ORIGINAL ARTICLE

Follow up of a randomised trial of two different courses of dexamethasone for preterm babies at risk of chronic lung disease

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Objectives: To report 18 month outcome of a randomised trial of two courses of dexamethasone to prevent chronic lung disease of prematurity.
Study design: Babies of birth weight 1250 g or less ventilated at 7 days of age were randomised to a 42 day reducing course (long) or a 3 day pulsed (pulse) course of dexamethasone.
Growth, cardiovascular status, and respiratory and neurodevelopmental outcomes were assessed at 18 months.
Results: Seventy six babies were enrolled. Nine died and three were lost to follow up. Babies receiving the long course were weaned off oxygen more quickly than those receiving the pulse course (47% *v* 69% on oxygen at 28 days; p = 0.01), but there were no differences in 18 month outcomes. However, children averaged −1 SD for growth parameters, half had moderate or severe disability, and 35% and 19% respectively required oxygen at 36 weeks and discharge.
Conclusions: The dexamethasone course used did not influence long term outcome. However, entry criteria for this study selected a group of babies at high risk of poor long term outcome.

Despite its use over many years, the role of dexamethasone in the management of preterm babies with chronic lung disease remains unclear. It is known to reduce the incidence of chronic lung disease in the high risk premature baby,[1] but controversy exists over the timing, dosage, and duration of treatment.[2–5] Short term side effects of dexamethasone are well documented, including impairment of linear growth and weight gain, glucose intolerance, adrenal suppression, myocardial hypertrophy, hypertension, and decreased bone mineral content.[6–11] Few studies have compared these effects in babies receiving different courses of dexamethasone. Recently there has been increased concern that dexamethasone may cause impaired neurodevelopment,[12] but to date few studies have addressed this specific issue. Furthermore, as babies with chronic lung disease have a poor overall outcome,[13 14] it is difficult to distinguish between the effects of chronic lung disease and those of dexamethasone. With growing concern over dexamethasone use, further studies comparing the short and long term effects of different courses are essential.

We previously reported a randomised trial[15] that directly compared short term outcomes of two different courses of dexamethasone given to preterm babies at risk of chronic lung disease: a three day repeatable pulsed course and a 42 day reducing course. This study of 40 babies showed that the pulsed course had fewer side effects but may have been less effective at preventing chronic lung disease. Twice as many babies in the pulse group as in the long course group required oxygen at 28 days and 36 weeks. However, the primary outcome of the study was leg growth, and it did not have adequate power to determine the efficacy of these different courses of dexamethasone in the prevention of chronic lung disease.

This earlier study was subsequently extended, and further babies were enrolled to allow comparison of the two courses of dexamethasone with regard to both prevention of chronic lung disease and long term outcomes. The present paper reports the findings of that enlarged study. We report the effects of two different courses of dexamethasone on the prevention of chronic lung disease and on long term growth, cardiovascular status, and respiratory and neurodevelopmental outcomes.

METHODS

Babies were eligible for the study if their birth weight was ⩽ 1250 g and if they were ventilated at ⩾ 15 cycles/minute at 7 days of age. Randomisation was by computer allocation to either a three day repeatable pulsed course of dexamethasone (the pulse group) starting immediately[2] or a 42 day reducing course[3] (the long group) starting at 14 days if they were still ventilated at ⩾ 15 cycles/minute and required ⩾ 30% supplemental oxygen in accordance with published protocols. The pulse course consisted of 0.5 mg/kg dexamethasone daily for three days, repeated every 10 days until infants no longer required ventilatory support or supplemental oxygen or until 36 weeks of age.[2] The long course consisted of dexamethasone starting at 0.5 mg/kg/day for three days, reduced to 0.3 mg/kg/day for three days, and thereafter reduced by 10% every three days to wean over 42 days.[3]

This study was approved by the regional ethics committee, and written informed consent was obtained from the parents of each child.

Babies enrolled in the original study[15] were included in this follow up study. One baby was found in retrospect to have a birth weight of 1305 g, but, as he had completed the study protocol, he was retained in the final analysis. Attempts were made to review all children at the National Women's Hospital at a chronological age of 18 months. Growth and cardiovascular measurements were usually taken on the same day, but in some instances this was not possible. Thus some children were reviewed on two occasions to obtain all information.

