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Decreasing Incidence of Chronic Lung Disease Despite the Gradual Reduction of Postnatal Dexamethasone Use in Very Low Birth Weight Infants

Dexamethasone has been widely used in very low birth weight infants (VLBWI) weighing less than 1,500 g at birth for the prevention or treatment of chronic lung disease (CLD). Recently, however the use of dexamethasone is being reduced, as its association with abnormal neurodevelopmental outcome is known. On the other hand, there have been persistent concerns about the increased risk of CLD according to the reduction of postnatal dexamethasone use. Hence, we did a retrospective cohort study to delineate the change in the incidence of CLD according to the reduction of dexamethasone use in VLBWI. The medical records of 559 VLBWI admitted to neonatal intensive care unit at Samsung Medical Center between November 1994 and December 2002 were reviewed with a focus on the use of postnatal dexamethasone and the incidence of CLD. The use of postnatal dexamethasone has significantly decreased over the study period. Especially, the use of high-dose regimen has markedly decreased. The day when postnatal dexamethasone therapy was begun has also been significantly delayed. The incidence of CLD has significantly decreased over the same period. In conclusion, the incidence of CLD has not increased despite the decreased use of postnatal dexamethasone.

Key Words : *Dexamethasone; Bronchopulmonary Dysplasia; Infant, Premature*

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INTRODUCTION

Chronic lung disease (CLD) is still one of the major causes of morbidity and mortality in very low birth weight infants (VLBWI). From the early 1980s, dexamethasone has been administered to ventilator-dependent infants with CLD, as several reports that dexamethasone improves the lung function and enables earlier extubation were published (1, 2). In the 1990s, postnatal dexamethasone was administered to preterm infants almost as a routine to reduce the time spent on the ventilator and to prevent CLD (3). However, it has been known that although postnatal dexamethasone reduces the length of assisted ventilation and the incidence of CLD both at the 28th day of life and at the 36th postmenstrual week, it does not reduce the length of hospital stay and mortality ultimately (4-9). Moreover, postnatal dexamethasone has been reported to be able to produce not only short-term adverse reactions such as gastrointestinal bleeding, intestinal perforation, sepsis, meningitis, and hyperglycemia, but also long-term adverse reactions such as adrenal suppression and growth failure (10-15). Even more remarkably, recently, there has been a series of reports that the use of postnatal dexamethasone is associated with developmental delay and cerebral palsy (16-19). Therefore, nowadays there is a trend not to use postnatal dexamethasone routinely simply for the prevention of CLD in many neonatal intensive care units (NICU) (20-22). Similarly, in our NICU, considering the potential harm of postnatal dexamethasone to the developing brain, we have been reducing the use of postnatal dexamethasone gradually. We have attempted to confine postnatal dexamethasone therapy to infants who were still ventilator-dependent beyond the second week of life and showed ongoing deterioration in ventilator settings and radiological finding for more than 3 to 7 consecutive days. Moreover, in case of postnatal dexamethasone therapy, we have tried to defer it after the second week of life, and use it in a low dose. However, there have been persistent concerns about the increased risk for the CLD due to the decreased use of postnatal dexamethasone (23, 24). Nevertheless, there are few studies looking at the change in the incidence of CLD according to the decreased use of postnatal dexamethasone. Therefore, we did this study to delineate the change in the incidence of CLD according to the gradual reduction of postnatal dexamethasone use in VLBWI in our NICU.

MATERIALS AND METHODS

Five hundred fifty nine VLBWI weighing less than 1,500 g at birth who were admitted to NICU unit at Samsung Medical Center between November 1994 and December 2002 were enrolled.

To see the trends over time, we divided the study period arbitrary by a two-year interval into four eras: Era 1, November 1994-December 1996; Era II, January 1997-December 1998; Era III, January 1999-December 2000; Era IV, January 2001-December 2002. We reviewed the medical records of subject infants with a focus on following variables: Demographic variables including birth weight, gestational age, and sex; Clinical characteristics including chorioamnionitis, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP) requiring laser or cryotherapy, high grade intraventricular hemorrhage (IVH ≥grade III, Volpe's grading system, 25), periventricular leukomalacia (PVL), the extent of initial physiological weight loss, the length of synchronized intermittent mandatory ventilation (SIMV), the length of nasal continuous positive airway pressure (NCPAP), the length of supplemental oxygen (fractional concentration of oxygen, $FiO_2 \geq 0.3$), and mortality; Variables associated with postnatal dexamethasone therapy and CLD including the use of antenatal steroid, the use of postnatal dexamethasone, the day when dexamethasone therapy was begun, the dose of dexamethasone used, and the incidence of CLD at the 28th day of life and at the 36th postmenstrual week.

