Early Postnatal Dexamethasone Therapy for the Prevention of Chronic Lung Disease in Preterm Infants With Respiratory Distress Syndrome: A Multicenter Clinical Trial

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ABSTRACT. *Objectives.* **To study whether early postnatal (<12 hours) dexamethasone therapy reduces the incidence of chronic lung disease in preterm infants with respiratory distress syndrome.**

Materials and Methods. **A multicenter randomized, double-blind clinical trial was undertaken on 262 (saline placebo, 130; dexamethasone, 132) preterm infants (<2000 g) who had respiratory distress syndrome and required mechanical ventilation shortly after birth. The sample size was calculated based on the 50% reduction in the incidence of chronic lung disease when early dexamethasone is used, allowing a 5% chance of a type I error and a 10% chance of a type II error. For infants who received dexamethasone, the dosing schedules were: 0.25 mg/kg/dose every 12 hours intravenously on days 1 through 7; 0.12 mg/kg/dose every 12 hours intravenously on days 8 through 14; 0.05 mg/kg/dose every 12 hours intravenously on days 15 through 21; and 0.02 mg/kg/dose every 12 hours intravenously on days 22 through 28. A standard protocol for respiratory care was followed by the participating hospitals. The protocol emphasized the criteria of initiation and weaning from mechanical ventilation. The diagnosis of chronic lung disease based on oxygen dependence and abnormal chest roentgenogram was made at 28 days of age. To assess the effect of dexamethasone on pulmonary inflammatory response, serial tracheal aspirates were assayed for cell counts, protein, leukotriene B_4, and 6-keto prostaglandin $F_{1\alpha}$. All infants were observed for possible side effects, including hypertension, hyperglycemia, sepsis, intraventricular hemorrhage, retinopathy of prematurity, cardiomyopathy, and alterations in calcium homeostasis, protein metabolism, and somatic growth.**

Results. **Infants in the dexamethasone group had a significantly lower incidence of chronic lung disease than infants in the placebo group either judged at 28 postnatal days (21/132 vs 40/130) or at 36 postconceptional weeks (20/132 vs 37/130). More infants in the dexamethasone group than in the placebo group were extubated during the study. There was no difference between the groups in mortality (39/130 vs 44/132); however, a higher proportion of infants in the dexamethasone group died in the late study period, probably attributable to infection or sepsis. There was no difference between the groups in duration of oxygen therapy and hospitalization. Early postnatal use of dexamethasone was associated with a significant decrease in tracheal aspirate cell counts, protein, leukotriene B_4, and 6-keto prostaglandin $F_{1\alpha}$, suggesting a suppression of pulmonary inflammatory response. Significantly more infants in the dexamethasone group than in the placebo group had either bacteremia or clinical sepsis (43/132 vs 27/130). Other immediate, but transient, side effects observed in the dexamethasone group are: an increase in blood glucose and blood pressure, cardiac hypertrophy, hyperparathyroidism, and a transient delay in the rate of growth.**

Conclusions. **In preterm infants with severe respiratory distress syndrome requiring assisted ventilation shortly after birth, early postnatal dexamethasone therapy reduces the incidence of chronic lung disease, probably on the basis of decreasing the pulmonary inflammatory process during the early neonatal period. Infection or sepsis is the major side effect that may affect the immediate outcome. Other observable side effects are transient. In view of the significant side effects and the lack of overall improvement in outcome and mortality, and the lack of long term follow-up data, the routine use of early dexamethasone therapy is not yet recommended.** *Pediatrics* **1997;100(4). URL: http://www.pediatrics.org/cgi/content/full/100/4/e3;** ***respiratory distress syndrome, prevention of chronic lung disease, early dexamethasone therapy.***

ABBREVIATIONS. CLD, chronic lung disease; RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; BUN, blood urea nitrogen; LTB_4, leukotriene B_4; 6-keto-$PGF_{1\alpha}$, 6-keto prostaglandin $F_{1\alpha}$.

Various studies suggest that pulmonary inflammation may play an important role in the early development of chronic lung disease (CLD) in preterm infants on mechanical ventilation.[1–5] Because the lung inflammation may occur early in the postnatal life[2,6] and the antiinflammatory effect of steroids is usually seen only after 48 to 72 hours of therapy,[7] we hypothesize that an early postnatal administration of dexamethasone within 12 hours after birth may prevent the subsequent development of CLD. Based on this hypothesis, we have conducted a multicenter randomized, double-blind clinical trial to answer the following four questions: 1) Does early intravenous dexamethasone therapy,

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given within 12 hours after birth for 1 week and then tapering off in 3 weeks, reduce the incidence of CLD? 2) Does early dexamethasone therapy reduce pulmonary inflammatory reaction and improve pulmonary status? 3) Does early dexamethasone therapy improve mortality and overall outcome? 4) What are the side effects of early dexamethasone therapy?

