The Minidex trial: does very low dose dexamethasone improve lung function in preterm infants?

The Minidex randomised controlled trial will assess the efficacy and safety of very low dose dexamethasone to facilitate the extubation of ventilator-dependent preterm infants who are at high risk of bronchopulmonary dysplasia (BPD). This article examines the controversy surrounding postnatal dexamethasone therapy and discusses how the information gathered in the Minidex trial will enable planning of a large pragmatic trial to determine dexamethasone’s effects on BPD and long-term neurodevelopmental outcomes.

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Keywords
Minidex; dexamethasone; clinical trial; corticosteroid; bronchopulmonary dysplasia; preterm; chronic lung disease

Key points
1. Higher doses of dexamethasone improve lung function in preterm infants and reduce BPD but are associated with poor neurodevelopmental outcomes.
2. The consequences of very low dose dexamethasone targeted to infants >1 week of age with a high risk of BPD are unknown.

BPD and corticosteroids
Bronchopulmonary dysplasia (BPD), or chronic lung disease, is one of the ongoing challenges of neonatal medicine. It affects approximately 35% of infants born at less than 30 weeks’ gestation who survive to discharge from neonatal care.¹ In the UK this equates to about 1,450 affected babies a year. BPD prolongs hospitalisation and is associated with a significant long-term respiratory and neurodevelopmental healthcare burden.³

One of the few interventions that have been proven to reduce the incidence or severity of BPD is corticosteroids, the most studied of these being dexamethasone. Corticosteroids facilitate the extubation of preterm infants and reduce the incidence of BPD;⁴ throughout the 1980s and 1990s they became a mainstay of neonatal care. However, in 2001 a meta-analysis⁵ found that infants treated with high dose regimens of postnatal corticosteroids have an increased risk of long-term adverse neurodevelopmental outcomes.

In response to this finding learned bodies such as the American Academy of Pediatrics (AAP) issued statements recommending that dexamethasone should not be used to prevent or treat chronic lung disease in preterm infants.⁶ Subsequently the popularity of postnatal corticosteroids declined sharply; this decline in popularity has been associated with an increase in BPD.⁷

Further investigation of the association between corticosteroids and adverse long-term neurodevelopmental outcomes has revealed that the likelihood of a poor outcome is modified by both the infant’s postnatal age at treatment⁷ and their underlying risk of developing BPD.⁸ Increased risk of adverse outcomes is seen in those infants treated at less than eight days of age,⁹ but not in infants with signs of evolving BPD treated at over seven days of age.¹⁰ Once the infant’s risk of developing BPD rises above about 50%, corticosteroid treatment may actually reduce the risk of the composite outcome of death or cerebral palsy.¹¹

This new evidence has tempered the initial backlash against corticosteroids. The policy statements of learned bodies have been revised and now advise clinicians to treat each patient according to their individual risk/benefit ratio.¹² Many clinicians now use low or very low dose...
regimens after seven days of life to improve pulmonary function in infants at high risk of BPD in the hope that it will be possible to maximise the pulmonary benefits while minimising the neurodevelopmental risks.

While this seems to be a reasonable standpoint there is no good evidence to support it. Previously, conducted trials of low dose dexamethasone failed to recruit due to lack of clinician “buy in,” or were stopped early in response to the policy statements that were made at the time. Now that there is a more complete picture of the possible relationship between corticosteroids and neurodevelopmental outcomes, investigators are in a better position to plan and conduct the necessary research to fully inform their use.

The Minidex trial

In a retrospective cohort study it was found that infants at risk of BPD who received a very low dose corticosteroid regimen, extubated significantly faster than controls who did not receive corticosteroids. This regimen, Minidex – 50mcg/kg/day of dexamethasone for 10 days followed by alternate days for six days – was derived from the physiological corticosteroid replacement dose. It now needs to be carefully evaluated in a randomised controlled trial to assess its efficacy at improving lung function and clinical acceptability. Once this is established it will be possible to proceed with a trial design to determine its effects on BPD and neurodevelopmental outcomes, as it is these outcomes that are needed to inform clinical practice.

The Minidex trial (FIGURE 1) will randomise 94 ventilator-dependent preterm infants of less than 30 weeks’ gestation to either a course of Minidex or placebo. The primary outcome will be time to extubation as a proxy measure of short-term improvement in lung function. Secondary outcomes will include morbidity and respiratory outcomes to 36 weeks’ postmenstrual age, safety data, measures of the parent/family involvement in their baby’s care and (in Leeds and Bradford infants only) changes to the inflammatory cytokine profile.

As this is an efficacy trial with a short-term measure as the primary outcome, contamination of the placebo group with off-label steroids will not be an issue; by the time it is deemed necessary to treat a baby with open-label steroids the primary outcome will have been measured.

However, the frequency with which off-label steroids are required will give additional information about the acceptability/suitability of the treatment. Eleven centres in the north of England have kindly agreed to participate in the study (TABLE 1). Recruitment will take place over an 18-month period, with the study lasting a total of 30 months. Given the size of the trial, it is not anticipated that more centres than this will be needed to reach the recruitment target.
Parental involvement

Parental involvement in care, positive touch and comfort holding are integral aspects of developmental care. Measuring the parent/family involvement in the infant’s care throughout the trial will allow the researchers to see if the different treatments have any impact on the way in which parents are able to contribute to their infant’s developmental care. This outcome will be captured by means of a ‘diary of care and cuddles’ that will be completed by the parents (FIGURE 2). The authors are not aware of any other trials that have sought to determine this effect.

Summary

If Minidex is found to help get these infants off of their ventilators, the information gathered regarding acceptability, recruitment and adherence to protocol, and open-label steroids use, will enable planning of the large pragmatic trial required to determine its effects on BPD and long-term neurodevelopmental outcomes. The authors would be delighted to hear from any units that may be interested in participating in this trial. Trial updates will be posted on the Minidex website at www.npeu.ox.ac.uk/minidex.

References

14. Yates H.L., Newell S.I. Minidex: very low dose dexamethasone (0.05 mg/kg/day) in chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2011;96;F190-94.

FIGURE 2 The Minidex diary of care.

Key topics

- Early identification of risks and prevention of premature labour
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