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Early postnatal dexamethasone for the prevention of chronic lung disease in high-risk preterm infants

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Abstract *Objective*: The purpose of this study was to evaluate the effect of early administration of dexamethasone on the incidence of chronic lung disease (CLD) in high risk preterm infants and to evaluate the side effects of the early steroid administration.
Design: Randomised clinical trial.
Setting: Neonatal intensive care unit.
Patients: 50 infants at high risk of CLD were randomly assigned after 72 h of life to the dexamethasone group ($n = 25$) or to the control group ($n = 25$). The treated infants received dexamethasone intravenously from the 4th day of life for 7 days (0.5 mg/kg per day for the first 3 days, 0.25 mg/kg per day for the next 3 days and 0.125 mg/kg per day on the 7th day). The control group received no steroid treatment.
Results: The incidence of CLD at 28 days of life and at 36 weeks' postconceptional age was significantly lower in the dexamethasone group than in the control group ($p < 0.001$). Moreover, infants in the dexamethasone group remained intubated and required oxygen therapy for a shorter period than those in the control group ($p < 0.001$). Hyperglycaemia, hypertension, growth failure and mainly hypertrophy of the left ventricle were the transient side effects associated with early steroid administration.
Conclusions: Early dexamethasone administration may be useful in preventing CLD, but its use should prudently be restricted to preterm infants at high risk of CLD.

Key words Preterm infants · Chronic lung disease · Dexamethasone

Introduction

Dexamethasone is widely used both for the treatment of established chronic lung disease (CLD) and for the prevention of CLD, but conflicting results about the effectiveness of early treatment have been reported [1–3]. In fact, some authors found no effect of steroids on the incidence of CLD with short courses of treatment [4–6], while others reported a significant reduction of CLD at 28 days and/or 36 weeks' postconceptional age with prolonged steroid treatment [7–9]. Moreover, the effectiveness of early treatment could be negatively influenced by the difficulty in the identification of infants at high risk of CLD.

The aim of this randomised clinical trial was to assess whether early dexamethasone treatment is effective in the prevention of CLD in preterm infants at very high risk for this pathology.

Patients and methods

This randomised clinical trial was carried out in the neonatal intensive care unit of Catholic University of Rome during a 2-year period ending in October 1998. The study protocol and consent forms were approved by the Ethical Committee of the Department of Paediatrics.

Infants were considered eligible for the study if they met the following criteria: birthweight ≤ 1250 g, gestational age

≤ 32 weeks, ventilator and oxygen dependent at 72 h of life and at high risk of CLD according to our scoring system. This score is based on gestational age, birthweight, respiratory distress syndrome, grade of respiratory support (in terms of peak inspiratory pressure and inspired oxygen concentration) and some major neonatal complications (pulmonary interstitial emphysema, patent ductus arteriosus, intraventricular haemorrhage > grade 2, sepsis).

A previous study indicated that more than 90 % of infants fulfilling these inclusion criteria would develop CLD at 28 days of age [10]. Using the sample-size table and using the 90 % CLD incidence in the control group and an expected 60 % reduction in the treated group, at least 20 infants in each group were required to detect a difference, allowing a 5 % chance of a Type I error. The randomisation, obtained by random number allocation, was revealed when numbered, sealed envelopes were opened and was carried out at 72 h of life; 25 neonates for both treatment and control groups were expected. Infants with prenatal infections, congenital malformations and evidence of sepsis at randomisation were excluded from the study.

The primary outcome measures were the incidence of CLD at 28 days of life and the requirement for supplemental oxygen at 36 weeks' postconceptional age. Additional measures included duration of mechanical ventilation and oxygen therapy, requirement for additional courses of steroids for established CLD and the incidence of side effects of dexamethasone treatment. The primary and additional outcomes were assessed by two clinicians (P.P., G.T.) who did not know the treatment allocation.

