School-age Follow-up of Prophylactic Versus Rescue Surfactant Trial: Pulmonary, Neurodevelopmental, and Educational Outcomes

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ABSTRACT. Background. Exogenous surfactant replacement has improved survival and reduced pulmonary complications of prematurity. Improved early outcomes for infants of <30 weeks’ gestation treated with a strategy of prophylactic versus rescue surfactant, if needed, were demonstrated in a multicenter, randomized trial conducted between 1985 and 1988. We reevaluated a subset of survivors from this trial to determine the pulmonary and neurodevelopmental outcomes at school age.

Methods. At 4.5 to 8 years of age, all survivors from one of the three centers were located, and 96% were evaluated. The original randomization included stratification by center and followed an intention-to-treat methodology in assessing the efficacy of prophylactic versus rescue treatment with surfactant. The follow-up test battery included a health-assessment questionnaire, spirometry, 88% saturation test, neurologic examination, and the McCarthy Scales of Children’s Abilities (MSCA) and the Conners’ Parent Rating Scale–48. Educational achievement was determined by school class placement and teachers’ reports of achievement.

Results. Of the 192 children originally enrolled, 154 survived. Evaluations were performed on 148 of these infants. An abnormal pulmonary history was found in 45 (30%) of the children: 16 (22%) in the prophylactic group and 29 (39%) in the rescue group. Formal pulmonary function was evaluated in 81 children: 29 (78%) in the prophylactic group and 33 (75%) in the rescue group were considered abnormal. No significant differences were found between the two groups on either cognitive or motor subscales of the MSCA, the Conners’ Parent Rating Scale–48, the neurologic examination, the education services received in school, or the teacher ratings of behavior, puberty, or educational outcome of treated children. Prophylactic surfactant administration to infants of <30 weeks’ gestation was associated with fewer long-term clinical pulmonary complications than assignment to rescue administration. Formal pulmonary testing at school age did not reveal significant differences between treatment groups in those infants who could be tested. There also were no group differences found on neurologic, cognitive, behavioral, or educational assessments at school age. Pediatrics 1998;101(5).

ABBREVIATIONS. RDS, respiratory distress syndrome; PRx, prophylactic surfactant group; RRx, rescue surfactant group; CGA, corrected gestational age; MSCA, McCarthy Scales of Children’s Abilities; CPRS–48, Conners’ Parent Rating Scale; GCI, general cognitive index; OR, odds ratio; BPD, bronchopulmonary dysplasia; CLD, chronic lung disease.

Exogenous surfactant has become accepted therapy for the prevention and treatment of respiratory distress syndrome (RDS) in small premature infants.1–5 Multiple studies have demonstrated short-term safety, improved survival, and decreased early morbidity with use of surfactant.1,7,8 However, important issues concerning surfactant therapy remain unanswered including the optimum timing of its administration and the long-term (school-age) pulmonary, neurodevelopmental, and educational outcome of treated children.

Prophylactic or immediate administration of surfactant offers theoretic advantages including optimal distribution in a fluid-filled lung and replacement before possible barotrauma.5 Several human studies have compared prophylactic surfactant treatment (PRx) and rescue surfactant treatment (RRx), but their conclusions have not been consistent. Kendig and associates studied 479 infants born at <30 weeks’ gestation who were treated either with PRx or with RRx surfactant and found a significant advantage to PRx.1 Survival was improved, and there were fewer episodes of pneumothorax. Other studies favoring prophylactic surfactant have found improved survival, decreased morbidity, decreased dependence on oxygen at the expected date of delivery, and lower risk of pneumothorax.3,9,10 However, some trials have found no significant advantage of PRx over RRx and recommend RRx because of unnecessary treatment of surfactant-sufficient neonates.8,11–13 Comparisons of the early neurodevelopmental outcomes of PRx versus RRx also have produced mixed results. An earlier analysis of part of the cohort from the present study demonstrated an advantage of prophylactic therapy, with fewer of the PRx infants having moderate to severe motor delays at 6