Growth

Head circumference was measured with a paper tape, and weight using electronic scales (Salter, Auckland, New Zealand). Length was obtained using a measuring board with a fixed headpiece and a sliding vertical footpiece (Holtain Ltd,

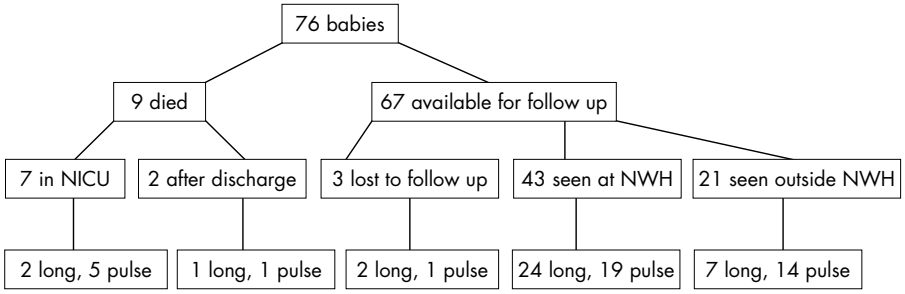

Figure 1 Follow up details of babies enrolled in each study group: long, 42 day reducing course of dexamethasone; pulse, three day pulsed course of dexamethasone. NICU, Neonatal intensive care unit; NWH, National Women's Hospital.

Crymych, Dyfed, Wales, UK). New Zealand sex specific postnatal centile charts[16] were used to calculate the standard deviation (z) scores for length, weight, and head circumference for each child's corrected age. The z score was the difference between the actual measurement and the population mean measurement for age divided by the standard deviation.

Cardiovascular status

Blood pressure was obtained using a Dynamap oscillometer (Johnson and Johnson, Arlington, Texas, USA). The average of three readings taken from the right arm was recorded. Interventricular septum thickness and left ventricular posterior wall thickness were measured in end diastole with calipers using M mode echocardiography images obtained with an ATL HDI 3000 (Advanced Technological Laboratories, Bethell, Washington, USA) ultrasound machine.

Respiratory outcome

The time on supplemental oxygen was calculated from the final date that each baby required supplemental oxygen. Similarly, the duration of any type of respiratory support (ventilation, continuous positive airways pressure, nasal cannula oxygen or air) was calculated from the final date on which any support was required.

Neurodevelopment

One developmental psychologist reviewed all children attending the National Women's Hospital Child Development Unit, where cognitive and motor function were assessed using Bayley Scales of Infant Development II.[17] The consultant paediatrician responsible for the child's follow up performed a detailed neurological examination. Children were classified into one of four outcome categories defined and modified from the work of Kitchen *et al*.[18] Severe disability was defined as including one or more of a Bayley mental score > 2 SDs below the mean, bilateral blindness, sensorineural deafness requiring hearing aids, or the presence of severe cerebral palsy. Moderate disability was classified as a Bayley mental score 1–2 SDs below the mean or mild-moderate cerebral palsy without developmental delay. Mild disability was the presence of tone disorder and/or motor delay but with normal mental development, and normal neurodevelopment was classified as the absence of tone disorder or developmental delay.

For babies who did not attend our hospital for follow up, the local paediatrician responsible for the child's care was asked to provide as much of the above information as could be collected including a detailed neurological assessment. Using this information, two paediatricians and one developmental psychologist independently categorised children into one of the previously defined outcome groups. Any minor differences in categorisation were resolved by discussion.

Statistical analysis

The primary outcome of this study was chronic lung disease defined by a requirement for supplemental oxygen at 36 weeks of postmenstrual age. Thirty six babies were required in each group to detect a 50% difference in the incidence of chronic lung disease with $\alpha = 0.05$ and 80% power. This was the difference observed between groups in our original study.[15]

Results were compared between groups using Student's *t* tests and multiple regression analysis for continuous variables and χ^2 for categorical variables. Data on duration of hospital stay, time on oxygen, and time on respiratory support were log transformed before analysis. All data were analysed using Statview version 5.0.1 (SAS Institute, Cary, North Carolina, USA).

