is a retrospective case series without primary research intent. An ethical or institutional review board (IRB) review is not applicable.

Consent for publication: The paper was reviewed by the USA Health Chief Compliance Officer who ruled that there were no patient identifiers that would require patient authorization or consent.

Availability of data and materials: Not applicable

Acknowledgements: Not applicable

Financial Support: No external funding or financial support was provided for this manuscript.

Author Contributions: Dr. Paul Henning drafted the initial manuscript, created the tables and was the primary writer and developer of the manuscript. Dr. Larry Mellick participated in editing of the manuscript, figures, and tables and preparing the article for submission.

Conflict of Interest Disclosures: The authors have no potential conflicts of interest to disclose.

References

1. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2016;374(18):1711-1722. doi:10.1056/NEJMoa1514204
2. Kudenchuk PJ, Leroux BG, Daya M, et al. Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest: The ALPS Study (Amiodarone, Lidocaine, or Placebo). Circulation. 2017;136(22):2119-2131. doi:10.1161/CIRCULATIONAHA.117.028624
3. Sanfilippo F, Corredor C, Santonocito C, et al. Amiodarone or lidocaine for cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2016;107:31-37. doi:10.1016/j.resuscitation.2016.07.235
4. Fernando SM, Mathew R, Sadeghirad B, et al. Epinephrine in Out-of-Hospital Cardiac Arrest. CHEST. 2023;164(2):381-393. doi:10.1016/j.chest.2023.01.033
5. Soar J. Epinephrine for cardiac arrest: knowns, unknowns and controversies. Curr Opin Crit Care. 2020;26(6):590-595. doi:10.1097/MCC.0000000000000763
6. Hohlfelder B, Douglas A, Wang L, Wanek M, Bauer SR. Association of Methylene Blue Dosing With Hemodynamic Response for the Treatment of Vasoplegia. J Cardiothorac Vasc Anesth. 2022;36(9):3543-3550. doi:10.1053/j.jvca.2022.04.003
7. Chalise SN, Sahib TA, Boyer GA, Pathak V. Methylene Blue in Refractory Shock. Cureus. Published online November 6, 2022. doi:10.7759/cureus.31158
8. Pruna A, Bonaccorso A, Belletti A, et al. Methylene Blue Reduces Mortality in Critically Ill and Perioperative Patients: A Meta-Analysis of Randomized Trials. J Cardiothorac Vasc Anesth. 2024;38(1):268-274. doi:10.1053/j.jvca.2023.09.037
9. Saha BK, Burns SL. The Story of Nitric Oxide, Sepsis and Methylene Blue: A Comprehensive Pathophysiologic Review. Am J Med Sci. 2020;360(4):329-337. doi:10.1016/j.amjms.2020.06.007
10. 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(2):496-499. doi:10.1016/S0003-4975(03)01510-8
11. Habib AM, Elsherbeny AG, Almehizia RA. Methylene Blue for Vasoplegic Syndrome Postcardiac Surgery. Indian J Crit Care Med. 2018;22(3):168-173. doi:10.4103/ijccm.IJCCM_494_17
12. Iolascon A, Bianchi P, Andolfo I, et al. Recommendations for diagnosis and treatment of methemoglobinemia. Am J Hematol. 2021;96(12):1666-1678. doi:10.1002/ajh.26340
13. Cwalinski T, Polom W, Marano L, et al. Methylene Blue—Current Knowledge, Fluorescent Properties, and Its Future Use. J Clin Med. 2020;9(11):3538. doi:10.3390/jcm9113538
14. Jennett B. ASSESSMENT OF OUTCOME AFTER SEVERE BRAIN DAMAGE A Practical Scale. The Lancet. 1975;305(7905):480-484. doi:10.1016/S0140-6736(75)92830-5
15. Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the Cerebral Performance Category Score and the Health Utilities Index for Survivors of Cardiac Arrest. Ann Emerg Med. 2009;53(2):241-248.e1. doi:10.1016/j.annemergmed.2008.03.018
16. Raina KetkiD, Callaway Clifton, Rittenberger JonC, Holm MargoB. Neurological and functional status following cardiac arrest: Method and tool utility. Resuscitation. 2008;79(2):249-256. doi:10.1016/j.resuscitation.2008.06.005
17. Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-Inotropic Score: Evolution, Clinical Utility, and Pitfalls. J Cardiothorac Vasc Anesth. 2021;35(10):3067-3077. doi:10.1053/j.jvca.2020.09.117
18. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*: Pediatr Crit Care Med. 2010;11(2):234-238. doi:10.1097/PCC.0b013e3181b806fc
19. Yamazaki Y, Oba K, Matsui Y, Morimoto Y. Vasoactive-inotropic score as a predictor of morbidity and mortality in adults after cardiac surgery with cardiopulmonary bypass. J Anesth. 2018;32(2):167-173. doi:10.1007/s00540-018-2447-2
20. Russell JA. Vasopressor therapy in critically ill patients with shock. Intensive Care Med. 2019;45(11):1503-1517. doi:10.1007/s00134-019-05801-z
21. Kessler MR, Eide T, Humayun B, Poppers PJ. Spurious Pulse Oximeter Desaturation with Methylene Blue Injection. Anesthesiology. 1986;65(4):435-436. doi:10.1097/00000542-198610000-00017
22. Stratta P, Barbe MC. Green Urine. N Engl J Med. 2008;358(11):e12. doi:10.1056/NEJMicm065416
23. Wiklund L, Sharma A, Patnaik R, et al. Upregulation of hemeoxygenase enzymes HO-1 and HO-2 following ischemia-reperfusion injury in connection with experimental cardiac arrest and cardiopulmonary resuscitation: Neuroprotective effects of methylene blue. In: Progress in Brain Research. Vol 265. Elsevier; 2021:317-375. doi:10.1016/bs.pbr.2021.06.009
24. Gureev AP, Sadovnikova IS, Popov VN. Molecular Mechanisms of the Neuroprotective Effect of Methylene Blue. Biochem Mosc. 2022;87(9):940-956. doi:10.1134/S0006297922090073
25. Katz A, Brosnahan SB, Papadopoulos J, Parnia S, Lam JQ. Pharmacologic neuroprotection in ischemic brain injury after cardiac arrest. Ann N Y Acad Sci. 2022;1507(1):49-59. doi:10.1111/

