

Letters to the Editor

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Methylene Blue

“Sirs: I have found you an argument. I am not obliged to find you an understanding.”

Dr. Samuel Johnson (1709-1784)

Comments on the study “Methylene blue for vasoplegic syndrome treatment in heart surgery. Fifteen years of questions, answers, doubts and certainties” authored by Full Professor Paulo Roberto Barbosa Evora, published in issue 24.3 of the Brazilian Journal of Cardiovascular Surgery [1].

The induction of an inflammatory state by endothelial dysfunction and an increased production of nitric oxide (NO) lead to vasodilatation of smooth muscle. These mechanisms would be by the action of NO in opening potassium channels, leading to decrease of calcium concentration and subsequent hyperpolarization with relaxation of vascular smooth muscle [2,3]. When this action becomes excessive, there is persistence of vasodilation and hyporesponsiveness to norepinephrine, characterizing vasoplegic syndrome (VS) [4].

When we analyze the risk factors for the development of VS, different mechanisms of action are presented to explain the endothelial dysfunction after a stress factor in the vascular wall. Persistent vasodilation by tissue accumulation of ACE inhibitor may be another factor. When seeking the most likely factors that could contribute to the VS, these same studies do not consider the possibility of withdrawal of these drugs in the preoperative period when such drugs are used [5].

The use of methylene blue (MB) by inhibiting guanylate cyclase and avoiding the increase of cyclic GMP (mediated by the action of NO), allows the action of norepinephrine in vascular tone [6]. The biggest problem found in the use of MB in the treatment of VS is that the majority of published studies refers to researches on clinical cases, variable incidence of VS (8.8 to 44%), and variable results regarding the MB treatment [6,7]. From the difficulty in recognizing a particular etiology, it lacks an experimental model suitable for the use of MB in cardiac surgery, despite its promising initial results.

When the “window of opportunity” (the period between 8 and 16 hours post-stress tissue) is noted carefully, in

which the action of MB is more effective, this time of 8 hours coincides with the end of the cardiovascular effects of CPB. The study by Fernandes [3] also mentions that in some vascular beds (renal and pulmonary) after using the MB, it may occur vascular vasoconstriction, worsening of clinical presentation and death.

In fact, after fifteen years of history, the MB in the treatment of VS presents with many questions, few answers, many doubts and uncertainties.

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Resposta

Dear Dr. Hélcio Giffhorn,

First of all, thank you for the interest in our review and by presentation of data in the literature that add interesting aspects to the matter still unresolved, that is the inhibition of guanylate cyclase as a therapeutic resource in vasoplegia resistant to adrenergic action of vasoactive amines. I also thank the citation by Samuel Johnson, which is extremely relevant.

In response to your comments I would like to comment on two aspects: the interpretation of the “window of opportunity” and the possibility of morbidity and mortality related to renal and respiratory functions, described by Fernandes [1].

In relation to the window of opportunity, You affirms “When we look more closely at the “window of opportunity” (the period between 8 and 16 hours post-stress tissue), in which the action of MB is more effective, this time of 8 hours coincides with the late cardiovascular effects of the CPB”. There is a major mistake in this interpretation, because the period from 8 to 16 hours is a period in which the action of MB is **less effective**, due to low expression of guanylate cyclase. When I did not know this experimental detail, I came to think of other mechanisms such as the already mentioned hyperpolarization-dependent potassium channels, and deficiency of vasopressin. The lesson given by the description of this “window of opportunity” is the possibility of late use of MB (up to 18-20 hours), when it occurs the synthesis “de novo” of guanylate cyclase. Thus, it is possible to hypothesize that the ineffectiveness of MB is due to hypoactivity of guanylate cyclase, which is probably due to the excessive production of NO by iNOS expression. In the next paragraph I reproduce the text of the original study.