Values are expressed as mean (SE) or median (range) as appropriate.

RESULTS

The study was performed between 1 January 1996 and 1 October 1997. Seventy six babies were enrolled, 40 of whom were included in the original report of short term respiratory outcomes[15] (fig 1). Three were lost to follow up. Eleven babies received steroids outside the study protocol and were not randomised.

Table 1 Clinical details of babies enrolled in the trial

	Long group	Pulse group
Birth weight (g)	793 (28) (560–1305)	776 (25) (440–1170)
Gestational age (weeks)	25.8 (0.3) (23.6–30.0)	25.8 (0.3) (23.0–31.0)
Antenatal steroids given	27 (73%)	37 (95%)*
Male	23 (62%)	24 (62%)
Small for gestational age (birth weight <10th centile)	8 (22%)	8 (21%)
Mean airway pressure at enrolment (cm H_2O)	7.8 (0.3)	8.0 (0.3)
F_{IO_2} at enrolment	0.30 (0.01)	0.30 (0.02)
Grade 3 or 4 intraventricular haemorrhage	2 (5%)	4 (10%)

Values shown are mean (SEM) (range) or number (%) for 37 babies in the long and 39 in the pulse group. Long group, babies receiving a 42 day reducing course of dexamethasone; pulse group, babies receiving a three day pulsed course of dexamethasone.
*p=0.05 compared with long group.

Table 2 Growth measurements with z scores at 18 month follow up in babies who received a long or pulse course of dexamethasone

	Long group	Pulse group
Corrected age (months)	16.2 (0.4) (12.7–20.3)	15.9 (0.6) (10.4–23.4)
Weight (kg)	9.6 (0.2) (7.4–11.9)	9.7 (0.2) (8.0–12.4)
Weight z scores	–1.13 (0.19) (–2.67–0.56)	–0.97 (0.15) (–2.21–1.01)
Length (cm)	77.6 (0.7) (72.0–82.7)	77.1 (0.6) (70.8–85.5)
Length z scores	–0.90 (0.21) (–3.10–1.03)	–1.00 (0.15) (–2.10–0.36)
Head circumference (cm)	46.9 (0.3) (43.6–49.5)	46.6 (0.2) (44.6–49.1)
Head circumference z scores	–0.85 (0.21) (–3.48–1.48)	–1.06 (0.16) (–2.61–0.47)

Values shown are mean (SEM) (range). Weight and head circumference measurements were obtained in 25 children, and length in 24 children in the long group. Measurements were obtained in 27 children in the pulse group.

Table 3 Cardiovascular measurements at follow up in babies who received a long or pulse course of dexamethasone

	Long group	Pulse group
Corrected age (months)	17.4 (0.7) (14.5–25.3)	17.4 (1.0) (14.0–33.7)
Systolic blood pressure (mm Hg)	93 (2) (74–108)	97 (3) (79–127)
Diastolic blood pressure (mm Hg)	62 (2) (50–75)	63 (3) (41–94)
Mean blood pressure (mm Hg)	77 (2) (69–89)	80 (3) (65–102)
Intraventricular septum thickness (cm)	0.45 (0.02) (0.32–0.60)	0.45 (0.02) (0.25–0.61)
Left ventricular wall thickness (cm)	0.43 (0.01) (0.32–0.48)	0.43 (0.02) (0.30–0.53)

The values are mean (SEM) (range). In the long group, blood pressure was measured in 16 children, and echocardiography measurements in 18 children. In the pulse group, blood pressure was measured in 17 children, and echocardiography in 19 children.

Table 4 Respiratory outcomes in babies who received a long or pulse course of dexamethasone

	Long group	Pulse group
Oxygen at 28 days	17/36 (47%)	25/36 (69%)**
Oxygen at 36 weeks	11/35 (31%)	13/34 (38%)
Home on oxygen	5/35 (14%)	8/34 (23%).
Length of time on oxygen (months)	3.0 (0.6) (0.03–16.6)	4.5 (1.1) (0.03–22.2)
Length of any respiratory support (months)	3.4 (0.6) (0.4–16.6)	5.0 (1.1) (0.3–22.2)

Values are the number/number of surviving babies (%), or mean (SEM) (range).
**p=0.01 compared with long group on multivariate analysis.

