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

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Propofol;
Midazolam

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

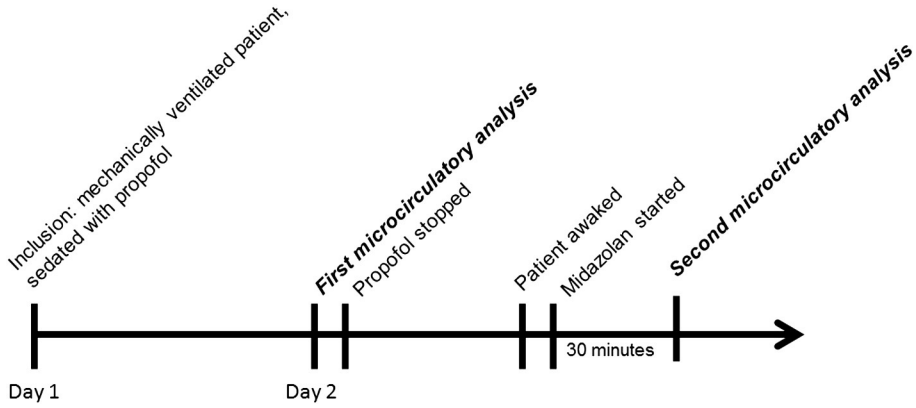

Fig. 1 Timeline of study protocol.

(absent or intermittent flow, the latter being absence of flow for at least 50% of the time). Densities were calculated as the total number of vessels (TVD), or number of perfused vessels (PVD), divided by the total length of the gridline in millimeters. The PPV was calculated with the following formula: 100 × (total number of vessel − [absent or intermittent flow])/total number of vessels. Large and small (<20 μm) vessels were analyzed separately.

The importance of the analysis of large vessels relies on quality control, to make sure that no excessive pressure on the SDF device is applied by the investigator because flow in these vessels is present even in dying patients [1,22].

2.3. Study protocol

Patients were assessed on 2 stages: (1) just before the interruption of PP and (2) 30 minutes after the onset of MDZ infusion (Fig. 1). Each assessment consisted of hemodynamic measurements and perfusion parameters: mean arterial pressure (MAP), heart rate, cardiac index, difference in CO_2 tension between venous and arterial blood (ΔCO_2), pulse pressure variation (ΔPP), central venous pressure, vasoactive requirements, arterial lactate, central venous oxygen saturation ($ScvO_2$), and base excess. If necessary, tidal volume would be temporarily set at 8 mL/kg to obtain a reliable ΔPP [23]. Microcirculatory parameters were also assessed at this moment.

Ventilator settings and fentanyl and dobutamine infusions (if needed) were kept constant throughout the study, and norepinephrine infusion rates were titrated to keep MAP greater than 65 mm Hg. No therapeutic intervention such as volume expansion or blood transfusion was instituted during the study period in any patient. Patients were followed for ICU mortality.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 16 for Windows (SPSS Inc, Chicago, Ill). Demographic variables were expressed as mean and SD or n and percentage, as appropriate. All numeric variables were tested for normality distribution with the Kolmogorov-Smirnov test. We compared continuous systemic and microcirculatory variables measured during PP and MDZ infusion, using the Wilcoxon signed rank test (nonparametric distribution). Data are presented as median (25th-75th percentiles). *P* value less than .05 was considered significant.

3. Results

3.1. Patient's characteristics

Sixteen consecutive patients with septic shock were included in this study between March and August 2011. Table 1 shows patient's characteristics. Sedation dose and time course of clinical, hemodynamic, and perfusion variables throughout the 2 sequential study steps are presented in

Table 1 Demographic, severity of illness, infection characteristics, and mortality of the study population

Variable	Mean (±SD) or n (%)
Age (y)	78 (±11.6)
APACHE II	19 (±6)
SOFA on admission	3 (±2.7)
SOFA on inclusion	10 (±2.7)
Days with antibiotics (before study start)	3 (±0.9)
Female sex	8 (50)
Bacteremia	3 (20)
Site of infection	
Lung	5 (31)
Abdomen	5 (31)
Urine	2 (13)
Catheter	1 (6)
Cholecystitis	1 (6)
Skin	1 (6)
Undefined	1 (6)
Time between 2 SDF examinations (min)	155 (48)
Hospital mortality	6 (37)

Data are reported as n (%) or mean (standard deviation).