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Prophylactic or immediate administration of surfactant offers theoretic advantages including optimal distribution in a fluid-filled lung and replacement before possible barotrauma.5 Several human studies have compared prophylactic surfactant treatment (PRx) and rescue surfactant treatment (RRx), but their conclusions have not been consistent. Kendig and associates studied 479 infants born at <30 weeks’ gestation who were treated either with PRx or with RRx surfactant and found a significant advantage to PRx.1 Survival was improved, and there were fewer episodes of pneumothorax. Other studies favoring prophylactic surfactant have found improved survival, decreased morbidity, decreased dependence on oxygen at the expected date of delivery, and lower risk of pneumothorax.3,9,10 However, some trials have found no significant advantage of PRx over RRx and recommend RRx because of unnecessary treatment of surfactant-sufficient neonates.8,11–13 Comparisons of the early neurodevelopmental outcomes of PRx versus RRx also have produced mixed results. An earlier analysis of part of the cohort from the present study demonstrated an advantage of prophylactic therapy, with fewer of the PRx infants having moderate to severe motor delays at 6

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to 12 months. Other authors found no differences in developmental outcome at 12 months adjusted age when their treatment groups were compared with respect to a categorical rating based on scores from the Bayley Scales of Infant Development. However, they did find that RRx resulted in a trend toward higher mean mental developmental indices on the Bayley Scales of Infant Development, although in that study, developmental assessments were performed on less than half of the original cohort. Our group has reported the school-age follow-up of a randomized trial comparing single-dose PRx with normal saline. We found the children had cognitive and motor functioning below average compared with term infants, but there was no increased risk in treating prophylactically with surfactant. To our knowledge, there are no previous reports of school-age neurodevelopmental and academic outcomes comparing PRx and RRx.

Formal pulmonary assessment is difficult in children, and only a few previous studies have reported it after surfactant treatment in neonates. No results comparing PRx and RRx have been published, nor have there been reports of formal pulmonary function testing at school age after multidose surfactant therapy. We report pulmonary, neurodevelopmental, and academic outcomes of school children after early treatment with either PRx or RRx. We also determined the predictive value of an oxygen requirement at 28 days and 36 weeks’ corrected gestational age (CGA) in this surfactant-treated population, because an oxygen requirement at 36 weeks' CGA has been reported to be more predictive of pulmonary sequelae than an oxygen requirement at 28 days in a presurfactant era.

METHODS

Subjects

The study cohort consisted of all surviving children born between 1985 and 1988 treated at the Children’s Hospital at Strong in Rochester, NY, one of the three centers that participated in the multicenter randomized clinical trial comparing PRx versus RRx replacement using a calf lung surfactant extract (Infasurf, ONY, Inc, Amherst, NY). A well-established follow-up program has been in place in Rochester since 1977. Women expected to deliver viable infants at 28 to 30 weeks’ gestation, and 21 infants assigned to the RRx group did not meet criteria for surfactant administration, 1 of whom was >30 weeks’ gestational age.

Evaluations

All 154 survivors were located and asked to return for a reevaluation when they were anticipated to be entering or already in school (4.5 to 8 years of age). The evaluation consisted of a parental interview and assessments by a pulmonologist, neurologist, and pediatric neuropsychologist. All evaluators were blinded to the children’s original treatment group. The parental interview was carried out in standard format and was a modification of the questionnaire developed by the American Thoracic Society and the Division of Lung Diseases, National Heart, Lung, and Blood Institute (ATS-DLD-78 questionnaire). Medical history, present and past medical status, medication use, family composition, environmental exposures such as smoking in the house, and previous needs for intervention services and specific therapies were determined.

Records since discharge from the nursery were reviewed including hospital records, evaluations from a neonatal high-risk follow-up clinic at 6 and 12 months’ corrected age, and yearly parent and pediatrician surveys that included questions regarding the child’s health. Additional pulmonary, neurodevelopmental, and educational history was obtained by contacting pediatricians, teachers, and other health care providers. Socioeconomic status was determined using the Hollingshead Scale.