Seven babies died after withdrawal of care in the neonatal unit. The causes of death were respiratory failure following septicaemia (four), severe intraventricular haemorrhage with hydrocephalus (two), and necrotising enterocolitis (one).

Two babies died after discharge. One had cerebral palsy with severe spastic quadraparesis and was reported to have died from sudden infant death syndrome at 9 months of age. The second died at 18 months from complications following an orthoptic liver transplant for extrahepatic biliary atresia. Development in this case was delayed, due in part to complications arising from liver disease. Outcome for these two babies is included in the results presented.

There were no differences between the groups at enrolment in birth weight, gestational age, sex, intraventricular haemorrhage, or severity of respiratory disease (table 1). However, more babies in the pulse group were exposed to antenatal steroids (95% *v* 75%, $p < 0.05$).

The mean age at measurement of growth variables was 16.0 (0.3) months (range 10.4–23.4) after term. About three quarters (76%) of the children were seen within the age range 14–18 months. There was no difference between groups in weight, length, or head circumference (table 2). Overall, these babies were about 1 SD below the mean for all measurements.

The mean age at cardiovascular follow up was 17.4 (0.6) months (range 14.0–33.7) after term. About three quarters (78%) of the echocardiograms were performed within the age range 14–18 months, and there was no change in cardiovascular measurements with age. There were no differences between the two groups with respect to blood pressure (systolic, diastolic, or mean), thickness of the interventricular septum, or thickness of the left ventricular posterior wall (table 3). All blood pressure measurements were within the normal range for corrected age.[19]

There was no significant difference in any respiratory outcome between the two groups (table 4). Half of all babies were still on supplementary oxygen at 28 days, and one third at 36 weeks. About 19% of babies were discharged on supplementary oxygen. When multivariate analysis was performed to take into account the difference in exposure to antenatal steroids between groups, babies in the long group were less likely to require supplemental oxygen at 28 days ($p = 0.01$). This difference was no longer significant by 36 weeks.

Neurodevelopmental outcome was not different between the two groups (table 5). Only one third of all babies were classified as having normal neurodevelopmental outcome at follow up, and 8% were severely disabled. Seven babies (five in the pulse group, two in the long group; $p = 0.22$) had grade 3 or 4 intraventricular haemorrhage, of whom four (three pulse, one long) had shunted hydrocephalus at discharge.

Multivariate analysis did not show any differences between groups in any of the other outcome variables measured.

Table 5 Neurodevelopmental outcome in babies who received a long or pulse course of dexamethasone

	Long group	Pulse group
Severe disability	1	4
Moderate disability	16	11
Mild disability	4	7
Normal	11	10

Values are number for 32 babies in the long group and 32 babies in the pulse group.

DISCUSSION

The aim of this study was to compare the effects of two different courses of dexamethasone on outcomes of babies at risk of chronic lung disease. We found no differences in measured outcomes at 18 months of age between babies treated with a 42 day reducing course and those treated with a three day repeatable course of dexamethasone. However, as a group, babies enrolled in this study did poorly: 12% died, 19% of surviving babies were discharged home on supplementary oxygen, and at 18 months on average they were small, with only one third having normal neurodevelopment.

We undertook this enlarged and longer term study because our previous study had suggested that the long course of dexamethasone may be more effective than the pulse course in preventing chronic lung disease.[15] In that study, half as many babies receiving the long course required supplemental oxygen at 28 days and 36 weeks, but the study did not have adequate power to determine the significance of those findings. This new study confirms the impression that babies receiving the long course show more rapid improvement in their respiratory status, with numbers receiving supplemental oxygen by 28 days reduced by about one third. However, this early improvement did not result in long term benefit. There was no difference in oxygen requirement at 36 weeks and no difference in longer term respiratory outcomes.

