

A Follow-up Study of Preterm Infants Given Budesonide Using Surfactant as a Vehicle to Prevent Chronic Lung Disease in Preterm Infants

Huang T. Kuo, MD, PhD, Hong C. Lin, MD, Chang H. Tsai, MD, PhD, I. C. Chouc, and Tsu F. Yeh, MD, PhD

Objective Our study of early intratracheal instillation of budesonide using surfactant as vehicle showed a significant decrease in death or chronic lung disease (CLD) in preterm infants with severe respiratory distress syndrome (RDS). We now report the long-term outcome at about 2 to 3 years of age.

Study design Of the 75 potential survivors, 67 (90%) were studied (35 budesonide-treated, 32 control). All infants had birth weight <1500 g and had severe RDS requiring intermittent mechanical ventilation shortly after birth. The treated group received a mixture of budesonide and surfactant every 8 hours. The control group received only surfactant.

Results The physical growth and the neurological examinations were comparable between the groups at follow-up. Infants in the group treated with budesonide tended to have higher PDI and MDI scores than infants in the control group (79 ± 20 vs 74 ± 18 and 80 ± 19 vs 75 ± 20), but these differences were not statistically significant. The incidence of neurodevelopmental impairment was 11 (31%) in the treated group and 13 (40%) in the control group ($P = .367$).

Conclusions Early intratracheal instillation of budesonide using surfactant as a vehicle significantly improved pulmonary outcome without causing long-term adverse effects. (*J Pediatr* 2010;156:537-41).

Chronic lung disease (CLD) continues to be an important complication in preterm infants after mechanical ventilation. Various studies indicate that pulmonary inflammation plays a central role in the development of CLD.¹ Glucocorticoids suppress lung inflammation and may improve pulmonary outcome, but because of their systemic side effects, they are not recommended for routine use.²⁻⁵ One alternative to systemic administration is delivery of glucocorticoids by inhalation.⁶⁻⁸ However, delivery of inhaled glucocorticoids including budesonide in preterm infants is technically difficult, and the effectiveness of glucocorticoids was limited. To achieve a better local effect of steroid on the airways, we conducted a pilot study of direct instillation of budesonide into the trachea using surfactant as a vehicle. There was a significant improvement in the combined outcome of death or CLD and immediate adverse reactions.⁹ However, budesonide is a potent corticosteroid, and its long-term effect on preterm infants is unknown. The present report summarizes the follow-up at about 2 to 3 years of age.

Methods

All infants born during the period September 1, 2004, to February 28, 2006, with a birth weight of less than 1500 g were eligible for the original double-blind trial. The selection criteria for the study included the following: (1) radiographic evidence of severe respiratory distress syndrome (RDS) requiring mechanical ventilation within 4 hours after birth; (2) requirement of fractional inspired oxygen (FIO₂) of ≥ 0.6 ; and (3) absence of severe congenital abnormalities and lethal cardiopulmonary disorders. We believed that these infants were at high risk of developing CLD. Infants received either a mixture of budesonide and surfactant (treatment group) or surfactant only (control group). In the treatment group, infants were administered a mixture of 0.25 mg/kg budesonide (Pulmicort nebulizing suspension, Astra Zeneca, Lund, Sweden) and 100 mg/kg beractant (Servanta, Abbott, Columbus, Ohio). In the control group, infants were given 100 mg/kg beractant only. The dosage of budesonide was chosen based on our in vitro study previously reported.⁹ In both groups, surfactant was given as rescue therapy. The first dose was usually given shortly after admission to the NICU. Repeated doses were given every 8 hours until the infant required <0.4 of FIO₂ or until the infant was extubated. The diagnosis of CLD was made at 36 weeks postmenstrual age if the infant continuously had respiratory distress

BSID-II	Bayley Scale of Infant Development-II
CLD	Chronic lung disease
IVH	Intraventricular hemorrhage
MDI	Mental Development Index
PDA	Patent ductus arteriosus
PDI	Psychomotor Development Index
RDS	Respiratory distress syndrome