MATERIALS AND METHODS

During a 30-month period (October 1992 to April 1995), all infants with birth weights of 500 to 1999 g (National Cheng Kung University Hospital, Chang Gung Children's Hospital, Mackay Memorial Hospital, China Medical College Hospital, Chung Shan Medical College Hospital, and Kuang Tien Hospital in Taiwan) were eligible for the study. The criteria of selection were: 1) severe radiographic respiratory distress syndrome (RDS) requiring mechanical ventilation within 6 hours after birth and 2) the absence of prenatal infection, complex congenital anomalies, and lethal cardiopulmonary status.

This study was approved by the scientific and human experimental committees of the participating hospitals. Informed consent was obtained from the parents.

Sample Size Calculation and Placebo/Dexamethasone Regimen

A previous survey in Taiwan indicated that approximately 40% of infants fulfilling the proposed inclusion criteria would develop CLD at 28 days of age. Using the sample-size tables of Fleiss[8] and using the 40% incidence in the placebo group and an expected 50% reduction in the dexamethasone-treated group, 127 infants in each group is required to detect the difference, permitting a 5% chance of a type I error and a 10% chance of a type II error. Allowing for attrition and exclusions from the final study groups, 135 was considered a safe target number for each group.

The numbers 1 through 270 were assigned at random either to the placebo or the dexamethasone group. When the first dose of placebo/dexamethasone was prescribed, the pharmacist in the central pharmacy of National Cheng Kung University Hospital would open the assignment list to determine whether dexamethasone or placebo should be dispensed. Four vials of either dexamethasone or saline placebo were prepared, one vial for each week. If placebo was indicated, each vial containing 10 mL of saline only would be prepared and if dexamethasone was indicated, each vial containing 10 mL of a solution of 20 mg, 10 mg, 5 mg, and 2.5 mg dexamethasone, respectively, would be prepared. A total of 56 doses of dexamethasone or saline solution were given intravenously for 4 weeks. This dosage corresponded to the following schedule (one dose every 12 hours) for the intravenously administered solution containing dexamethasone sodium phosphate: days 1 through 7, 0.25 mg/kg/dose; days 8 through 14, 0.12 mg/kg/dose; days 15 through 21, 0.05 mg/kg/dose; and days 22 through 28, 0.02 mg/kg/dose.

Diagnosis and Treatment of RDS

The diagnosis of RDS was made according to clinical and radiographic features. A protocol for the treatment of infants with RDS was followed by the participating hospitals. Blood gas samples were obtained through an umbilical arterial catheter or from a peripheral artery. The criteria for initiation of continuous positive airway pressure (CPAP) would include either of the following: 1) arterial partial pressure of oxygen <50 mm Hg with the fraction of inspired oxygen (F_{IO_2}) $\geq .4$, or 2) apnea. Intermittent mandatory ventilation was initiated if there was: 1) failure to respond to CPAP; 2) arterial partial pressure of oxygen <50 mm Hg; $F_{IO_2} \geq .6$; 3) arterial partial pressure of carbon dioxide >60 mm Hg; or 4) repeated or prolonged apnea. Weaning from mechanical ventilation started as soon as there was an improvement in blood gas values and clinical condition. Once the peak ventilatory pressure was <25 cm H_2O, the inspired oxygen concentration was decreased, with a 5% reduction each time, and the arterial or arterialized oxygen tension was maintained at appropriate levels. When the inspired oxygen concentration had been reduced to 40%, attempts were made to speed up the weaning process by decreasing the ventilatory rate. Once the rate has been reduced to 5 to 10 per minute, continuous distending pressure was instituted, with pressure adequate to maintain appropriate blood gas values. The pressure was then reduced until it reached 2 cm H_2O. If the blood gas values remained appropriate, attempts to remove the endotracheal tube were initiated. After endotracheal suction and manual ventilation, the tube was removed during a full inflation of the lungs. The infant was then placed in a hood with an environmental oxygen concentration 10% higher than that before removal of the tube. Total fluid intake was adjust to 80 mL/kg/d in the first postnatal day and increased daily to 150 mL/kg/d by day 5 and onward. Because of the possible risk of infection associated with steroid therapy, all infants were given ampicillin and gentamicin for 7 days. Subsequently the use of antibiotics was judged by the service attending physician. Blood culture was obtained for any infant suspected to have sepsis. Clinical suspicion of sepsis was made if the infant had clinical signs of lethargy and poor sucking and had increases in immature neutrophile or elevation of C-reactive protein.[9]

After completion of the study at 4-weeks postnatal day, the infants were treated at the discretion of the attending physician and house staff who were not aware of the therapy. Surfactant was not commercially available in Taiwan at the time when this study was started; therefore, none of these infants received surfactant.