Our previous study also showed that the long course was associated with poorer growth, more hypertension, and more adrenal suppression than the short course, although there were no differences in growth or cardiovascular parameters by 36 weeks. Thus the increased short term adverse effects of the long course were accompanied by short term respiratory benefit, but no apparent long term advantage or disadvantage in comparison with the pulse course. Although adrenal axis function would have been of interest at follow up, we did not feel that invasive testing of asymptomatic children could be justified. Growth and cardiovascular outcomes were not available for all children not followed up at our centre. However, this is unlikely to have altered the results, as a similar proportion of children from each group were seen in our centre.

Although randomisation to either a long or pulse course of dexamethasone occurred at 1 week of age, babies randomised to the long course did not begin steroid treatment until 2 weeks of age, in accordance with the published protocol.[3] We expected that not all babies randomised at 1 week would be eligible at 2 weeks, as some babies would improve in the 2nd week of life and thus avoid receiving a prolonged course of dexamethasone. However, only one baby randomised to the long course failed to meet criteria for starting dexamethasone at 2 weeks. Thus respiratory status at 1 week appeared to be very predictive of status at 2 weeks. This raises the question of whether the long course would be more efficacious if given at 1 week of age. Inflammatory mediators have been found in the lungs of ventilated infants within the first few days of life, and the major effect of dexamethasone may be reduction of inflammation.[20 21] Administration of dexamethasone at 7–14 days of postnatal age reduces both mortality and the incidence of chronic lung disease,[1] whereas its administration at a later stage may reduce oxygen requirement in the short term but not mortality or quality of life.[22] Thus there appears to be little advantage in delaying the start of dexamethasone treatment beyond the period required to establish that the infant falls into a high risk group likely to benefit from such treatment. In our nursery, criteria for recruitment into this trial appeared to select a high risk group at the end of the first week of life.

In our study, the overall rate of chronic lung disease as defined by a requirement for oxygen at 36 weeks was 35% of survivors. However, this was not a complete reflection of all babies with respiratory problems at 36 weeks of corrected age. Seven babies (9%) required continuous positive airway pressure but not supplemental oxygen at 36 weeks. These babies clearly had a continuing requirement for respiratory support, but did not meet the current definition of chronic lung disease. With continuing changes in neonatal care and the increasingly widespread use of continuous positive airway pressure for long term respiratory support of preterm babies, the definition of chronic lung disease may need amendment. It would be useful to report respiratory outcomes in terms of any respiratory support as well as requirement for supplemental oxygen in future reports on treatment of respiratory disease in preterm babies.

Babies recruited to this study had a high incidence of chronic lung disease (53% at 28 days and 34% at 36 weeks), and 19% of infants required home oxygen therapy. This reflects the high risk group recruited, rather than a high rate of chronic lung disease with our nursery population. Over the study period, the incidence of chronic lung disease in babies less than 1250 g in our nursery was 28% (70/254) at 28 days and 16% (41/254) at 36 weeks. Seven percent (19/254) were discharged home on supplemental oxygen. Thus entry criteria for enrolment into this study correctly selected a group of babies at high risk of chronic lung disease. Indeed enrolled babies constituted 59% of all babies with chronic lung disease treated over this period.

The respiratory outcomes we report are similar to those reported elsewhere.[1 2] Although Cummings *et al*[3] compared the 42 day course with an 18 day course, finding no benefit of the latter, there are no other trials comparing two different courses of dexamethasone. Papille *et al*[23] compared a two week course of dexamethasone started at 2 weeks of age with the same course started at 4 weeks of age and found no difference in the incidence of chronic lung disease overall (67% overall, with 48% and 52% requiring home oxygen for a median of 5 and 5.5 months respectively). No other long term outcomes were measured. Respiratory outcomes were measured until 1 year of corrected age and may not have accurately reflected long term respiratory outcome of some babies. A number of babies in our study still required supplemental oxygen after 1 year of corrected age, and therefore our results include the total duration that each baby required supplemental oxygen.