Gestational age was based on obstetrical record and survival was defined as when a VLBWI left the hospital alive fulfilling the indication of discharge in our NICU: weighing over 1,800 g and gaining weight steadily about 20-30 g/day; ability to maintain temperature in an open crib; no need for any parenteral drugs or fluids. Chorioamnionitis was defined as histological chorioamnionitis or umbilical cord vasculitis of grade 2 or greater according to the grading system suggested by Salafia et al. (26) and assessed by a single pathologist. The diagnosis of RDS required the presence of respiratory distress, increased oxygen requirement ($FiO_2 \geq 0.4$) and radiological and laboratory findings consistent with RDS in the absence of the evidence of other causes of respiratory distress. PDA was diagnosed by echocardiography and only symptomatic cases were identified. A single pediatric ophthalmologist made the diagnosis and the treatment decision of ROP. IVH and PVL were assessed with cranial ultrasonography by a single pediatric radiologist. CLD was defined by the need for supplemental oxygen ($FiO_2 \geq 0.3$) at the 28th day of life or at the 36th postmenstrual week with consistent radiological finding. In our NICU, postnatal dexamethasone therapy regimen was either high-dose or low-dose. High-dose regimen was as follows: starting at 0.5 mg/kg/day divided every 12 hr for 48 hr, then halving the dose every 48 hr for the next 5 days completing a total of 7 day-regimen. Low-dose regimen was the same as high-dose regimen except that the starting dose was 0.2 mg/kg/day.

All categorical variables were designated as percent (%), and continuous variables were designated as mean±standard deviation. We sought to see the trends in the variables across the four study eras. For this purpose, we used score test for trend (Jonckheere-Terpstra test for continuous variables, and linear by linear association for categorical variables). We used SPSS version 11.5 for these statistical analyses. *p*-value lower than 0.05 was regarded significant.

RESULTS

The trends in demographic and clinical characteristics across the four study eras

There were no significant difference in gestational age and sex by the four study eras (Table 1). However, birth weight showed a significant trend to decrease as the time elapses from era I to era IV ($p<0.01$). There were no significant differences in the incidence of RDS, PDA, ROP requiring laser and cryotherapy, and IVH (≥grade III) by the four study eras except the incidence of PVL that revealed a significant trend

Table 1. Trends in demographic and clinical characteristics of very low birth weight infants across the four study eras

	Era I n=106 ('94-'96)	Era II n=140 ('97-'98)	Era III n=116 ('99-'00)	Era IV n=197 ('01-'02)	*p*-value†
Birth weight (g)	1,172±219	1,145±252	1,118±248	1,087±262	<0.01
Gestational age (wk)	$29^{+4}\pm2^{+5}$	$29^{+2}\pm2^{+3}$	$29^{+0}\pm2^{+4}$	$28^{+5}\pm2^{+5}$	NS
Male sex (%)	51	51	53	50	NS
CA (%)	17	20	32	26	NS
RDS (%)	58	49	62	58	NS
PDA (%)	52	44	51	52	NS
ROP (%)	8	8	9	7	NS
IVH (%)	11	8	4	5	NS
PVL (%)	12	2	6	4	<0.05
% Initial weight loss	9±14	10±17	17±20	13±10	<0.001
SIMV length (d)	22±29	15±28	15±35	9±16	<0.001
NCPAP length (d)	2±5	6±10	6±10	8±12	<0.001
Suppl. O_2* length (d)	9±13	6±8	6±16	2±4	<0.001
Hospital stay (d)	62±44	60±37	71±46	63±37	NS
Mortality (%)	19	17	10	9	<0.01

CA, Chorioamnionitis; RDS, Respiratory distress syndrome; PDA, Patent ductus arteriosus; ROP, Retinopathy of prematurity that requiring laser or cryotherapy; IVH, Intraventricular hemorrhage (≥grade III, Volpe's grading system); PVL, Periventricular leukomalacia; SIMV, Synchronized intermittent mandatory ventilation; d, day; NCPAP, Nasal continuous positive airway pressure. *, Supplemental oxygen (fractional concentration of inspired oxygen≥0.3); †, *p*-value of score test for trend (Jonckheere-Terpstra test for continuous variables; and linear by linear association for categorical variables).

