Postnatal corticosteroids in preterm infants: systematic review of effects on mortality and motor function

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Authors' objectives
To review the evidence on the effects of postnatal corticosteroids in preterm infants on long-term mortality and motor dysfunction, including cerebral palsy.

Searching
The search strategy followed the guidelines of the Cochrane Collaboration (see Other Publications of Related Interest no.1). Searches were conducted of the Cochrane Controlled Trials Register, MEDLINE, published systematic reviews, and abstracts from the annual meeting of the Society for Pediatric Research for the years 1995 to 1999. Studies published in full or as abstracts were included.

Study selection
Study designs of evaluations included in the review
Randomised (RCTs) or quasi-randomised trials were eligible. Duration of follow-up ranged from 28 days to 3 years of age.

Specific interventions included in the review
Parenteral or oral corticosteroids were eligible. Studies with only inhaled steroids were excluded. Dose of dexamethasone or equivalent dexamethasone dose ranged from 0.4 mg/kg to 8 mg/kg. Co-interventions included antenatal corticosteroid therapy and surfactant. The rate of antenatal corticosteroid therapy was low (<50%) in most studies (range 0% to 85%). The rate of surfactant therapy ranged from 0% to 100%. Contamination rates (% of controls ultimately treated with postnatal steroids) where stated, ranged from 0% to 83%.

Participants included in the review
Newborn infants at risk of, or with, established chronic lung disease were eligible. In most studies, infants were all ventilator dependent at trial entry. Infants studied were mostly of birth weight < 1000g (range, where stated, 750g to < 1500g) and gestational age < 30 weeks (range, where stated, from 25 to 32 weeks). Postnatal age at trial entry ranged from < 0.5 days to 47 days.

Outcomes assessed in the review
The primary outcomes were mortality, motor dysfunction in survivors (including cerebral palsy) and survival free of motor dysfunction. Mortality was that reported at the latest age from a particular trial. The rigour of follow-up assessments for motor dysfunction varied from questionnaires to parents or health visitors, through to full paediatric and psychological assessments. Only one study specified diagnostic criteria for cerebral palsy.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report a method for assessing validity. Two observers independently reviewed validity. The second reviewer was blind to the authors and institutions of the studies.

Data extraction
Each of the two authors extracted the following data independently before comparison and resolution of differences:
dose of dexamethasone (mg/kg) expected in the treated group; demographic details; rates of antenatal corticosteroid and postnatal surfactant therapy; and the ultimate use of postnatal steroids in infants initially allocated to placebo/control groups (contamination). Studies of other corticosteroids had the dose converted to the equivalent dose of dexamethasone. Results were expressed as event rate differences (ERD) and 95% confidence intervals (CI).

Methods of synthesis
How were the studies combined?
Pooled event rate differences (ERD) and 95% confidence intervals (CI) were calculated.

How were differences between studies investigated?
Sensitivity analyses for mortality were planned a priori and included trials where the following subgroups could be identified: time of starting therapy (< 5 days, 7 to 14 days, and > 14 days); dose of corticosteroid therapy above the median equivalent of dexamethasone (2.9 mg/kg); high (> 50%) rates of antenatal corticosteroid therapy; and surfactant therapy; and low contamination rate (<= 33%). Similarly, sensitivity analyses for motor dysfunction were also planned around postnatal age and the diagnosis of cerebral palsy.

Results of the review
Twenty-seven RCTs were included (3260 infants).

1. Overall mortality rate.
The latest age of reported mortality varied from 28 days to 3 years of age.

There was a non-significant difference between treatment groups favouring corticosteroids. ERD = -0.1% (95% CI: -2.9%, 2.8%). In no individual study was the reported mortality significantly different between groups. ERD ranged from -26.5% to + 16.7%.

After excluding two RCTs (early dexamethasone compared with selective dexamethasone at a later stage and dexamethasone started at 14 days compared with selective treatment at 28 days): difference between treatment groups was not significant. ERD = -0.7% (95% CI: -4.0%, 2.6%).