From the Division of Developmental and Behavior Pediatrics (H.T.K.), the Division of Neonatology (H.C.L., T.F.Y.), and the Division of Pediatric Neurology (H.T.K., C.H.T., I.C.C.), College of Medicine, China Medical University, Taichung, Taiwan; the Department of Biotechnology (C.H.T.), Asian University, Wufeng, Taiwan; and the Department of Pediatrics (T.F.Y.), John H. Stroger Jr Hospital of Cook County, Chicago, IL

Supported in part by the National Science Council Taiwan (NSC96-2314-B-039-008-MY2). The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. Copyright © 2010 Mosby Inc.
All rights reserved. 10.1016/j.jpeds.2009.10.049

requiring supplemental oxygen therapy since birth and had abnormal chest radiographic findings. The details of the study methods were described previously.⁹

A total of 116 infants were included in the initial study: 60 in the budesonide-treated group and 56 in the control group.¹⁰ Infants in the treatment group had better pulmonary status than those in the control group during the first 3 days after intervention. There were no significant differences in mortality or CLD morbidity between the treatment and control groups; however, the total number of infants who either died or developed CLD was significantly lower in the treatment group than in the control group (19/60 vs 34/56 $P = .003$). With the exception of a higher incidence of transient elevated blood pressure in the treatment group, the 2 groups were comparable in somatic growth, incidence of intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), retinopathy of prematurity, and sepsis during the initial study period. There was no significant difference between the groups followed and those not seen with respect to birth weight (940 ± 292 vs 890 ± 340 g), gestational age (26.8 ± 2.5 vs 26.4 ± 2.6 weeks), Apgar score, and severity of RDS at birth.

Follow-up Study

The follow-up study was conducted at about 2 to 3 years of age. The study was approved by the institutional review board of the hospital, and consent was obtained from parents or guardians of each infant. Of the 75 potential survivors at about 2 years of age, 67 (90%) were studied: 35 in the budesonide-treated group and 32 in the control group (Table I).

At each follow-up visit, an interim medical history was obtained and a physical examination was performed. Weight, occipito-frontal head circumference, and standing height were measured. Each medical examination was accompanied by a neurological assessment of mental status, motor development (including coordination, general reflex, and muscle tone), and cranial nerves by a senior pediatrician and pediatric neurologist. Neuromotor dysfunction was classified as mild, moderate, or severe, based on the mobility of the child, as described by Costello et al.¹⁰ Motor dysfunction that was

not severe enough to interfere with the mobility was defined as mild. Dysfunction was defined as moderate if the child was independently mobile when provided hand-holding and severe if the child was not independently mobile even with hand-holding. A standard 12-lead monopolar and bipolar electroencephalogram (EEG) also was performed and included visual stimulation (visual evoked potential, VEP) and auditory stimulation (brainstem auditory evoke potential, BAEP) at 15 to 100 dB.

Psychomotor evaluations were performed using the Bayley Scale of Infant Development (BSID-II) by a pediatric psychologist. All tests were performed in the presence of the child's parents or guardians, with the examiners blinded to group assignment. For analysis of physical growth and developmental performance, the child's postnatal age was corrected by the degree of prematurity before term (40 weeks). Data on family background and socioeconomic status were obtained from parents or occasionally from a guardian. Maternal education level was classified into 4 categories, below high school graduation (compulsory 9-year education), high school graduate (12 years), some college education (12 to 16 years), and college graduate (>16 years). The parents' occupation was evaluated by using a scoring system modified from Hollingshead and Redlich.¹¹

Statistics

The data were analyzed by a statistician using the SAS System (SAS Institute, Inc, Cary, North Carolina). Analysis of variance and, where appropriate, the t test was used to make group comparisons of continuous variables. The χ^2 test was used to compare the groups with respect to categorical variables. Except where indicated otherwise, values are expressed as mean \pm 1 SD. A P value of $<.05$ was considered significant.

