Failure of early postnatal dexamethasone to prevent chronic lung disease in infants with respiratory distress syndrome

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Abstract

Objective—To study the effect of early postnatal dexamethasone (days 1–3) on the incidence and severity of chronic lung disease in preterm infants with respiratory distress syndrome.

Methods—A multicentre, randomised, placebo controlled, blinded study was carried out in 18 neonatal intensive care units in Israel. The primary outcome measure was survival to discharge without requirement for supplemental oxygen therapy beyond 28 days of life. The secondary outcome measures were requirement for mechanical ventilation at 3 and 7 days, duration of ventilation or oxygen therapy, need for subsequent steroids for established chronic lung disease and incidence of major morbidities.

Results—The study consisted of 248 infants (dexamethasone $n=132$; placebo $n=116$). No differences were found in the outcome variables except for a reduction in requirement for mechanical ventilation at age 3 days in treated infants (dexamethasone 44%, placebo 67%; $P=0.001$). Gastrointestinal haemorrhage, hypertension, and hyperglycaemia were more common in treated infants, but no life threatening complications, such as gastrointestinal perforation, were encountered. **Conclusions**—These data do not support the routine use of early postnatal steroids, but may justify further study in a selected, high risk group of infants.

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Keywords: respiratory distress syndrome, steroids, surfactant, chronic lung disease.

The incidence of chronic lung disease (CLD) in premature infants remains distressingly high in spite of the reduction in acute morbidity and mortality resulting from the recent introduction of surfactant treatment for respiratory distress syndrome (RDS).^{1–3} Steroid treatment has been shown to be effective in ameliorating established CLD, presumably mainly by its anti-inflammatory actions.^{4–7} Cellular and biochemical studies have shown inflammatory changes in the lungs of ventilated infants as early as the first few days of life,^{8–10} and dexamethasone has been shown to reduce this inflammation.^{11 12} Thus it has been postulated that steroid treatment administered shortly

after birth may prevent the inflammatory insult to the lung and thereby reduce the likelihood of CLD.¹³ Early steroid treatment may also increase the postnatal induction of surfactant synthesis and secretion. Five randomised controlled trials of early postnatal steroid treatment have been reported, with mixed results.^{13–17} Three of these studies were conducted before the routine availability of surfactant therapy and they all had relatively small study populations. Three of the studies used a long course of treatment of 12–28 days, which was felt by this group of investigators possibly to incur a significant risk of steroid related adverse events. The two other studies used an extremely short course of treatment (2 doses) which may possibly have been inadequate.

Thus we report a multicentre, randomised, blinded, placebo-controlled trial of a three day, early postnatal course of dexamethasone treatment in preterm infants with respiratory distress syndrome, who were treated with surfactant.

Methods

The study protocol was approved by the Human Investigation Committee of each participating centre and also by the Ministry of Health of Israel. Informed parental consent was obtained for each infant.

All infants meeting criteria were considered for inclusion in the study. The inclusion criteria were: clinical and radiographic diagnosis of RDS; requiring mechanical ventilation and $FiO_2 > 0.4$ with a PaO_2 of 50–80 mm Hg; birthweight 500–2000 g; less than 12 hours of age; no contraindications to steroids, such as bleeding tendency, hypertension, hyperglycaemia or active infection; and no lethal congenital malformation.

The primary outcome measure was survival to discharge without requirement for supplemental oxygen beyond 28 days of life. The secondary outcome measures were the requirement for mechanical ventilation or oxygen at the end of the study drug course – three days – and before subsequent steroid treatment for established CLD was permitted after 7 days of age. Additional measures of outcome included oxygen requirement at 36 and 40 weeks, corrected gestational age, duration of mechanical ventilation or oxygen treatment, requirement for subsequent steroids for established CLD, and the incidence of major associated morbidity. The minimum study sample size was

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Table 1 Baseline characteristics of the infants in both study groups (continuous variables are expressed as mean (SEM))

	Dexamethasone (n=132)	Placebo (n=116)
Birthweight (g)	1185 (35)	1174 (34)
Gestational age (weeks)	29 (0.2)	29 (0.2)
Sex (M/F)	76/56	66/49
ROM >24 hours	13 (10)	14 (12)
Apgar at 5 minutes	7.5 (0.2)	7.8 (0.2)
Caesarean section delivery	77 (58)	70 (60)
Singleton birth	98 (74)	83 (72)
Inborn	129 (99)	115 (99)
Antenatal steroids		
None	97 (73)	86 (74)
Partial	13 (10)	11 (9)
Complete	21 (16)	19 (16)

Discrete variables are expressed as the n with % in parentheses. ROM=rupture of membranes.