The infants assigned to the treatment group received intravenous dexamethasone sodium phosphate (Soldesam, Farmac. Mil.) from the 4th day of life for 7 days according to the following regimen: 0.5 mg/kg per day for the first 3 days of treatment, 0.25 mg/kg per day for the next 3 days and 0.125 mg/kg per day on the day 7 of treatment. The control group received no steroid treatment. A diagnosis of CLD at 28 days of life was made if the baby required supplemental oxygen to maintain an arterial oxygen tension (PaO_2) > 50 mmHg or an oxygen saturation > 90 % and had abnormal radiological findings [11–13]. A diagnosis of CLD at 36 weeks' postconceptional age was made in every baby who was oxygen-dependent at that time. During the study period, patient care practices were uniform among the neonatologists, according to the standard protocols of the unit. Caffeine was administered intravenously at a dosage of 2.5 mg/kg per day from birth to week 33 of postconceptional age to treat apnoeic spells. Conventional mechanical ventilation with pressure-limited time-cycled ventilators (Bear-Cub) was used. The goals of respiratory management were to maintain blood gas values with pH 7.30–7.45, arterial carbondioxide tension 45–55 mmHg and PaO_2 50–70 mmHg with O_2 saturation between 88 and 93 %; 200 mg/kg of a pig-derived natural surfactant (Curosurf, Chiesi) was given to each infant with hyaline membrane disease as soon as the diagnosis was made. The policy of weaning during the recovery stage of their illness was similar for all infants studied. The peak inspiratory pressure and ventilator rate were reduced until a peak pressure of 18 cmH_2O and a ventilator rate of 15 breaths/min (bpm) were achieved. The fractional inspired oxygen concentration (FIO_2) was reduced when the PaO_2 exceeded 70 mmHg till FIO_2 reached 0.30. Positive end-expiratory pressure was maintained at 4 cmH_2O and inspiratory time was maintained constant at 0.4 s. When these parameters were reached and maintained for at least 6 h, the ventilator rate was reduced by 2 to 4 bpm every 6 h to a minimum rate of 5 bpm, and then the infants were extubated to nasal continuous airway pressure (5 cmH_2O). After extubation, oxygenation and heart and respiratory rate were continuously monitored and FIO_2 was adjusted as necessary to maintain the goals of respiratory management.

Infants diagnosed as having CLD at 28 days of life received furosemide (2 mg/kg per day i.v.) and theophylline (1 mg/kg per day i.v.) instead of caffeine. All babies still ventilated at 28 days of life were treated with steroids to reduce the severity of CLD and to achieve extubation as soon as possible. All babies received parenteral nutrition following our fluid intake protocol [14]; enteral feeding was begun by the 1st week of life. Ranitidine was administered for minor gastrointestinal bleeding associated with treatment. Necrotising enterocolitis (NEC) was diagnosed when gastrointestinal signs and symptoms were associated with specific radiological findings [15]. Echographic monitoring of intracranial haemorrhage and periventricular leucomalacia was made on days 1, 3, 5 and 7 of life and then weekly until discharge. Patent ductus arteriosus was diagnosed clinically and by echocardiography and treated by surgical closure only if indomethacin treatment had failed. Left ventricle morphology was studied echocardiographically before treatment, at the 3rd and at the 6th day of treatment and 3 days after treatment. Left ventriclar hypertrophy was diagnosed if there was a systolic intraventricular septum thickness greater than 5 mm. A diagnosis of sepsis was made when a clinically septic baby had a positive blood culture. Hypertension was diagnosed if three consecutive systolic or diastolic blood pressure readings more than 2 SD above the normal mean for age were recorded in a 24-h period [16]. Hyperglycaemia was defined as plasma glucose levels > 200 mg/dl. Screening for retinopathy of prematurity was performed by a paediatric ophthalmologist and graded according to the international classification [17].

Group differences were analysed with the use of Student's *t*-test for continuous variables and Fisher's exact test for discrete variables. A p value < 0.05 was considered statistically significant.

Results

During the study period, 50 infants were enrolled in the study. Among the control infants, 1 had posthaemorrhagic hydrocephalus and required repeated surgical interventions, and 1 infant had a severe acquired cytomegalovirus infection. Among the treated babies, in 1 therapy was stopped because of severe sepsis, and in 1 there were no complete data to evaluate the outcomes. These infants were included in the analysis of results on an "intention to treat" basis.

Table 1 reports the baseline characteristics and the respiratory status at enrolment in the study. The two study groups were well matched for birthweight, gestational age, sex, incidence of premature rupture of membranes, treatment with steroids antenatally and for the respiratory status at the enrolment. There were no differences in the incidence of major morbidity among the study groups as reported at discharge from the unit (Table 2). All preterm infants survived until 28 days of life while the survival rate at discharge was 88 % in the control group and 92 % in the dexamethasone group. Table 3 reports the respiratory outcomes of the study groups. Twenty-one infants in the dexamethasone group were extubated between the 2nd and 6th days of treatment; 15 babies in the control group underwent extubation between the 5th and 20th day of life, but 3 of them were reintubated before the 28th day of life because of

Table 1 Baseline characteristics and respiratory status at enrolment in the study. Values are expressed as median (range) or number (per cent) (*PROM* premature rupture of membranes, *PIP* peak inspiratory pressure, *MAP* mean airway pressure; FIO_2 fractional inspired oxygen, *ClDyn* dynamic compliance, *EspRes* expiratory resistances)

