O Azul de Metileno e o Seu Papel no Doente Crítico

Methylene Blue and its Role in the Critically Ill Patient

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Mr. Editor:

Methylene blue is a versatile drug that is a powerful aid in different clinical contexts, especially in the context of critically ill patients, especially in states associated with profound vasodilatation such as distributive shock (septic shock). Historically, the use of methylene blue has been used as an antimalarial treatment, in the treatment of gonococcal infections, as well as in the treatment of methemoglobinemia (MetHB), although in this particular condition, the use of methylene blue is only used in selected cases of patients with respiratory symptoms associated with MetHB levels above 920%.[1] It has been used as an antidote for cyanide poisoning, which makes the use of this type of compound relevant. These types of pharmacological aids are conditioned to their use, since, if used early and rationally, they constitute an improvement in the survival of patients. The versatility of the use of methylene blue allows it to be used in multiple medical conditions; its use in intensive care units is described below, especially in states of "shock" in the care of critically ill patients.[2]

The mechanism of action of methylene blue is given mainly in the inhibition of soluble guanylate cyclase, therefore it plays a role in the inhibition of nitric oxide (NO) formation, thus reversing the hypotension induced by endotoxins, it also has an antagonistic role in the hyporeactivity to vasoconstrictors. The doses of administration of the drug in shock conditions are usually indicated at 2 mg/kg as a bolus and then continued as an infusion at 0.25- 1.2 mg/kg/hour.[3,4] The side effects described secondary to the use of methylene blue in the literature date initially from blue staining of the urine and skin, as well as the generation of symptoms associated with nausea, vomiting, and abdominal pain.[5]

Kirov *et al* conducted in 2001 the first study related to the use of methylene blue in the treatment of patients with septic shock, where it was found that the early use of methylene blue could reduce the requirement of vasopressors; the survival of the population in this study did not have sufficient statistical power to find differences in mortality.[6] Another study by Juffermans *et al* aimed to evaluate the use of methylene blue in the treatment of patients with severe septic shock; multiple doses of methylene blue were used at a rate of 1-3-7 mg/kg during 20 minutes in 15 patients with the diagnosis, the use of methylene blue improved several variables in these patients such as cardiac index and mean pulmonary artery arterial pressure, decreased serum lactate and less oxygen requirement in patients under invasive mechanical ventilation.[7]

A recent study by Ibarra-Estrada *et al* aimed to evaluate methylene blue as an early adjuvant in patients with refractory septic shock in order to measure primary and secondary outcomes associated with vasopressor reduction during ICU stays. This study included 91 patients who were randomized and compared with 46 placebos. The primary outcome was that patients who used methylene blue had a shorter time of vasopressor use compared to the placebo group (69 h [IQR 59–83] *vs* 94 h [IQR 74–141]; *p* 0.001), as well as a decrease in the requirement for norepinephrine in the group that used methylene blue. Other important secondary outcomes were related to one day less vasopressor requirement at day 28 ($p = 0.008$), a shorter ICU stay by 1.5 days ($p = 0.039$), and a shorter hospital stay by 2.7 days ($p = 0.027$). Other results showed that the days of invasive mechanical ventilation and mortality were similar to those in the comparison group without obtaining statistical significance. The most important adverse effects were related to 93% of cases, which presented bluish-green urine coloration (93%), as an increase in MetHB saturation (2.9% [RIC 2.2–3.3] *vs* 0.5% [RIC 0.4–0.7]; *p* 0.001). Some serum markers, such as serum creatinine, bilirubins, and hepatic aminotransferases, did not show statistically significant changes versus the comparison group.[8]

In a randomized controlled clinical trial conducted by Aguilar Arzapalo *et al*, where 60 individuals were divided into two groups respectively, within which were critically ill, with different stages of septic shock and/or vasodilated shock, the administration of methylene blue was monitored, and monitored

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in one of the two groups. The results obtained in the group to which it was administered were associated with methylene blue being effective as an adjuvant in the treatment of individuals with septic, vasodilated or distributive shock. Shock time, as well as vasopressor consumption, is significantly reduced with the use of methylene blue. An important advance in lactate clearance and improvement in central venous saturation was also demonstrated, a significantly better result with the use of methylene blue, and mortality was reduced, being lower with the use of methylene blue at 28 days after hospital discharge.[9]