Table 2 Severity of initial disease

	Dexamethasone (n=132)	Placebo (n=116)
<i>First 12 hours of life</i>		
Highest FIO ₂	0.85 (0.2)	0.82 (0.2)
Lowest pH	7.22 (0.01)	7.22 (0.01)
Lowest MABP (mm Hg)	31 (0.7)	29 (0.6)
Age at MV (hour)	1.2 (0.3)	1.5 (0.4)
Age at first surfactant (hour)	4.4 (0.4)	4.8 (0.4)
x Ray grade	2.9 (0.1)	2.8 (0.1)
<i>Settings before study drug</i>		
a:A PO ₂	0.15 (0.01)	0.15 (0.01)
MAP (cm H ₂ O)	8.9 (0.2)	8.4 (0.2)
Oxygenation index	12 (0.8)	12.8 (0.8)

MV=mechanical ventilation; MABP=mean arterial blood pressure; a:A PO₂=arterial:alveolar oxygenation ratio; MAP=mean airway pressure.

calculated assuming 5% error and a power of 80%, therefore estimating that it would be possible to detect an increase from 50% to 70% in the primary outcome variable with a sample size of 206 infants (103 pairs).

Eighteen centres participated in the study with four to 50 infants per centre. (In view of the small number of infants enrolled from some centres, no analysis of the effect of centre allocation was performed.) Each participating unit was supplied with numbered sets of syringes containing either dexamethasone 1 mg in 0.25 ml or physiological saline. The syringes were prepared with full sterile technique under a laminar flow hood by the study pharmacist in the Pharmacy Department at Soroka Medical Center, Beersheva. Following preparation, each syringe was stored in a sealed, nylon sleeve. Syringes containing dexamethasone were not distinguishable from those containing saline. Syringe sets were numbered according to a random number list. Randomisation was stratified by centre and by two birthweight groups – 500–1000 g and 1001–2000 g – to prevent chance sampling inequality. The drug assignment was not

known to any of the investigators until after the three month observation period of the last enrolled infant. When an infant who met inclusion criteria was identified, the local investigator telephoned the central randomisation unit in the Department of Neonatology at Soroka Medical Center, Beersheva, and a study number was assigned corresponding to the syringe set to be administered. The syringe set was opened and 0.75 ml saline was added to achieve a final concentration of 1 mg/ml of dexamethasone (or its placebo equivalent). The dosage regimen was 0.25 mg/kg intravenously, every 12 hours for a total of six doses. Subsequent steroid treatment for established CLD was permitted after 1 week of age. Otherwise, routine clinical care was at the discretion of the attending neonatologist.

Bovine surfactant (Surfactant TA, Surfacten) was supplied by Tokyo Tanabe, Japan and administered to all infants as a rescue treatment according to the manufacturer's guidelines. Each dose of surfactant was 100 mg/kg (30 mg/ml) and up to 4 doses per infant were permitted.

Data collection included: baseline patient characteristics (birthweight, gestational age, sex, multiplicity); obstetric data (inborn/outborn, antenatal steroids, rupture of membranes, delivery type, Apgar score); severity of initial disease (age at mechanical ventilation and age at surfactant treatment, chest x-ray grade,¹⁸ highest FIO₂, lowest pH and lowest mean arterial blood pressure in the first 12 hours of life); ventilatory and oxygen requirements and arterial blood gasses before and after surfactant and at age 24 hours and age 3 and 7 days; number of doses of surfactant and study drug received and, if the full six doses of study drug were not administered, the reason for discontinuation; adverse events attributed by the attending neonatologist to dexamethasone, such as hypertension, hyperglycaemia, infection, gastrointestinal haemorrhage, etc; outcome in terms of mortality and associated major morbidity, such as CLD and the need for subsequent steroid treatment, intraventricular haemorrhage, periventricular leucomalacia, retinopathy of prematurity, patent ductus arteriosus, pulmonary air leak, pulmonary haemorrhage, sepsis, pneumonia, necrotising enterocolitis, apnoea and seizures.