Pulmonary

The past and present clinical pulmonary status was determined by reports from the parents and the child’s pediatrician and medical record review, including an evaluation of oxygen requirements at 28 days and 36 weeks’ CGA. Parent and guardian interviews at school age included questions about hospitalizations for pulmonary disorders, respiratory illnesses (asthma, bronchitis, bronchiolitis, or pneumonia), and the need for pulmonary medications including oxygen, diuretics, or bronchodilators. Pulmonary function was assessed with spirometry, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak flow rate, and maximal forced expiratory flow (FEF) between 25% and 75% of vital capacity (FEF25–75%) with pulmonary function results expressed as percent predicted based on height and weight. The 88% saturation test was performed as described previously.

Based on the history, spirometry, and 88% saturation test, each child’s pulmonary condition was classified as normal or abnormal in two categories: pulmonary history and pulmonary laboratory testing. The pulmonary history was considered abnormal if there were rehospitalizations for any pulmonary disorder, if the pediatrician reported that the pulmonary status was abnormal, or if the child was requiring pulmonary medication (oxygen, diuretic, or bronchodilator). Children having an abnormal saturation test or any abnormal measure of pulmonary function on spirometry (FVC, FEV1, peak flow rate, and maximal FEF25–75%) were considered to have abnormal pulmonary laboratory testing.

Neurodevelopment

Neurodevelopmental assessment included cognitive, behavioral, and motor assessments. The neurologic examination was performed by a pediatric neurologist and consisted of an evaluation of mental status, activity, cranial nerves, motor system (including tone, strength, deep tendon reflexes, and coordination), cerebellar system, and sensation. To measure IQ, a pediatric neuropsychologist administered the McCarthy Scales of Children’s Abilities (MSCA). Impaired children unable to be tested with the MSCA were given the Peabody Picture Vocabulary Test. School-administered IQ testing was used if the child was uncooperative, unable to be tested during the clinic visit, or lived out of state. The 48-question Conners’ Parent Rating Scales (CPRS–48) were completed by the parent and scored by the pediatric neuropsychologist to obtain standardized measures of behavior. The CPRS–48 has five subscales that assess behaviors indicative of learning problems, anxiety, conduct problems, hyperactivity, and impulsivity/hyperactivity based on age-appropriate norms.

Education

Educational assessment was determined using a teacher questionnaire and a structured parent interview, both of which requested information regarding the need for services in school. Educational placement ratings were classified in accordance with the New York State defined class size categories as: 1) no special services needed; 2) consultation—children in regular classes who have a special teacher work with them one-on-one at regular intervals; 3) option I, a special classroom with a 15:1 pupil-teacher
ratio; 4) option II, a special classroom with a 12:1 pupil:teacher ratio and 1 additional paraprofessional; 5) option III, a classroom with an 8:1 pupil:teacher ratio and 1 paraprofessional; and 6) option IV, a classroom with a 12:1 pupil:teacher ratio and 1 additional adult for every 3 children in the class. Academic performance ratings were based on teacher reports. Teachers were asked to rate a child’s academic performance based on age-appropriate school performance. A subjective 1 to 5 rating scale was used as follows: 1) far below average; 2) below average; 3) average; 4) above average; and 5) far above average.

**Statistical Analysis**

Data were analyzed using two-sample student’s t test (unequal variance), \( \chi^2 \)/Fisher’s exact or Mann–Whitney rank tests. All P values were based on two-tailed tests. For pulmonary history (normal/abnormal), the groups were compared using multiple logistic regression with adjustment for birth weight, smoking in the home, socioeconomic status, and the possibility of an interaction between smoking status and surfactant treatment.

Positive predictive values for normal and abnormal pulmonary history were calculated for an oxygen requirement at 28 days or 36 weeks’ CGA. These latter two variables also were examined as independent predictors of pulmonary history with logistic regression (normal/abnormal), the groups were compared using multiple logistic regression with adjustment for birth weight, smoking in the home, socioeconomic status, and the possibility of an interaction between smoking status and surfactant treatment.

