

Microbiome in Critical Illness

Microbiome in Sepsis and COVID-19, *F. Forfori, S. Ferrari, A. Isirdi, F. Corradi*

The Intestinal Microbiome in Critical Illness, *N.J. Klingensmith, C.M. Coopersmith*

Microbiome and Pneumonia in Children, *C. Guitart, I. Jordan, E. Esteban*

Microbiome and Probiotics: Do They Really Work? *Y. Longhitano, C. Zanza, T. Romenskaya et al.*

Clostridioides difficile Infection: A Serious Complication of Intestinal Microbiome Alteration

in Critical Patients, *M.G. Olvera-Ramos, G. Castillo-Gutiérrez, G.A. Bautista-Aguilar et al.*

The Role of the Microbiome and Nutritional Therapy in Critical COVID-19, *V.A. Bolaños-Toscano, S.E. Martínez-Vázquez, A. Kammar-García et al.*

Safer Intubation Practices in Critically Ill Patients – What We Learned During the COVID-19 Pandemic That Should Not Be Forgotten, *P.V. Mendes, B.A. Besen, L. de Azevedo*

Methylene Blue for Vasoplegic Syndrome Post Cardiac Surgery, *B. Gladwin, P. Young*





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Cardiac surgery is one of the most frequently performed major surgical procedures, with more than 1 million operations annually. Major cardiac surgery requiring cardiopulmonary bypass commonly results in post-operative haemodynamic instability and requires specialised management in Intensive Care Unit (ICU). As many as half of all patients requiring cardiopulmonary bypass develop a degree of shock following surgery. In patients responsive to first line vasopressor therapy, the duration of time in ICU and the overall mortality is relatively low. Significant vasoplegia refractory to vasopressors may be seen in between 5 and 25% of patients and increases to 40% in high risk groups (Lenglet et al. 2011a; Fischer and Levin 2010; Lenglet et al. 2011b; Argenziano et al. 1999). Patients like this are considered to have vasoplegic syndrome and often require prolonged ICU care and prolonged hospitalisation (Lenglet et al. 2011b; Ortoleva et al. 2020). Patients with vasoplegic syndrome have high risk of developing renal failure and of adverse neurological, cardiac outcomes and death (Shaefi et al. 2018; Levin et al. 2004; Ortoleva and Cobey 2019; Lenglet et al. 2011b; Liu et al. 2017; Gomes et al. 1998). Given the increasing frequency of invasive cardiac surgery, the investigation and effective management of

Methylene Blue for Vasoplegic Syndrome Post Cardiac Surgery

Post-operative cardiac surgical patients are encountered commonly in the intensive care unit. Methylene blue might be a useful treatment for patients with vasopressor-refractory vasoplegia but high quality evidence is lacking.

post-cardiac surgical vasoplegic syndrome is of critical importance.

Definitions of vasoplegic syndrome vary (Lenglet et al. 2011b; Stawicki et al. 2008; Gomes et al. 1998; Donati et al. 2002; Lambden et al. 2018; Orozco Vinasco et al. 2019). In addition to the requirement for the condition to develop within 24 hours of cardiopulmonary bypass, a combination of clinical parameters including low blood pressure, low central venous pressure and pulmonary capillary wedge pressure, elevated cardiac index, and low peripheral resistance combined with a minimum vasopressor requirement are used in the literature to define the syndrome. In practical terms, clinicians recognise vasoplegic syndrome when they encounter a patient with a combination of high cardiac output and low blood pressure.

Pathophysiology of Vasoplegic Syndrome

Cardiopulmonary bypass-induced vasoplegia results from a combination of inciting factors including the immunological response to ischaemia reperfusion injury of the heart and lung, endotoxin release from mucosal surfaces, and complement activation after exposure of blood to the cardiopulmonary bypass circuit (Shaefi et al. 2018; Hall et al. 1997). These processes result in increased production of oxygen free radicals, thromboxane A₂, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF). Inducible nitric oxide synthase is stimulated via these cytokines and leads to an overproduction of nitric oxide (NO) (Lenglet et al. 2011b). NO increases vasodilation primar-

ily via activation of guanylyl cyclase, which results in production of cyclic guanosine monophosphate (cGMP) (Booth et al. 2017). The normal role of cGMP is inhibition of calcium entry via voltage-gated channels and therefore cardiopulmonary-bypass induced NO production leads to a rapid reduction in intracellular calcium and vasodilation. NO also activates ATP-sensitive potassium channels causing membrane hyperpolarisation which causes a further reduction in vascular smooth muscle tone (Ortoleva and Cobey 2019; Ortoleva et al. 2020).

