

# Methylene blue is not a pure vasoconstrictor drug

The Editor,

The modern era of heart surgery began when the cardiopulmonary bypass (CPB) technique was introduced in the early 1950s. CPB is essential for the majority of cardiac surgery, but an undesirable inflammatory reaction occurs because of its use.

There is a frequent misconception that methylene blue (MB) is a vasopressor drug. The MB effect appears in conditions of nitric oxide (NO) upregulation; it is not a vasoconstrictor and it is receptors-independent. MB blocks the cyclic guanosine monophosphate (cGMP) pathway through a “cross-talk” mechanism, thereby facilitating the cyclic adenosine monophosphate-dependent epinephrine vasoconstrictor effect. In an excellent systematic review of pharmacologic agents for acute hemodynamic instability, Morozowich and Ramakrishna included MB as a “pure vasoconstrictor” and mentioned “an *passant*” that the MB use is justified as “rescue therapy.”<sup>[1]</sup>

Targeting MB for vasoplegic syndrome (VS) in a personal statement including questions, answers, doubts, and certainties, the following conclusions were drawn:<sup>[2,3]</sup> (1) The recommended doses are safe (the lethal dose is 40 mg/kg); (2) MB did not cause endothelial dysfunction; (3) the MB effect appears in cases of NO upregulation; (4) MB is not a vasoconstrictor; (5) it is possible that the MB acts through this “crosstalk” mechanism; (6) the most used dosage is 2 mg/kg as intravenous bolus followed by the same continuous infusion because the plasma concentrations strongly decay in the first 40 min; (7) there are no definitive multicentric studies, MB, at present, is the best, maybe it is the safest and cheapest option, but (8) there is a possible “window of opportunity” for the MB’s effectiveness.<sup>[2,3]</sup>

Many times, hemodynamic and metabolic MB effects were not observed because there is a potential “window of opportunity” for MB’s effectiveness.<sup>[4]</sup> In the first 8 h, there was an increased nitric oxide synthase (NOS) activity and guanylyl cyclase (GC) upregulation. In the next 8 h, there was a lack of GC expression and downregulation of NOS. In the third 8-h window, there was an upregulation of GC and NOS. Other authors and we have been emphasizing, over and over, two practical aspects: (1) The disclosure in using MB treatment without considering the window of opportunity and (2) the need for the establishment of this window in humans, perhaps choosing cGMP as a biomarker because the attempt to use nitrite/nitrate, measured by chemiluminescence was frustrating. In summary, there are two opposing concepts: (1) The use of MB as a rescue therapy to treat VS and (2) the use of MB as an early adjuvant drug (window 1). There is a possibility that MB does not act (second window) or acts too late (third window) when the circulatory shock is metabolically irreversible, presenting high lactate levels and uncontrollable metabolic acidosis. Maybe, it would be more sensible to consider MB, not a late rescue treatment, but as an adjuvant drug to be used early (window 1). In the absence of a protocol for the MB use as an adjuvant therapy, maybe the persistent vasoplegia and the increased needs of vasoconstrictors would be indicative signals for the MB use. By sharing again the discussed concepts, we hope that they are complimentary to the Morozowich and Ramakrishna’s review.

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#### Conflicts of interest

There are no conflicts of interest.

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