Completed data sheets were sent to the Data Coordinating Unit for double data entry computerisation on the spreadsheet package Quattro Pro for Windows. The range of acceptable values for each data field was predefined and discrepancies were rechecked at source.

Cranial ultrasound scans were performed at 1 and 6 weeks of age and were assessed for the presence of localised, intraventricular or parenchymal haemorrhage, ventricular dilatation, and parenchymal cysts.¹⁹ Retinopathy of prematurity was defined according to the standard international classification.²⁰ Patent ductus arteriosus was diagnosed by standard clinical, radiographic, and echocardiographic criteria.

Statistical analysis was performed using the SPSS for Windows software package.

Table 3 Primary and secondary outcome variable

	Dexamethasone (n=132)	Placebo (n=116)	Odds ratio (95% CI)
<i>Primary outcome</i>			
Survival, no O ₂ >28 d	72 (55)	71 (61)	0.76 (0.46, 1.26)
Survival, O ₂ >28 d	29 (22)	23 (20)	1.14 (0.62, 2.1)
Died	31 (24)	22 (19)	1.31 (0.71, 2.4)
<i>Secondary outcome needing MV</i>			
3 Days	54/122 (44)	71/106 (67)*	0.4 (0.24, 0.68)*
7 Days	27/113 (24)	34/100 (34)	0.61 (0.34, 1.11)

Denominators at 3 and 7 days represent number of survivors at each age. *P=0.001.

Table 4 Markers of chronic lung disease (CLD)

	Dexamethasone (n=132)	Placebo (n=116)
Days MV	9 (1.2)	11 (1)
Days in O ₂	20 (3)	19 (3)
Days in >40% O ₂	8 (1)	10 (4)
O ₂ at 28 days	32 (24)	24 (21)
O ₂ at 36 weeks	15 (11)	11 (9)
O ₂ at 40 weeks	6 (5)	6 (5)
Steroids for CLD	24 (27)	30 (26)
Days of steroids for CLD	3 (1)	6 (1)
<i>Duration of hospital stay (days)</i>		
Survivors	63 (3)	65 (4)
Died	12 (3)	10 (4)

Student's *t* test was used for comparison of means of continuous variables. For variables with marked skewness of distribution, the Mann-Whitney U-Wilcoxon Rank Sum Test was used. χ^2 or Fisher's exact test was used for categorical variables and odds ratios and 95% confidence intervals were also calculated. A *P* value of less than 0.05 was considered significant. All comparisons were made between the complete treated and placebo groups.

Results

BASELINE CHARACTERISTICS AND INITIAL SEVERITY OF DISEASE

During the study period, April 1993 to January 1994, 255 infants were enrolled in the study. Seven infants were subsequently excluded from analysis. Three infants had major congenital abnormalities (two myotonic dystrophy and one cyanotic congenital heart disease) which had not been diagnosed at the time of randomisation. Three infants had errors in drug administration and one was randomised beyond 12 hours of age. Thus the final study sample consisted of 248 infants, of whom 132 received dexamethasone and 116 received placebo. In the 500–1000 g group there were 108 infants, with 59 receiving dexamethasone and 49 placebo. Of the 140 infants in the 1001–2000 g group, 73 received dexamethasone and 67 placebo. Table 1 shows the

baseline characteristics of the groups. No significant differences were noted. In particular, the incidence of antenatal steroid use was low, overall, and no difference was found between the study groups.

Severity of disease before the study intervention was analysed. Table 2 shows that there were no significant differences between the treated and placebo infants.

OUTCOME

No differences were found between the treated and placebo groups in survival without chronic lung disease – that is, the primary outcome variable (table 3).