The diagnosis of CLD was made if the infant had: 1) respiratory distress requiring supplemental oxygen therapy for 28 days or longer, and 2) an abnormal chest radiograph.

Evaluation of Possible Side Effects

All infants were observed for hypertension, hyperglycemia, sepsis, intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and somatic growth. Cardiac echocardiograph and calcium homeostasis were also evaluated in the first 50 infants. The following variables were measured before and on days 1, 3, 5, 7, 10, 14, 21, and 28 after starting the study: urine output, urine electrolytes and osmolality, urine calcium, phosphorous and creatinine, serum electrolytes, creatinine, blood urea nitrogen (BUN), osmolality, calcium, phosphorous, and parathyroid hormone. Body weight, length, head circumference, and bone length and width by radiograph (longest axis and midpoint medullary diameter of femur) were all recorded weekly during the study.

Tracheal Aspirate

To evaluate the effect of dexamethasone on lung inflammation, tracheal aspirate samples were obtained before the study and at 3, 7, 14, 21, and 30 days after starting the study in the first 60 infants in one hospital (National Cheng Kung University Hospital). The technique of sampling followed the method of Merritt et al.[2] Total protein was measured by the Lowry method.[10] Leukotriene B_4 (LTB_4) and 6-keto prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) were determined by radioimmunoassay according to the methods provided by the manufacturer (New England Nuclear, Dupont, Boston, MA).

Statistics

The data were analyzed at 28 days of age with CLD as the primary outcome variable. Analysis of variance and, where appropriate, the *t* test were used to make group comparisons for continuous variables. Fisher's exact test was used to compare groups with respect to categorical variables. Except where indicated otherwise, values are specified as mean plus or minus one standard deviation.

RESULTS

During the 30-month study period, there were 637 eligible infants admitted to the neonatal intensive care units. Three hundred and forty-one infants fulfilled the inclusion criteria. Of these, parental consents were obtained in 270 infants; they were all included into study. However, 8 infants were excluded from data analysis; 6 died of culture-proven sepsis within 12 hours after birth and 2 had severe asphyxia requiring resuscitation since birth until the time of death.

Thus, the total number of infants included for final

data analysis was 262; 130 in the placebo group and 132 in the dexamethasone group. Table 1 lists the perinatal characteristics which shows no significant difference between the study groups. The proportion of infants receiving prenatal steroid therapy was similar in both groups (Table 1).

Table 2 shows that the two groups were comparable in their clinical, biochemical, and other laboratory variables at the time of admission to the study. The mean postnatal age of infants when they received their first dose of dexamethasone was 7.4 ± 5.2 hours (range, 0.5 to 12 hours).

Pulmonary Status

Infants in the dexamethasone group required a significantly lower mean airway pressure on days 2, 3, 4, and 6 (7.2 ± 3.1, 7.1 ± 3.4, 6.3 ± 2.9, and 5.2 ± 3.3 cm H_2O, respectively) and lower fractional inspired oxygen on days 3, 4, and 6 (0.41 ± 0.22, 0.35 ± 0.19, 0.30 ± 0.24, respectively) than the infants in the placebo group (mean airway pressure: 8.5 ± 3.1, 8.2 ± 3.4, 7.0 ± 2.5, and 6.2 ± 1.9 cm H_2O, respectively; FIO_2: 0.51 ± 0.24, 0.44 ± 0.17, and 0.39 ± 0.21, respectively). There was no significant difference between the groups in oxygen tension, but significantly lower carbon dioxide tension and a higher pH value were seen in the dexamethasone group on days 4, 6, and 21 (36.2 ± 11.9, 37.4 ± 12.7, 36.3 ± 11.2 mm Hg vs 42.3 ± 12.6, 43.3 ± 12.5, 43.1 ± 11.2 mm Hg) and on days 14 and 21, respectively (7.39 ± 0.07, 7.39 ± 0.08 vs 7.31 ± 0.07, 7.32 ± 0.06). The proportion of infants who had weaned from intermittent mandatory ventilation or CPAP among the survivors was significantly ($P < .05$) higher in the dexamethasone treated than in the control group at 1, 3, and 4 weeks of postnatal age (78/117, 80/96, and 77/88 vs 55/105, 65/95, and 66/91, respectively).