**RESULTS**

Of the 192 infants originally enrolled in the study, 154 (80%) survived to school age. Thirty infants died in the nursery (12 PRx and 18 RRx infants), and 8 died after discharge (4 in each group). All 154 survivors were located and families of 148 (96.1%) children agreed to participate in this study. Of the children, 138 (93.2%) were evaluated at the Children’s Hospital at Strong and 2 by our staff in their home; 8 out-of-state children received neurodevelopmental testing by other professionals. There were 78 survivors from the original PRx group and 76 from the RRx group. Four families of 6 infants (two sets of twins) (5 children in the PRx group and 1 in the RRx group) declined to participate, leaving 73 infants in the PRx group and 75 in the RRx group. PRx and RRx study groups were similar in demographic, neonatal pulmonary, and nonpulmonary complications (\( P > .05 \)), as shown in Table 1, except for a statistically significant greater number of infants in the RRx group requiring oxygen at 36 weeks’ CGA (\( P = .043 \)).

**Pulmonary**

More than half of the homes contained smokers: 39 (53%) homes in the PRx group and 41 homes (55%) in the RRx group. An oxygen requirement at 28 days was diagnosed in 34 (46%) of the PRx group versus 33 (44%) of the RRx group. At 36 weeks’ CGA, 6 (8%) of the PRx group and 15 (20%) of the RRx group still required oxygen. There were 13 children in the PRx group and 10 in the RRx group discharged from the nursery on oxygen. Of the PRx group and RRx groups, respectively, 29 (40%) and 26 children (35%) were either discharged home from the nursery on an apnea monitor or readmitted and sent home on a monitor.

Pulmonary history was assessed on all 148 infants. There were 32 children rehospitalized for pulmonary reasons after discharge, 12 (16%) in the PRx group and 21 (28%) in the RRx group. Seven children in the PRx group and 14 in the RRx group were reported by their pediatrician to have respiratory problems. There were 29 children in the PRx group and 36 in the RRx group who had experienced pulmonary ill-

### Table 1. Demographics of 148 Surfactant Follow-up Participants

<table>
<thead>
<tr>
<th></th>
<th>PRx</th>
<th>RRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children evaluated</td>
<td>73</td>
<td>75</td>
</tr>
<tr>
<td>Male</td>
<td>36 (49%)</td>
<td>43 (57%)</td>
</tr>
<tr>
<td>Gestational age at birth in weeks (mean ± SD)</td>
<td>28.2 ± 2.7</td>
<td>28.4 ± 1.9</td>
</tr>
<tr>
<td>Birth weight in grams (mean ± SD)</td>
<td>1087 ± 437</td>
<td>1102 ± 322</td>
</tr>
<tr>
<td>White</td>
<td>49 (63%)</td>
<td>49 (64%)</td>
</tr>
<tr>
<td>Neonatal pulmonary complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2 (3%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>PIE</td>
<td>4 (5%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Median days of supplemental oxygen</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Median days of assisted ventilation</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Oxygen at 28 days</td>
<td>34 (46%)</td>
<td>33 (44%)</td>
</tr>
<tr>
<td>Oxygen at 36 weeks’ corrected gestational age</td>
<td>6 (8%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>Nonpulmonary neonatal complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>37 (51%)</td>
<td>37 (49%)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage I–II</td>
<td>10 (14%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage III–IV</td>
<td>9 (12%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (pneumatosis or portal venous air)</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Retinopathy of prematurity (any stage or grade)</td>
<td>34 (47%)</td>
<td>28 (37%)</td>
</tr>
<tr>
<td>Determinations at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) at follow-up (mean ± SD)</td>
<td>6.1 ± 0.7</td>
<td>6.1 ± 0.8</td>
</tr>
<tr>
<td>Socioeconomic status by Hollingshead (mean ± SD)</td>
<td>34.3 ± 15.4</td>
<td>36.3 ± 16.5</td>
</tr>
<tr>
<td>Smoking in the home (yes)</td>
<td>39 (53%)</td>
<td>41 (55%)</td>
</tr>
</tbody>
</table>