Table 2 Sedative dose and hemodynamic, respiratory, neurologic, and metabolic parameters of patients with septic shock in the beginning of PP and MDZ infusions

Variable	PP	MDZ	*P*
BIS	51 (47-57)	44 (40-50)	.004
Ramsay	5 (5-5)	5 (5-6)	1
MAP (mm Hg)	78 (69-93)	78 (71-83)	.5
Heart rate (beats/min)	79 (66-99)	82 (67-99)	.03
Cardiac Index (L min^{-1} m^{-2})	2.5 (2.2-2.7)	2.5 (2.3-2.8)	.08
ΔPP (%)	10 (7-11)	9 (7-12)	.6
Temperature (°C)	36.5 (36.2-36.7)	36.6 (36.3-37)	.7
ΔCO_2	6 (3-7)	5 (4-6)	.6
$Scvo_2$ (%)	76 (74-82)	78 (72-82)	.8
pH (log(L/mol))	7.4 (7.4-7.5)	7.5 (7.37-7.49)	.5
Bicarbonate (mEq/L)	23.5 (19.6-24.9)	24 (20-25)	.8
Lactate (mmol/L)	1.8 (1.2-2.4)	1.6 (1.1-2.2)	.6
Tidal volume (mL/kg)	6.7 (5.4-8.4)	6.4 (5.7-7.8)	.2
PEEP (mm Hg)	8 (6-10)	8 (6-10)	1
Noradrenaline (μg kg^{-1} min^{-1})	0.21 (0.04-0.4)	0.22 (0.05-0.38)	.5
Sedative dose (mg kg^{-1} h^{-1})	0.96 (0.59-1.23)	0.07 (0.06-0.09)	–
Hematocrit (%)	28.1 (24-31)	28.1 (24-32)	.2
Po_2/Fio_2	320 (256-348)	290 (246-363)	.4

Data are presented as median (25th-75th percentiles).

Table 2. Ten patients (62%) had already been treated with hydrocortisone, all of them for at least 12 hours. Norepinephrine was administered to all patients. Three patients (18%) were also treated with dobutamine and 2 other (12%) with fentanyl. The ICU mortality rate was 37% (6 patients). Temperature, MAP, cardiac index, ΔCO_2, ΔPP, central venous pressure, vasoactive requirements, arterial lactate, $Scvo_2$, base excess, and Ramsay scale score were similar when patients were on sedative infusion. Heart rate was slightly lower, and BIS index was higher when patients were on PP in comparison with MDZ infusion. When patients were awake, MAP and BIS index were higher, whereas Ramsay scale score was lower compared with those obtained with PP or MDZ, as expected (87 [82-101] vs 78 [69-93] and 78 [71-83] mm Hg, 84[80-90] vs 51 [47-57] and 44 [40-50], and 2 [2-3] vs 5 [5-5] and 5 [5-6], respectively; $P < .001$).

3.2. Microcirculatory results

We performed 32 SDF studies on 16 septic patients. The average time between the 2 examinations was 155 minutes. We observed an increase in the PPVs between PP and MDZ stages, owing to alterations on small-vessel perfusion because no large vessel presented unsatisfactory blood flow at any given moment. Therefore, the proportion of perfused small vessels was lower when patients were on PP as compared with MDZ. The MFI was higher with MDZ compared with PP, whereas FHI was higher with PP (Table 3). The time course of PPV (of total and small vessels), FHI, and MFI during the study period is depicted in Fig. 2, respectively. No significant difference was seen between PP and MDZ in terms of TVD and PVD.

4. Discussion

To our knowledge, this is the first time that microcirculatory effects of sedative drugs management were studied in patients with septic shock. We have demonstrated that changing sedative infusion from PP to MDZ improves sublingual microcirculatory perfusion in patients with septic shock, independently of changes on global hemodynamic

Table 3 Microcirculatory perfusion variables during PP and MDZ infusions

Variable	PP	MDZ	*P*
Density of total vessels (n/mm)	13.1 (11.5-14.9)	13 (12-14.2)	.68
Density of perfused small vessels (n/mm)	11.1 (9.5-12.7)	11.6 (10.9-12.4)	.13
Proportion of perfused total vessels (%)	93.4 (89.3-95.2)	96.6 (94.2-97.7)	.001
Proportion of perfused small vessels (%)	92.7 (88.3-94.7)	96.4 (93.7-97.6)	.001
MFI	2.3 (1.9-2.6)	2.8 (2.4-2.9)	.002
FHI	0.49 (0.2-0.8)	0.19 (0.1-0.4)	.016

Data are presented as median [25th-75th percentiles].

