

Commentary

Steroids in sepsis: another swing of the pendulum in our clinical trials

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Abstract

Many studies have been conducted to try and find interventions to treat patients with severe sepsis, but with little success. In several cases, initial apparent beneficial effects have not been confirmed in later trials. The story of steroids in sepsis is one example of this pendulum effect, with initial success in the study by Annane *et al.* tempered by the more recent negative results of the Corticus study. The reasons for this pendulum effect are likely related, at least in part, to issues of clinical trial design and the way in which clinical trials in intensive care unit patients are developed, conducted and assessed needs to be critically reassessed.

The search for effective interventions in sepsis has, in several cases, been associated with rather inconsistent results from clinical studies, as the pendulum seems to swing from a benefit effect through no effect to potential harm and all the way back to benefit, leaving the practicing clinician with a real therapeutic dilemma. This pendulum in clinical trial results is demonstrated well by the use of steroids in the treatment of patients with sepsis.

Forty years ago, high-dose steroids were used in the belief that, because sepsis is an inflammatory response, the anti-inflammatory properties of steroids could be useful. Initial studies were encouraging, with Schumer demonstrating that treatment with one or two doses of intravenous dexamethasone (3 mg/kg) or methylprednisolone (30 mg/kg) was associated with reduced mortality compared with saline treatment in patients with septic shock [1]. Two large, double-blind, randomized controlled trials later failed to confirm these findings [2,3], however, and two meta-analyses in the mid 1990s concluded that steroids were ineffective [4] or indeed were potentially harmful [5] in sepsis.

Then, in the late 1990s, several studies were published suggesting a role for much smaller, so-called stress, doses of steroids in reducing vasopressor requirements in patients with septic shock [6-8]. These results led to a study by Annane and colleagues in which patients with relative adrenal insufficiency – as assessed by nonresponse to a cortico-

tropin test – who were treated with hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 µg orally daily) for 7 days had a reduced mortality compared with nonresponders treated with placebo [9]. Despite concerns regarding the lack of statistical significance in overall mortality rates at 28 days, the results from this study led to steroids being recommended in the treatment of patients with septic shock [10]. Steroid use was also incorporated into the so-called sepsis bundles, with the recommendation that all patients with septic shock should receive low-dose corticosteroids within 24 hours of diagnosis.

Doubts remained, however, and a large, international, multicenter study was conducted to confirm the results of the earlier study [9]. The Corticus – Corticosteroid Therapy of Septic Shock – study, which included close to 500 patients, recently showed that hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not respond to a corticotropin test [11]. The results from the Corticus study were somewhat disappointing, and, in the accompanying editorial, Dr Finfer suggested the need for a further study to explore the effects of steroids in septic shock in a much larger population [12]. With no signal from the Corticus study, however, merely increasing the size of the study is unlikely to show mortality differences.

Importantly, apart from the differences in effects on outcome, there were other notable differences between the Corticus study [11] and Annane and colleagues' study [9], including the larger number of postoperative patients, the more common abdominal source of the sepsis, and, in particular, the lower severity of illness in the Corticus study. This latter factor is particularly important and can be explained by the fact that many patients with severe septic shock were treated with steroids in accordance with guidelines current at the time of the study [10], and hence were excluded from enrollment – so the included population, by definition, consisted of less severely ill patients. As a result of this lower

severity of illness, the mortality rate in the Corticus study was about one-half that of Annane and colleagues' study. It is therefore still possible that steroids may decrease mortality in very ill patients, just not in those with moderately severe shock.

Similar observations were made with activated protein C, another adjunct therapy for sepsis, which was shown to reduce mortality in very ill patients [13] but not in those patients with a lower risk of death [14]. I believe we *do* need another trial of steroids in sepsis, but specifically in patients with *severe* septic shock rather than just in a larger general population of septic shock patients.

In this age of evidence-based medicine, we urgently need well-designed, appropriately targeted clinical trials to provide convincing and reliable data on which we can base future guidelines and recommendations for the treatment of patients with septic shock. Importantly there can be no ideal global clinical trial model – the design of each clinical trial must be adapted according to the question it is attempting to answer; however, general principles of clinical trial design can be developed. To this end, a round table held in March 2008 joined 26 leaders in critical care medicine to create a think-tank on the subject of improving clinical trials in the critically ill. Participants presented, discussed, and debated all aspects of clinical trial conduct, including inclusion and exclusion criteria, sample sizes, timing, ethical issues, selection of endpoints, power calculations, the benefits of multicenter studies over single-center studies, logistics, and much more.

There is no doubt there is an urgent need to improve outcomes for patients with sepsis, but – in our rush to produce that all-powerful randomized controlled trial – details of clinical trial design can be overlooked, making the end result less than ideal. Perhaps the time has come to take a step back and reflect on past efforts so that future clinical trials will be conducted in an optimal manner to limit the pendulum effect and to provide results that stand up to scrutiny and can be immediately introduced into clinical practice to the benefit of our patients.

Competing interests

The author declares that they have no competing interests.

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