JOURNAL OF SURGICAL RESEARCH 193 (2015) 849–855

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Propofol increases preload dependency in septic shock patients

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ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form
23 July 2014
Accepted 28 August 2014
Available online 6 September 2014

Keywords:
Sedation
Propofol
Midazolam
Preload dependency
Passive leg raising
Preload dependency
Septic shock

ABSTRACT

Background: Predicting fluid responsiveness is crucial for fluid administration in septic shock patients. Midazolam and propofol decrease vascular tone and venous return, which may influence preload dependency. However, little is known about the effects of these two sedatives on preload dependency in septic shock patients. We evaluated the effects of sedation with propofol or midazolam on preload dependency in septic shock patients who have been fluid resuscitated.

Methods: Forty-three septic shock patients who were undergoing early goal-directed therapy resuscitated within 24 h were enrolled. The patients were randomly divided into the midazolam group and the propofol group. An initial passive leg-raising test (PLR1) was performed to evaluate passive leg raising test (PLR) responsiveness. Then, the patients were infused with midazolam or propofol. After increasing the doses of the sedatives to titrate to a Ramsay 4 score, a second passive leg raising test (PLR2) was conducted to evaluate PLR responsiveness. The primary end-point was the preload dependency before and after sedation with midazolam or propofol.

Results: In the midazolam-PLR1-negative patients, there was no difference between the changes in the cardiac index induced by PLR1 (PLR1-Δ cardiac function index [CI]) and the changes in the cardiac index induced by PLR2 (PLR2-Δ CI) (+1.4% ± 7.4% *versus* +1.7% ± 6.4%, $P > 0.05$). However, in the propofol-PLR1-negative patients, there was a significant increase in the PLR-Δ CI after sedation to a Ramsay 4 score compared with a Ramsay 3 score (+7.3% ± 4.8% *versus* +3.2% ± 4.7%, $P = 0.008$). There were no differences between PLR1-Δ CI and PLR2-Δ CI within the midazolam-PLR1-positive patients or within the propofol-PLR1-positive patients.

Conclusions: In titrating the sedation level from a Ramsay 3 score to a Ramsay 4 score, propofol but not midazolam increased preload dependency in septic shock patients with fluid nonresponsiveness.

Trial registration: Clinicaltrials.gov identifier: NCT 02050893

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http://dx.doi.org/10.1016/j.jss.2014.08.050

1. Introduction

Volume expansion is commonly used in critically ill patients to improve their hemodynamic conditions, which is based on their volume responsivity. In a previous report, fewer than 50% of the patients responded to the volume expansion that was deemed necessary by the clinicians [1]. In other studies, exacerbated pulmonary edema and septic shock concurrent with an increased extravascular lung water index caused significant challenges to the lifesaving procedures in preload unresponsive patients [2,3]. Therefore, it is of prime importance to improve the preload dependency of septic shock patients.

Infection, trauma, pain, a prolonged mechanical ventilation time, and/or septic shock forces critically ill patients into a state of severe stress, which can contribute to myocardial ischemia, arrhythmia, gastrointestinal tract ischemia, and stress ulcers. In addition, catecholamine (CA) levels are markedly increased in severe stress reactions in the intensive care unit (ICU) setting [4]. As CA is able to attenuate the preload dependency of the heart in patients [5], we speculated that a decreased preload dependency may exist in those with a severe stress reaction.

Currently, propofol and midazolam are the most widely used drugs for the sedation of patients in the ICU [6,7]. As blocking agents for the sympathetic nervous system, they can inhibit the activity of the autonomic nervous system [8,9]. Sedation can attenuate the release of CA *in vivo* [10,11] leading to remarkable decreases in the stress reaction caused by noxious stimulation as well as potential decreases in the cardiac preload and peripheral resistance. In our previous observational study [12], we confirmed that a propofol infusion, but not a dexmedetomidine infusion, can increase the preload dependency in circulatory failure patients. Nevertheless, the study included pooled septic and nonseptic patients. The effect of sedative drugs on preload dependency in septic shock patients remains unclear. The vascular tone and the ability to respond to drugs in septic shock are different compared with nonseptic shock conditions because of vasoparesis. Forty-three patients with the clinical manifestations of septic shock were included in this study. A passive leg raising test (PLR) test was performed to evaluate the patients' cardiac preload dependency before and after increasing the sedation level (using propofol or midazolam) from a Ramsay score 3 to a Ramsay score 4.

