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ORIGINAL ARTICLE

Long-term sequelae of postnatal surfactant and corticosteroid therapies for BPD

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Objective: This retrospective analysis assessed the relationship between medical treatment (postnatal steroids, surfactant) received neonatally and outcomes at 3 and 8 years using a longitudinal sample of children with bronchopulmonary dysplasia (BPD).

Study Design: Four groups were formed retrospectively based on the type of neonatal medical treatment received: no drug intervention ($n = 37$), surfactant only ($n = 29$), postnatal steroids only ($n = 13$) and combined surfactant and postnatal steroids ($n = 16$). Groups were compared on neurological and medical outcomes.

Result: Combined postnatal steroids and surfactant treatment was associated with more days on supplemental oxygen than no intervention or surfactant only. Surfactant replacement therapy alone was not associated with adverse consequences; however, postnatal steroid exposure appeared to be related.

Conclusion: Although retrospective analyses make statements about causation impossible, the differential relationships of therapies with cognitive outcomes argues for careful monitoring of therapeutic agents with very low birth weight infants.
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Introduction

Bronchopulmonary dysplasia (BPD) is the leading chronic lung disease in infancy in the United States.[1–3] During the early 1990s, the most commonly used treatment for infants with BPD and very low birth weight (VLBW) was postnatal corticosteroids, which treated the inflammation assumed to play a pathogenic role in chronic lung disease.[4] Although corticosteroids helped to wean children off respirators, neonatologists became increasingly aware of adverse outcomes associated with steroid use.[5–8] In 2002, the American Academy of Pediatrics and the Canadian Paediatric Society, following a review of studies, concluded that corticosteroids should not be used with VLBW infants in the treatment of chronic lung disease.[9] Three Cochrane reviews have reported on the adverse effects of postnatal steroids in both the infancy and the preschool periods based on randomized, controlled trials.[10–12] They further note that long-term follow-up of postnatal steroids is sparse and has been difficult to obtain due to small sample size.

As concerns about postnatal steroids surfaced, alternative management strategies were advanced.[13] Currently, surfactant replacement therapy has become the standard of care for preterm babies with respiratory distress.[6] Short-term results suggest that survival of VLBW infants has improved with surfactant, with no short-term contraindications for neurological outcomes.[14,15] More specifically, results from a 2002 meta-analysis based on 13 randomized controlled trials revealed no neuropsychological differences at both 1 and 2 years of age for infants treated with surfactant and controls.[16] The long-term, school age consequences of surfactant on cognitive development and the use of surfactant in combination with postnatal steroids have not been examined.

The present reanalysis of the BPD data published in Pediatrics[17] was conducted to assess the relationship between postnatal treatment with surfactant and/or steroids in our cohort of VLBW infants diagnosed with BPD and school-aged developmental outcomes. In our previous work with this sample,[17] we demonstrated that steroid use was associated with poorer neurodevelopmental outcomes in the BPD group as a whole; however outcome differences within the BPD group as a function of surfactant treatment were not examined nor were direct comparisons made between children receiving different

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management strategies. Examining the long-term effects of several treatment options in a BPD cohort that varied in terms of disease severity will help generate hypotheses about how treatment procedures selected to manage BPD are associated with risk factors.

Methods

Participants

The children with BPD in the current study were part of a prospective study of VLBW children and term controls who were recruited from birth in Cleveland between 1989 and 1991.[17,18] Recruitment strategies for this study have been detailed elsewhere.[17–19]

A total of 122 infants with BPD were enrolled in this prospective longitudinal study, however 7 died after enrollment. Ninety-eight and 104 children were seen at 3 and 8 years, respectively. Although there were 105 children with either or both 3- and 8-year data, 10 were excluded due to missing steroid and/or surfactant information, leaving 95 children or 83% of living children in the current analyses. Children with missing information were less likely to have septicemia and had a lower mean Home Observation for Measurement of the Environment (HOME) score than the children retained in these analyses.

Neonatal medical and demographic information was obtained from the hospital charts. Cranial ultrasound studies were performed and reviewed by board certified radiologists at 3, 10, 28 days and prior to discharge. Severity of intraventricular hemorrhage (IVH) was based on the most severe lesion diagnosed, with identifiable lesions graded on a scale from 1 to 4, based on the criteria of Papile.[20] A total neurological risk score was calculated based on the total number of neurological abnormalities (neurologic malformations, seizures, echodense lesions, porencephaly, hydrocephalus, ventriculoperitoneal shunt, meningitis and periventricular leukomalacia) plus the four gradations of IVH, with the neurological risk score ranging from 0 to 12. The validity of the summary score has been demonstrated in previous research.[19] The severity of BPD was determined according to the criteria detailed in the 2001 consensus workshop conducted by NICHD and NHLBI.[2] Four treatment groups were examined based on physician medical management strategy: steroids only, surfactant only, combined steroid and surfactant treatment and neither steroid nor surfactant treatment. Subjects treated with steroids received dexamethasone, as it was routinely used postnatally in 1989.