\( \dagger P = .043. \)

### Table 2. Pulmonary Follow-up Data of Surfactant Study Survivors

<table>
<thead>
<tr>
<th></th>
<th>PRx</th>
<th>RRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary history abnormal</td>
<td>16/73 (22%)</td>
<td>29/75 (39%)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>12/73 (16%)</td>
<td>21/75 (28%)</td>
</tr>
<tr>
<td>Abnormal physician report</td>
<td>7/33 (10%)</td>
<td>14/75 (19%)</td>
</tr>
<tr>
<td>Pulmonary medications</td>
<td>3/73 (4%)</td>
<td>7/75 (9%)</td>
</tr>
<tr>
<td>Pulmonary laboratory testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal spirometry</td>
<td>3/34 (9%)</td>
<td>9/44 (20%)</td>
</tr>
<tr>
<td>Abnormal 88% saturation</td>
<td>28/39 (72%)</td>
<td>27/43 (63%)</td>
</tr>
</tbody>
</table>

\* n (%); the denominator for each test reflects the number of children tested successfully. \( \dagger P = .027. \)
nesses at some time since discharge from the nursery (including asthma, reactive airway disease, bronchi-
tis, bronchiolitis, respiratory syncytial virus, or pneu-
monia). Thirty children had a history of asthma, 11
(15%) in the PRx group and 19 (25%) in the RRx
group. Only 3 of the PRx and 7 of the RRx children
still were receiving pulmonary medications at fol-
low-up. Therefore, there were 16 of 73 children (22%)
in the PRx group and 29 of 75 (39%) in the RRx
group considered to have an abnormal pulmonary history
\( \chi^2 = 4.90; \text{df} = 1; P = .027 \). This difference between
treatment groups on pulmonary history remained signif-
icate \( (P = .036) \) when adjusted for the covari-
ates of birth weight, smoking in the home, and so-
cioeconomic status.

**Pulmonary Laboratory Testing**

Formal pulmonary function testing with both spi-
rometry and the 88% saturation test was completed
successfully by 81 children. Of the 67 children not
completing formal pulmonary functions, 37 were un-
cooperative, unable to perform the testing proce-
dures, or lived out of state. Thirty-three of the 81
spirometry test performances were technically unsat-
sfactory. Twenty-nine of 111 children completing
the 88% saturation test had to be excluded from
analysis post hoc when it was discovered that an
incorrect oxygen mixture was used (14 in the PRx
group and 15 in the RRx group). Sixty-two children
were found to be abnormal on the 88% Sao2 or spi-
rometry tests, 29 (78%) in the PRx group and 33
(75%) in the RRx group. (Pulmonary follow-up data
are summarized in Table 2 and Fig 1).

**Neurodevelopment**

A summary of the neurodevelopmental assess-
ments is shown in Table 3. Ninety-nine children
(68%) had a normal neurologic examination, and no
difference was found between the PRx (68%) and
RRx (69%) groups. There were 15 children with ce-
cerebral palsy, 8 (11.0%) in the PRx group and 7 (9.3%)
in the RRx group. Intellectual testing for IQ showed
an average general cognitive index (GCI) of 86 (nor-
mal mean = 100; SD = 15) with no difference be-
 tween the PRx and RRx groups (86.4 PRx vs 85.9
RRx). Similar numbers (13 vs 15) and percentages
(18% vs 20%) of children with a GCI <70 were found
in the PRx vs RRx groups, respectively. Motor scores
on the MSCA (normal mean = 50; SD = 10) were
within the normal range and similar for the two
groups (44 PRx and 46 RRx). The CPRS-48 revealed
no differences between treatment groups on subscale
scores. However, 37 (52%) of the children in the PRx
group had an abnormality on one or more of the
subcales, as did 48 (62%) in the RRx group. Both
treatment groups had similar rates of problems with
seizures and the need for shunts. Early intervention
services had been received by ~40% of the children
in both groups (26 in the PRx group and 30 in the
RRx group).

