The Internet Journal of Pediatrics and Neonatology
Volume 7 Number 1

# Respiratory Morbidity and Pulmonary Function in 5-6 Year Old Children Born Prematurely and Treated With Intratracheal Recombinant Human Cu Zn Superoxide Dismutase

D Vaysman, J Davis, W Rosenfeld, S Pollack, P Puch, H Lee

**Citation**

D Vaysman, J Davis, W Rosenfeld, S Pollack, P Puch, H Lee. *Respiratory Morbidity and Pulmonary Function in 5-6 Year Old Children Born Prematurely and Treated With Intratracheal Recombinant Human Cu Zn Superoxide Dismutase*. The Internet Journal of Pediatrics and Neonatology. 2006 Volume 7 Number 1.

**Abstract**

Objective: We performed a pilot study to investigate whether the administration of recombinant human Cu Zn superoxide dismutase (rhSOD) in premature infants has an impact on respiratory morbidity and lung function at 5-6 years of age and would warrant expansion to a larger cohort of patients from a multicenter study.

Study design: 16 of 23 children from one center, who had participated in a multicenter rhSOD trial, were recruited for this study. All patients had moderate to severe RDS requiring ventilator therapy. Eight patients received SOD and 8 received placebo. The respiratory histories were obtained and physical examinations and pulmonary function tests were performed. Student t-test, Fisher's exact test and Pearson product-moment correlation coefficient were used for statistical analysis.

Results: There was no difference in neonatal course between the groups. At the time of follow up three of 7 rhSOD patients (42.9%) and 7 placebo patients (87.5%) had evidence of hyperinflation and air trapping (p=0.1). Three rhSOD (37.5%) and 6 (75%) placebo had cough/wheezing and had used bronchodilators within the previous year (p=0.3). There was no significant difference in mean PFT values between the groups.

Conclusion: The RhSOD-treated group had less respiratory morbidity and less hyperinflation and air trapping, although differences did not reach statistical significance. This was a pilot study and expansion to the original patient population may yield a better understanding.

## INTRODUCTION

BPD remains the most common long-term complication in very low birth weight infants, and a variety of strategies have been attempted to decrease the incidence of BPD. Included in these is the administration of antioxidants, as premature neonates are particularly vulnerable to oxidant injury due to deficient antioxidant enzyme activity at birth.[1] Animal and human studies have demonstrated that the administration of recombinant human Cu-Zn superoxide dismutase (rhSOD) decreases acute and chronic lung injury from hyperoxia.[2,3,4,5,6] To determine if rhSOD improved BPD, a multicenter, randomized, placebo controlled study which enrolled 302 premature infants was conducted between January 1997 and June 1998.[7] Although there was no acute reduction in the incidence of BPD, there was a significantly lower incidence of respiratory morbidity, use of corticosteroids and bronchodilators, ER visits and hospitalizations in rhSOD treated infants at one year of corrected age. The aim of this pilot follow up study was to assess the effect of rhSOD on respiratory morbidity and pulmonary function at 5-6 years of age in a small number of children who had participated in the aforementioned study and to determine if a more extensive study would be warranted.

## MATERIALS AND METHODS

The study was approved by the hospital institutional review board. The parents of the patients who had participated in the multicenter intratracheal rhSOD trial at our institution between January 1997 and June 1998 were contacted by a letter. Sixteen of 23 patients agreed to participate. Three letters were returned due to the change of address and 4 patients did not respond. Informed consent was obtained from the parents of all children. A detailed questionnaire was used to obtain the patients' clinical history since discharge from NICU, including use of prenatal corticosteroids, surfactant, wheezing with/without cold, daytime and nighttime cough, family history of respiratory illness and allergies, use of inhaled and oral corticosteroids, bronchodilators, hospitalizations, and ER visits, presence of smokers in the household, pets and RSV infection. Copies of medical records from their pediatricians were obtained after parents authorized the release of medical records. All patients had a physical examination performed by one of the investigators participating in the study.

## PULMONARY FUNCTION TEST (PFT)

A pulmonary function test was performed at least a month after any recent respiratory tract infection. Bronchodilators were withheld for 24 hours before the test. PFT was performed with Sensor Medics $V_{max}$22/V6200Autobox pulmonary function equipment (Sensormedics, Yorba Linda, CA) by the same technician in the morning, and pretest calibration was performed before the test according to the manufacturer's instructions. All children were tested in the standing position wearing a nose clip. Each patient performed three FVC maneuvers for the spirometry including FVC, $FEV_1$, $FEV_1$/FVC, $FEF_{25-75}$ and PEF. The test with the largest sum of FVC and $FEV_1$ was selected for analysis. All patients received an albuterol sulfate inhalation solution 0.083%, (DEY, Napa, CA) 2.5 mg via Misty-Neb nebulizer with adapter and mouthpiece (Allegiance Healthcare Corporation, McGaw Park, IL) and a PFT was repeated 15 minutes later. Airway obstruction was defined as FEV1 and/or FEV1%   80% predicted, RV and/or FRC > 120% predicted. Bronchial responsiveness to $\beta_2$-agonist was defined as an increase in FVC ≥ 12% and/or $FEV_1$≥ 12%. Lung volumes including TLC, FRC, RV, RV/TLC were measured by the nitrogen washout technique. Normal predicted values for expiratory flow rates and lung volumes were obtained from Polgar and Promadhat.[8] A measured value more than 2 standard deviations (SD) above or below the predicted value was considered abnormal. Investigators were not aware of the patient's treatment assignment during the neonatal period.