All assessments were completed in the behavioral laboratory of the project by examiners who were uninformed about neonatal history. Families were reimbursed for transportation and given a stipend of $100. The Institutional Review Boards of the hospitals approved this study, and informed consent from parents/guardians was obtained at all time points, and child assent was obtained at 8 years.

Procedures

The measures used in this study were designed to assess four general areas: cognitive, psychomotor, academic and language skills. Questionnaires/interviews from both parents and teachers were utilized to obtain school outcomes (that is, school placements, grade retention and enrollment in special education services).

Three-year outcome measures. The Bayley Scales of Infant Development (2nd ed.; BSID-II)[21] assessed overall cognitive and psychomotor development, producing standard scores for the mental development index and psychomotor development index (PDI).

The communication domain from the Battelle Developmental Inventory[22] produced standard scores for receptive, expressive and total language.

The total composite score from the HOME[23] assessed the quality of the home environment and controlled for environmental differences between the groups.

Eight-year outcome measures. The Wechsler Intelligence Scale for Children-III (WISC-III)[24] assessed general cognitive ability, producing standard scores for verbal, performance and full-scale IQ, as well as subscores for perceptual organization and verbal composites.

Academic achievement was measured using the Woodcock Johnson Test of Achievement-Revised (WJTA-R),[25] producing four standard scores: reading recognition, passage comprehension, calculation and applied problem solving skills.

The Clinical Evaluation of Language Fundamentals (3rd ed.; CELF-3)[26] produced standard scores for receptive, expressive and total language.

Statistical analysis

Data were summarized as median and inter-quartile range, mean and s.d. or frequency and percent, as appropriate. The Kruskal–Wallis rank sum and Fisher's exact tests were used to compare treatment groups on infant and maternal demographic and medical characteristics at birth. The relationships between drug treatment for children with BPD on cognitive, language and achievement outcomes were analyzed using analysis of covariance (ANCOVA). The ANCOVA models for the treatment groups were adjusted for covariates related to prematurity, including birth weight, head circumference and HOME score.

All ANCOVA analyses were followed up with planned contrasts; since it was hypothesized that management with postnatal steroids would be negatively associated with cognitive outcomes.[5–9,13–17] To assess this prediction, the group performance by BPD children who received neither steroids nor surfactant was compared to the average performance by children in the two groups that received postnatal steroids (that is, steroids only and steroid/surfactant combination). In contrast, no negative associations were predicted

for surfactant treatment based on the limited available research.[14,16] To test this hypothesis, two comparisons were performed: (1) performance by children who received surfactant was compared to children who had received neither form of treatment and (2) performance of children who had received surfactant was compared to the average performance of the two groups who had received steroids. The fourth comparison was designed to assess differences between performances in the steroids alone group compared to the combination group. While no specific hypothesis was generated regarding this comparison, it was designed to determine whether the administration of both medications occurred for the most severely impaired children and whether the presence of surfactant minimized the negative association of steroids with outcomes.

Finally, the percentage of children meeting clinical criteria for developmental disabilities (scoring two s.d. below the mean on the WISC-III and WJTA-R) was calculated for all groups. A significance level of 10% was chosen to perform the planned pair-wise testing, with all significant planned comparisons using a 0.025 significance level. For continuous outcomes, any planned difference of 10 points or more was considered clinically significant and highlighted in the text and tables. The four planned contrasts described below were performed and were selected based on *a priori* hypotheses.

Results

Demographics

Maternal characteristics at infant birth. 62% of the sample was married, 55% was of low socioeconomic status and mean educational attainment was 13 years. No differences in maternal characteristics were noted among the treatment groups.

Infant characteristics. Treatment groups differed only in birth weight and head circumference, with both factors used as covariates in subsequent analyses. Although no treatment differences appeared related to the NICHD severity classification, treatment group differences were observed in duration of use of supplemental oxygen and total oxygen received. Infants receiving any combination of steroid treatment were administered more total oxygen for a longer period of time than either the no steroid/surfactant or surfactant only groups (Table 1).