**Education**

At school age, 39 (55%) of the children who had
received PRx and 35 (47%) of the RRx group were in
regular education with no services. No differences
between groups were seen in those receiving addi-
tional or special education services in school (46%
PRx vs 53% RRx), those rated as performing academ-
ically below average by their teachers (45% PRx vs
48% RRx), or those having a special education clas-
sification and being in a self-contained special edu-
cation class (options I to IV: 27% PRx vs 24% RRx).

Among the 146 study children schooled outside of
the home (2 were home-schooled), 109 (75%) were in
regular classrooms; 74 (51%) of these children re-
ceived no additional services, and 35 (24%) were
receiving consultation services. Overall, 37 (25%) of
the children were in special education classes (op-
tions I to IV), but only 10 children (29%) (5 each in

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**TABLE 3. Neurodevelopmental and Academic Functioning at 4.5 to 8 Years of Age**

<table>
<thead>
<tr>
<th>Psychological Assessment, Cognitive and Behavior</th>
<th>PRx</th>
<th>RRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal neurologic examination</td>
<td>68% (50/73)</td>
<td>69% (52/75)</td>
</tr>
<tr>
<td>Shunt or seizures</td>
<td>8.2% (6/73)</td>
<td>6.7% (5/75)</td>
</tr>
<tr>
<td>McCarthy Scales of Children’s Abilities (or other IQ test***)</td>
<td>86.4 ± 24 (73)</td>
<td>85.9 ± 24.8 (75)</td>
</tr>
<tr>
<td>Motor t score‡</td>
<td>44.5 ± 12.5 (56)</td>
<td>45.8 ± 10.4 (59)</td>
</tr>
<tr>
<td>Conners’ Parent Questionnaire, Subscale Score†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct problem</td>
<td>50.6 ± 11.6 (71)</td>
<td>51.8 ± 14.1 (74)</td>
</tr>
<tr>
<td>Learning problem</td>
<td>57.4 ± 16.8 (71)</td>
<td>59.8 ± 19.2 (74)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>53.2 ± 13.9 (71)</td>
<td>56.2 ± 15.1 (74)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>50.2 ± 8.8 (71)</td>
<td>51.6 ± 8.7 (74)</td>
</tr>
<tr>
<td>Impulsive/hyperactive</td>
<td>50.5 ± 11.6 (71)</td>
<td>53.1 ± 14.3 (74)</td>
</tr>
<tr>
<td>Academic functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early intervention received</td>
<td>35.6% (26/73)</td>
<td>40.0% (30/75)</td>
</tr>
<tr>
<td>Regular education (no services currently)</td>
<td>55% (39/71)</td>
<td>47% (35/75)</td>
</tr>
<tr>
<td>Consult teacher service</td>
<td>18% (13/71)</td>
<td>29% (22/75)</td>
</tr>
<tr>
<td>Special education class (options I–IV)</td>
<td>27% (19/71)</td>
<td>24% (18/75)</td>
</tr>
<tr>
<td>Academic performance below average</td>
<td>46% (31/68)</td>
<td>49% (36/74)</td>
</tr>
</tbody>
</table>

* ‡ % or mean ± SD (n), (denominators reflect the number of children for whom there were data obtained) as appropriate.
** Alternative IQ test administered in 21% of each group: 15 in PRx group and 16 in RRx group.
‡ Expected mean = 100 ± 15.
† Expected mean = 50 ± 10.
PRx and RRx) were in option IV, the children needing the most intense educational services. Academic data are summarized in Table 3.