TABLE 1. Clinical Characteristics in the Perinatal Period

Characteristics	Placebo	Dexamethasone
n	130	132
Birth weight (g)	1312 ± 361*	1286 ± 345
<1000	26	29
1000–1500	59	66
1501–1999	45	37
Gestational age (wk)	29.2 ± 2.6	29.5 ± 2.7
≤28	55	48
29–32	64	71
33–36	11	13
Appropriate for gestational age/ small for gestational age	102/28	93/39
Sex (M/F)	70/60	75/58
Type of delivery		
C-section	59	56
Vaginal	71	76
Apgar score 1-minute		
≤3	28	28
4–6	71	81
>6	31	23
Apgar score 5-minute		
≤3	8	6
4–6	38	39
>6	84	87
Prenatal steroid	44	39

* Mean ± SD.

TABLE 2. Clinical, Biochemical and Laboratory Characteristics at Time of Study Entry

Characteristics	Placebo (n = 130)	Dexamethasone (n = 132)
Age of study (h)	7.0 ± 5.3*	7.4 ± 5.2
Fluids intake (mL/kg/d)	79 ± 20	82 ± 30
IMV		
Rate/min	32 ± 7	35 ± 10
Peak inspiratory pressure/ positive end expiratory pressure (cm H_2O)	19 ± 4/4 ± 1	18 ± 3/4 ± 1
Mean airway pressure (cm H_2O)	9.1 ± 5.1	8.9 ± 3.2
FIO_2	0.6 ± 0.2	0.6 ± 0.3
PO_2 (mm Hg)	110 ± 86	96 ± 82
PCO_2 (mm Hg)	44 ± 16	44 ± 13
pH	7.29 ± 0.07	7.30 ± 0.08
Base deficit (meq/L)	5.9 ± 5.1	5.8 ± 5.2
Blood pressure		
Systolic (mm Hg)	49 ± 12	50 ± 14
Diastolic (mm Hg)	29 ± 8	29 ± 11
Hematocrit (%)	44 ± 7.3	45 ± 7.2

* Mean ± SD. Peak inspiratory pressure/positive and expiratory pressure

Mortality

Thirty-nine infants (30%) died in the control group and 44 (33%) died in the dexamethasone group. This difference in mortality between the groups is not statistically significant. Figure 1 shows the cumulated number of infants that died during the 1st, 2nd, 3rd, and 4th week of postnatal age. There was no significant difference between the groups in mortality at 1, 2, 3, and 4 weeks. In the control group, 80% of the deaths occurred in the first 2 weeks (31/39), whereas in the dexamethasone group, 50% (22/44) died in the first 2 weeks. There was no difference between groups in mortality at 6 weeks (41/130 vs 45/132) and 8 weeks (42/130 vs 46/132).

The causes of death judged by terminal clinical events in the control versus dexamethasone group were: intractable respiratory failure (20 vs 12, $P < .05$); severe IVH (5 vs 7); sepsis (12 vs 18); and other (2 vs 7).

CLD Morbidity

Forty infants (31%) in the placebo group and 21 (16%) in the dexamethasone group had CLD ($P <$

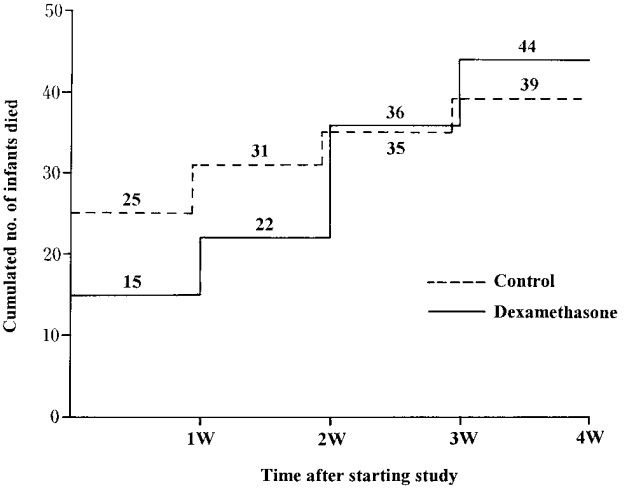

Fig 1. The cumulated number of infants that died at 1, 2, 3, and 4 weeks after starting the study.

.05). The incidence of CLD among the survivors was 44% (40/91) in the placebo group and 24% (21/88) in the dexamethasone group ($P < .01$). If we defined CLD at 36 days postconceptional age, 37 (28%) in the placebo group and 20 (15%) in the dexamethasone group had CLD ($P < .05$). Among the survivors, there were no significant differences between the placebo and dexamethasone groups in the total duration of oxygen therapy (36 ± 29 days vs 33 ± 24 days) and hospitalization (65 ± 44 days vs 62 ± 54 days). Infants in the control group, however, required a significantly longer duration of high oxygen therapy (FIO_2 >0.4) than infants in the dexamethasone group (13.4 ± 12.1 days vs 7.2 ± 7.4 days; $P <$ .01). The proportion of infants who either died or survived with CLD was comparable between the groups (79/130 vs 65/132).

