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Original Contribution

Improved sepsis bundles in the treatment of septic shock: a prospective clinical study ☆

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ABSTRACT

Background: Sepsis bundles can decrease mortality in patients with severe sepsis or septic shock. However, current methods of measuring pressure, such as central venous pressure, are inadequate. This study investigated the effect of improved sepsis bundles informed by pulse-indicated continuous cardiac output.
Methods: We compared the outcome of treatment with sepsis bundles informed by either conventional pressure measurements or pulse-indicated continuous cardiac output. Patients in 2 groups received fluid resuscitation, standard antibiotics, and oxygen therapy.
Results: A total of 105 patients with septic shock were randomly divided into 2 groups: the conventional sepsis bundle group (n = 52) or the improved sepsis bundle group (ISBG, n = 53). The ISBG significantly reduced the mean Acute Physiology and Chronic Health Evaluation II and Sepsis-related Organ Failure Assessment scores. Significantly fewer ISBG-treated patients received vasoactive drugs compared to conventional sepsis bundle group–treated patients. In addition, patients in the ISBG exhibited a significantly increased arterial blood lactate clearance rate and required less total fluid resuscitation and a shorter duration of mechanical ventilation and stay in the intensive care unit.
Conclusions: Pulse-indicated continuous cardiac output–directed sepsis bundles can reduce the severity of septic shock, provide more accurate fluid resuscitation, and reduce the duration of mechanical ventilation and stay in the intensive care unit.

1. Introduction

Severe sepsis and septic shock are systemic inflammatory response syndromes characterized by impaired function in multiple organs. Although they are closely related, severe sepsis and septic shock are not identical conditions. *Severe sepsis* is defined as sepsis that is complicated by organ failure [1]. *Septic shock* is defined as sepsis that is complicated by hypotension that is refractory to treatment with fluids or by hyperlactemia [1].

Together, severe sepsis and septic shock remain one of the most common causes of death in intensive care units (ICUs). The high degree of morbidity and mortality in patients who are diagnosed with severe sepsis or septic shock remains a major unmet medical challenge, and an effective treatment protocol is urgently needed [2,3].

The current standard of care uses sepsis treatment bundles, which are groups of evidence-based interventions that provide greater benefit for the patient when administered together as compared with any single intervention. The therapeutic bundles have been codified in guidelines and implemented throughout care units. In 2004, the Surviving Sepsis Campaign and the Institute for Healthcare Improvement collaboratively wrote sepsis guidelines that incorporated 2 sepsis bundles, the 6-hour resuscitation and 24-hour management bundles [4-6]. Evidence suggested that achieving patient resuscitation within a 6-hour time frame significantly decreases mortality in patients with severe sepsis or septic shock [7,8]. The care bundles were revised in 2012 to include a 3-hour and a 6-hour resuscitation bundle [2]. However, the 6-hour resuscitation bundle from the 2004 sepsis guidelines is still considered as conventional treatment for severe sepsis and septic shock [9,10].

The concept of the "golden six hours" has been proposed for sepsis treatment bundles to achieve maximum therapeutic effect. To gauge the success of the bundles, there are several clinical parameters that must be achieved within that time, including (1) the central venous pressure (CVP) should be stable between 8 and 12 mm Hg, (2) mean artery pressure (MAP) should be greater than or equal to 65 mm Hg, (3) urinary production should be greater than or equal to 0.5 mL/kg per hour, and (4) venous oxygen saturation (SvO_2) should be greater

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than or equal to 70%. Recently, it has been found that pressure measurements such as CVP or pulmonary capillary wedge pressure (PCWP) lack sensitivity and precision. These parameters are susceptible to alterations of the intrathoracic pressure, cardiac and vascular adaptation effects, vasoactive drugs, valvular regurgitation, and positive end-expiratory pressure. Thus, CVP or PCWP measurements can result in an inaccurate estimation of volume load [11-13].

Pulse-indicated continuous cardiac output (PiCCO) is a novel technique that continuously monitors cardiovascular volume status using arterial pulse contour analysis, combined with a transpulmonary thermodilution technique. This technique can be used to calculate volume load parameters, such as the intrathoracic blood volume index (ITBVI) and global end-diastolic volume index (GEDVI) [14]. Both ITBVI and GEDVI are sensitive and reproducible measures of cardiac preload that are not affected by respiratory motion and cardiac compliance [15,16].

The objective of the current study was to investigate the clinical value of PiCCO to measure volume load in patients being treated for severe sepsis and septic shock. Procalcitonin (PCT) and arterial blood lactate clearance rate were monitored as treatment end points. Procalcitonin, a propeptide of calcitonin, can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis [17,18]. Arterial blood lactate clearance rate during the early stages of disease (within 6 hours) is a specific and sensitive indicator of mortality for patients with severe sepsis and septic shock [19-21]. We hypothesized that PiCCO-directed treatment bundles would improve treatment outcome compared to conventional sepsis bundles.