Predicting Long-term Pulmonary Outcome

We used logistic regression models to determine whether an infant’s oxygen status at 28 days and 36 weeks’ CGA would predict an abnormal pulmonary history. Significant contributing factors to predicting an abnormal pulmonary history based on the infant’s status at 28 days included an oxygen requirement at 28 days (odds ratio [OR], 4.15; \( P = .0007 \)), smoking in the home (OR, 2.10; \( P = .056 \)), and being in the RRx group (OR, 2.54; \( P = .015 \)). At 36 weeks’ CGA, the predictive variables were an oxygen requirement at that time (OR, 5.35; \( P = .0013 \)) and smoking in the home (OR, 2.43; \( P = .025 \)). The effect of surfactant group assignment was not significant in this second model (OR, 1.87; \( P = .11 \)). There was no interaction between surfactant treatment and either oxygen at 28 days or 36 weeks’ CGA.

Table 4 shows the specificity, sensitivity, and positive and negative predictive values for an abnormal pulmonary history based on an oxygen requirement both at 28 days and at 36 weeks’ CGA. An oxygen requirement at 28 days had a positive predictive value for an abnormal pulmonary history of 43.3% and a negative predictive value of 80%. At 36 weeks’ CGA, the positive and negative predictive values for an abnormal pulmonary history were 62% and 75%, respectively.

### DISCUSSION

Our hypothesis was that early normalization of pulmonary function would reduce barotrauma from early ventilatory support and prevent establishment of more chronic pulmonary conditions. We found reduced long-term pulmonary morbidity in children treated with PRx at birth compared with RRx when assessed by measures of pulmonary history and pulmonary status at school age. In this study, only the results of the pulmonary history reached statistical significance, showing a continued advantage of PRx when children reach school age. If our findings are corroborated by others, this supports the use of PRx for infants of <30 weeks’ gestation.

To date, long-term pulmonary function evaluations of infants treated with surfactant are extremely limited and vary in length of follow-up and methodologic.15,23–26 Our study is the first to compare the two different modes of surfactant administration with regard to formal pulmonary assessment in long-term follow-up. However, formal pulmonary function evaluations did not distinguish between these two groups in the limited subset of patients in whom testing could be completed.

Infants who have RDS are at an increased risk for chronic lung disorders such as bronchopulmonary dysplasia (BPD) or reactive airway disease, and many require repeated hospitalizations. These pulmonary disorders also may be associated with neurodevelopmental impairments.27–30 A diminished severity of BPD generally has been accepted as a result of surfactant use, although its incidence remains significant in the premature population having had RDS.11,29,31–34 Chronic lung disease (CLD) is not defined uniformly among published studies; thus, we examined it in two ways. First we evaluated an oxygen requirement at 28 days in children who required ventilatory assistance during the first week of life, and then we examined infants having an oxygen requirement at 36 weeks’ CGA.16 We found no significant group difference in the requirement for oxygen at 28 days in the survivors. However, the group treated with PRx did have a significantly decreased requirement for oxygen at 36 weeks’ CGA (8% in the PRx vs 20% in RRx group; \( P = .043 \)), with a combined group incidence of 14%. This finding differs from that of Vaucher and colleagues.14 They used a requirement for oxygen at 38 weeks’ CGA as the definition of CLD and found that 33% of the infants had CLD. They reported that the rescue group had better pulmonary outcomes (19% vs 44% CLD). Our findings also differ from those of Dunn et al.9 They found no difference between RRx and PRx administration in the incidence of CLD defined as an oxygen requirement at 36 weeks (odds ratio [OR], 5.49; \( P = .025 \)). The effect of surfactant group assignment was not significant in the second model (OR, 1.26; \( P = .11 \)). There was no interaction between surfactant treatment and either oxygen at 28 days or 36 weeks’ CGA.