The mortality and CLD morbidity based on specific birth weight categories are shown in Table 3. Significant differences in CLD morbidity between the groups were seen in infants with weight <1000 g and in infants with weight 1000 to 1500 g ($P < .05$).

Tracheal Aspirate (Figure 2)

Infants in the dexamethasone-treated group had significantly lower cell count, total protein, and 6-keto-$PGF_{1\alpha}$ on days 3 and 7, and lower LTB_4 on days 3, 7, and 14 than infants in the control group.

Side Effects

A summary of side effects is shown in Table 4. Infants in the dexamethasone group had significantly higher blood pressure, blood glucose, BUN, serum potassium, osmolality, and parathyroid hormone levels, and higher urinary fractional excretion of phosphate and higher left ventricle free wall/left ventricle chamber ratio on echocardiogram than infants in the control group. However, these differences between the groups were not statistically significant on day 21 and later. There was no difference between the groups in serum sodium, chloride, calcium, phosphorous, and in femur length and width measured by radiograph during the study.

Despite comparable fluid and caloric intakes, infants in the dexamethasone group had significantly lower body weight at 1, 2, and 3 weeks. By 4 weeks, there was no difference between the groups (Fig 3). Infants in the dexamethasone group took a significantly ($P < .01$) longer time to regain to birth weight (22.4 ± 6.5 days) than infants in the control group (17.6 ± 7.6 days). There was no difference between the groups in body length and head circumference at any time during the study (Fig 3).

TABLE 3. Mortality and CLD Morbidity

	No. of Infants	Mortality	CLD Morbidity
Placebo			
<1000 g	26	10 (38.5%)	14 (53.8%)
1000–1500 g	59	17 (28.9%)	18 (30.5%)
>1500 g	45	12 (26.7%)	8 (18%)
Dexamethasone			
<1000 g	29	13 (44.8%)	7 (24.1%)*
1000–1500 g	66	21 (31.8%)	9 (14%)*
>1500 g	37	10 (27.0%)	5 (14%)

* $P < .05$ (dexamethasone vs placebo).

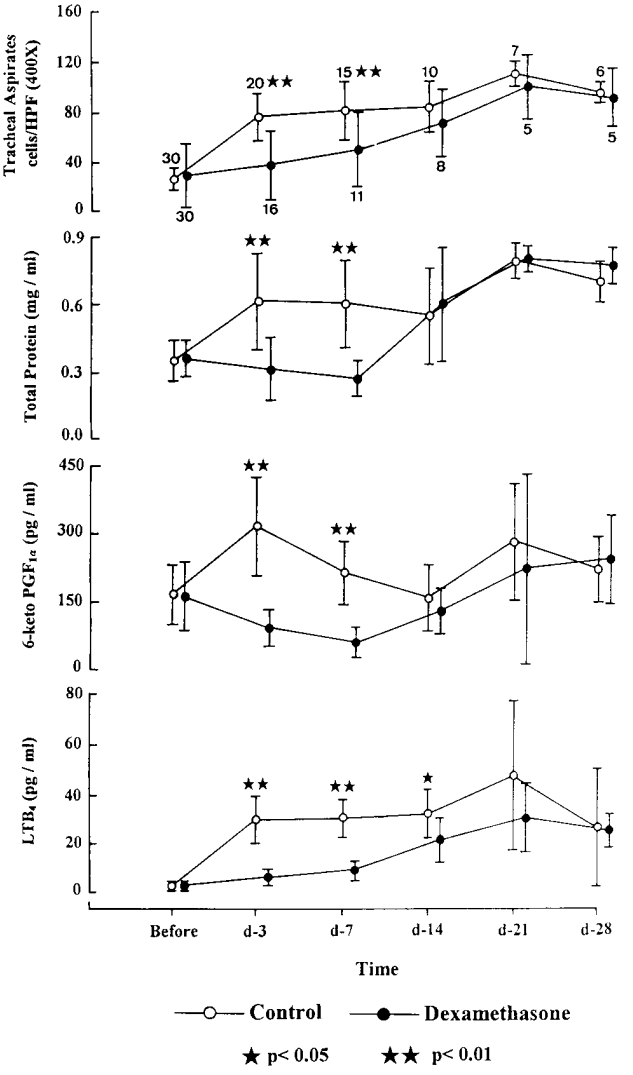

Fig 2. Comparison of cell counts, protein, 6-keto-$PGF_{1\alpha}$ and LTB_4 in tracheal aspirates between the groups before and during the study.