Results

Perinatal Characteristics and Socioeconomic Background

There were no significant differences in the perinatal characteristics and socioeconomic background between the groups (Table II). There were no significant differences between the groups in mode of delivery (vaginal delivery: 17 vs 15 and C-section: 18 vs 17 in treated vs control, respectively) and in Apgar score at 1 minute (≤ 3 : 14 vs 13; 4 to 6: 16 vs 16; >6 : 5 vs 3 in treated vs control, respectively) and at 5 minutes (≤ 3 : 2 vs 2; 4 to 6: 8 vs 9; >6 : 25 vs 21, respectively). None of the mothers had a history of drug abuse. The initial cardiopulmonary status on admission to NICU was also comparable between the groups. The mean postnatal age at the time of the first dose of budesonide was 2.3 ± 0.3 hours. Both groups were comparable with respect to maternal age, maternal education level, parental occupation score, and marital status. Most of the children came from middle class families, and their medical care was covered by the Taiwan National Health Insurance Program.

Table I. Infants studied

	Budesonide treatment (n = 35)	Control (n = 32)
No. of infants in the initial study	60	56
No. of infants died in the initial study period	10	18
No. of infants died after discharge from hospital and before the age of 2 years	8	5
No. of infants that could not be located	4	1
No. of infants without consent to participate or lack of cooperation	3	0
No. of infants included in the current study	35	32

Table II. Perinatal characteristics, social background, initial course, and outcome

	Budesonide-treated (n = 35)	Control (n = 32)
Perinatal characteristics		
Gestational age (wk)	26.9 ± 2.1	26.7 ± 2.5
Birth weight (g)	947 ± 265	934 ± 243
Sex (M/F)	20/15	16/16
Prenatal steroid	28 (80%)	20 (63%)
Social background		
Maternal age (y)	28.4 ± 7.2	30.7 ± 4.5
Maternal education		
Not a high school graduate	3 (9%)	6 (19%)
High school graduate	17 (48%)	12 (38%)
Some college	10 (29%)	11 (34%)
College graduate	5 (14%)	3 (9%)
Occupational score		
Father	3.7 ± 1.2	3.5 ± 1.0
Mother	3.5 ± 0.9	3.8 ± 0.8
Marital status		
Married and living together	30 (86%)	30 (94%)
Married not living together	0	0
Unmarried and living together	1 (3%)	0
Single parent	4 (11%)	2 (6%)
Initial course		
Doses of surfactant		
1 dose	19 (54%)	10 (31%)*
2 doses	14 (40%)	17 (53%)
3 doses	2 (6%)	5 (16%)
Outcome		
CLD	6 (17%)	11 (34%)
PDA	18 (51%)	22 (68%)
ROP	10 (29%)	8 (25%)
IVH (Grade II or higher)	8 (22%)	5 (16%)
Duration of IMV (d)	12.8 ± 14.2	16.2 ± 21.6
Duration of O ₂ therapy (d)	44.2 ± 22.6	51.6 ± 32.4

CLD, Chronic lung disease; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.

* $P = .049$.

Initial Course and Outcome

The proportion of infants that required only 1 dose of surfactant was higher in the budesonide-treated group than in the control group (19/35 vs 10/32, $P = .049$) (Table II). As in the original study, there was a trend of lower incidence of CLD in the budesonide-treated group than in the control group (6/35 vs 11/32, $P = .102$). There was no significant difference between the groups in incidence of PDA, ROP, IVH (Grade II or higher), or in the duration of assisted ventilation and supplemental oxygen therapy.

General Health

The mean postnatal age at the time of follow-up was 31.3 ± 4.3 months in the budesonide-treated group and 31.8 ± 3.6 months in the control group. The corrected age was 28.0 months in the budesonide-treated group and 28.6 months in the control group. Of the infants who had CLD, 1 in the treatment group and 2 in the control group still had mild respiratory distress and required occasional supplemental oxygen therapy by nasal cannula at the time of follow-up. The mean frequency of upper respiratory infection per year was 8.2 ± 4.1 in the budesonide-treated group and 8.9 ± 3.2 in

the control group. Twenty-six infants in the budesonide-treated group (76%) and 21 infants in the control group (67%) were admitted to the hospital because of various respiratory problems during the first 2 to 3 years of life.