Neurodevelopmental assessment at follow up showed that half of the babies enrolled in this study had moderate or severe neurodevelopmental disability. Once again, this reflects the severity of illness of babies recruited, rather than a high overall incidence of disability among survivors in our nursery. Of the babies of birth weight < 1000 g cared for in our unit in 1996[24] and 1997, 42/116 (36%) were classified as having severe or moderate neurodevelopmental disability at 18 months of age. Thirty of these infants (71%) were enrolled in our study; thus these babies formed a substantial proportion of those children with poor neurodevelopmental outcome discharged from our unit.

Previous studies have shown that babies with chronic lung disease are at increased risk of poor neurodevelopmental outcome.[25] This is a consistent finding even when other possible causative factors such as periventricular haemorrhage and patent ductus arteriosus are taken into account. Before the

widespread use of dexamethasone, it is likely that some preterm babies with severe chronic lung disease did not survive. Dexamethasone treatment may improve survival of some infants who are at increased risk of neurological injury. However, concern is increasing that postnatal dexamethasone may also have direct adverse effects on central nervous system growth and development in premature infants. Perinatal corticosteroids cause significant changes to the rodent brain, including decreased brain weight and changes to neural cell division and differentiation.[26] To date there are few studies on long term follow up of infants enrolled in placebo controlled dexamethasone trials. Recent reports have suggested that postnatal use of dexamethasone may be associated with an increased rate of cerebral palsy and sensorineural impairment in surviving children,[27–29] but each of these reports has methodological or sample problems.

Our study did not include a placebo group, and thus any potential adverse effects of dexamethasone and chronic lung disease on neurodevelopment cannot be differentiated. At the time this study was started, dexamethasone had been shown to reduce death and chronic lung disease, and available follow up data suggested no adverse effects on neurodevelopmental outcome.[2] Thus withholding dexamethasone from a high risk group was thought to be unethical. However, given more recent concerns about an apparent association between dexamethasone treatment and adverse neurodevelopmental outcome,[27–29] and the overall poor outcome of babies enrolled in this study, placebo treated groups and long term neurodevelopmental follow up should be considered in future studies of the use of dexamethasone in preterm babies.

Our original study showed that, although growth was reduced in the neonatal period when babies received dexamethasone, there were no longer any differences between groups by 36 weeks of corrected age.[15] Despite this, children enrolled in this study were small at follow up, being on average 1 SD below the mean for all measurements. When factors such as very low birth weight, low gestation, poor respiratory outcome, and poor neurodevelopmental outcome are taken into account, this result is not surprising, and is consistent with other long term studies of growth of children with chronic lung disease.[30] However, it is also possible that dexamethasone itself may have an adverse effect on long term growth. Once again, potential adverse effects of chronic lung disease and those of dexamethasone on long term growth cannot be differentiated in this study.

In our original study, babies who received the long course of dexamethasone had a greater increase in left ventricular wall thickness and intraventricular septal thickness than those in the pulse course, and this difference persisted at 36 weeks.[15] However, by 18 months these effects had resolved, and both measurements were within normal limits for both groups.[31] This finding is consistent with other studies reporting the reversible cardiac effects of dexamethasone.[32] However, the mechanism of these effects is unclear. Left ventricular and intraventricular septal hypertrophy are also associated with conditions causing hyperinsulinism, suggesting that the cardiac effects of dexamethasone may be through similar pathways, perhaps by reversible upregulation of cardiac myocyte insulin or insulin-like growth factor-I receptors.[32 33] Babies receiving the long course of dexamethasone also had a greater increase in blood pressure earlier in the course, but this difference had resolved by 36 weeks.[15] Again there was no evidence of any persisting difference in blood pressure between groups at follow up, and all measurements were within normal limits for corrected age.[19] Thus there do not appear to be lasting effects of early dexamethasone use on cardiovascular parameters, at least up to 18 months of age.

We conclude that, in preterm infants at high risk of chronic lung disease, treatment with a long course of dexamethasone is associated with more rapid respiratory improvement but more side effects in the short term than treatment with a repeated pulse course of dexamethasone. However, there were no long term differences between groups in respiratory, growth, cardiovascular, or developmental outcomes. The overall outcome for babies enrolled in this study was poor. From this study it is not possible to differentiate between the adverse consequences of chronic lung disease and potential additional adverse effects of dexamethasone.

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