The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis

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CRD summary
This review concluded that low dose steroids may improve mortality rates in people with septic shock who were at high risk of death, but further trials were required. The conclusions were appropriate, although there was a risk that studies that showed no benefit with low dose steroids were not found; therefore, the benefit with steroids could have been over-estimated.

Authors’ objectives
To investigate the effects of steroids during sepsis and determine whether illness severity, drug dose and response to adrenocorticotrophic stimulation testing predicted treatment effects.

Searching
MEDLINE, EMBASE and The Cochrane library were searched for the period January 2004 to December 2008 (search terms were provided). Abstracts from national and international critical care conferences and the references of published meta-analyses were searched. These searches updated those conducted for an earlier review, for which MEDLINE was searched for the period 1988 to December 2003 (see Other Publications of Related Interest).

Study selection
Randomised controlled trials (RCTs) that compared glucocorticoid treatment with a placebo or no treatment control in people with sepsis or septic shock were eligible for inclusion. Studies had to report either shock reversal or survival outcomes. The criteria used for determining sepsis or septic shock in the primary studies had to be consistent with the American College of Chest Physicians/Society of Critical Care Medicine consensus definitions.

Nine included studies were published prior to 1989 and 12 after 1997. In studies published before 1989, median corticosteroid dose (expressed as hydrocortisone equivalent) was 23,975mg (range 1,050 to 42,000mg) and median duration of treatment was one day (range four hours to six days); none used a tapered steroid dose. After 1997, median dose was 1,209mg (range 330 to 1,880mg) and median duration of treatment was six days; more than half the studies used a tapering steroid regimen. Where specified, steroids used were hydrocortisone, betamethasone, dexamethasone, methylprednisolone and prednisolone. Methylprednisolone was most commonly investigated in the studies prior to 1989 and hydrocortisone after 1997. Cointerventions included antibiotics, fluids, vasopressors and standard care.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Method of randomisation, use of blinding and reporting of withdrawals were assessed using the Jadad scale and each study was given a score up to a maximum of 5 points. Two reviewers independently assessed study quality. Discrepancies were resolved by a third reviewer.

Data extraction
The numbers of events for the outcomes of interest were extracted and the odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Doses of steroids used in the included studies were converted to hydrocortisone equivalents.

Methods of synthesis
Studies were pooled using random-effects meta-analyses. Studies were pooled regardless of data of publication and also stratified by early publication (pre-1989) and late publication (post-1997). Heterogeneity was assessed using Cochran’s Q statistic and the I² test.
Regression analysis was used to investigate the relationship between the odds ratios of death and the variables steroid dose and severity of illness. The impact of removing individual studies from the analysis was assessed in a sensitivity analysis.

A funnel plot and Egger's test were used to assess publication bias.

**Results of the review**

Twenty-one RCTs were included. Most studies were of at least adequate quality; with the exception of two studies the Jadad score was at least 3 (out of a maximum 5). The funnel plot of trials published after 1997 and the associated Egger's test indicated the possibility of publication bias.

**Deaths**: In studies published before 1989 (high dose) there was a statistically significant increase in deaths with steroids compared to control (OR 1.39, 95% CI 1.04 to 1.86; eight studies) and after 1997 (low dose) there was a decrease in deaths with steroids (OR 0.64, 95% CI 0.45 to 0.93; 12 studies). In the analysis of studies before 1989 heterogeneity was low. In the post-1997 analysis it was moderate. Regression analysis that combined all studies indicated a statistically significant increase in deaths at higher doses and with less severe illness.

**Shock reversal**: There was a statistically significant increase in 28-day shock reversal with steroids compared to control based on seven (low dose) studies published after 1997 (OR 1.66, 95% CI 1.25 to 2.20). Two studies that reported this outcome pre-1989 showed no statistically significant benefit with steroids.

**Treatment related complications**: Based on trials published after 1997, there was no statistically significant increase in secondary infection (nine studies), gastrointestinal bleeding (nine studies) or neuropathy (two studies) with steroids compared to control.

**Authors' conclusions**

Low dose steroids seemed to improve mortality rates in people with septic shock who were at high risk of death, but further trials were required to definitively determine the role of low dose steroids during sepsis in this population.

**CRD commentary**

This review answered a clearly stated review question. There was a possibility that relevant studies were missed as the earlier review that was updated used only one source to identify relevant studies and analysis suggested a possibility of publication bias in the low dose steroid studies. In addition, it was unclear whether there was a risk of language bias and whether more than one reviewer was involved in study selection. Appropriate methods were used to minimise error and bias in data extraction and quality assessment. Relevant details were provided from the primary studies. The analysis seemed appropriate and statistical heterogeneity was assessed and possible sources investigated. The authors’ conclusions were appropriate and likely to be reliable, although the risk that studies that showed no benefit with low dose steroids were not found should be kept in mind.

**Implications of the review for practice and research**

**Practice**: The authors stated that the decision to administer low-dose steroid therapy to a patient with sepsis should be made on an individual basis and take into account illness severity and the risk of adverse events. They suggested a total daily dose of 200mg to 300mg of hydrocortisone in divided doses or as a continuous infusion, followed by a tapered regimen over three to five days. The authors suggested that adrenocorticotropic hormone stimulation testing should not be used to determine who received steroids.

**Research**: Trials were required of low-dose steroids used to treat patients who were severely ill with refractory septic shock.

**Funding**

Not stated.
Bibliographic details

PubMedID
19416302

DOI
10.1111/j.1469-0691.2009.02752.x

Original Paper URL

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents /therapeutic use; Humans; Sepsis /drug therapy /mortality; Steroids /therapeutic use; Treatment Outcome

AccessionNumber
12009105779

Date bibliographic record published
02/09/2009

Date abstract record published
11/11/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.