### TABLE 4. Predicting Pulmonary History

<table>
<thead>
<tr>
<th>Oxygen at 28 Days</th>
<th>Oxygen at 36 Weeks’ CGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>64.4</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>63.1</td>
</tr>
<tr>
<td>+ Predictive value (%)</td>
<td>43.3</td>
</tr>
<tr>
<td>− Predictive value (%)</td>
<td>80.2</td>
</tr>
</tbody>
</table>

Sensitivity indicates proportion with abnormal pulmonary history who require oxygen at time point (28 days or 36 weeks’ CGA); specificity, proportion with normal pulmonary history who did not require oxygen at time point; positive predictive value, proportion requiring oxygen at time point who have abnormal pulmonary history; negative predictive value, proportion not requiring oxygen at time point who have normal pulmonary history.
requirement at 36 weeks’ CGA. They did report a difference between the groups at 28 days, favoring the RRx group. Kattwinkel et al found that the PRx group had a decreased need for supplemental oxygen at 28 days, but did not report outcome at 36 weeks’ CGA. Explanations for these differences include statistical arguments of power, surfactant preparation (human-, calf-, or porcine-derived), timing, method of dosing (bolus vs aliquot, immediate vs early administration with or without suppression of the infant’s first breath), and population differences.

We evaluated the ability of an oxygen requirement at 28 days or 36 weeks’ CGA to predict an abnormal pulmonary history in an effort to replicate the work of Shennan et al. We found similar results in that an oxygen requirement at 28 days had a positive predictive value for an abnormal pulmonary history of 43.3% and a negative predictive value of 80% compared with Shennan’s results of 38% and 93%, respectively. At 36 weeks’ CGA, we found the positive and negative predictive values for an abnormal pulmonary history to be 62% and 75%, respectively, compared with Shennan’s values of 63% and 90%. Of note, our criteria for an abnormal pulmonary history differed from those of Shennan, whose follow-up only went until 2 years of age and involved patients from the presurfactant era. He did, however, perform his analysis on a larger cohort of patients (605 patients with birth weights <1500 g, of whom 119 had abnormal pulmonary findings at 2 years of age; 113 had an oxygen requirement at 36 weeks’ CGA). One also must appreciate that the evaluation of an oxygen requirement at a particular time point has its own inherent limitations. Several of the infants in our study who were not requiring supplemental oxygen at 36 weeks’ CGA went on to require oxygen therapy at a later date and were discharged home on this therapy. This underscores the difficulties in defining CLD.

The effects of smoking in the home on abnormal pulmonary outcome in our regression models reinforce the public health concern that has been addressed in many other publications. Smoking was present in more than half of the homes in which these study patients reside. A reduction in home exposure of children <6 years of age to ≤20% is a stated goal of the US Public Health Service in its Healthy People 2000 report.

At school age, we found a high rate of neurodevelopmental problems, but no statistically significant difference between treatment groups either on cognitive testing or on neurologic examination. We evaluated the children’s neurodevelopment at school age because tests of development in infants and toddlers are not always predictive of later developmental outcome. Both the cognitive measure we used, the MSCA, and the neurologic examination are standard instruments for evaluating school children and have been used in previous surfactant follow-up studies. Our overall findings are consistent with previous reports of school-age follow-up of premature infants’ neurodevelopment and of the neurodevelopment of infants treated with a single dose of surfactant at birth. Our data do not indicate any cognitive or neurologic advantage of PRx over RRx.

We found a high frequency of behavioral problems in our cohort. Behavioral changes, including hyperactivity, distractibility, and conduct disorders, have been reported frequently in association with prematurity. However, there were no differences between treatment groups observed. Our cohort was evaluated at the beginning of their school experience, however, and behavior problems may not appear until later. Academic underachievement and a need for extra educational assistance were frequent problems in this cohort. Previous studies of prematurity also have reported an increased need for educational assistance and decreases in academic achievement. However, no differences between PRx and RRx groups were identified.

CONCLUSIONS

Children <30 weeks’ gestation who received PRx showed significantly fewer indicators of clinical pulmonary problems through school-age follow-up than those randomized to receive RRx. No significant differences between the treatment groups were found on formal pulmonary testing or on neurologic, cognitive, or behavioral testing; however, the prevalence of neurodevelopmental problems was high, as reported previously in children born prematurely. Problems with academic achievement and the need for special educational services also were frequent, but the two treatment groups were similar. Based on our data showing a reduction of clinical pulmonary symptomatology up to school age, we feel that PRx at delivery of very premature infants who are at high risk for RDS should be seriously considered.

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