Very low-dose dexamethasone to facilitate extubation of preterm babies at risk of bronchopulmonary dysplasia: the MINIDEX feasibility RCT

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Scientific summary

The MINIDEX feasibility RCT

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Scientific summary

Background

Bronchopulmonary dysplasia (BPD) poses a significant health-care burden for babies born prematurely, adversely affecting both long-term respiratory and neurodevelopmental outcomes. Postnatal corticosteroids have been used to improve lung function and reduce the incidence of BPD [relative risk (RR) 0.77, 95% confidence interval (CI) 0.67 to 0.88], yet concerns were raised that postnatal corticosteroids may be associated with adverse long-term neurological outcomes when a meta-analysis published a cerebral palsy RR of 1.92 (95% CI 1.41 to 2.61).

Further analysis of the available evidence led to the discovery that the adverse neurodevelopmental outcomes were associated with treating babies in the first 7 days of life with dexamethasone, treating babies at a low risk of developing BPD with corticosteroids, and treating babies with high doses (i.e. a cumulative dose > 3.0 mg/kg) of dexamethasone.

These findings have resulted in many clinicians in the UK treating babies older than 1 week of age, who are deemed to be at high risk of developing BPD, with very low-dose regimens of dexamethasone in the hope that the beneficial pulmonary effects will be seen, and the baby is spared from adverse neurodevelopmental outcomes. There is no clear evidence to support this use of very low-dose dexamethasone.

Objectives

The objective of the study was to assess the efficacy of very low-dose dexamethasone at facilitating the extubation of ventilator-dependent preterm babies born at < 30 weeks' gestation and who are at high risk of developing BPD.

Research questions

1. How effective is very low-dose dexamethasone at reducing the duration of invasive intermittent positive-pressure ventilation in ventilator-dependent preterm babies born at < 30 weeks' gestation and who are at high risk of developing BPD?
2. What is the safety of very low-dose dexamethasone?
   - Does very low-dose dexamethasone increase the risk of adverse effects that are seen with high-dose dexamethasone, for example hypertension, hyperglycaemia, confirmed/suspected sepsis and gastrointestinal perforation/necrotising enterocolitis?
   - Does very low-dose dexamethasone therapy result in changes in babies' cranial ultrasound scans between randomisation and 36 weeks' postmenstrual age (PMA)?
   - Does very low-dose dexamethasone therapy result in changes in babies' neonatal growth?
3. Will it be possible to perform a large multicentre randomised controlled trial to assess the 2-year neurodevelopmental outcomes of treatment with very low-dose dexamethasone?
4. Is a novel assessment of the family's involvement with their baby feasible?
5. Does very low-dose dexamethasone affect changes in babies' biochemical inflammatory cytokine profile?

Methods

This was a multicentre, randomised, masked, parallel-group, placebo-controlled Phase 2b trial.

The trial was designed as a feasibility study for a subsequent study of the clinical effectiveness of very low-dose dexamethasone in reducing the incidence of BPD at 36 weeks' PMA. As such, the study had a surrogate outcome as a primary aim but collected information about a range of clinical outcomes and trial characteristics.

Inclusion criteria

Inclusion criteria included:

- babies born at < 30 weeks' gestation
- babies aged between 10 and 24 postnatal days (i.e. ≥ 10 and ≤ 24 postnatal days)
- babies at high risk of developing BPD – receiving mechanical ventilation, via an endotracheal tube, receiving at least 30% inspired oxygen when the positive end-expiratory pressure is at least 4 cmH_2O and, in the opinion of the treating physician, unlikely to be extubated within 48 hours
- babies receiving caffeine therapy
- written informed parental consent
- babies born to a mother aged ≥ 16 years.

Exclusion criteria

Exclusion criteria included babies:

- receiving postnatal steroid treatment for prevention or treatment of respiratory disease
- with no realistic prospect of survival
- with a severe congenital anomaly affecting the lungs, heart or central nervous system
- having undergone a surgical abdominal procedure or patent ductus arteriosus ligation
- who are ill or receiving medication for which postnatal corticosteroid would be contraindicated (e.g. an active fungal infection, confirmed or suspected acute sepsis, acute necrotising enterocolitis/focal intestinal perforation or cyclo-oxygenase therapy)
- participating in another trial that would preclude the baby from inclusion in the MINIDEX feasibility trial.

Babies were recruited from 11 UK neonatal units and randomised (1 : 1) to the active intervention [once-daily 50 µg/kg dexamethasone on days 1–10 after randomisation (i.e. 10 doses), then dexamethasone was given on alternate days (i.e. on days 12, 14 and 16), making a total of 13 doses (a cumulative dose 0.65 mg/kg)] or a matched saline placebo.

Data were collected on the case report form at trial entry, daily throughout Investigative Medicinal Product administration and at 36 weeks' PMA.

Results

The trial was delayed in starting and, once open, recruitment was lower than predicted because of a shortage of eligible babies. After 9 months of recruiting, 22 babies of the planned sample size of 94, had been randomised to the trial. There was a higher than anticipated discontinuation rate among the recruited babies (i.e. 12 babies of the 22 randomised were discontinued, 11 of them for confirmed/suspected sepsis or requirement for open-label steroid therapy). Following this poor recruitment and high discontinuation rate the funder decided to stop recruitment. It was agreed that the final report should provide only a descriptive analysis because of the small number of babies recruited to the trial.

It is not possible to report the primary outcome; however, a few secondary outcomes can be given as descriptive statistics. It was found that, compared with the placebo group, a higher proportion of babies extubated were at day 7 of life [5/8 (62.5%) for the very low-dose dexamethasone group vs. 2/6 (33.3%) for the placebo group] and a reduced duration of invasive ventilation (a median of 23 days in the very low-dose dexamethasone group vs. a median of 31 days in the placebo group) in the very low-dose dexamethasone group. This is supported by a trend for an increased requirement for open-label rescue steroids in control group babies (41.7% in the very low-dose dexamethasone group vs. 80% in the placebo group).

Conclusions

The trial addressed the question of whether or not giving very low-dose dexamethasone to ventilator-dependent preterm babies < 30 weeks' gestation facilitates extubation. The trial used a surrogate outcome and was designed to facilitate the design of a definitive large pragmatic trial using substantive outcomes. The MINIDEX trial has made it clear that in the contemporary clinical context it is not possible to recruit to a large pragmatic trial of very low-dose dexamethasone that would give the substantive outcomes needed to inform clinical practice. The research question remains open.

Future work

Assessment of very low-dose dexamethasone in this patient group requires careful consideration.

Study registration

The study is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry as number ISRCTN81191607.

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This report

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