Table 2. Trends in the frequency of postnatal dexamethasone use and the incidence of chronic lung disease at the 28th postnatal day or at the 36th postmenstrual week across the four study eras

	Era I n=106 ('94-'96)	Era II n=140 ('97-'98)	Era III n=116 ('99-'00)	Era IV n=197 ('01-'02)	*p*-value†
Antenatal steroid use (%)	24	59	68	76	<0.001
Postnatal DXT use (%)	49	30	19	20	<0.001
High-dose (cycle)*	0.8±1.5	0.2±0.6	0.4±0.9	0.1±0.4	<0.01
Low-dose (cycle)*	2.2±2.4	2.1±2.1	2.0±1.8	1.4±0.9	NS
Start day (d)*	14±7	17±11	30±23	29±14	<0.001
CLD at 28th PND (%)	46	37	34	31	<0.05
CLD at 36th PMW (%)	26	19	11	8	<0.001

DXT, Dexamethasone; CLD, Chronic lung disease; PND, Postnatal day; PMW, Postmenstrual week. *, In case of postnatal dexamethasone use, *p*-value of score test for trend (Jonckheere-Terpstra test for continuous variables, and linear by linear association for categorical variables).

to decrease as the time passes ($p<0.05$). There were no significant differences in the length of hospital stay by the study eras. However, the length of SIMV and supplemental oxygen, and mortality showed a significant trend to decrease as the time elapses ($p<0.001$, $p<0.001$, $p<0.01$, respectively), while the extent of initial physiological weight loss and the length of NCPAP revealed a significant trend to increase as the time passes ($p<0.001$).

The trends in postnatal dexamethasone use and the incidence of CLD across the four study eras

The use of antenatal steroid showed a significant trend to increase as the time elapses from era I to era IV ($p<0.001$). However, the use of postnatal dexamethasone in VLBWI has significantly decreased as the time passes ($p<0.001$) (Table 2). Especially, the use of high-dose regimen has markedly decreased ($p<0.01$), while the use of low-dose regimen did not reveal a significant trend across the study eras. The incidence of CLD at the 28th day of life and that at the 36th postmenstrual week have all decreased significantly as the time elapses with the latter more evident ($p<0.05$, $p<0.001$, respectively).

DISCUSSION

Around the year of 1999, a number of investigators reported that postnatal dexamethasone therapy for the prevention or treatment of CLD might produce adverse neurodevelopmental outcome (11, 16-19, 27, 28). Recognizing this potential neurodevelopmental risk of postnatal dexamethasone, we have tried to reduce the use of postnatal dexamethasone for the prevention or treatment of CLD in our NICU. The results of present study indicate that in our NICU, the use of postnatal dexamethasone, especially high-dose regimen has remarkably decreased as the time elapses from era I to era IV. Moreover, a large majority of the studies that reported the neurodevelopmental risk of postnatal dexamethasone dealt with the early treatment regimen that dexamethsone is given to VLBWI within the first two weeks of life, particularly within the first four days of life. Therefore, we have also tried to delay postnatal dexamethasone therapy after the second week of life. Actually, our results demonstrated a trend that the time when dexamethasone therapy was begun has been deferred from 14±7 postnatal day in era I to 29±14 postnatal day in era IV.

