Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: a systematic review of placebo-controlled trials
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CRD summary
This review concluded that higher cumulative doses of dexamethasone administered after the first week of life may decrease the risk of bronchopulmonary dysplasia without increased risk of neurodevelopmental sequelae in ventilated preterm infants. A large randomised controlled trial was needed to confirm or refute these findings. These cautious conclusions appear likely to be reliable.

Authors' objectives
To determine the impact of cumulative dexamethasone dose on mortality and pulmonary and neurodevelopmental sequelae in preterm infants.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Dates ranged from 1966 to 1982 onward (final search dates not reported). Search terms were reported. Previous review articles and abstracts of Pediatric Academic Societies and European Society for Paediatric Research (ESPR) were searched from 1990 onward.

Study selection
Placebo-controlled randomised controlled trials (RCTs) of a standardised dosage regimen of systemic dexamethasone in ventilated preterm infants initiated after seven days postnatal age were eligible for inclusion in the review. Trials were required to report at least one of the outcomes: incidence of hypertension, sepsis or hyperglycemia during hospitalisation; duration of mechanical ventilation; failure to extubate at day three and day seven after initiation of therapy; use of rescue therapy with glucocorticoids; mortality at 36 weeks postmenstrual age or discharge; bronchopulmonary dysplasia (BPD) (oxygen dependency at 36 weeks postmenstrual age); and long-term neurodevelopmental sequelae including cerebral palsy and Bayley Scales of Infant Development (Mental Development Index) scores at between one and four years corrected gestational age.

Included studies used cumulative doses of dexamethasone (range 0.9 to 7.8mg/kg). Variations in the use of antenatal glucocorticoids and exogenous surfactant were present in the included trials, largely as a function of differences in publication date. Average gestational age ranged from 24 to 28.5 weeks in the dexamethasone group and 25 to 28.6 weeks in the placebo group. Average birth weight ranged from 652g to 1,000g in the dexamethasone group and 700g to 1,029g in the placebo group.

The authors did not state how many reviewers selected papers for the review.

Assessment of study quality
Two reviewers independently assessed studies for validity using criteria of allocation concealment, blinding, completeness of follow-up and blinding of outcome measurements.

Data extraction
Two reviewers independently extracted data on outcomes to permit calculation of relative risks (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean differences with 95% CI for continuous data. Arbitrary thresholds were used to classify included studies into one of three subgroups on the basis of cumulative dexamethasone dose (<2.0mg/kg, >2.0<4.0mg/kg, >4.0mg/kg). Studies were classed as having moderately early onset of therapy (seven to 14 days) or delayed onset (over three weeks). Crossover trials were assessed only for short-term outcomes. Authors were contacted to assess the accuracy of data extraction and for any additional data.

Methods of synthesis
Studies were combined in a meta-analysis using the predefined cumulative dexamethasone dose subgroups and pooled relative risks and weighted mean differences with 95% CI were calculated. Where a scatter plot suggested a potential linear relationship, weighted meta-regression was used to explore the relationship between cumulative dexamethasone dose and effect size. Fixed-effect models were used in the absence of heterogeneity significant at the p=0.05 level; otherwise, random-effects models were used.

**Results of the review**

Sixteen RCTs (n=1,136) were included in the review. Methodological quality of the trials was considered to be fair to good. Nine RCTs used moderately early treatment and seven used delayed treatment.

There were no statistically significant differences between treatment and placebo groups in mortality rates for either moderately early or delayed treatment trials. There was a statistically significantly lower risk of the combined outcome of 36-week postmenstrual age mortality and BPD in treatment groups in the moderately early trials (RR 0.70, 95% CI 0.57 to 0.86) and a trend towards a significant effect in trials of delayed treatment (RR 0.91, 95% CI 0.84 to 1.00); the authors stated that the risk of BPD as a single outcome was also reduced.

Subgroup analysis showed that these effects were most pronounced in trials that uses cumulative doses of at least 4mg/kg (BPD alone RR 0.53, 95% CI 0.28 to 0.98 and combined outcome RR 0.57 95% CI 0.39 to 0.84). However, metaregression did not show a significant relationship between the cumulative dose of dexamethasone and risk of mortality or bronchopulmonary dysplasia.

A statistically significant inverse relationship with dose was found for the risk of the combined outcome of mortality or cerebral palsy in the moderately early trials with a decrease of 6.2% for each incremental mg/kg cumulative dexamethasone dose; this was not the case for the delayed treatment trials. This pattern of results was also found for the outcome of an MDI score 2 standard deviations below the mean with a decrease of 6.6% for each incremental mg/kg cumulative dexamethasone dose. There was no relationship between dose and short-term respiratory benefits.

**Authors’ conclusions**

Higher cumulative doses of dexamethasone administered after the first week of life may decrease the risk of BPD without increased risk of neurodevelopmental sequelae in ventilated preterm infants. A large RCT was needed to confirm or refute these findings.

**CRD commentary**

The review question and the inclusion criteria were clear. The authors searched several relevant databases and did not report restrictions on language or publication status, which may have reduced risks of omission of relevant studies and bias. Use of methods designed to reduce reviewer bias and error was reported at all stages of the review process except study selection. Appropriate criteria were used in the assessment of validity. The use of meta-analysis and meta-regression were appropriate.

The authors’ showed appropriate caution in interpreting the results of a subgroup analysis that used arbitrary thresholds, particularly given the lack of a statistically significant finding in the metaregression analysis. Their cautious conclusions appear likely to be reliable.

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

**Practice**: The authors stated that dexamethasone should not be given outside American Academy of Pediatrics guidelines or the context of a well-designed and implemented controlled clinical trial.

**Research**: The authors stated that a large RCT that compared low and high doses of dexamethasone and placebo administered moderately early in life in ventilated preterm infants was needed to assess the impact of treatment and cumulative dexamethasone dose on mortality, bronchopulmonary dysplasia and neurodevelopmental outcomes including cerebral palsy.
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