	Control group ($n = 25$)	Dexamethasone group ($n = 25$)
Gestational age (weeks)	28 (25–30)	28 (25–31)
Birthweigth (g)	940 (610–1250)	940 (590–1250)
Sex ratio (M/F)	13/12	14/11
PROM	8 (32)	7 (28)
Antenatal steroids	11 (44)	13 (52)
PIP (cmH_2O)	21 (17–32)	20 (16–30)
MAP (cmH_2O)	6.8 (4.9–13.9)	7 (5.5–13)
FIO_2	0.30 (0.23–0.6)	0.30 (0.23–0.55)
Score	6.8 (4.5–10.5)	6.8 (4.5–10.9)
ClDyn (ml/cmH_2O per kg)	0.408 (0.198–0.769)	0.389 (0.183–0.742)
ExpRes (cmH_2O/ml per s)	221 (123–389)	211 (107–362)

Table 2 Survival and major morbidity of the study groups. Baseline characteristics and major morbidity. Values are numbers (per cent) (*PDA* patent ductus arteriosus, *ICH* intracranial haemorrhage, *PVL* periventricular leucomalacia, *NEC* necrotising enterocolitis, *ROP* retinopathy of prematurity)

	Control group ($n = 25$)	Dexamethasone group ($n = 25$)
Survivors at 28 days	25 (100)	25 (100)
Survivors at discharge	22 (88)	23 (92)
PDA	17 (68)	13 (52)
ICH > grade 2	6 (24)	5 (20)
PVL	2 (8)	2 (8)
Sepsis	7 (28)	8 (32)
NEC	3 (12)	2 (8)
ROP > grade 2	8 (32)	9 (36)

respiratory failure. The number of babies still ventilated at 28 days was significantly lower in the treated group than in the control group ($p = 0.0157$). The incidence of CLD at 28 days of life was significantly higher in the control group than in the treatment group (96 vs 44 %; $p = 0.0001$). Between the 28th day of life and 36 weeks' postconceptional age, 4 infants died, 2 in each study group. Two control babies died because of bronchopulmonary dysplasia, complicated by NEC in 1 case; 2 treated infants died, 1 because of bronchopulmonary dysplasia and 1 because of NEC. Three of the 23 surviving infants (13 %) in the dexamethasone group had CLD at 36 weeks' postconceptional age compared with 17 of 23 survivors (73.9 %) in the control group ($p < 0.0001$). Infants in the dexamethasone group remained intubated for a shorter period than those in the control group ($p = 0.0009$). Moreover, a significant decrease in the number of days on oxygen therapy was observed in the treated group in respect to the control group ($p = 0.0006$).

The side effects of dexamethasone treatment are reported in the Table 4. Seven cases of transient hyperglycaemia were observed; in all cases the reduction of glucose intake and a short course of insulin therapy normalised serum glucose levels. Two babies had a transient elevation of blood pressure, but none needed treatment. Despite comparable fluid and caloric intakes, 20 treated babies had a weight loss or no weight gain during dexamethasone administration compared with none of the control infants ($p < 0.0001$). Left ventriclar hypertrophy was observed in 3 control infants (12 %) and in 13 treated infants (52 %), the difference reaching statistical significance ($p = 0.0054$). The incidence of sepsis and of NEC was similar in the two study groups.

Discussion

The rationale for early postnatal steroid administration in preterm infants suffering from the respiratory distress syndrome is supported by several observations. Firstly, it is well known that the inflammatory activity leading to CLD occurs in the first few days of life [18–22]. Secondly, corticosteroids may improve lung function by increasing antioxidant activity and surfactant synthesis and reducing both lung inflammatory changes and fibrosis [23, 24]. Thirdly, early adrenal insufficiency has been suggested as a possible cause of bronchopulmonary dysplasia [25]. Finally, late steroid treatment failed to reduce the incidence of CLD in preterm infants with the exception of the studies starting at 7 days of age [1–3, 26].

Data about the effectiveness of early postnatal steroid treatment in high-risk neonates are conflicting because of the differences in dose and duration of steroid therapy and in the incidence of CLD in investigated populations [4–9]. Some authors have treated infants starting on the 1st day of life, for only 1, 3 or 5 days (total doses of dexamethasone of 1, 0.75 and 2.5 mg/kg, respectively) without any effect on CLD incidence [4–6]. On the contrary, Yeh et al. [8] and Rastogi et al. [7], starting steroid administration in the first 12 h of life, reported a reduction of CLD at 28 days and 36 weeks' postconceptional age with a 28-day steroid course (total dose of 6.16 mg/kg) and with a 12-day steroid course (total dose of 3.3 mg/kg), respectively. Moreover, a 12-days of steroid therapy (total dose of 2.79 mg/kg) permitted Tapia et al. [9] to obtain a reduction of O_2 dependency at 36 weeks' postconceptional age. These observations suggest that a too brief steroid treatment, even if started early, may be ineffective in preventing CLD. In a re-