2. Methods

2.1. Patients

Forty-three septic shock patients admitted to the ICU from May 2012–May 2013 were included in this prospective, nonblinded, randomized, controlled study. The study was registered as project number NCT02050893 with clinicaltrials.gov and was approved by the Ethics Committee of the Zhongda Hospital of Southeast University (2012ZDllKY24.0). Informed consent was obtained. The inclusion criteria were as follows: the need for sedative therapy due to anxiety and/or the need for mechanical ventilation in the absence of baseline sedative agent administration. *The* criteria of *septic shock* were based on American College Of Chest Physicians/Society Of Critical Care Medicine (ACCP/SCCM) Consensus 2012. The patients met early goal-directed therapy (EGDT) criteria including [13]: [1] a central venous pressure (CVP) of 8–12 mm Hg; [2] a mean arterial pressure of ≥65 mm Hg; [3] urine output of >0.5 mL/kg per hour; and [4] a central venous blood oxygen saturation ($ScvO_2$) of 70% or higher or a mixed venous oxygen saturation (SvO_2) of 65% or higher. The exclusion criteria were as follows: (1) aged <18 y; (2) an intra-abdominal pressure of >12 mm Hg; (3) a central nervous system pathology; (4) a second-degree heart blockage or third-degree heart blockage, bradycardia, heart blockage, acute coronary syndrome, cardiac shock, or use of intra-aortic balloon pump; (5) contraindications to PLR, such as a craniocerebral injury and venous thrombosis; (6) severe liver disease (Child–Pugh class C); or (7) a systolic blood pressure of <90 mm Hg despite vasopressor infusion.

2.2. Measurements

An opiate drug was administered to induce analgesia before the study. No modulation was performed in the doses of the vasoactive agent and analgesics, respirator parameters, and fluid infusion rate. The patients were monitored by CVP measurements, using an invasive arterial pressure and a $PiCCO_2$ (Pulsion Medical Systems, Munich, Germany) device. Previous studies have confirmed the utility of PiCCO measurements for assessing the preload dependency in septic shock patients [5,14]. The cardiac output (CO) and stroke volume were determined with a $PiCCO_2$ device and measured by transpulmonary thermodilution before and after the study drug (propofol or midazolam) infusion and by a pulse contour analysis before and after the PLR tests. The maximal pressure developed by the left ventricle (dP/dtmax) and global end-diastolic volume (GEDI) index were determined with the $PiCCO_2$ device.

2.3. Study design

An initial PLR test (PLR1) was performed in all the patients to evaluate the preload dependency at baseline. PLR was performed by transferring the patients from a semirecumbent position to a horizontal position with the legs elevated at 45° [12]. Propofol and midazolam were infused and titrated according to the Ramsay scale; the goal of the sedation was to increase the sedation level from Ramsay score 3 to Ramsay score 4. Preload dependency was assessed by a PLR test according to the previously documented methods [5]. A patient was considered to have a positive PLR test finding if the change in the cardiac function index (CI) induced by the PLR increased by ≥10% during the PLR test [5]. An initial bolus dose of 0.05 mg/kg of midazolam, followed by a continuous infusion with 0.05–0.1 mg/kg/h or an initial bolus dose of 0.5 mg/kg propofol, and then continuous infusion with 0.5–2.0 mg/kg/h was administered. The infusion rate of the propofol or midazolam was titrated to maintain the target sedation depth of Ramsay score 4. After 40 min, when a suitable sedation level was achieved and the hemodynamic variables were stabilized, a second PLR test (PLR2) was then performed. Treatment