Physical Growth

There were no significant differences in mean body weight (BW), height (Ht) and head circumference (HC) between the groups, either in boys and or in girls (treated vs control, respectively: boys: BW: 11.7 ± 2.4 vs 12.5 ± 3.4 kg; Ht: 85.2 ± 6.4 vs 87.7 ± 3.9 cm; HC: 46.3 ± 1.8 vs 47.0 ± 3.0 cm; girls: BW: 11.6 ± 1.4 vs 11.4 ± 2.6 kg; Ht: 85.7 ± 5.2 vs 85.7 ± 6.1 cm; HC: 47.0 ± 1.7 vs 46.1 ± 1.5 cm). Five infants in the treatment group and 5 in the control group had body weight below the third percentile. Four infants in the treatment group and 6 in the control group had a head circumference below the third percentile. Six infants in the budesonide-treated group and 3 in the control group had a height below the third percentile.

Neurological Assessment

Two children in the budesonide-treated group and 1 in the control group had a history of clinical seizures. Table III summarizes the neurological diagnoses. There was no significant difference in the incidence of abnormal neurological findings between the budesonide-treated group and the control group (11/35 vs 8/32, $P = .559$). There was no significant difference in the severity of neuromotor dysfunction between the 2 groups. Seven infants in the budesonide-treated group and 4 in the control group had an abnormal EEG demonstrating epileptic-form discharge. There was no significant correlation between abnormal EEG patterns and neurological outcome. Twelve infants in the budesonide group and 11 infants in the control group had eye problems, including nystagmus and strabismus. One infant in the budesonide group and 2 infants in the control had significant vision impairment. Two of these infants (1 in each group) also had severe neurological problems. There was no significant difference between the groups either in incidence of abnormal BAEP (4/35 vs 2/32 $P = .675$) or in the mean amplitude and latency of BAEP and VEP. Two infants in each group required hearing aids.

Intellectual Development

There is a trend toward a higher mean Mental Development Index score (MDI) and Psychomotor Development Index (PDI) score in the budesonide-treated group as compared with the control group, but these differences were not statistically significant ($P = .433$ for MDI and $P = .214$ for PDI) (Table III). The difference in proportion of low MDI (≤ 69) or low PDI scores (≤ 69) between the groups were not statistically significant. Neurodevelopmental Impairment (NDI) either due to moderate to severe neurologic defects or significant intellectual defects (MDI and/or PDI ≤ 69) and/or hearing deficit requiring hearing aid or bilateral blindness were seen in 11 infants in the budesonide-treated group and in 13 infants in the control group ($P = .367$) (Figure).

Table III. Neurodevelopment assessment

	Budesonide-treated (n = 35)	Control (n = 32)
Neurological examination		
Normal	24 (69%)	24 (75%)
Abnormal	11 (31%)	8 (25%)
Tetraparesis	3	2
Hemiparesis	1	1
Diplegia	4	2
Hypotonia	3	3
Severity		
Mild	6	4
Moderate	3	3
Severe	2	1
Development (BSID II) assessment		
MDI	80.1 ± 20.0*	74.9 ± 20.6*
≥115	0	1
85-114	18	10
70-84	7	9
≤69	10 (28%)	12 (37%)
PDI	79.9 ± 20.8*	74.1 ± 18.3*
≥115	0	1
85-114	18	7
70-84	7	11
≤69	10 (28%)	13 (40%)

*Values are mean ± SD.

Discussion

Infants who received early intratracheal budesonide and surfactant therapy were comparable in body weight, height and head circumference, and neurodevelopment outcome to infants who received surfactant only.

