EDITORIAL

Hydrocortisone for Septic Shock, Bolus or Infusion: Pro, Con, May be

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Sepsis is conceptually defined by Sepsis 3 criteria as life-threatening organ dysfunction caused by a dysregulated host response to infection. The operational definition is infection with a Sequential (sepsis-related) Organ failure (SOFA) score of 2 or more. Septic shock is identified as sepsis-related hypotension with the requirement of vasopressor to maintain a mean arterial pressure (MAP) of 65 mm Hg or more and a serum lactate level of 2 mm Hg or more, as this cohort has a high mortality rate of 40% or more.[1] The subset of sepsis patients with hypotension requiring a vasopressor but lactate less than 2 mm Hg still carries a substantial mortality and is also a common criteria used by physicians to start adjunctive therapy like steroids. The current tendency to start vasopressor early along with fluid resuscitation will create a subset of patients who will be defined as having septic shock by the present criteria but are not yet fully volume resuscitated. Moreover, the term refractory septic shock has not been well-defined in the current guidelines. It is variably defined as persistent hypotension despite optimum volume resuscitation and requiring increasing doses of a vasopressor with an arbitrary dose cutoff.[2] The surviving sepsis guideline suggests, with a weak recommendation and a moderate quality of evidence, the use of intravenous hydrocortisone at a dose of 200 mg/day in patients with septic shock with an ongoing requirement of vasopressors (Epinephrine or Norepinephrine) at a dose of 0.25 μg/kg/min for 4 hours or more to maintain a target MAP. It suggests using hydrocortisone as a 50 mg intravenous bolus every 6 hours or 200 mg as a continuous infusion.[3]

The common clinical practice is to give a bolus dose of hydrocortisone, but there is a growing interest in using continuous infusions to attain better glycemic control. Moreover, continuous infusions have been found to attenuate the inflammatory response and lead to an early reversal of shock. It may also decrease the nursing workload. One of the disadvantages of continuous infusion is the need for a dedicated line, which might be an issue with patients on multiple vasopressor and antibiotic infusions. Thus, the issue of comparing bolus vs continuous infusion of steroids is of clinical importance.

The present recommendation for glucose control in critically ill patients is to keep blood sugar between 140 and 180 mg/dL. Hyperglycemia, (>180 mg/dL) hypoglycemia and glycemic variability have been associated with adverse outcome in critically ill patients.[4] We have earlier described a worse outcome with increasing glycemic variability, especially in critically ill patients whose blood sugars are in a desirable euglycemic range.[5] In critically ill diabetic patients, the target for hyperglycemia and glycemic variability control may be different from non-diabetics.[6]

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In clinical practice, keeping blood sugars within a desirable range during the ICU stay is difficult, as it depends not only on the patient's pre-morbid diabetic status but also on the frequency of blood glucose measurements, medications like steroids, nutritional factors, etc. Various indices of glycemic variability over time have been described.[7] The proposed advantage of continuous steroid infusion is decreased variability and better glucose control. Previous large randomized studies of steroid use in septic shock have used bolus doses (APROCCHSS) and also continuous infusions (ADRENAL) of hydrocortisone.[8,9]

In this issue of the journal, a randomized study has been conducted in 40 patients with septic shock requiring a vasopressor comparing a hydrocortisone bolus of 50 mg 6 hours a day with a continuous infusion of hydrocortisone of 200 mg over 24 hours. The primary outcome measures were average blood glucose control over the study period of 5 days and secondary outcome measures were episodes of hyperglycemia, hypoglycemia, daily average insulin requirement, nursing workload, reversal of shock and time to shock reversal. The study did not show a difference between the two groups among all the primary and secondary outcome parameters.[10]

The findings of this study are in contrast with a similar prospective randomized trial in 48 septic shock patients, which showed significantly more episodes of hyperglycemia and the need for more frequent insulin dosage changes with bolus doses of steroids. Nursing workload was less with continuous infusion. Episodes of hypoglycemia and shock reversal were not different between the two groups.[11] These findings may be attributed to various measures taken to decrease glucose variability by other confounding factors in the study cohort, apart from steroids. These measures were the use of protocolized enteral nutrition, a predefined frequency of blood glucose measurement, and protocolized insulin administration.

The authors of the current study should be commended to perform a prospective, randomized study in critically ill patients in the current environment of constraints faced by researchers to perform interventional studies in India. Probably, a more meticulous control of confounding factors and protocolization of care may have resulted in a different conclusion. Use of a single initial loading dose of hydrocortisone may also be considered in the continuous infusion group. Glycemic variability indices have not been addressed in both of these studies and may be an important parameter to study as they have an impact on patient outcomes. In the meantime, one of the approach that can be suggested is to individualize the mode of steroid administration based on the patients' glucose profile. Patient with a greater degree of glucose fluctuation and hyperglycemic episodes after a steroid bolus, necessitating insulin therapy may benefit from continuous infusion. We hope future trials may compare this strategy to the standard practice of bolus doses of steroids.

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