Mortality sensitivity analyses.
Postnatal age: mortality rate was non-significantly lower only in the subgroup with treatment starting between 7 and 14 days. Age < 7 days: ERD = 1.3% (95% CI: -2.3%, 4.9%). Age 7 to 14 days: ERD = -5.0 (95% CI: -11.0, 1.1). Age > 14 days: ERD = 0.3% (95% CI: -6.4%, 7.1%).

Rate of antenatal corticosteroids > 50%: there was a non-significant difference favouring the control group. ERD = 4.9% (95% CI: -1.5%, 11.4%).

There were no major differences in subgroup analyses restricted to higher dose of corticosteroids, where surfactant was given, or where contamination rate was low. Results were presented.

2. Motor dysfunction (5 RCTs reported this outcome beyond infancy).

Ages of follow-up ranged from 1 to 3 years. Follow-up rates were > 90% in all but one study. The rate of motor dysfunction overall was significantly higher in the corticosteroid group. ERD favouring controls = 11.9% (95% CI: 4.6%, 19.2%). In two studies (including one with no contamination) the rate was significantly higher in the corticosteroid groups.

Excluding one study where treatment started early (< 4 days postnatal age): there was no significant difference in the rate between treatment groups. ERD = 7.7% (95% CI: -0.6%, 16%).

Cerebral palsy (3 RCTs with treatment with postnatal steroids started after 14 days postnatal age): the overall rate was
significantly higher in the corticosteroid group. ERD = 8.7% (95% CI: 0.3%, 17.0%).

3. Survival free of motor dysfunction (5 RCTs).

After excluding children lost to follow-up the rate of survival free of motor dysfunction was significantly higher in the control groups. ERD = 7.8% favouring controls (95% CI: 0.5%, 15.1%).

Assuming all those survivors lost to follow-up to have a bad outcome, the difference remained statistically significant. ERD = 9.5% (95% CI: 2.5%, 16.5%).

Assuming all those survivors lost to follow-up to have a good outcome, the difference became non-significant. ERD = 5.4% (95% CI: -1.7%, 12.4%).

Authors’ conclusions
Although postnatal corticosteroids have short-term benefits, they do not increase the survival rates, and they may cause motor dysfunction in survivors. A large-scale, placebo controlled randomised trial, with survival free of sensorineural impairment and disabilities as the major end-point, is urgently needed.

CRD commentary
The aims were stated and inclusion criteria defined in terms of study design, participants, intervention and outcome. The search strategy was conducted according to the Cochrane Collaboration guidelines though no details were given of keywords or language restrictions and methods used to select studies were not described. Included studies were restricted to randomised or quasi-randomised studies and validity was reported as being assessed but criteria used were not specified and the results of the validity assessment were not reported or incorporated into the analyses. Methods used to extract data were described and some relevant details of the included studies presented in tabular format. Data were pooled in a meta-analysis but no assessment of statistical heterogeneity was undertaken and thus it was not clear whether a meta-analysis was appropriate. The studies appeared to differ considerably on patient characteristics and co-interventions. Several sensitivity analyses were conducted to investigate the influence of various factors on the results and analyses were conducted assuming drop-outs to have good or bad outcomes.

Without an assessment of the validity of the included studies, the quality of the evidence presented cannot be assessed and without an assessment of heterogeneity it cannot be determined whether meta-analysis was appropriate. Hence caution is required when interpreting the results.

Implications of the review for practice and research
Practice: The authors state that although postnatal corticosteroids have short-term benefits, they do not increase the survival rates and they may cause motor dysfunction in survivors.

Research: The authors state that a large-scale, placebo-controlled randomised trial, with survival free of sensorineural impairment and disabilities as the major end-point, is urgently needed. Design issues for such as trial include entry criteria (severity of lung disease and postnatal age) and aspects of the corticosteroid regimen (type, dose, duration and route of administration).

Bibliographic details

PubMedID
10760004

Other publications of related interest

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Subject indexing assigned by NLM

**MeSH**
Adrenal Cortex Hormones /adverse effects /therapeutic use; Cerebral Palsy /chemically induced /mortality; Disease-Free Survival; Female; Humans; Infant, Newborn; Infant, Premature; Motor Activity /drug effects; Postnatal Care; Randomized Controlled Trials as Topic /statistics & numerical data; Survival Analysis

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**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.