Commentary

Effect of sepsis therapies on health-related quality of life

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See related research by Longo *et al.*, http://ccforum.com/content/11/6/R128

Abstract

Sepsis is one of the most common conditions encountered in the intensive care unit and is the 10th leading cause of death overall in the United States. Both long-term survival and health-related quality of life are reduced in survivors of sepsis, yet there is little knowledge of the effect of sepsis-specific interventions on either long-term survival or health-related quality of life. The present article discusses the importance of studying health-related quality of life as it relates to sepsis management strategies, particularly in the context of pharmacologic therapy with recombinant human activated protein C.

Sepsis affects more than 750,000 patients each year in the United States; it is the 10th leading cause of death and one of the leading causes for admission to the intensive care unit [1-4]. The estimated mortality from sepsis is 20–30%, meaning that approximately 500,000 patients survive their septic episode annually in the United States alone [3,4]. What happens to these sepsis survivors? Are they able to resume their lives and regular activities, or does sepsis have far-reaching effects that extend beyond the hospitalization? Ten years ago, Quartin and colleagues were the first to show that sepsis has long-lasting effects and increases the risk of death up to 5 years after hospitalization for the septic episode [5]. Mounting evidence has since demonstrated that survivors of sepsis have a higher long-term risk of death and a lower health-related quality of life (HRQoL) when compared with the general population [6-8].

In 2001, recombinant human activated protein C (rhAPC) was shown to significantly reduce the 28-day mortality in patients with severe sepsis [9]. A subgroup analysis demonstrated that patients who were more severely ill, with multiple organ dysfunction or with Acute Physiology and Chronic Health Evaluation (APACHE) II scores ≥25, accrued the greatest benefit from rhAPC, resulting in drug approval focused on these sepsis populations [10]. A subsequent randomized controlled trial that evaluated rhAPC use in patients with severe sepsis and a low risk of death (APACHE II score <25) found no survival benefit with rhAPC [11]. Given the high cost of rhAPC, the attendant bleeding risk associated with its use, and the lack of clinical trials confirming its efficacy, there continues to be debate and controversy regarding its appropriate use [12].

With the increasing emphasis on patient-centered outcomes in clinical trials, we are now more frequently assessing short-term and long-term survival and, at least sometimes, HRQoL. In assessing long-term outcomes among sepsis survivors from the original rhAPC trial, the short-term survival benefit for more severely ill patients (APACHE II scores ≥25) treated with rhAPC was also evident at 3, 6 and 12 months, while there was no difference in survival for those less severely ill patients [8].

In the previous issue of *Critical Care*, Longo and colleagues evaluated the effect of rhAPC on long-term HRQoL and resource utilization in patients with severe sepsis [1]. Using an observational cohort of 100 patients with severe sepsis (36 patients received rhAPC and 64 patients received standard care) who survived to day 28, the patients' HRQoL was measured using the Short Form 36 (SF-36) at 3, 5 and 7 months, and resource utilization was measured using patients' self-reports recorded in a diary. Patients who were treated with rhAPC had significantly better physical component scores on the SF-36 throughout the follow-up period, without significant differences in other components of the SF-36. Patients treated with rhAPC also had a significantly shorter hospital stay compared with patients in the standard care group, and showed statistically nonsignificant improvements in the rate of return to employment.

APACHE = Acute Physiology and Chronic Health Evaluation; HRQoL = health-related quality of life; rhAPC = recombinant human activated protein C; SF-36 = Short Form 36.

One of the major limitations of their study is that rhAPC was administered in a nonrandomized fashion, meaning the use of rhAPC was left to the discretion of the attending physician. Unfortunately, we are given little information about what factors the attending physicians considered when deciding to treat patients with rhAPC. Without the design of a randomized controlled trial, the results are subject to bias and confounding by unmeasured factors. The authors recognize these limitations and demonstrated that the two groups of patients (rhAPC vs. standard care) were similar in illness severity (APACHE II score) and had similar numbers of comorbidities. However, patients who received rhAPC were significantly younger and more likely to have been admitted through the emergency department. These dissimilarities suggest that there may have been other important unmeasured differences between groups. Further, there are no data provided about other factors that may have influenced survival and HRQoL such as the type or severity of comorbities (HIV, malignancy) [13-15], organ dysfunction [2,3], use of vasopressors or need for mechanical ventilation. These unmeasured differences may fully or partially account for the observed differences in long-term HRQoL. For example, younger patients with minor comorbidities (for example, hypertension) and a better chance of long-term survival may have been more likely to receive rhAPC than an elderly patient with metastatic cancer. Other limitations include the small sample size and the limited power to detect smaller but meaningful differences in other components of the SF-36 or resource utilization.

Despite the limitations of the study, Longo and colleagues address an important issue – evaluating the long-term effects of a sepsis therapy. Their findings suggest that treatment with rhAPC may result in improved long-term physical functioning in patients with severe sepsis. The authors hypothesize that rhAPC may reduce acute organ dysfunction, thereby diminishing the likelihood of chronic dysfunction and thus improving long-term HRQoL. As noted by the authors, this study does not provide conclusive evidence that rhAPC improves long-term HRQoL, and nor does this study provide any insight into the mechanisms responsible for the improvement in physical functioning. Instead, the study offers intriguing preliminary data that should provide the foundation for a larger, more rigorously designed clinical trial examining the long-term effects of rhAPC on HRQoL. Certainly, if rhAPC is shown to improve long-term health outcomes, including HRQoL, it will open new windows for drug evaluation and provide more evidence to help us determine the optimal use of this controversial medication.

Competing interests

The authors declare that they have no competing interests.

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