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Critically Appraised Articles

Early corticosteroid therapy does not improve the prognosis of paediatric septic shock

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English key words: septic shock, adrenal cortex hormones, prognosis, mortality.
Palabras clave en español: choque séptico, corticosteroides, pronóstico, mortalidad.

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Early corticosteroid therapy does not improve the prognosis of paediatric septic shock

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Abstract

Authors' conclusions: early corticosteroid therapy in children with septic shock, before they develop adrenal insufficiency, can shorten the shock reversal time without increasing mortality.

Reviewers' commentary: there is no evidence that early corticosteroids therapy improves prognosis in children with septic shock and it could increase mortality.

Key words: septic shock, adrenal cortex hormones, prognosis, mortality.

En pacientes pediátricos con *shock* séptico, el uso precoz de corticoides no mejora el pronóstico

Resumen

Conclusiones de los autores del estudio: el uso precoz de corticoides en pacientes con shock séptico antes de que exista insuficiencia suprarrenal, puede acortar el tiempo de reversión del shock sin aumentar la mortalidad.

Comentario de los revisores: no hay evidencia de que el uso precoz de corticoides en pacientes pediátricos con shock séptico mejore el pronóstico y sí podría aumentar la mortalidad.

Palabras clave: choque séptico, corticosteroides, pronóstico, mortalidad.

STRUCTURED ABSTRACT

Objective: to assess and compare early corticosteroid treatment at the onset of septic shock (in the first stage) with conventional administration of corticosteroids in the third stage of treatment.

Design: randomised clinical trial (RCT).

Setting: tertiary level university hospital in Alexandria (Egypt).

Study sample: the study included 96 patients aged 1 month to 4 years admitted to the intensive care unit (ICU) with a diagnosis of septic shock based on international criteria. Patients who were immunosuppressed, patients with adrenal diseases or diseases affecting the pituitary function and patients treated with long-term corticosteroids within the past 6 months or short-term corticosteroids within the past 4 weeks were excluded.

Intervention: patients were divided in four groups: group A, with 32 patients, received conventional treatment; group B, with 32 patients, received the same treatment as group A with the addition of the adrenocorticotropic hormone (ACTH) stimulation test, considered positive if there was an increase in cortisol of more than < 9 µg over the baseline level; group C, with 32 patients, received an intravenous stress dose of hydrocortisone (50 mg/m2/24 h) with continuous infusion for 5 days (intervention group [IG]); and group D, consisting of patients from group A or B that required corticosteroids in the third stage of treatment (36 patients) (control group [CG]).

The patients were randomized by "block randomization" with allocation concealment. The physicians, nurses, data collectors and statistician were blinded to the use of early corticosteroid therapy.

Outcome measures: the outcome measures were the Pediatric Index of Mortality score (PIM); the Pediatric Logistic Organ Dysfunction score (PELOD); shock reversal time in days (maintenance of systolic blood pressure at or above the 5th percentile in infants aged less than 1 year and of 70 mmHg or greater + (2 × age in years) in children aged 1 to 10 years without vasopressor support for 24 hours or more); length of ICU stay, complications; and fate (discharge or death).

Main results: there were significant differences between groups A, B and C in the baseline PIM and PELOD scores and reversal of shock time (p values of.041,.035 and.046, respectively), while the groups had similar demographic and clinical characteristics. The basal serum ACTH level was normal, and serum cortisol was elevated, with no differences between groups. The authors did not find a statistically significant association between nonresponse to adrenal stimulation and the development of complications, the outcome, and the length of stay (*p*- values of.131,.057 and.959, respectively).

The comparison of the IG (early corticosteroid treatment) and CG (corticosteroid therapy in the third stage of treatment, adhering to conventional protocol) showed that while the PIM and PELOD scores at day 1 were worse in the IG (*p*-values of.009 and.044), there was a significant difference in favour of the IG on day 3, with a shorter shock reversal time (2.5 ± 0.9 days versus 5.8 ± 1.8; *P* =.001) and an improved better PELOD *score* (reduced from 38 ± 11.3 to 16.2 ± 21.5; *P* =.001). There was no difference in the cumulative hazard of mortality based on length of stay (calculated by means of a Kaplan-Meier survival curves) between groups A, b and C.

Conclusion: early use of corticosteroids in patients with septic shock may shorten shock reversal time without increasing mortality or the incidence of superinfection. Mortality is disappointing as a primary outcome, while shock reversal time is a more plausible endpoint that is also clinically relevant.

Conflicts of interest: none disclosed.

Funding source: none.

COMMENTARY

Justification: a 2015 Cochrane review of studies conducted mainly in adults found evidence of low and moderate quality that corticosteroid therapy reduces mortality in patients with sepsis, with an increase in metabolic disorders.[1] The latest specific recommendations for the management of children with sepsis include administration of corticosteroids to children at risk of adrenal insufficiency in the third stage of treatment.[2] The authors aimed at comparing the effects of advancing administration of corticosteroids to the first stage of treatment in a paediatric ICU.

Scientific rigour or validity: the research question was not clear enough, as there was no introductory explanation on how the authors intended to compare the groups with and without early corticosteroid treatment, and the endpoints that would be considered. Thus, it seems that the study did not include an *a priori* calculation of the sample size required to analyse a primary endpoint. The need for stratifying the sample into three groups is also unexplained, as is the creation of a fourth group from the first and second groups, which suggests the possibility that they may have been created posterior to the recruitment of the patients. Although it is clear that group C is the intervention group, the statistical analyses compared groups A, B and C (which does not seem appropriate in light of the original purpose) or groups C and D, so that there is no clear control group. The methods used for randomisation and blinding were not explained. The authors did not specify whether the analysis was made by intention to treat. There was no control for covariates. It is not clear whether there were any losses to followup or the reasons they may have happened, as there is no chart on the subject nor any reference to a source where this information could be retrieved.

It is worth noting that the study did not find significant differences between groups in the primary outcome of mortality (this study documents 30-day mortality). However, the compared groups were small, and if the sample size had been four times larger and the mortality percentages remained the same, more patients would have died within 30 days in the intervention group compared to the group with conventional treatment (43.7% versus 31.2%), and the difference would have been statistically significant.

More patients died (or were lost) after shock reversal in the intervention group compared to the control group (6 versus 2), as can be seen in the supplementary information linked to the article. Under these circumstances, the advantage of shortening the shock reversal time is not clear, as it could come at the cost of fatal side effects.

The lack of internal validity of the study limits its external validity, and thus precludes its application to clinical practice in Spain.

Clinical relevance: given its methodological limitations, this study should not influence therapeutic decision-making. Since mortality was higher in the group with early corticosteroid therapy compared to the group with standard treatment in which corticosteroids were given in the third stage (although the difference was not statistically significant), we ought to question the benefits of advancing the administration of corticosteroids in children with sepsis, and consider the potential associated risks.

Applicability to clinical practice: this study is not applicable to clinical practice. Physicians that care for children with septic shock should continue to follow current guidelines while awaiting further evidence from new paediatric studies.

Conflicts of interest: the authors of the commentary had no conflicts of interest.

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