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Changing sedative infusion from propofol to midazolam improves sublingual microcirculatory perfusion in patients with septic shock☆,☆☆

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Abstract

Purpose: The goal of this study was to explore possible microcirculatory alterations by changing sedative infusion from propofol to midazolam in patients with septic shock.

Materials and Methods: Patients (n = 16) were sedated with propofol during the first 24 hours after intubation, then with midazolam, following a predefined algorithm. Systemic hemodynamics, perfusion parameters, and microcirculation were assessed at 2 time points: just before stopping propofol and 30 minutes after the start of midazolam infusion. Sublingual microcirculation was evaluated by sidestream dark-field imaging.

Results: The microvascular flow index and the proportion of perfused small vessels were greater when patients were on midazolam than when on propofol infusion (2.8 [2.4-2.9] vs 2.3 [1.9-2.6] and 96.4% [93.7%-97.6%] vs 92.7% [88.3%-94.7%], respectively; $P < .005$), and the flow heterogeneity index was greater with propofol than with midazolam use (0.49 [0.2-0.8] vs 0.19 [0.1-0.4], $P < .05$). There were no significant changes in systemic hemodynamics and perfusion parameters either during propofol use or during midazolam infusions. Data are presented as median (25th-75th percentiles).

Conclusions: In this study, sublingual microcirculatory perfusion improved when the infusion was changed from propofol to midazolam in patients with septic shock. This observation could not be explained by changes in systemic hemodynamics.

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1. Introduction

The presence of microvascular alterations in patients with septic shock has been clearly recognized over the last decade. Acute microvascular alterations are associated with severe sepsis and septic shock [1], and the degree of microvascular impairment is associated with prognosis in different types of shock [2,3]. In addition, increased microcirculatory flow during resuscitation was associated with reduced organ failure at 24 hours after the initiation of septic shock treatment, and this could not be explained by differences in global hemodynamics [4]. Nevertheless, interventional procedures focused on improving microcirculation still remain to be proven beneficial. However, it does not prove that microvascular alterations are a consequence rather than a cause of morbidity because they are likely to be involved in the pathophysiology of shock and are independent, aside from being one of the most powerful predictors of outcome [3,5]. Hence, recently, an expressive number of studies were aimed at associating different therapeutic interventions for severe sepsis, such as fluids, norepinephrine, dobutamine, nitroglycerine, hydrocortisone, and red blood cell transfusion, with alterations in microcirculatory blood flow [6–11]. Furthermore, different experimental studies have tried to couple new possible therapeutic drugs for septic shock and microcirculatory blood flow [12,13].

Patients with septic shock usually need mechanical ventilation, making the use of sedative drugs almost imperative to treat anxiety and agitation and to facilitate their care. Propofol (PP) and midazolam (MDZ) are the most commonly used drugs for continuous infusion in these patients [14]. However, little is known about the microcirculatory effects of sedative drugs. In healthy women, PP reduced microcirculatory perfusion [15], whereas, in critically ill nonseptic patients, MDZ induced a deterioration of vasomotion and microvascular response to ischemia [16]. Therefore, it is important to explore possible microcirculatory alterations because of management of sedative drugs in patients with septic shock.

2. Materials and methods

This prospective nonrandomized study was approved by the Research Ethics Committee of the State University of Rio de Janeiro and was registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01618396). Informed consent was obtained from patient's closest relatives. Patients were recruited from within the medical-surgical intensive care unit (ICU) of a tertiary hospital, between the months of March and August 2011. We included patients with septic shock [17] needing mechanical ventilation in a pressure- or volume-controlled mode. Exclusion criteria were being younger than 18 years, pregnancy, non–sinus rhythm, and contraindication of daily interruption of sedative drug, mainly with the use of neuromuscular blocking drugs, or patients with intracranial hypertension or *status epilepticus*.

We recorded the Acute Physiology and Chronic Health Evaluation (APACHE) II score [18] upon admission, and the Sepsis-Related Organ Failure Assessment (SOFA) score [19] upon inclusion.

2.1. Sedation management

All patients were initially sedated with PP after intubation. On the second day of mechanical ventilation, PP infusion was interrupted, in accordance to the current sedation protective strategy [20]. At this point, the decision whether the patient had clinical condition for weaning within the next 48 hours was made. If not, when the patient awoke, MDZ infusion would be initiated after a loading dose of 0.05 mg/kg. Sedation target was a Ramsay scale score of 4 to 5. Fentanyl would be added if necessary, and the infusion rate was maintained the same throughout the study. Bispectral index (BIS) was used to access sedation depth, and at this stage, all patients had cardiac output and other flow-based hemodynamic variables measured by the FloTrac/Vigileo device (Edwards Lifesciences LLC, Irvine, CA, USA).

2.2. Microcirculatory measurements and analysis

The microcirculatory network was evaluated in the sublingual mucosa by the sidestream dark-field imaging (SDF) device (Microscan; Micro Vision Medical, Amsterdam, the Netherlands) [21] and instantaneously recorded on a personal computer (Sony Model PCG-7184l, Tokyo, Japan) using the software AVA 3.0. Image acquisition and analysis were performed following international recommendations [22]. After gentle removal of saliva, 20-second images were recorded from at least 4 different sites. Adequate focus and contrast adjustment were verified, and poor-quality images were discarded. All sequences were acquired by the same investigator (G.L.P.) and then blindly and randomly analyzed by another investigator (F.F.) using a semiquantitative method.

The image analysis determined the following: proportion of perfused vessels (PPV), microvascular flow index (MFI), total vascular density (TVD), perfused vascular density (PVD), and flow heterogeneity index (FHI). As previously described, to determine the MFI, the image was divided into 4 quadrants and the predominant flow type was assessed in each one of them and characterized either as follows: absent, 0; intermittent, 1; sluggish, 2; or normal, 3. The values of the 4 quadrants were averaged. Flow heterogeneity index was calculated as FHI = (MFImax − MFImin)/mean MFI of all sublingual sites at a single time point. For TVD and PVD, a gridline consisting of 3 horizontal and 3 vertical equidistant lines was superimposed on the image [22]. All vessels crossing the lines were counted and classified as either being perfused vessels (continuous flow) or non–perfused vessels