Table 3 Respiratory outcomes. Values are expressed as mean ± SD or number (per cent) (*CLD* chronic lung disease)

	Control group ($n = 25$)	Dexamethasone group ($n = 25$)	p	Odds ratio or difference between means	95 % confidence interval
Ventilated at 28 days	13 (52)	4 (16)	0.0157	5.688	1.509 to 21.43
CLD at 28 days	24 (96)	11 (44)	0.0001	30.55	3.554 to 262.5
CLD at 36 weeks	17 : 23 (73.9)	3 : 23 (13)	< 0.0001	18.89	4.091 to 87.20
Steroids after 28 days	13 (52)	3 (12)	0.0054	7.944	1.883 to 33.51
Mechanical ventilation (days)	34.2 ± 22.2	16.1 ± 10.2	0.0009	18.10 ± 5.09	– 28.37 to – 7.82
Oxygen therapy (days)	43.2 ± 20.2	25.2 ± 12.0	0.0006	18.00 ± 4.89	– 27.88 to – 8.11

Table 4 Side effects of dexamethasone administration. Values are numbers (per cent)

	Control group ($n = 25$)	Dexamethasone group ($n = 25$)	p	Odds ratio	95 % confidence interval
Hyperglycaemia	0	7 (28)	0.0096	0.0483	0.002 to 0.901
Hypertension	0	2 (8)	0.4898	0.1843	0.008 to 4.044
Growth failure	0	20 (80)	< 0.0001	0.0052	0.0002 to 0.1009
Left ventricular hypertrophy	3 (12)	13 (52)	0.0054	0.1259	0.029 to 0.530
Sepsis	2 (8)	3 (12)	1.00	0.6377	0.097 to 4.190
Necrotising enterocolitis	1 (4)	2 (8)	1.00	0.4792	0.040 to 5.655

cently published study [27], we demonstrated that dexamethasone therapy induces a significant improvement in lung function in preterm infants in the first 3–5 days of treatment and that it is associated with major reported modifications of inflammatory response in the bronchoalveolar lavage fluid. For these reasons we chose for our study a course of dexamethasone treatment of 7 days with a total dose of 2.375 mg/kg.

The conflicting results on CLD prevention are likely to be explained also by the wide range of incidence of CLD in the control/placebo groups reported in the literature. The incidence of CLD at 28 days of life varies from 21 % in Shinwell et al.'s placebo group [6] to 65.6 % in Rastogi et al.'s placebo group [7], while O_2 dependency at 36 weeks' corrected age varies from 9 to 33 %; this implies that their study populations have different risks for CLD. Moreover, it is noteworthy that the best results come from those studies which involve the babies with the highest risk for CLD [7, 9]. On this basis, we decided to treat only those preterm infants still being ventilated after 72 h of life in whom our scoring system [10] is able to identify subjects with a > 90 % risk for CLD; this choice allowed us to avoid useless treatments.

The results of our study confirm that a 7-day postnatal course of 2.375 mg/kg dexamethasone, started on the 4th day life, significantly reduces the incidence of CLD both at 28 days of life and at 36 weeks' postconceptional age. Moreover, the treated babies required mechanical ventilation and oxygen therapy for a shorter time as compared with control babies.

As regards the side effects of steroid administration, it has to be emphasised that transient hyperglycaemia always resolved with a lower glucose intake and a short course of insulin therapy, while hypertension had a very low incidence, even if there is no agreement on what level of blood pressure constitutes hypertension requiring treatment. The two main adverse effects were growth retardation and left ventricular hypertrophy. A transient lack of weight gain was observed during dexamethasone administration in the vast majority of treated babies; this effect was of short duration and was followed by significant catch-up growth, so that no differences were then observed between treated and untreated infants at 28 days of life and at discharge.

Left ventricular hypertrophy occurred in 52 % of treated babies and slowly resolved in a 15-day period after the discontinuation of therapy. It was never associated with insulin therapy, and 25 % of affected infants had left ventricular outflow tract reduction and therapy had to be discontinued during the 6th day of treatment. In our opinion, an echocardiogram is mandatory to assess left ventricular morphology and function and to prevent left ventricular outflow obstruction. The long-term consequences of early steroid treatment are currently under investigation.

In conclusion, we think that early steroid administration is effective in preventing CLD, but it should prudently be restricted to the preterm infants with the highest risk of CLD on the basis of a cost–benefit ratio, in order to reduce useless treatments and to avoid side effects.

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