nyas.14613

26. Choudhary RC, Shoaib M, Sohnen S, et al. Pharmacological Approach for Neuroprotection After Cardiac Arrest—A Narrative Review of Current Therapies and Future Neuroprotective Cocktail. Front Med. 2021;8:636651. doi:10.3389/fmed.2021.636651
27. Lu Q, Tucker D, Dong Y, Zhao N, Zhang Q. Neuroprotective and Functional Improvement Effects of Methylene Blue in Global Cerebral Ischemia. Mol Neurobiol. 2016;53(8):5344-5355. doi:10.1007/s12035-015-9455-0
28. Johannsen CM, Nørholt C, Baltsen C, et al. The effects of methylene blue during and after cardiac arrest in a porcine model; a randomized, blinded, placebo-controlled study. Am J Emerg Med. 2023;73:145-153. doi:10.1016/j.ajem.2023.08.041
29. Miclescu A, Basu S, Wiklund L. Methylene blue added to a hypertonic–hyperoncotic solution increases short-term survival in experimental cardiac arrest*: Crit Care Med. 2006;34(11):2806-2813. doi:10.1097/01.CCM.0000242517.23324.27
30. Miclescu A, Basu S, Wiklund L. Cardio-cerebral and metabolic effects of methylene blue in hypertonic sodium lactate during experimental cardiopulmonary resuscitation. Resuscitation. 2007;75(1):88-97. doi:10.1016/j.resuscitation.2007.03.014
31. Wiklund L, Basu S, Miclescu A, Wiklund P, Ronquist G, Sharma HS. Neuro- and Cardioprotective Effects of Blockade of Nitric Oxide Action by Administration of Methylene Blue. Ann N Y Acad Sci. 2007;1122(1):231-244. doi:10.1196/annals.1403.016
32. Xavier MS, Vane MF, Vieira RF, et al. Methylene blue as an adjuvant during cardiopulmonary resuscitation: an experimental study in rats. Braz J Anesthesiol Engl Ed. 2024;74(2):744470. doi:10.1016/j.bjane.2023.10.003
33. Semenas E, Nozari A, Thiblin I, Rubertsson S, Wiklund L. Modulation of nitric oxide expression with methylene blue does not improve outcome after hypovolemic cardiac arrest. Resuscitation. 2011;82(10):1344-1349. doi:10.1016/j.resuscitation.2011.04.027
34. Jeroukhimov, Avi Weinbroum, Ron Ben I. Effect of Methylene Blue on Resuscitation After Haemorrhagic Shock. Eur J Surg. 2001;167(10):742-747. doi:10.1080/11024150152707716
35. 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(1):110. doi:10.1186/s13054-023-04397-7
36. Sari-Yavuz S, Heck-Swain KL, Keller M, et al. Methylene blue dosing strategies in critically ill adults with shock—A retrospective cohort study. Front Med. 2022;9:1014276. doi:10.3389/fmed.2022.1014276
37. Naoum EE, Dalia AA, Roberts RJ, Devine LT, Ortoleva J. Methylene blue for vasodilatory shock in the intensive care unit: a retrospective, observational study. BMC Anesthesiol. 2022;22(1):199. doi:10.1186/s12871-022-01739-w
38. Ballarin RS, Lazzarin T, Zornoff L, et al. Methylene blue in sepsis and septic shock: a systematic review and meta-analysis. Front Med. 2024;11:1366062. doi:10.3389/fmed.2024.1366062
39. Puntillo F, Giglio M, Pasqualucci A, Brienza N, Paladini A, Varrassi G. Vasopressor-Sparing Action of Methylene Blue in Severe Sepsis and Shock: A Narrative Review. Adv Ther. 2020;37(9):3692-3706. doi:10.1007/s12325-020-01422-x
40. Wildhirt SM, Dudek RR, Suzuki H, Bing RJ. Involvement of inducible nitric oxide synthase in the inflammatory process of myocardial infarction. Int J Cardiol. 1995;50(3):253-261. doi:10.1016/0167-5273(95)02385-A
41. Schneider F, Lutun Ph, Hasselmann M, Stoclet JC, Tempé JD. Methylene blue increases systemic vascular resistance in human septic shock: Preliminary observations. Intensive Care Med. 1992;18(5):309-311. doi:10.1007/BF01706481
42. Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. Biochem Pharmacol. 1993;45(2):367-374. doi:10.1016/0006-2952(93)90072-5
43. Juffermans NP, Vervloet MG, Daemen-Gubbels CRG, Binnekade JM, Jong MD, Groeneveld ABJ. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide. 2010;22(4):275-280. doi:10.1016/j.niox.2010.01.006.