Significantly fewer of the treated infants required ventilation at the completion of steroid treatment at age 3 days than placebo infants (dexamethasone 44%, placebo 67%, *P*=0.001). However, at 7 days of age, this difference was much less noticeable and no longer met statistical significance.

RESPONSE TO SURFACTANT

Surfactant administration was followed by a substantial and rapid improvement in oxygenation with the a:A ratio rising by 233 (46%) from before (0.14 (0.12)) to one hour after administration (0.33 (0.19)). The mean number of doses of surfactant administered was 1.74 per infant and no significant differences were noted between the treated and placebo groups in terms of number of doses or improvement in a:A PO₂ in response to surfactant.

CHRONIC LUNG DISEASE

Various measures were used to assess the severity and duration of CLD. Table 4 shows the duration of mechanical ventilation and oxygen treatment, the need for and duration of steroid treatment for established CLD and the duration of hospital stay for both survivors and for infants who died. No significant differences were found between the treated and placebo groups.

MAJOR MORBIDITY

Table 5 shows the incidence of major morbidities. No significant differences were found between the treated and placebo infants. The incidence of complications attributable to steroids in treated and placebo infants are shown in table 6. Treated infants had a significantly higher incidence of gastrointestinal haemorrhage than the placebo group. Hypertension and hyperglycaemia were seen more often in treated infants but this difference did not meet significance.

CAUSES OF DEATH

No significant differences were found between treated and placebo infants in the relative frequencies of the different causes of death (table 7).

Table 5 Major morbidity

	Dexamethasone (n=132)	Placebo (n=116)	Odds ratio (95% CI)
Intraventricular haemorrhage grade II+	7/88 (8)	10/76 (13)	0.57 (0.21, 1.56)
Ventricular dilatation	7/88 (8)	6/76 (8)	1.01 (0.32, 3.13)
Periventricular leucomalacia	16/88 (18)	9/76 (12)	1.63 (0.7, 3.82)
ROP (grade 3+)	10 (8)	8 (7)	1.11 (0.42, 2.89)
Pneumothorax	9 (7)	13 (11)	0.58 (0.24, 1.4)
PIE	6 (5)	6 (5)	0.87 (0.27, 2.79)
PDA	25 (19)	32 (28)	0.61 (0.34, 1.11)
NEC	10 (8)	10 (10)	0.87 (0.35, 2.17)
Sepsis	32 (24)	37 (32)	0.68 (0.39, 1.19)

ROP=retinopathy of prematurity; PIE=pulmonary interstitial emphysema; PDA=patent ductus arteriosus; NEC=necrotising enterocolitis. Ventricular dilatation refers to hydrocephalus >4 mm above the 97th percentile. Denominators in IVH, ventricular dilatation, and PVL refer to number of available ultrasound examinations.

Table 6 Complications attributed to study drug by local investigator

	Dexamethasone (n=132)	Placebo (n=116)	Odds ratio (95% CI)
Hypertension	8 (6)	2 (2)	3.05 (0.86, 10.82)
Hyperglycaemia	16 (12)	9 (8)	1.62 (0.71, 3.69)
Sepsis	4 (3)	8 (7)	0.43 (0.14, 1.38)
Gastrointestinal haemorrhage	28 (21)	12 (10)	2.23 (1.13, 4.38)
Less than 6 doses of drug/placebo course	17 (13)	6 (5)	2.49 (1.06, 5.87)

Table 7 Causes of death

	Dexamethasone (n=31)	Placebo (n=22)	Odds ratio (95% CI)
Acute respiratory	7 (23)	6 (27)	0.78 (0.22, 2.74)
Intraventricular haemorrhage	10 (32)	8 (36)	0.84 (0.27, 2.62)
Chronic respiratory	3 (10)	0	5.92 (0.57, 61.57)
Infection	3 (10)	3 (14)	0.68 (0.12, 3.75)
Congenital anomaly	0	0	1
Other	8 (26)	5 (23)	1.18 (0.33, 4.14)

Discussion

This study has shown that an early, short post-natal course of dexamethasone does not prevent the development of CLD or reduce mortality in severe RDS. The only significant difference between the groups which may suggest benefit was the improved respiratory status of the treated infants group at 3 days of age. This difference, however, was not sustained at 7 days of life. In addition, this finding did not find expression in a reduction in either incidence or severity of chronic lung disease.