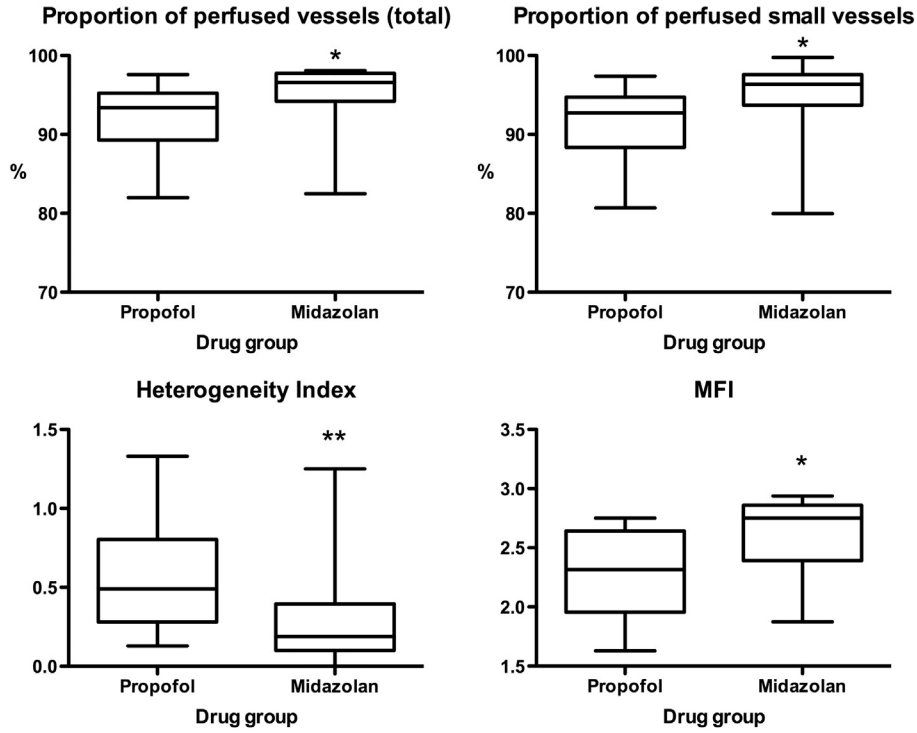

Fig. 2 Comparison of microcirculatory parameters measured during PP and MDZ infusions. *$P < .01$ and **$P < .05$.

variables. The mechanism accounting for this microvascular improvement is, however, uncertain.

The administration of PP has hemodynamic effects, of which the most significant is arterial hypotension primarily elicited by decreasing vascular tone and venous return [24]. With regard to the microcirculation, PP directly affected capillary blood flow in young healthy humans, and its infusion induced a significant reduction in the density of total small vessels, and although not significant, the proportion of small vessels containing red blood cells with intermittent or no flow increased [15]. This is in line with our study and further suggests that PP induces an increase in microvascular blood flow heterogeneity, contributing to reduction in oxygen extraction capability. In experimental models of hemorrhagic shock, compared with ketamine and pentobarbital, capillary blood flow was mainly reduced by PP, both at baseline and during hemorrhage [25]. In a recent crossover study, norepinephrine markedly increased gastromucosal hemoglobin oxygenation in dogs during sevoflurane anesthesia, but this was not observed during PP anesthesia. So, PP appeared to blunt regional response to norepinephrine, not predictable through its systemic effects [26]. On the other hand, effects of MDZ on the microcirculation were rarely evaluated. In a study using laser Doppler flowmetry to assess the microcirculation of 10 nonseptic patients, MDZ induced an increase in cutaneous microcirculatory blood flow, secondary to vasodilatation, and alterations of vasomotion [16]. In an experimental study, the hepatosplanchinic microcirculation of rats was assessed to compare the effects of several different intravenous anesthetics. Functional capillary density was higher during PP when compared with MDZ infusion, but MAP was significantly lower during MDZ infusion, which could explain the result. Both MFI and FIH were not obtained in this study [27].