There was no significant difference between the placebo and dexamethasone group with respect to incidence of IVH (≥Gr II) (20 vs 25), active ROP (22 vs 23), and necrotizing enterocolitis (12 vs 11). More infants in the dexamethasone group had gastrointestinal hemorrhage (21 vs 10). Infants in the dexamethasone group had a significantly ($P < .01$) lower incidence of clinically significant PDA (14/132) than infants in the placebo group (34/130) during the study.

Clinical suspicion of sepsis was observed more commonly in the dexamethasone group (30/132) than in placebo group (19/130). Culture-proven bacteremia was seen in 13 infants in the dexamethasone group and in 8 infants in the control group. The total number of infants with bacteremia and/or clinical sepsis was significantly ($P < .05$) higher in the dexamethasone group (43 or 33%) than in control infants (27 or 21%). Fungus cultures were available in three participating hospitals. Four infants in the control

TABLE 4. A Summary of Side Effects Following Early Postnatal Dexamethasone Therapy

		Age (days)							
		2	3	5	7	10	14	21	28
Systolic blood pressure	C	57 ± 13	56 ± 10	62 ± 14	64 ± 14	63 ± 11	67 ± 12	70 ± 16	72 ± 15
(mm Hg)	D	58 ± 16	60 ± 12**	67 ± 17	71 ± 15**	69 ± 12**	74 ± 16**	77 ± 16	73 ± 15
Diastolic blood pressure	C	35 ± 10	34 ± 7	38 ± 11	41 ± 11	38 ± 9	40 ± 10	43 ± 12	44 ± 11
(mm Hg)	D	36 ± 11	37 ± 9**	42 ± 12	46 ± 13**	44 ± 11**	46 ± 12**	49 ± 11	43 ± 11
Glucose	C	129 ± 84	133 ± 95	123 ± 63	125 ± 75	119 ± 84	117 ± 90	101 ± 47	90 ± 34
(mg %)	D	151 ± 92**	146 ± 85**	150 ± 84**	151 ± 99**	138 ± 80**	122 ± 66	120 ± 56	93 ± 44
Blood urea nitrogen	C	24 ± 13	19 ± 11	18 ± 12	15 ± 13	14 ± 11	9 ± 7	7 ± 6	6 ± 4
(mg %)	D	29 ± 12*	31 ± 13**	36 ± 15**	33 ± 15**	24 ± 17**	19 ± 17**	11 ± 8	10 ± 8
Serum potassium	C	4.9 ± 1.3	4.7 ± 1.2	4.5 ± 1.1	4.6 ± 0.9	4.7 ± 0.8	4.6 ± 0.7	4.6 ± 0.8	4.7 ± 0.8
(meq/L)	D	5.6 ± 1.1*	5.3 ± 1.0*	5.1 ± 1.8*	4.9 ± 0.9	4.9 ± 0.9	4.9 ± 1.1	4.9 ± 0.7	4.8 ± 0.8
Osmolality	C	276 ± 26	285 ± 29	278 ± 29	275 ± 25	274 ± 25	279 ± 14	275 ± 23	275 ± 11
(mosm)	D	285 ± 24	292 ± 31	285 ± 39	286 ± 34*	287 ± 16*	280 ± 24	281 ± 9	275 ± 13
Echo	C	0.20 ± 0.06	0.21 ± 0.06		0.25 ± 0.08		0.29 ± 0.08	0.25 ± 0.11	0.29 ± 0.11
LVFW/LVC	D	0.24 ± 0.15	0.27 ± 0.12		0.35 ± 0.17*		0.30 ± 0.12	0.34 ± 0.11*	0.26 ± 0.09
FE_P	C	39 ± 27	43 ± 32		35 ± 27	25 ± 21	23 ± 17	54 ± 51	30 ± 28
(%)	D	57 ± 27*	60 ± 27*		39 ± 27	31 ± 22	35 ± 34	44 ± 20	27 ± 26
PTH	C	98 ± 55	99 ± 53		82 ± 80	92 ± 91	57 ± 29	57 ± 45	55 ± 31
(pg/mL)	D	233 ± 182*	165 ± 125*		131 ± 92*	111 ± 64	117 ± 82	62 ± 34	73 ± 25

Abbreviations: C, control; D, dexamethasone treated; LVFW/LVC, left ventricle free wall/left ventricle chamber; FE_p, urinary fractional excretion of phosphate; PTH, parathyroid hormone.
* $P < .05$.
** $P < .01$ (C vs D).