Three-year-old outcomes as a function of neonatal medical treatment

Cognitive outcomes. Treatment group differences on Bayley PDI Scores emerged, with infants who had received the steroid only and the combined steroid and surfactant treatments performing more poorly (13 to 19 point difference) than infants who had received surfactant only or neither drug (Tables 2 and 3).

Language outcomes. Children who received the combined drug treatment or the postnatal steroids alone performed more poorly on all language scores compared to those children who received neither steroids nor surfactant. Additionally, the children in the surfactant only group were superior to the children in the postnatal steroid group and the combined postnatal steroid/surfactant group in total language scores.

Eight-year-old outcomes as a function of neonatal medical treatment

Cognitive outcomes. Treatment group differences emerged for performance IQ and perceptual organization on the WISC-III, with children who received any form of steroids performing more poorly than children who received no drug treatment or surfactant only. In addition, children who did not receive steroids scored 14 points higher on average on full-scale IQ than children who received any form of steroids (Tables 2 and 3).

Language outcomes. No statistically or clinically significant treatment group differences emerged for the language outcomes at 8 years of age.

Achievement outcomes. Contrary to our hypotheses, children in the postnatal steroids group performed better than children in the combined treatment group in both letter-word identification and reading comprehension. In contrast, children in both steroid groups performed more poorly in math achievement as compared to the children who received no drug treatment or surfactant only.

Categorical analyses of educational outcomes. Therapy and educational outcomes at 8 years are reported in Table 3. Although groups did not differ in speech-language therapy, children who received any form of postnatal steroid management were more apt to be enrolled in special education, occupational therapy and physical therapy than the children who had received no drug treatment. Also, children managed with postnatal steroids were more apt to be enrolled in special education and occupational therapy than children who received surfactant only. Medical management appeared to be related to subaverage scores on intelligence tests at both 3 and 8 years. A higher percentage of children in our sample who had received some form of postnatal steroid treatment achieved intelligence scores less than 85 or in the borderline range of cognitive functioning compared to children who had not received steroids.

Discussion

This prospective, longitudinal study assessed the relationship between type of neonatal medical management strategy and the cognitive, psychomotor, language and achievement outcomes of children with BPD during preschool and early school age years.

Table 1 Neonatal characteristics for treatment groups ($n = 95$)

Treatment	*None* n = *37* *Median (IQR)*	*Surfactant only* n = *29* *Median (IQR)*	*Steroids only* n = *13* *Median (IQR)*	*Both* n = *16* *Median (IQR)*	P-*value*
Birth weight (g)	909 (805–1029)	1072 (895–1267)	810 (708–967)	945 (769–1213)	0.06[a]
Gestational age (week)	27 (26–28)	28 (27–29)	26 (25–27)	28 (26–30)	0.12
Total oxygen	60 (37–97)	62 (45–98)	87 (51–211)	94 (44–130)	0.11[b,c]
Duration ventilator	23 (7–38)	26 (14–36)	46 (34–63)	44 (29–65)	0.002[b,c]
Head circumference	25 (24–26)	26 (24–27)	24 (23–24)	26 (24–27)	0.02[a,d]
Neurological risk	0.0 (0–3)	0.0 (0–2)	1.0 (0–3)	0.5 (0–2)	0.72
HOME score	41 (37–43)	42 (40–43)	40 (40–44)	42 (38–43)	0.42
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Race (Caucasian)	21 (57)	17 (59)	6 (46)	12 (75)	0.45
Gender (male)	20 (54)	17 (59)	4 (31)	10 (63)	0.34
Single birth	28 (76)	22 (76)	12 (92)	11 (69)	0.52
Septicemia (yes)	17 (46)	18 (62)	5 (39)	9 (56)	0.43
PVL	2 (5)	1 (3)	1 (8)	4 (25)	0.08
Intraventricular hemorrhage					
1	5 (14)	6 (21)	3 (23)	3 (19)	0.81
2	4 (11)	3 (10)	2 (15)	2 (12)	
3	4 (11)	4 (14)	2 (15)	0 (0)	
4	2 (5)	0 (0)	0 (0)	2 (12)	
None	22 (59)	16 (55)	6 (46)	9 (56)	
BPD severity classification					
Mild	20 (55)	15 (52)	6 (46)	7 (47)	0.62
Moderate	6 (17)	5 (17)	0 (0)	2 (13)	
Severe	10 (28)	9 (31)	7 (54)	6 (40)	

Abbreviations: BPD, bronchopulmonary dysplasia; HOME, Home Observation for Measurement of the Environment; PVL, periventricular leukomalacia.
[a]Surfactant differed from steroids.
[b]None differed from steroids.
[c]None differed from both.
[d]Steroids differed from both.

