Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review

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CRD summary
The review concluded that post-natal hydrocortisone had few beneficial or harmful effects when used for prevention and treatment of bronchopulmonary dysplasia in pre-term infants. These conclusions reflected the data presented, but should be interpreted with caution given the limited number of small heterogeneous studies available and weaknesses in the reported review methods.

Authors' objectives
To assess the effectiveness of post-natal hydrocortisone for the prevention and treatment of bronchopulmonary dysplasia in pre-term infants.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2009. Search terms were reported. Additional articles were sought by handsearching paediatric and perinatal journals (not specified) and from examining previous review articles and contacting practicing neonatologists.

Study selection
Randomised controlled trials (RCTs) that compared post-natal hydrocortisone with placebo for the treatment or prevention of bronchopulmonary dysplasia in ventilator-dependent pre-term infants were included. Outcome measures were: mortality; bronchopulmonary dysplasia; death or bronchopulmonary dysplasia; late rescue with corticosteroids; survivors discharged home on oxygen; failure to extubate; complications during the primary hospitalisation (as defined in the review); and long-term outcomes including cerebral palsy.

Most trials looked at prevention of bronchopulmonary dysplasia. Two trials looked at treatment of hypotension. Where reported, birth weight ranged from 500g to 2,805g and gestational age ranged form 23 to 36 weeks. Total hydrocortisone dose (oral or intravenous) used ranged from 5.8mg/kg to 30mg/kg. Controls received placebo or no treatment. Study duration ranged from one to 15 days. All trials were started in the first week of life. All trials were conducted between 1972 and 2007.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they assessed methodological quality, but information was sought on methods of randomisation and blinding.

Data extraction
Data were extracted on the number of infants in each study arm in the main outcome categories: death; bronchopulmonary dysplasia; death or bronchopulmonary dysplasia; cerebral palsy; and death or cerebral palsy. These data were used to calculate the relative risk (RR), with 95% confidence interval (CI), for each outcome.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Meta-analysis (model not specified) was used to calculate pooled estimates of relative risks with 95% confidence intervals. Where appropriate, number needed to treat/harm was calculated.

Between-study heterogeneity was assessed using $I^2$ and was considered significant for $I^2$ values that exceeded 50%.
For the main outcomes, sensitivity analyses were conducted for studies where the primary aim was prevention of bronchopulmonary dysplasia.

**Results of the review**

Eight RCTs (n=880 infants, range 34 to 360) were included in the review. All studies were described as methodologically sound. Treatment allocation was concealed from the study investigators. Investigators were blinded to the intervention. There was blinding of outcome measures. There was complete reporting of in-hospital outcome measures and follow-up rates of at least 85% after discharge.

There was no significant difference between hydrocortisone and placebo for any of the specified outcome measures, (death, bronchopulmonary dysplasia, death or bronchopulmonary dysplasia, cerebral palsy, death or cerebral palsy). These results did not change when the analyses were restricted to studies with the primary aim of preventing bronchopulmonary dysplasia.

Analyses of early complications revealed that use of hydrocortisone was associated with a decreased risk of patent ductus arteriosus (RR 0.85, 95% CI 0.73 to 0.99; six RCTs, significant between-study heterogeneity) and with an increased risk of gastrointestinal perforation (RR 2.02, 95% CI 1.13 to 3.59; six RCTs). Results were similar when analyses were restricted to studies with the primary aim of preventing bronchopulmonary dysplasia.

There were no significant differences between hydrocortisone and placebo for the outcomes of discharged on oxygen and failure to extubate.

**Authors' conclusions**

Post-natal hydrocortisone in the doses and regimens used in reported studies had few beneficial or harmful effects. There are no randomized trials to substantiate use of hydrocortisone in chronically ventilator-dependent infants with established or evolving bronchopulmonary dysplasia.

**CRD commentary**

The review addressed a clearly stated research question defined by appropriate inclusion criteria. A number of sources were searched for relevant studies. No restrictions by language and publication status were reported. Reporting of review methods was limited and it was unclear whether any measures were taken to minimise potential for error and bias in study selection and data extraction. Although no quality assessment of included studies was specified, a summary of key components of methodological quality was provided and all included studies were considered to be methodologically sound.

A degree of between-study clinical heterogeneity was apparent (differences in study duration and weight and gestational age of infants) and there was some evidence of statistical heterogeneity. Relatively few studies were included, sample sizes were small and one study was conducted approximately 30 years earlier than the others. Meta-analytic methods used to generate pooled estimates were not reported.

The authors' conclusions reflected the raw data presented, but should be interpreted with caution given the limited number of small heterogeneous studies available and weaknesses in the reported review methods.

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

**Practice:** The authors stated that post-natal hydrocortisone could not be recommended for prevention of bronchopulmonary dysplasia.

**Research:** The authors stated that future RCTs of hydrocortisone should focus on those infants most at risk of dying or surviving with neurological disability as a consequence of prolonged assisted ventilation and evolving bronchopulmonary dysplasia.

**Funding**
Partly supported by National Health and Medical Research Council, Australia.

Bibliographic details

PubMedID
20150750

DOI
10.1159/000279992

Original Paper URL
http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract&ArtikelNr=279992

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents /therapeutic use; Bronchopulmonary Dysplasia /drug therapy /mortality /prevention & control; Humans; Hydrocortisone /therapeutic use; Infant, Newborn; Infant, Premature; Intestinal Perforation /etiology; Randomized Controlled Trials as Topic; Survival Rate; Treatment Outcome

AccessionNumber
1201006266

Date bibliographic record published
10/11/2010

Date abstract record published
20/07/2011

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.