Complications, which were attributable, in the opinion of the attending neonatologist, to steroid treatment, were more common in the treated group. Gastrointestinal haemorrhage was significantly more common in treated infants and there was also a non-significant increase in hypertension and hyperglycaemia. No cases of gastrointestinal perforation were recorded. In spite of the slight increase in hypertension, there was no difference between the groups in the incidence of intracranial haemorrhage. The mean number of doses of dexamethasone administered was 5.5 out of a possible six in both groups and, in total, only 23 infants (9%) did not receive the complete course of the study drug, suggesting that the severity of the side effects was relatively mild.

Previous reports of the use of early postnatal steroid treatment have provided mixed results. Baden *et al*¹⁴ in 1972 were unable to demonstrate any immediate benefit from the administration of two doses of hydrocortisone within the first day of life. No improvement was found in requirement for oxygen or ventilation in the first 72 hours and no difference in mortality was found between treated and untreated infants. In addition, no benefit was seen in the subgroup of infants whose mothers had received antenatal steroids. Yeh *et al* in 1990¹³ demonstrated improved acute respiratory status, increased extubation by 14 days, and less chronic lung disease with a 12 day tapering course of dexamethasone. Treated infants showed a transient decrease in mean airway pressure and sustained improvement in pulmonary compliance. Yeh also noted a trend toward decreased mortality. Hypertension and hyperglycaemia were significantly more common in the dexamethasone group. Sanders *et al*¹⁵ studied the effect of two doses of dexamethasone in the first 24–36 hours of life. Treated infants had improved survival, shorter duration of hospital stay, and fewer days of ventilation or oxygen therapy. Two subsequent studies have been reported in abstract form. Yeh *et al*¹⁶ reported a multicentre study of early and prolonged (four weeks) dexamethasone administration in which they found a

Table 8 Summary of reported randomised controlled clinical trials of early postnatal steroids in RDS

Author	Year	Steroid	Duration of treatment	Steroids (n)	Placebo (n)
Baden	1972	Hydro	1 Day	22	22
Yeh	1990	Dex	12 Days	28	29
Sanders	1992	Dex	1 Day	19	21
Yeh	1993	Dex	28 Days	75	67
Rastogi	1993	Dex	12 Days	32	32
Present study	1994	Dex	3 Days	132	116

Hydro=hydrocortisone; Dex=dexamethasone.

reduction in the incidence of chronic lung disease and lower PCO₂ values in treated infants. There were no differences in mortality or acute respiratory status. Rastogi *et al*¹⁷ reported a study of the 12 day tapering course of dexamethasone as in Yeh's first study, but in conjunction with surfactant therapy, and found a reduction in chronic lung disease, improved pulmonary function, and no change in mortality.

None of the studies described above was designed with a sample size sufficient to evaluate many of the major complications seen in severe RDS. This study is much larger, thus increasing the statistical power of the results (table 8). However, in view of the conflicting results of the studies, it clearly will be necessary to undertake a much larger trial in order to determine whether a true significant reduction in the incidence of chronic lung disease can be achieved with early postnatal steroid treatment.

Several possible explanations can be proposed for the lack of effect of the three day course of dexamethasone despite the solid theoretical basis for the intervention. The moderate improvement in respiratory status at 72 hours in treated infants which disappeared later may support the hypothesis that a longer course of steroid treatment is required in order to suppress sufficiently the inflammatory response in the lungs and allow the process of recovery to take place. Another possible explanation is that postnatal steroid treatment is in fact not effective and that differences found in smaller trials were not generalisable. Also, it may be that the effect of steroid treatment is masked by the improvement in outcome resulting for surfactant therapy. Only one of the trials reporting a positive effect of steroids included surfactant administration for all infants.

We conclude that the present study does not support the routine use of early postnatal steroid treatment for the prevention of chronic lung disease, but that there is sufficient evidence to justify a much larger multicentre study of early prolonged dexamethasone treatment.

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