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Clinical Investigation

CLINICAL INVESTIGATION

Continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock is associated with decreased mortality rates up to 90 days

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Abstract

Background. There is growing evidence that beta-blockade may reduce mortality in selected patients with sepsis. However, it is unclear if a pre-existing, chronic oral beta-blocker therapy should be continued or discontinued during the acute phase of severe sepsis and septic shock.

Methods. The present secondary analysis of a prospective observational single centre trial compared patient and treatment characteristics, length of stay and mortality rates between adult patients with severe sepsis or septic shock, in whom chronic beta-blocker therapy was continued or discontinued, respectively. The acute phase was defined as the period ranging from two days before to three days after disease onset. Multivariable Cox regression analysis was performed to compare survival outcomes in patients with pre-existing chronic beta-blockade.

Results. A total of 296 patients with severe sepsis or septic shock and pre-existing, chronic oral beta-blocker therapy were included. Chronic beta-blocker medication was discontinued during the acute phase of sepsis in 129 patients and continued in 167 patients. Continuation of beta-blocker therapy was significantly associated with decreased hospital (P=0.03), 28-day (P=0.04) and 90-day mortality rates (40.7% *vs* 52.7%; P=0.046) in contrast to beta-blocker cessation. The differences in survival functions were validated by a Log-rank test (P=0.01). Multivariable analysis identified the continuation of chronic beta-blocker therapy as an independent predictor of improved survival rates (HR = 0.67, 95%-CI (0.48, 0.95), P=0.03).

Conclusions. Continuing pre-existing chronic beta-blockade might be associated with decreased mortality rates up to 90 days in septic patients.

Key words: adrenergic beta-antagonists; critical care outcomes; mortality; sepsis

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Editor's key points

- Evidence is emerging that beta-blockade may be beneficial in some patients with sepsis.
- In this study there was an association between continuation of beta-blocker and decreased in-hospital, 28-day and 90-day mortality in patients with sepsis.
- However, the data are from a retrospective secondary analysis of a single centre study, with possible confounding factors.
- These results add to the evidence that beta-blockade may influence outcome in sepsis but should be interpreted with caution.

The high prevalence of cardiovascular diseases leads to an increasing proportion of hospital patients taking chronic oral beta-blocker therapy.[1] Physicians have to decide on a daily basis whether or not to continue chronic beta-blocker medication and these decisions can markedly influence outcome. For example, continuing chronic beta-blocker therapy has been associated with reduced mortality in patients with acute respiratory failure.[2]

In septic patients, limiting beta-adrenergic stimulation may also be beneficial.[3] In a randomized controlled trial, a newly initiated esmolol infusion in fluid resuscitated septic shock patients with tachycardia increased stroke volume, reduced norepinephrine and fluid requirements and lowered 28-day mortality rate.[4] Furthermore, a pre-existing chronic beta-blocker therapy was associated with improved 28-day survival despite a higher risk profile in this cohort.[5] However, whether oral beta-blockers were continued or not during sepsis in that study is unknown. Notably, current guidelines give no recommendation how to manage chronic beta-blocker medication during sepsis.[6]

The primary aim of the present study was to compare 90-day mortality rates for discontinued or continued chronic beta-blocker therapy in patients with severe sepsis and septic shock. Secondary outcomes included length of stay, ICU (intensive care unit), hospital and 28-day mortality.

Methods

Design

The present secondary analysis of a single-centre prospective observational trial[7] on critically ill patients with severe sepsis or septic shock was performed at an interdisciplinary, surgical ICU of the tertiary University Hospital of Greifswald, Germany. The original study was conducted as part of the local quality improvement program for the improvement in diagnosis and treatment in patients with severe sepsis or septic shock. Data were entered into a study database (Sepsis Information System for Quality Assurance, SIQ; G.punkt Medical Services, Magdeburg, Germany). The local ethics committee approved the study (Identifier: BB 133/10) and waived a written informed consent because of the observational nature of this quality improvement initiative and the anonymous data collection. The study was performed from January 1st, 2010 to December 31st, 2013.

Study population

During the study period, all patients of the ICU were screened daily by study nurses for the first episode of a systemic inflammatory response syndrome (SIRS) and at least one organ dysfunction within the last 24 h. SIRS, organ failure, severe sepsis and septic shock were defined according to ACCP/SCCM consensus criteria.[8] SIRS was diagnosed if at least two of the following criteria were fulfilled: body temperature $>38\,^{\circ}C$ or $<36\,^{\circ}C$, heart rate $>90\,min^{-1}$, respiratory failure with a respiratory rate $>20\,min^{-1}$ or a partial carbon dioxide pressure of <4.3 kPa and a white blood cell count of $>12{,}000$ cells μL^{-1} or <4000 cells μL^{-1} or the presence of more than 10% immature neutrophils. Organ dysfunctions were defined as systolic bp below 90 mm Hg in the absence of other causes and despite adequate fluid resuscitation, lactate acidosis (>1 mmol L^{-1}), oliguria (urine output <0.5 mL kg^{-1} h^{-1} for at least two h despite adequate fluid resuscitation) or an acute alteration in mental status. In a second step, the records were screened for signs of severe sepsis (to specify organ failure) or septic shock (hypotension or need of catecholamines despite adequate fluid replacement) and for the focus of infection (microbiological probes, X-rays etc.). Experienced intensivists in the study team (4 consultants) reviewed every case and decided based on all available documents whether SIRS and organ failure were probably caused by an infection or not. The study team did not change during the study period. All patients aged$\geq$18 yr, who met the criteria for the first episode of severe sepsis or septic shock, were included in the study. A second episode of sepsis was not registered to exclude phenomena such as the compensatory anti-inflammatory response syndrome.[9]

Definitions

The onset of sepsis was defined as the first time point when patients fulfilled the ACCP/SCCM criteria for severe sepsis or septic shock.[8] The onset of severe sepsis or septic shock was identified retrospectively by study nurses and validated by intensivists based on laboratory and haemodynamic variables and notes in the patient management system.

The place where sepsis was deemed to have occurred was determined according to dates of onset of sepsis, admission to hospital and ICU. Community-acquired sepsis was defined as an infection that occurred <48 h after hospital admission. ICU-acquired sepsis was defined as an infection >48 h after ICU admission. Otherwise, sepsis was categorised as hospital-acquired sepsis. Pre-existing chronic health problems were defined as at least one of the following: chronic kidney failure, metastatic cancer, haematological malignancies, AIDS, other causes of immunosuppression, severe hepatic failure, NYHA class IV and pre-existing chronic severe hypoxia.

The electronic patient management system or the patient's documents were reviewed, or the general practitioner was contacted to find which patients were receiving chronic beta-blocker medication. Pre-existing oral beta-blocker therapy was defined as a treatment started at least seven days before sepsis onset. The individual indications for beta-blockers could not be evaluated in detail but maybe inferred from the comorbidities (Table 1). Discontinuation was defined as an interruption of a pre-existing beta-blocker therapy for more than 24 h within the acute phase of severe sepsis and septic shock. The acute phase of severe sepsis and septic shock was narrowly defined as the period ranging from two days before to three days after sepsis onset, to evaluate the impact of beta-blockade during the period of highest haemodynamic instability and highest sympathetic tone.

Mortality rates were determined in ICU, hospital, and 28 days and 90 days after sepsis onset. Study nurses determined