In addition to this well accepted pathway, other NO-independent pathways resulting from the cascade of factors above have been proposed. Cardiopulmonary bypass-induced release of IL-1 and IL-2 results in vasodilation in the absence of NO via direct guanylate cyclase activation and this effect can be reversed with administration of methylene blue (Beasley and McGuiggin 1994; Samlowski et al. 2011). Endogenous soluble guanylate cyclase activating factors such as carbon monoxide (CO) and the hydroxyl free radical (OH) also contribute to vasoplegia by direct activation of guanylate cyclase (Schmidt 1992). Lastly, vasopressin deficiency due to haemodilution during cardiopulmonary bypass has been suggested as an exacerbating feature of post cardiac surgical vasoplegia.

Management of Vasoplegic Syndrome

Accurate pre-operative determination of patients who will develop vasoplegic syndrome is not possible at present. Risk factors which are associated with vaso-

plegic syndrome include pre-operative use of angiotensin-converting enzyme inhibitors or beta-blockers, higher comorbid disease burden before surgery (Shaefi et al. 2018; Riha and Augoustides 2011), low pre-operative left ventricular ejection fraction (Shaefi et al. 2018), preoperative use of heparin, congestive heart failure, prolonged duration of cardiopulmonary bypass, advanced age, and the use of opioid analgesia (Ortoleva et al. 2020).

Early recognition and differentiation of vasoplegic syndrome from other common causes of shock in the post-operative cardiothoracic setting is complex as cardiogenic, obstructive, hypovolaemic and vasoplegic shock often coexist. Fluid responsiveness and post-operative anaemia should be treated with combination of blood product replacement, crystalloid and colloid with a focus on restrictive resuscitative targets (Murphy et al. 2015). Early use of vasopressors and simultaneous investigation and elimination of reversible causes is necessary. Ultimately, the identification of vasoplegic syndrome requires a high index of suspicion and remains a diagnosis of exclusion.

The action of soluble Guanylate Cyclase represents an important target for the management of vasoplegic syndrome. Methylene blue is a low cost therapy which acts via both direct and indirect mechanisms to counteract the vasoplegic effects of cardiopulmonary bypass (Omar et al. 2015). The direct action of methylene blue is via oxidation of both inducible nitric oxide synthase and endothelial nitric oxide synthase resulting in significantly reduced NO levels. Secondly, methylene blue acts

via indirect pathways by binding to the haem complex of the guanylate cyclase enzyme. This further reduces vasoplegia by targeting the common final pathway of both nitric oxide dependent and independent mechanisms, reducing the formation of cyclic GMP and increasing intracellular calcium levels and vascular tone.

Only one previous randomised clinical

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trial has evaluated the use of methylene blue in patients with post cardiac surgery vasoplegia (Levin et al. 2004). A total of 56 patients with post cardiopulmonary bypass vasoplegia were included. Of these, 28 received an infusion of 1.5 mg/kg of methylene blue over 1 hour and 28 received placebo. Mortality in the group treated with methylene blue was 0% compared with 21.4% in the placebo group respectively ($P=0.01$). There was also a significant difference in the duration of vasopressor support with all patients in the methylene blue group successfully weaned from vasopressor support within 4 hours of the treatment (Levin et al. 2004).

Another randomised clinical trial compared the use of a single 2mg/kg dose of methylene blue given 1hr prior to

surgery in patients at high risk of developing vasoplegia (Ozal et al. 2005). In this study, vasoplegic syndrome was not observed in any patients in the treatment group but occurred in 26% of the control. In a second prospective randomised controlled trial, a dose of 3mg/kg vs placebo was given immediately post cardiopulmonary bypass and was observed to significantly reduce post-operative phenylephrine and noradrenaline requirements (Maslow et al. 2006).

Finally, a single centre retrospective analysis evaluating the use of 2 mg/kg of intravenous methylene blue followed by a 12-hour infusion at 0.5 mg/kg/h demonstrated that the use of methylene blue was associated with significant reductions in major adverse events defined as permanent stroke, renal failure, reoperation, deep sternal wound infection, and prolonged ventilation in addition to operative mortality (in-hospital or 30-day) (Mehaffey et al. 2017).

Despite these encouraging data, further research is now needed to establish whether methylene blue can be effectively applied to severe post-operative cardiothoracic vasoplegia to reduce both mortality, duration of vasopressor therapy and ICU length of stay. Given how rapidly the burden of cardiac disease and the frequency of cardiac surgical intervention is increasing, a large randomised controlled trial to determine the safety and efficacy of this therapy is a high priority.

Conflict of Interest

None. ■

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