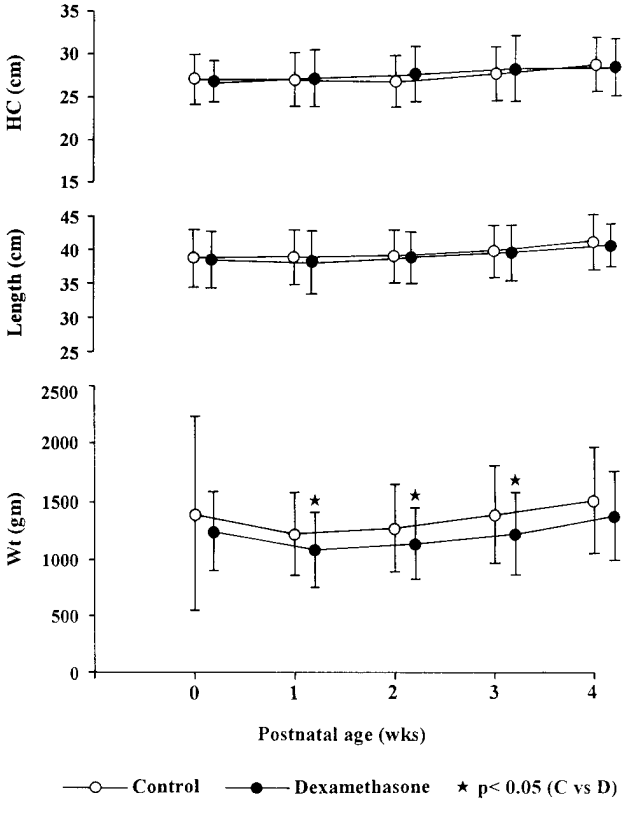

Fig 3. Comparison of body weight, head circumference, and length between the groups at 1, 2, 3, and 4 weeks postnatal age.

group and 4 in the dexamethasone group had fungemia (*Candida albicans*).

DISCUSSION

The present study demonstrated that administration of dexamethasone shortly (<12 hours) after birth for 1 week followed by a stepwise reduction of dosage throughout a 3-week period improved pulmonary status, facilitated weaning from respirator, and significantly reduced the incidence of CLD in the survivors. However, early postnatal use of dexamethasone was associated with various significant side effects including infection and sepsis. There was no apparent improvement in overall outcome and mortality.

The present study was conducted in a developing country in which the neonatal intensive care was only recently applied. The neonatal mortality rate and CLD morbidity, particularly in those infants that weighed <2000 g, are much higher than those of the respective weight group in developed countries. Furthermore, surfactant was not commercially available in Taiwan until early 1995. It is not possible to compare our data with those reported from the United States and Europe. The main purpose of our study was to test the hypothesis that early postnatal use of dexamethasone would prevent CLD. Our results strongly indicated this possibility.

The use of dexamethasone has been associated with a short-term but substantial improvement in pulmonary function, permitting rapid weaning from mechanical ventilation in some studies.[11–14] However, the majority of these previous studies were done in infants whose postnatal age was 2 weeks or older and their underlying changes of CLD was probably already established. It is, therefore, not surprising that none of these previous studies has shown any improvement in CLD morbidity. The present study was designed based on the following observations and hypotheses: 1) pulmonary inflammation after oxygen and ventilatory therapy occurs early in the course of RDS.[2,6,15,16] Therefore, any therapy to be beneficial in preventing CLD might have to start shortly after birth (eg, within the first day of life during which the infants have the highest risk of oxygen exposure and barotrauma). 2) Previous experience indicated that a 48- to 72-hour period of therapy was usually needed before the improvement of pulmonary function was seen.[7] Therefore, if dexa-

methasone is to be used for preventing CLD, the drug might have to be administered very early after birth. 3) Recent studies suggested that in some of the preterm infants who eventually developed CLD, their adrenal response may be immature and, in the face of stress, they may be in a state of adrenal insufficiency.[17,18] An early physiological replacement of cortisol may be needed. The physiological amount of cortisol in these infants has not been well-defined. The dosage of dexamethasone we used in this study is for antiinflammatory effect and may be higher than physiologically needed.