“Recently, a doctoral thesis very well prepared was defended at Federal University of Florianópolis. This thesis has been published and brings some very important data to attempt to answer this question [1]. A model of sepsis in mice allowed the authors to demonstrate, in a period of 24 hours divided into three periods of eight hours, that there is a dynamic action of guanylate cyclase in such a way as to create a “window of opportunity” for the effectiveness of MB to help restore systemic vascular resistance. This phase coincides with the increased expression of iNOS. Between 8 and 16 hours, the expression of guanylate cyclase is absent, probably due to excessive production of nitric oxide and thus, in this phase the MB **can not act**. Later, between 16 and 24 hours there would be a synthesis “de novo” of guanylate cyclase, becoming the MB effective.”

As the statement that in certain vascular beds (renal

and pulmonary) after using the MB, there may be vascular vasoconstriction, worsening of clinical presentation and death, I can not effectively comment very much about such statements [1]. Due to the fact that this model of sepsis is in rats, in my opinion, it is not enough cause for concern. Our studies in pigs and analysis of the literature on human patients attest to the safety of the use of MB. Although there is mention of the use of doses up to 10 mg/kg, I have never surpassed, in my personal experience, the dose of 6 mg/kg.

I echo your words when You said that, in fact, the MB in the treatment of VS has a history of 15 years with many questions, few answers, many doubts and uncertainties. But one certainty I have: it is a measure with wide margin of safety and it can be a life-saving therapy [2,3].

Finally, I suggest to the readers of this response to read two reviews that, in my opinion, have the best “state of the art” on the use of MB in the treatment of vasoplegic syndrome [4,5].

Paulo Roberto B. Evora, Ribeirão Preto/SP/Brazil,

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Incentive spirometry versus breathing exercises in physiotherapy routine

Dear Editor,

We would like to congratulate Dr. Julia A. Renault and collaborators for the article: “**Comparison between deep breathing exercises and incentive spirometry after CABG**”

surgery” [1] (Brazilian Journal of Cardiovascular Surgery 2009, 24 (2): 165-172), for discussing a pertinent theme of routine care of the physiotherapist.

Patients undergoing coronary artery bypass grafting (CABG), regardless of the use of cardiopulmonary bypass will present impairment of pulmonary function in the postoperative period of cardiac surgery (POP), due to multifactorial reasons [2].

The physiotherapist has been requested in this period in order to reduce or prevent complications [3]. But different techniques are used [4], and controversies still remain about the superiority between them and the proper prescription of breathing exercises [5]. As the techniques vary according to the routine of each Service [3], more research on the subject is necessary.

The physiotherapy techniques are justified by the reduction of lung volume and capacity, that lead to atelectasis and hypoxemia [3]. In addition, sternal instability and the consequent decrease in diaphragmatic motion also lead to a decrease in volumes. In 1915, MacMahon had already described the use of breathing exercise for patients with chest trauma. Since then the technique of deep breathing has been implemented and studied as a component in caring for the POP of cardiac surgery by increasing lung volume through expansion of the lower rib cage, by the tactile and verbal stimuli. Thus, the stimuli through deep breathing, ventilate collapsed alveoli and result in smaller decrements in lung function [4].

The study [1] mentioned above showed no statistically significant differences in spirometric variables, maximum respiratory pressures and oxygen saturation, with the use of an incentive spirometer and deep breathing. Despite the similar results of these techniques, the use of an incentive spirometer [4] requires more physiotherapy. However, one should be aware of ventilatory patterns, due to the risk caused by the Valsalva maneuver, that may increase blood pressure to levels not recommended for this period, if the patient is poorly guided and not receiving the necessary follow-up for learning of the exercise.

However, these techniques should be used with caution in defined cases, by trained professionals, in order to ensure the quality of the postoperative period. What seems to be unanimous is the benefit of early mobilization. The definition of the best technique would reduce costs for institutions in the acquisition of therapeutic materials, however, the standardization of studies is necessary to improve the prescription of physiotherapy in the POP of cardiac surgery.

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