## STATISTICAL METHODS

Student t-test and Fisher's exact test were used for continuous and categorical statistical analysis, respectively. The linear correlation analysis between the current symptoms status and neonatal course, and between the pulmonary function, current symptoms status and neonatal course were performed using the Pearson product-moment correlation coefficient. Various neonatal variables were evaluated including birth weight, gestational age, duration of intubation, oxygen therapy and BPD. A two-tailed p-value of 0.05 was the threshold for significance. As parametric and non-parametric results were very similar, only parametric results are reported.

## RESULTS

There were no significant differences between the groups in gestational age, birth weight, diagnosis of BPD, duration of oxygen therapy, intubation and a family history of asthma and atopy, use of prenatal corticosteroids and surfactant. (Table 1)

### Figure 1

Table 1: Neonatal data.

| Characteristics | RhSOD n=8 | Placebo n=8 | *P* value |
|---|---|---|---|
| Gestational Age (wk) | 26.6 ±1.3(25-28) | 26.5 ± 1.4(24-29) | NS(0.9) |
| Birth Weight (gm) | 915.1 ± 177.4 (606-1175) | 881.5 ± 128.9 (693-1083) | NS(0.7) |
| Sex male/female | 4/4 | 2/6 | NS(0.6) |
| BPD | 5 | 4 | NS(1.0) |
| Oxygen Therapy (days) | 42.9 ± 14.4 (7-76) | 40 ± 24.2 (20-58) | NS(0.8) |
| Intubation (days) | 15.4 ± 11.9 (3-32) | 10.8 ± 11.8 (2-34) | NS(0.4) |
| Prenatal Corticosteroids | 4/4 | 4/4 | NS(1.0) |
| Surfactant | 7/8 | 8/8 | NS(1.0) |

History of respiratory symptoms and atopy.(Table 2)

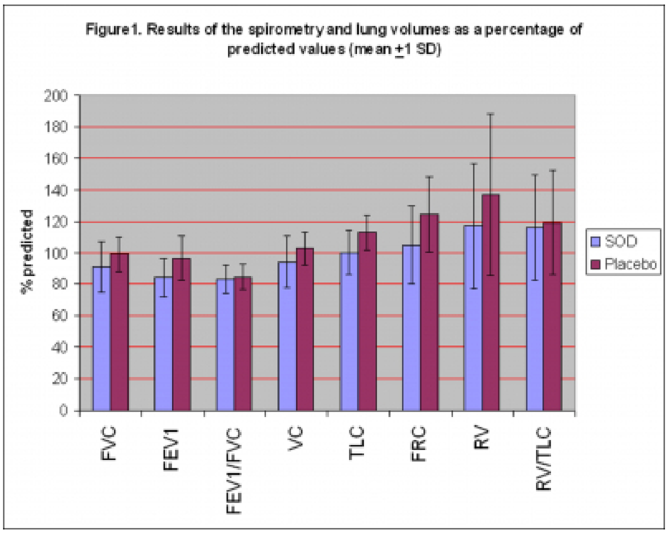
### Figure 2

Table 2: Respiratory Morbidity.

| Symptoms | rhSOD (8) n | Placebo (8) n | Fisher's exact test p-value |
|---|---|---|---|
| Cough/Wheezing 0-3 years | 6/8 (75%) | 7/8 (87.5%) | 1.00 |
| Cough/Wheezing 3-6 years | 3/8 (37.5%) | 6/8 (75%) | 0.315 |
| Cough/Wheezing previous year | | | |
| | 3/8 (37.5%) | 6/8 (75%) | 0.315 |
| Hospitalizations | | | |
| | 2/8(25%) | 2/8 (25%) | 1.000 |
| ER visits | | | |
| | 2/8 (25%) | 2/8 (25%) | 1.000 |
| Corticosteroids | | | |
| | 4/8 (50%) | 4/8 (50%) | 1.000 |
| Bronchodilators use previous year | | | |
| | 3/8 (37.5%) | 6/8 (75%) | 0.315 |
| Allergies | | | |
| Allergic rhinitis | 1/8 (12.5%) | 3/8 (37.5%) | 0.569 |
| Asthma | 2/8 (25%) | 5/8 (62.5%) | 0.315 |
| Smokers in the household | 4/8 (50%) | 6/8 (75%) | 0.608 |
| | 0/8 (0%) | 3/8 (37.5%) | 0.200 |
| Pets | | | |
| RSV | | | |
| | 3/8 (37.5%) | 4/8 (50%) | 1.000 |
| | 1/8 (12.5%) | 0/8 (0%) | 1.000 |