2. Methods

2.1. Patient enrollment

This study was approved by the Human Research Ethics Committee of the Affiliated Hospital at Yangzhou University. Written informed consent was obtained from the patient's next of kin before enrollment. The patients included in the study were 18 years or older and had been diagnosed with septic shock. The diagnoses were made in accordance with the surviving sepsis campaign guidelines criteria for management of severe sepsis and septic shock: systolic blood pressure less than 90 mm Hg, a systolic blood pressure decrease greater than 40 mm Hg, or less than 2 SDs below normal for age in the absence of other causes of hypotension [2]. Patients were excluded from the study, if (*a*) they had acute myocardial infarction, (*b*) they were younger than 18 years, (*c*) they were pregnant women, (*d*) they were undergoing immunosuppressive therapy, (*e*) they were terminally ill, or (*f*) they had ever received fluid resuscitation in another hospital.

2.2. Experimental procedure

A total of 105 patients were enrolled to participate in the study. They were divided into 2 groups and treated with either the conventional sepsis bundle (conventional sepsis bundle group [CSBG]; n = 52) or with the improved PiCCO-guided sepsis bundle (improved sepsis bundle group [ISBG]; n = 53).

Treatment with the conventional sepsis bundle involved fluid resuscitation, vasoactive drugs, antibiotics, and oxygen therapy (oxygen supply or invasive or noninvasive ventilator-assisted breathing) and was performed according to relevant guidelines. The therapeutic goals to be achieved within 6 hours included (1) stabilizing the CVP between 8 and 12 mm Hg, (2) stabilizing the MAP greater than or equal to 65 mm Hg, (3) urinary production greater than or equal to 0.5 mL/kg per hour, and (4) stabilizing SvO_2 greater than or equal to 70%. If venous oxygen saturation target was not achieved (SvO_2 <70%), packed red blood cells were transfused to a hematocrit of greater than or equal to 30%, and/or dobutamine infusion was administered.

Treatment with the improved sepsis bundles was guided by PiCCO measurements. However, patients received interventions with vasoactive drugs, antibiotics, and oxygen therapy following the same guidelines as the CSBG. To measure volume load, an indwelling venous catheter and PiCCO tube (PULSION Medical Systems SE, Fedkirchen, Germany) were placed beneath the subclavian or internal jugular vein and connected to a PiCCO monitor (PULSION Medical Systems SE). Fluids were administered depending on the intrathoracic blood volume to normalize the ITBVI between 850 and 1000 mL/m^2. If venous oxygen saturation target was not achieved ($SvO_2 < 70\%$), packed red blood cells were transfused to a hematocrit of greater than or equal to 30%. If necessary, cardiac function was improved by administering dobutamine based on the left ventricular contractility and stroke volume. The mean arterial blood pressure was maintained at greater than or equal to 65 mm Hg. In addition, in the CSBG, lasix was administered according to the physician's clinical experience. In the ISBG, the level of extravascular lung water and ITBVI were monitored to select the appropriate volume of solution to infuse and to determine whether to administer lasix. In this group, 20-mg lasix was used for both (1) ITBVI greater than 1000 mL/m^2, extravascular lung water index greater than 7.0 mL/kg or (2) ITBVI, 850 to 1000 mL/m^2, with MAP greater than or equal to 65 mm Hg and with a small dose of vasopressors (dopamine ≤ 5 μg/kg per minutes or norepinephrine ≤ 0.1 μg/kg per minute) or without vasopressors.

Before treatment, the patient's general condition and underlying disease were recorded. Patients were evaluated pretreatment and posttreatment using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sepsis-related Organ Failure Assessment (SOFA) score indices. Clinical measurements were also taken pretreatment and posttreatment including the mean artery pressure, oxygenation index, arterial blood lactate level and lactate clearance rate, PCT level, exposure to vasoactive drugs, the amount of fluid resuscitation administered over 6 hours and 72 hours, hospital mortality, duration of mechanical ventilation, and the length of the patient's ICU stay. The instant arterial blood lactate clearance rate was calculated using the following formula: [(initial level of arterial blood lactate − instant level of arterial blood lactate)/initial level of arterial blood lactate] × 100%.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL) to compare between groups with regard to hospital mortality and the number of patients who received vasoactive drugs. All other comparisons between groups were conducted using the *t* test. The data are presented as mean ± SD, and $P < .05$ was considered statistically significant.

3. Results

There were 105 patients enrolled in this study; the CSBG contained 52 patients, including 33 men and 19 women (Table 1). The average age of the CSBG patients was 61.5 ± 14.4 years (Table 1). Their average body mass index (BMI) was 26 ± 7 kg/m^2, and 38 of the 52 patients received mechanical ventilation. The ISBG contained 53 patients, including 35 men and 17 women (Table 1). Their average age was 60.8 ± 15.1 years. The average BMI of the ISBG was 26 ± 10, and 40 of the 53

Table 1
Patient demographics

	Conventional bundle	Improved bundle
n	52	53
Age (y)	61.5 ± 14.4	60.8 ± 15.1
Ratio of men/women	33/19	35/17
BMI (kg/m^2)	26 ± 7	26 ± 10
Mechanical ventilation (n)	38	40

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