We have chosen the SDF technique to visualize the microcirculation because it is noninvasive, is easy to use in an ICU setting, and allows identification of capillaries and venules [1]. Sidestream dark-field imaging requires a semiquantitative approach to estimate vessel density and flow, it does not allow identical vessels to be examined over time, and estimation of blood flow and blood cell velocity provides a 2-dimensional projection of the 3-dimensional microvascular network. However, Kanoore and coworkers [28] recently demonstrated that quantitative and semiquantitative microcirculatory parameters have similar performances. We have studied the effects of sedation on sublingual microcirculation, and this may not reflect perfusion in other microcirculatory beds. However, this area is easily accessed and has a good correlation with splanchnic perfusion, as demonstrated by several studies [29,30]. Other techniques have presented important limitations. Laser Doppler flowmetry, for example, averages velocities in all explored vessels and does not take into account blood flow heterogeneity.

Our study has some limitations. Patient mortality was higher than expected by APACHE II score (37% vs 32%), but it is important to note that at the moment of the study inclusion, they were much sicker than on ICU admission, as SOFA score indicates (3 vs 10).

The study design did not include randomization between the 2 steps. Patients stayed a longer period of time on PP infusion than on MDZ when the microcirculation was

analyzed. Therefore, we cannot rule out the possibility that if MDZ infusion time were longer, microcirculatory alterations could be worse than observed. In other words, it is not possible to deduce that MDZ is less detrimental for the microcirculation than PP. The interruption of sedative infusion leading to awakening of the patient may have been partially responsible for observed microcirculatory improvement.

On the other hand, a carryover effect may interfere when studying the microcirculatory effects of MDZ because we cannot exclude the possibility of residual effects of PP during this period. However, patients awoke before the initiation of MDZ infusion, BIS levels were higher, and, most importantly, microcirculatory variables improved during MDZ infusion. In fact, we have designed our study according to widely accepted sedation guidelines to be as close as possible to routine clinical practices. Our study lasted a total of about 2.6 hours, and longer follow-up periods are difficult in practice because of the inevitable therapeutic alterations and patient manipulation. Still, a spontaneous improvement of microcirculatory variables over time cannot be ruled out, once it happens in surviving patients. Three patients (18%) were on dobutamine infusion and another 2 on fentanyl, but infusion rates remained the same during the study period, and even excluding these patients, the result would still be the same (data not shown). Heart rate was slightly lower when patients were on PP infusion (although with no clinical significance—79 vs 82 beats/min), but cardiac index was not different in both moments. Ten patients (62%) were using hydrocortisone, all for more than 12 hours when microcirculatory alterations had already occurred, so effects of steroid on the microcirculation in this setting are improbable [10]. Although BIS was significantly lower during MDZ infusion, it was at the same range (between 40 and 60) for the whole study protocol. Finally, one may argue that these microcirculatory changes might have caused no significant consequences on organ function in these already volume-resuscitated patients with septic shock. It is true that maybe the study was underpowered to show a significant difference in density of perfused small vessels and that the proportion of perfused small vessels was relatively preserved during PP infusion, despite a significant increase in microvascular perfusion observed during MDZ administration. However, it is important to note that the MFI was consistently lower during PP infusion, whereas the FHI was higher in this moment, compared with MDZ infusion. These observations suggest that increasing the heterogeneity of microvascular blood flow in already hypoperfused tissues areas of patients with septic shock may worsen microvascular flow, as recorded during PP administration. Furthermore, in patients with an early severe septic shock, administration of PP may induce additional microcirculatory alterations with important consequences to organ function. As previously suggested, increased microcirculatory flow during resuscitation was associated with fewer organ failures and fewer deaths [3,4]. Hence, avoiding interventions that could impair microvascular flow makes sense in septic shock treatment.

Therefore, in patients with septic shock, changing sedative infusion from PP to MDZ results in an improvement of the microcirculation, independently of changes in global hemodynamic variables. Our study raises the question of whether the choice of a sedative agent in patients with septic shock has a direct effect on the microcirculation and if the sedation with PP is worse for the microcirculation than MDZ. However, more experiments are needed to evaluate this issue. To our knowledge, this is the first study addressing the microcirculatory effects of sedative drug management in patients with septic shock.

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