Our results also show that the incidence of CLD has not increased, instead it has decreased despite the reduced use of postnatal dexamethasone during the same period. Many factors might be responsible for this decrease in the incidence of CLD. In the present study, we observed the trends in the factors that have been previously known to be associated with the development of CLD over time during the study period. Birth weight, gestational age, and the incidence of pathologically proven chorioamnionitis, RDS, and PDA have not changed significantly during the study period. However, the extent of initial physiological weight loss, the length of SIMV and NCPAP showed a significant change over time during the study period. The extent of initial physiological weight loss has increased as the time elapses from era I to era IV. This change in the extent of initial physiological weight loss might reflect the alteration in fluid management strategy in our NICU. We applied fluid restriction therapy (less than 80 mL/kg/day during the first week of life) since 1999. There have been several reports that excessive fluid administration in the early postnatal period is associated with the development of CLD (29, 30). Therefore, it is possible that the increased extent of initial physiological weight loss might have contributed to the decreased incidence of CLD during the study period. However, the effect of fluid restriction therapy on the prevention of CLD remains to be further evaluated by randomized case-control study. The decrease in the length of SIMV and the increase in the length of NCPAP are related to each other, because we have tried to wean the infants from SIMV to NCPAP as soon as possible since the latter half of the study period. Early weaning from SIMV to NCPAP is one of the strategies to reduce the ventilator-induced lung injury, and has also been applied in many other NICUs (20-22). Its preventive effect on CLD is supported by several studies (31-33). In our study, the decrease in the incidence of CLD might be partly attributable to this weaning strategy. The incidence of CLD has significantly decreased not only at the 36th postmenstrual week but also at the 28th day of life. Considering that in the latter half of the study period, the era III and IV, the mean day when dexamethasone therapy was begun was

around end of the 4th week, the decrease in the incidence of CLD at the 28th day of life in our cohort is not thought to be the effect of postnatal dexamethasone.

In contrast to the postnatal dexamethasone, the use of antenatal steroid to the mothers of VLBWI has increased across the four study eras. Antenatal steroid is known to facilitate the fetal lung maturation resulting in the improvement of the pulmonary function in the postnatal period (34), and is being widely used routinely when preterm labor is anticipated unless the case is contraindicated. However, the neurodevelopmental adverse effects that antenatal steroid might produce have been controversial. Baud et al. reported that the VLBWI whose mothers had been given antenatal betamethasone developed PVL on cranial ultrasonography 2 times less frequently than the VLBWI whose mothers had not, while the VLBWI whose mothers had been given antenatal dexamethasone developed PVL 1.5 times more frequently than the VLBWI whose mothers had not (35). Shankaran et al. reported that there were no differences in the neurodevelopmental prognosis of VLBWI according to the use of antenatal steroid (36). All the more, they asserted that antenatal steroid decreased the incidence of high-grade (≥grade III) IVH. Similarly, LeFlore et al. reported that antenatal steroid did not affect the incidence of PVL and the scores of Bayley Scales of Infant Development (37). Our results also revealed that the incidence of PVL has, at least, not increased across the four study eras, while the use of antenatal steroid has markedly increased during the same period. However, according to the study of Jobe et al.'s, antenatal steroid can cause symmetrical intrauterine growth retardation (38, 39). From the above contradicting results, at present, the neurodevelopmental safety of antenatal steroid may not be guaranteed yet, and it requires further investigations.

Aside from the probable neurodevelopmental risk of antenatal steroid, the inverse relationship between the trends in the frequency of antenatal steroid use and the incidence of CLD across the study eras suggests a possibility that the decrease in the incidence of CLD might be due to the increased use of antenatal steroid considering its beneficial effect to the lung function. However, that possibility might be low, because the incidence of RDS that is thought to be the ultimate outcome of the beneficial effect of antenatal steroid did not show a significant change over time during the same study period. Moreover, in our recent epidemiologic study to assess the risk factors for CLD in out NICU, RDS was not a significant risk factor for CLD (40).

Our results demonstrated that although the use of postnatal dexamethasone has been reduced, the incidence of CLD has not increased. The incidence of CLD has rather decreased. This favorable outcome is thought to be attributable to the introduction of other measures for the reduction of the lung injury such as early weaning from SIMV to NCPAP and fluid restriction therapy in the early postnatal period. Therefore, as long as the possibility that postnatal dexamethasone produces neurodevelopmental adverse effect remains, it may be desirable to refrain from the routine use of postnatal dexamethasone for the prevention of CLD and restrict postnatal dexamethsone therapy to the ventilator-dependent VLBWI who aggravates relentlessly clinically and radiologically beyond the second week of life.

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