Budesonide is a potent, nonhalogenated corticosteroid and has been used for years in children with asthma.¹² The pharmacological effects of budesonide include anti-inflammatory and bronchodilator activity.¹³ The mechanisms responsible for the pulmonary improvement in preterm infants are not completely clear but could be due to a local anti-inflammatory effects on the lungs and the overall

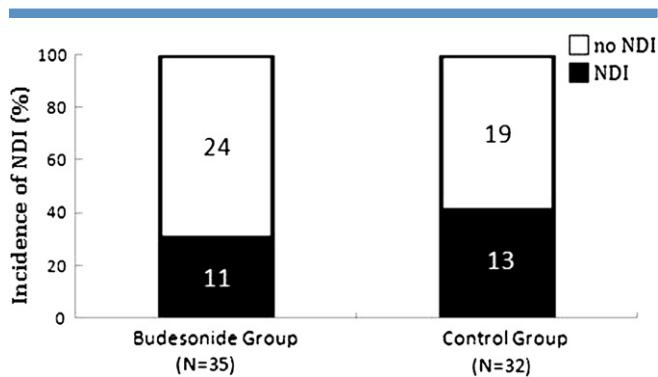


Figure. Incidence of neurodevelopmental impairment (NDI), defined as either due to moderate to severe neurological defects or significant intellectual defects (MDI and/or PDI ≤69) and/or hearing deficit requiring hearing aid or bilateral blindness. No significant difference in incidence of NDI between the groups ($P = .367$).

improvement of cardiopulmonary status.⁹ The long-term effects of using budesonide in preterm infants are not known. Most previous studies on inhaled budesonide in preterm infants with RDS did not show beneficial effects; however, they also did not show immediate adverse effects.^{6,14}

There are several possibilities as to why intratracheal instillation of budesonide did not cause immediate or long-term adverse effects. For example, our pharmacokinetic data indicated that after instillation of the budesonide-surfactant mixture, a significant amount of budesonide might remain in the lungs for some time.¹⁵ This may explain the rapid and prolonged effect on the lungs.⁹ Furthermore, surfactant may enhance solubilization of budesonide, thereby increasing absorption into cells.^{16,17} Once budesonide is absorbed, it can be conjugated extensively with fatty acids, resulting in the formation of budesonide ester at the C21-hydroxyl group.¹⁸ This conjugation process is reversible, and the conjugates can be hydrolyzed intracellularly, gradually releasing free budesonide. Budesonide is not metabolized in lung cells. The reversible conjugation may improve airway selectivity and prolong the local anti-inflammatory action in the airways. This, perhaps, explains why minimal doses (1 or 2) of budesonide were effective for some time.⁹ Our previous study¹⁵ showed that the terminal half-life of plasma budesonide is 4.13 hours, much shorter than most of the medications reported in preterm infants. This short half-life and the simultaneous increase in one of its major metabolites, 16 α -hydroxyprednisolone, indicates that budesonide is rapidly metabolized in the liver or other tissue.¹⁹ The systemic effects of the metabolites are minimal.¹⁹

The present study was conducted in children about 2 to 3 years of age. However, only about half of study population has had a longitudinal follow-up since the initial discharge from the hospital. Many of these infants were followed in private clinics throughout the country. The interim medical history was obtained from the parents. The 13 infants (8 in the budesonide-treated group and 5 in the control group) who died before reaching the age of 2 to 3 years, 10 (6 in the budesonide treated and 4 in the control group) had birth weight of <1000 g, 4 (2 in each group) had neurological defects according to the mother's statement, and 7 (3 in the budesonide-treated group and 4 in the control) had respiratory problems. None of these infants underwent autopsy, and the causes of death could not be defined. Although we were able to follow nearly 90% of the potential survivors, the imbalance in number of infants followed between the 2 groups may favor better outcomes in the budesonide-treated groups. Furthermore, the number of deaths by 2 to 3 years of age was 18 in the budesonide group and 23 in the control group; this would substantially reduce the significance of the difference in primary outcome of the pilot study. A large sample size study is needed. ■

We thank Hsiang-Ling Hung for statistical analysis, Chi-fen Lian and Shyh-Herng Wong for developmental assessment, and Yu-Chen Pan and Melanie Li-Kastanes for manuscript preparation.