Consistent with the findings advanced by the American Academy of Pediatrics and the Canadian Paediatric Society[9] and the Cochrane Reviews,[10–12] the use of postnatal steroids in the medical management of children with BPD was associated with more adverse outcomes in this cohort of children. Compared to VLBW children with BPD who received no drug treatment, children who received combined steroid and surfactant treatment or steroids alone were more likely to receive special education services and had significantly more difficulties in perceptual motor, cognitive and language skills. These differences persisted after controlling for head circumference, birth weight and home environment. While treatment group differences could not be attributed to socioeconomic status, maternal education, race, gender, neurological complications or the global NICHD severity of BPD classification, the use of steroid therapy was associated with neuropsychological impairment for children who have BPD during the preschool and school-age period. Our findings that the use of postnatal steroids is associated with adverse neuropsychological outcomes extend those reported by the American Academy of Pediatrics and the Canadian Paediatric Society[9] by the inclusion of data from both the preschool and school-age period. Nonetheless, the fact that this study was not a randomized controlled trial precludes us from ruling out other factors, including poor nutrition, physiologic instability, and ongoing hypoxia as the primary or secondary reasons underlying the adverse neuropsychological outcomes.

Surfactant replacement therapy has become a standard of care for VLBW infants with BPD.[6] This retrospective analysis is one of the first prospective, longitudinal examinations that specifically examined the relationship of surfactant treatment to cognitive, language and achievement outcomes in VLBW infants with BPD during both the preschool and school age years. Although our

Table 2 Cognitive and linguistic outcomes for sample at 3 and 8 years

	None *Mean (s.d.)* n = *31*	*Surfactant only* *Mean (s.d.)* n = *28*	*Steroids only* *Mean (s.d.)* n = *12*	*Both* *Mean (s.d.)* n = *14*	P-*value*
Bayley[a]					
MDI	89.7 (22)	89.6 (18)	79.6 (20)	81.4 (27)	0.21
PDI	94.4 (22)	89.8 (26)	75.3 (29)	76.6 (35)	0.09[b,c]
Battelle[d]					
Receptive	91.2 (20)	86.8 (18)	75.5 (11)	83.8 (13)	0.06[b]
Expressive	102.8 (22)	96.9 (20)	80.6 (16)	90.4 (23)	0.01[b]
Total	99.5 (22)	93.0 (20)	76.6 (14)	86.5 (21)	0.004[b,c]
	$n = 34$	$n = 25$	$n = 12$	$n = 16$	
WISC-III[e]					
Verbal	92.4 (17)	92.0 (16)	87.8 (13)	82.6 (26)	0.57
Performance	87.5 (17)	86.6 (14)	76.3 (18)	70.3 (19)	0.007[b,c]
Full scale	88.7 (17)	88.3 (15)	80.6 (16)	74.4 (24)	0.11[b]
Verbal composite	93.2 (16)	93.6 (17)	90.6 (12)	83.2 (24)	0.50
Perceptual organization	87.3 (17)	88.3 (14)	76.0 (16)	72.4 (20)	0.01[b,c]
CELF-3[f]					
Receptive	93.3 (16)	92.8 (16)	86.8 (18)	79.5 (26)	0.24
Expressive	95.5 (18)	94.2 (16)	92.4 (12)	84.3 (25)	0.40
Total	93.6 (17)	92.6 (16)	88.7 (14)	81.3 (25)	0.31
Woodcock Johnson achievement test-R[g]					
Letter word identification	99.8 (20)	96.0 (17)	100.1 (13)	77.9 (28)	0.02[b,h]
Passage comprehension	100.4 (19)	101.6 (20)	100.3 (12)	79.5 (31)	0.08[b,h]
Calculations	89.8 (20)	91.7 (17)	82.8 (17)	77.3 (29)	0.32
Applied problems	97.9 (20)	100.7 (19)	86.5 (14)	82.7 (31)	0.01[b,c]

Abbreviations: MDI, mental developmental index; PDI, psychomotor developmental index.
[a]Bayley Scales of Infant Development (2nd edn.).
[b]None differed from both and steroids.
[c]Surfactant differed from both and steroids.
[d]Battelle Developmental Inventory.
[e]Wechsler Intelligence Scales for Children (3rd edn.).
[f]Clinical Evaluation Language Fundamentals (3rd edn.).
[g]Woodcock Johnson Tests of Achievement (revised).
[h]Steroids differed from both.

