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LETTER TO THE EDITOR

Comments on: Methylene blue? Therapeutic alternative in the management of septic shock refractory to norepinephrine

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Dear Editor,

We read with pleasure the paper "*Methylene blue? Therapeutic alternative in the management of septic shock refractory to norepinephrine*", published by Aragon-Benedi C *et al*. [1] in the last issue of Signa Vitae. It is a very interesting case report that is focusing the attention on an important topic.

Shock, defined as an acute syndrome of circulatory failure leading to inadequate oxygen delivery to the cells, is most of the time "distributive" (62% of the cases) [2]. This is characterized by a decrease of systemic vascular resistances (SVR) and abnormal distribution of blood flow, with normal or increased cardiac output (CO) [3]. Sepsis is the most common cause of distributive shock, and the referred "case report" is a classic example. In septic shock, the response to pathogen-associated molecular patterns (PAMPS) and damage-associated molecular patterns (DAMPS) generates a combination of vasodilation and increased capillary permeability. Capillary leak, coupled with greater vessel capacitance mediated by vasoplegia, may result in absolute or more commonly relative hypovolemia [3].

Whatever the cause might be, hemodynamic shock is characterized by a decrease in tissue perfusion associated with cellular and metabolic abnormalities. If not reversed, end-organ hypoperfusion results in significant morbidity. Mortality rate reached 50% in observational studies [4, 5]. Hence, the goal of shock resuscitation is to improve tissue perfusion by restoring perfusion pressure of vital organs, ensuring an adequate oxygen delivery (DO2). When possible, it should improve microvascular alterations to avoid cellular damages. This is possible only adopting an adequate and complete monitoring of cardiovascular functions. Moreover, it should restore the oxygen consumption (VO2), and maintain a correct mixed venous oxygen blood saturation (SvO2) [6]. To achieve these goals, the management of shock should remove the initial cause and adopt specific treatments (mainly antibiotics). Moreover, it should carefully provide volume replacement, and (in most of the patients) infusion of vasopressors, to maintain a perfusing blood pressure [7, 8]. This should ensure adequate systemic and microcirculatory flow and tissues oxygenation [3, 8, 9], but this is not always enough. Sometimes, the shock condition becomes resistant to the infusion of vasopressor drugs, especially in advanced phase.

The L-arginine nitric oxide (NO) pathway plays a pivotal role in regulating cardiovascular hemodynamics and vascular permeability [10]. Nitric oxide stimulates guanylate cyclase that causes vascular smooth muscle relaxation from cyclic guanosine monophosphate production [11].

Methylene blue inhibits inducible NO synthase (NOS) and guanylate cyclase, thereby reversing NO induced vasodilation [10, 11]. In septic shock, it was firstly used at the beginning of the 1990s [12]. This drug has resulted beneficial and safe in randomized clinical trials [13, 14] and case reports [1, 15, 16]. Recently, its clinical use has been deeply reviewed [17, 18], and we are strongly convinced that it would deserve further attention and prospective, randomized, clinical trials. In particular, we believe that its use should be precocious, and not be reserved at patients in advanced conditions of shock. Accordingly, this is the reason why we have recently proposed a specific protocol for approval by the Ethics Committee. The study will be conducted on adults in septic shock, with precise inclusion and exclusion criteria, randomly assigned to two different groups. One of the groups will initially receive only norepinephrine, and only at a later stage will receive methylene blue. The second group will be treated with methylene blue at an earlier stage.

Kind regards.

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CONFLICT OF INTEREST

The authors have no conflict of interest in this article.

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