Submitted for publication May 7, 2009; last revision received Sep 11, 2009; accepted Oct 29, 2009.

Reprint requests Dr Tsu F. Yeh, Department of Pediatrics, College of Medicine, China Medical University, 91 Hsieh Shi Road, Taichung, Taiwan. E-mail: tsufuhy@yahoo.com.

References

1. Speer CP. Pre and postnatal inflammation mechanism in chronic lung disease of preterm infants. *Pediatr Respir Rev* 2004;5:S241-4.
2. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics* 1998;101. Available at: www.pediatrics.org/cgi/content/full/101/5/e7.
3. Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2003;1:CD001146.
4. Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH, et al. Outcome at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N Engl J Med* 2004;350:1304-13.
5. Committee on fetus and newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics* 2002;109:330-8.
6. Shah SS, Ohlsson A, Halliday H, Shah VS. Inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birth weight neonates. *Cochrane Database Syst Rev* 2003;CD002058.
7. Kovács L, Davis GM, Faucher D, Papageorgiou A. Efficacy of sequential early systemic and inhaled corticosteroid therapy in the prevention of chronic lung disease of prematurity. *Acta Paediatr* 1998;87:792-8.
8. Cole CH, Colton T, Shah BL, Abbasi S, Mackinnon BL, Demissie S, et al. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. *N Engl J Med* 1999;340:1005-10.
9. Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, et al. Early Intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. *Pediatrics* 2008;121:1310-18 or www.pediatrics.org/cgi/content/full/121/5/1310.
10. Costello de L, Hamilton PA, Baudin J, Townsend J, Bradford B, Stewart AL, et al. Prediction of neurodevelopmental impairment at four years from brain ultrasound appearance of very preterm infants. *Dev Med Child Neurol* 1988;30:711-22.
11. Hollingshead AB, Redlich FC. Social stratification and psychiatric disorders. In: Rose AM, editor. *Mental Health and Mental Disorders: A Sociological Approach*. New York, NY: WW Norton and Co; 1955.
12. National Asthma Education and Prevention Program. Expert Panel Report: guidelines for the diagnosis and management of asthma update on selected topics: 2002. *J Allergy Clin Immunol* 2002;110(suppl 5):S141-219.
13. Brattsand R, Thalen A, Roempke K, Kallström L, Gruvstad E. Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur J Respir Dis* 1982;122(suppl 2):62-73.
14. Nimmo AJ, Carstairs JR, Patole SK, Whitehall J, Davidson K, Vink R. Intratracheal administration of glucocorticoids using surfactant as a vehicle. *Clin Exp Pharmacol Physiol* 2002;29:661-5.
15. Wu TS, Agrawal V, Lin HC, Su BH, Pyati S, Yeh TF. Intratracheal instillation of budesonide (B) by using surfactant (S) as vehicle in VLBW infants at high risk for chronic lung disease: pharmacokinetics and bioavailability of budesonide. *E-PAS* 2007;616292.1.
16. Pham S, Wiedmann TS. Note: dissolution of aerosol particles of budesonide in Survanta TM, a model lung surfactant. *J Pharmaceutical Sci* 2001;90:98-104.
17. Wiedmann TS, Bhatia R, Wattenberg LW. Drug solubilization in lung surfactant. *J Control Release* 2000;65:43-7.
18. Miller-Larsson A, Mattsson H, Hjertberg E, Dahlbäck M, Tunke A, Brattsand R. Reversible fatty acid conjugation of budesonide: novel mechanism for prolonged retention of topically applied steroid in airway tissue. *Drug Metab Dispos* 1998;26:623-30.
19. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000;60:1141-78.