sample size is quite small, no relationship between groups treated with surfactant without postnatal steroids and cognitive and language outcomes at 3 and 8 years was observed. In addition, the surfactant group performed comparably across a host of cognitive and language measures for children with BPD who had received neither drug. While causality cannot be determined in this sample due to lack of random assignment to treatment, the data lend further support to meta-analytic findings by Sinn and colleagues that rates of mild disabilities were lower at 1 and 2 years of age when infants had been treated with surfactant.[16]

These data provide additional support for the concerns about the negative relationship between use of postnatal steroids and development in VLBW infants. Our findings provide further support for Hintz *et al*.[15] who found that the use of postnatal steroids alone or in combination with surfactant appears to be related to some of the adverse medical, cognitive and language consequences associated with BPD. Unfortunately, it is impossible from these data to determine whether steroid use prolonged or decreased time on the ventilator, nonetheless our finding that prolonged oxygen use was associated with poorer cognitive outcomes is consistent with findings of Robertson *et al*.[27] Since both groups of VLBW children who received steroids required more oxygen than the nonsteroid groups, it seems that BPD may not be the only factor related to the delays. The combination of steroid treatment selected to manage

Table 3 Educational outcomes for the sample at 3 and 8 years

	None N (%)	*Surfactant only* N (%)	*Steroids only* N (%)	*Both* N (%)	P-*value*
Special education (yes)	12 (40)	11 (44)	11 (92)	10 (67)	0.01[a,b]
Repeat grade (yes)	2 (7)	6 (24)	0 (0)	4 (27)	0.07
Physical therapy (yes)	11 (32)	11 (44)	8 (67)	12 (75)	0.03[a]
Occupational therapy (yes)	13 (38)	11 (44)	8 (67)	12 (75)	0.05[a,b]
Speech therapy (yes)	13 (38)	12 (48)	9 (73)	9 (56)	0.22
Bayley % <85[c]					
MDI	10 (32)	7 (25)	7 (58)	5 (36)	0.16
PDI	9 (19)	8 (29)	6 (50)	6 (43)	0.08[a]
WISC-III % <85[d]					
Verbal	11 (32)	8 (32)	8 (67)	7 (44)	0.27
Performance	11 (32)	9 (36)	8 (67)	12 (75)	0.001[a,b]
Full scale	14 (41)	8 (32)	8 (67)	10 (63)	0.09[a]

Abbreviations: MDI, mental developmental index; PDI, psychomotor developmental index.
[a]None differed from both and steroids.
[b]Surfactant differed from both and steroids.
[c]Bayley Scales of Infant Development (2nd edn.).
[d]Wechsler Intelligence Scales for Children (3rd edn.).

the BPD condition and the need for supplemental oxygen are both related to developmental delays in this sample.

The simultaneous use of steroid and surfactant for the treatment of BPD was also associated with lower perceptual, motor and processing speed abilities in this cohort. This finding is consistent with Majnemer *et al*.[28] who found that at 10 years of age, 50% of children with BPD who had required home oxygen therapy had gross and fine motor skill deficits. The findings are also consistent with outcomes found in this cohort at 3 years of age, which indicated that history of BPD predicted poor motor skills beyond the effects of other medical and demographic factors.[29]

Thus, medical conditions such as BPD and possibly the treatments used to manage BPD are associated with negative cognitive, academic, psychomotor and language development. Physicians should continue to exercise great care when selecting treatment programs for management of BPD.[30] This research further underscores the need for continued monitoring of children with BPD, particularly those children who were administered both steroids and surfactant, in order to identify, refer and intervene with children most at risk for diagnosable school problems.

Limitations and implications

Data from this sample were collected prior to the routine use of surfactant replacement therapy, which enabled examination of cases of BPD which were not managed with surfactant or steroids. Physicians selected to use none, one or both forms of treatment for BPD, with no formalized criteria specified for this study. Thus, this is not a randomized, controlled evaluation. While the prospective, longitudinal nature of this sample makes it ideal for examining the long-term consequences of BPD, the relatively small sample size precludes the simultaneous comparison of disease severity and treatment strategy. Additionally, no negative associations were noted between use of surfactant and outcomes at 3 and 8 years. Finally, postnatal steroid exposure appeared to be related to long-term developmental outcomes in this sample.

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