Although there is little scientific evidence or lack of randomized clinical trials on the use of methylene blue, alternative uses have been shown, such as in the treatment of anaphylaxis; a study conducted by Moreia Rodriguez *et al* employed the use of this pharmacological agent in a series of cases, mainly in bronchospasm. Although the authors do not explain the mechanisms directly involved in the use of this drug due to the low evidence of its use, they propose a synergy mechanism with the previous use of adrenaline, especially as first-line treatment in this type of conditions.[10]

Given the above, several annotations arise concerning the use of methylene blue in the intensive care unit. Initially, it could be considered or its use could be considered as a secondary alternative to the use of the vasopressor of choice described throughout the available literature as norepinephrine, even in the initial stages of septic shock; however, it is necessary to explore the literature with more evidence and which is more conclusive for the aforementioned. Methylene blue will have to be used according to the clinical conditions of each patient, individualizing each case, considering each comorbidity or patient's condition, according to the criteria of the intensivist or specialist if considered relevant; however, it should be noted that its efficacy is linked to early onset of the same.

As a commentary, in Colombia, especially in the health centre of the present authors, we use methylene blue in refractory septic shock when adjuvant therapy with norepinephrine and vasopressin is not effective in controlling hypotension despite the parallel medical management established with antibiotics and steroids, sometimes requiring renal replacement therapy, among others. We do not have a study on their use in our institution in a standardized way; however, their use promises encouraging horizons. ■

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JSST, SGBM, JDED - Concepção da ideia, pesquisa bibliográfica, redação e aprovação final do manuscrito.

Todos os autores aprovaram a versão final a ser submetida.

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JSST, SGBM, JDED - Idea conception, literature search, writing and final approval of the manuscript.

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REFERENCES

1. Skold A, Cosco DL, Klein R. Methemoglobinemia: Pathogenesis, diagnosis, and management. South Med J. 2011;104:757–61. doi:10.1097/SMJ.0b013e318232139f
2. Saha BK, Burns SL. The story of nitric oxide, sepsis and methylene blue: a comprehensive pathophysiologic review. Am J Med Sci. 2020;360:329–37. doi.org/10.1016/j.amjms.2020.06.007
3. Paciullo CA, McMahon Horner D, Hatton KW, Flynn JD. Methylene blue for the treatment of septic shock. Pharmacotherapy. 2010;30:702-15. doi: 10.1592/phco.30.7.702.
4. Shanmugam G. Vasoplegic syndrome - The role of methylene blue. Eur J Cardio-thoracic Surg. 2005;28:705–10. doi.org/10.1016/j.ejcts.2005.07.011
5. Dumbarton TC, Gorman SK, Minor S, Loubani O, White F, Green R. Local cutaneous necrosis secondary to a prolonged peripheral infusion of methylene blue in vasodilatory shock. Ann Pharmacother. 2012;46:e6. doi.org/10.1345/aph.1Q560
6. Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjørnsson B, et al. Infusion of methylene blue in human septic shock: A pilot, randomized, controlled study. Crit Care Med. 2001;29:1860–7.
7. Juffermans NP, Vervloet MG, Daemen-Gubbels CRG, Binnekade JM, Jong M de, Groeneveld AB. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide - Biol Chem. 2010;22:275–80. doi:10.1016/j.niox.2010.01.006

8. Ibarra-Estrada M, Kattan E, Aguilera-González P, Sandoval-Plascencia L, Rico-Jauregui U, Gómez-Partida CA, et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. Crit Care. 2023;27:110. doi:10.1186/s13054-023-04397-7
9. Francisco M, Arzápalo A, Gabriel V, Avendaño L, Castillo AE, José J, et al. Eficacia del azul de metileno como coadyuvante en el tratamiento de pacientes con choque séptico. Rev Asoc Mex Med Crit Ter Int. 2016;30:102–10.
10. Rodrigues JM, Pazin Filho A, Rodrigues AJ, Vicente WV de A, Evora PR. Methylene blue for clinical anaphylaxis treatment: A case report. Sao Paulo Med J. 2007;125:60–2. doi.org/10.1590/s1516-31802007000100012