Six of the rhSOD (75 %) and 7 of the placebo (87.5 %) patients had cough/wheezing until 3 years of age. Cough/wheezing persisted between 3 and 6 years of age in 3 rhSOD (37.5%) and 6 placebo (75%) patients, and all patients in both groups who wheezed up to 6 years of age continued to have cough/wheezing up to the time of the study. Three rhSOD (37.5%) and 6 placebo (75%) patients used an inhaled bronchodilator during the previous year. Two patients in the rhSOD (25%) and 5 in the placebo group (62.5%) had diagnosed allergic rhinitis, 4 patients in the rhSOD (50%) and 6 in the placebo (75%) had physician diagnosed asthma, 3 patients (37.5%) in placebo and none in rhSOD have been exposed to cigarette smoke, 3 patients (37.5%) in rhSOD and 4 in the placebo (50%) had pets, 1 patient (12.5%) in rhSOD and none in the placebo group had RSV infection. There was no difference between the groups in frequency of ER visits, hospitalizations and corticosteroids use. There was no correlation between long-term respiratory symptoms and the diagnosis of BPD or duration of intubation and oxygen therapy in the neonatal period for either group.

### Figure 3




## LUNG FUNCTION

One rhSOD patient was unable to perform lung volume measurements due to lack of cooperation. There was no significant difference in mean pulmonary function values between the groups, (Figure 1) and no significant response to inhaled bronchodilator.

Lung volumes measurements showed increased FRC in one rhSOD patient (14.3%) and 4 placebo patients (50%) ($p=0.28$), and increased RV in 2 rhSOD patients (28.6%) and 5 placebo patients (62.5%) ($p=0.3$).

Four patients in the rhSOD (50%) and 1 in the placebo group (12.5%) had abnormal spirometry indicating airway obstruction. Six rhSOD (75%) and 7 (87.5%) placebo patients had abnormal lung volumes with evidence of airway obstruction.

## SIGNIFICANCE

Multiple strategies have been attempted to prevent the development of BPD, including the use of surfactant, corticosteroids, heliox, high frequency ventilation, vitamin A, and antioxidants. The intratracheal administration of rhSOD, whilst it did not decrease the development of BPD, did have a significant effect on respiratory morbidity at one year of corrected age. The significant improvement in respiratory status at one year of age may be an important marker for the effectiveness of strategies used for ventilation in at risk preterm neonates. Palta et al [9], in an attempt to validate the various definitions of BPD in the neonatal period against later respiratory problems, compared 5 definitions for BPD ((oxygen at 30 days, BPD score, BPD diagnosed, x-ray score, and oxygen at 36 weeks post conceptional age) and found x-ray score to be the best. The sensitivity ranged from 56-74% and specificity from78-79% depending on the long-term variable. Similarly Davis et al [10] showed the sensitivity and specificity of his most accurate criteria (oxygen at 28 days) were 67% and 54% when compared to poor long-term pulmonary outcomes. These studies suggest that it is imperative to look at the long term rather than short-term outcomes to accurately reflect the effectiveness of neonatal interventions to prevent chronic lung disease in former preterm infants. Extending our observations on rhSOD patients to one year of age allowed demonstration of a significant beneficial effect not seen in the first months of life. Our pilot study demonstrates that rhSOD treated patients had a trend towards a lower incidence of respiratory morbidity at 5-6 years of age as indicated by a lower incidence of hyperinflation and air trapping in rhSOD treated patients. In view of the small number of patients in this pilot study, the results must be evaluated cautiously but are encouraging. Inclusion of other patients from the multicenter study may show statistical significance. Power analysis demonstrates that if the present trend remains constant only 52 patients will be required in the expanded study to demonstrate significance.

In conclusion, the administration of rhSOD to premature infants with RDS in a large study plays a role in decreasing respiratory morbidity at one year of corrected age when these infants are most vulnerable to severe respiratory disease. Its role in the later development of respiratory symptoms is not as clear. The trend towards the lower incidence of hyperinflation and air trapping, which are the markers of airway obstruction, and the lower incidence of respiratory morbidity in rhSOD patients at 5-6 years may reflect a beneficial effect of rhSOD. This is a pilot study to evaluate the long-term effect of rhSOD and results should be interpreted with caution due to small number of patients. Expansion of the study to include the entire original patient population of the multicenter rhSOD trial may yield a better understanding of its long-term effect.

## CORRESPONDENCE TO

Haesoon Lee, MD SUNY Health Science Center at Brooklyn Department of Pediatrics 450 Clarkson Ave BOX 49 Brooklyn, NY Email: HL1008@aol.com

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### Author Information

**Dmitriy Vaysman, M.D.**
Department of Pediatrics, Good Samaritan Hospital Medical Center

**Jonathan M. Davis, M.D.**
Department of Pediatrics, SUNY Stony Brook School of Medicine

**Warren Rosenfeld, M.D.**
Department of Pediatrics, SUNY Stony Brook School of Medicine

**Simcha Pollack, Ph.D.**
Department of Biostatistics, SUNY Stony Brook School of Medicine

**Peter Puch, RRT**
Department of Pediatrics, SUNY Stony Brook School of Medicine

**Haesoon Lee, M.D.**
Department of Pediatrics, SUNY Health Science Center at Brooklyn