Early postnatal use of dexamethasone had been studied first by Yeh et al[7] and recently by other investigators.[19–23] The results of these studies are mixed and some are conflicting. It is difficult to interpret these results because each of these studies was designed differently with respect to time of starting the therapy, dosage and duration of the therapy, and the sample size chosen. The study by Shinwell et al[23] is somewhat similar to our study in terms of sample size and the time of starting therapy. They could not demonstrate the benefit of early dexamethasone therapy in preventing CLD. In Shinwell's study, dexamethasone was given for a maximum of only 3 days (6 doses) and surfactant was routinely given to all infants. As explained by the authors, that failure to demonstrate the beneficial effect of dexamethasone may be due to inadequate duration of therapy or the effect of steroid was masked by the improvement in outcome resulting from surfactant therapy. In our previous study,[7] a higher dosage (1 mg/kg/d) and a shorter duration (2 weeks) were given and the end point of assessment was successful weaning from the ventilator. In the present study, a lower dosage but a longer duration of tapering process was used, with the hope that by giving a lower dosage, side effects could be decreased to a minimum, and by a longer duration of tapering, the prolonged inflammation that occurred in the late neonatal period could also be suppressed. The significantly lower tracheal aspirate cell counts, protein content, and lower LTB_4 and 6-keto-$PGF_{1\alpha}$ in the dexamethasone-treated group suggests a blunted inflammatory response as compared with the placebo group (Fig 3). However, there seemed to be an increase in inflammatory response in the dexamethasone group from day 7 onward (Fig 3), suggesting an insufficient suppression of inflammation. Because of the small number of tracheal samples, it is not clear whether this insufficient suppression is attributable to a relatively low dosage of dexamethasone administered at this time. We did not observe an increase in urine output after dexamethasone, one of the possible mechanisms to reduce lung edema, as reported by Gallstone et al.[24]

One of the intriguing observations in this study is the significant decrease in incidence of PDA in the dexamethasone-treated infants. This finding is consistent with the earlier observation that prenatal steroid was associated with a decrease in PDA incidence.[25,26] Eronen et al[27] have also shown that antenatal administration of steroid may promote spontaneous closure of PDA in premature infants. Glucocorticoids may have an effect on PDA through an interference with prostaglandin synthesis[28] or through a reduction in sensitivity of ductus muscle to prostaglandin E2.[29] In the present study, we have also shown a good association of PDA and the subsequent development of CLD. Significant PDA shunt may cause pulmonary congestion, leading to more oxygen therapy and ventilatory support.[30] Early closure of the ductus would reduce the oxygen and ventilatory therapy and theoretically would decrease the incidence of CLD. However, previous studies of early prophylactic closure of the ductus, either by surgical or medical means,[31–33] did not show improvement in CLD morbidity. The role of PDA in the development of CLD in premature infants remains to be investigated.

The potential side effects of glucocorticoid therapy have been reported by various authors[7,11–14] and extensively reviewed by Taeusch[34] and by Ng.[35] Similar to these reports, we have shown a transient increase in blood glucose and blood pressure and development of cardiomyopathy. A transient increase in serum BUN, potassium, amino acid concentrations, and urinary excretion of 3-methylhistidine[36,37] indicated an increase in tissue catabolism and protein breakdown.

A transient elevation of serum parathyroid hormone level was noted after dexamethasone therapy. However, we did not observe any change in serum calcium and phosphorus and bone growth. Bone density was not measured in this study, however, osteoporosis was reported in infants treated with dexamethasone.[35,36] Similar to our previous report,[7] we have seen a transient weight loss and a delay in the rate of weight gain after dexamethasone. Although we did not evaluate the adrenal function, a transient suppression might have occurred, similar to our previous observation[38] and those of others.[39] These changes reflect the important pharmacological effect of steroid. The transient nature of the effects gives us some assurance in the use of this intervention. Whether a modified therapeutic regimen, with an even lower dosage and shorter duration than the present study or with pulse therapy, may achieve the same beneficial effect with less complication remains to be proven.

Infection and sepsis are important side effects associated with dexamethasone therapy. Of the 43 infants in the dexamethasone group who had bacteremia or clinical sepsis, 30 occurred at 2 weeks or later when prophylactic antibiotics were no longer administered. It is possible that this high incidence of infection may account for the relatively high mortality rate observed in the late course of the therapy. The increased risk of infection must therefore be considered before using dexamethasone.

Summary

1. Early postnatal dexamethasone therapy, given within 12 hours after birth for 1 week and tapering off in 3 weeks, significantly reduced the incidence of CLD judged at 28 postnatal days or at 36 postconceptional weeks. The use of dexametha-

sone was also associated with a significant decrease in incidence of clinical PDA.
2. Early dexamethasone therapy significantly suppressed pulmonary inflammation and improved pulmonary status of the infants, permitting earlier weaning from mechanical ventilation.
3. Early dexamethasone therapy was associated with the following immediate but transient side effects: 1) increase in blood glucose, BUN, and serum potassium; 2) increase in blood pressure and cardiac hypertrophy; 3) increase in parathyroid hormone and in urinary excretion of phosphate; and 4) increase in degree of weight loss.
4. Dexamethasone therapy was associated with a higher incidence of infection. This could contribute to an increased death rate in the late course of therapy.
5. Early dexamethasone therapy did not alter the incidence of ROP, IVH (≥GrII), head circumference, height, or bone growth.

In view of the significant, although transient, side effects of the early postnatal use of steroid and the lack of overall improvement in outcome and mortality, our recommendation regarding its routine use remains cautious until the result of a long-term follow-up study is available.

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