Early Cortisol Replacement to Prevent Bronchopulmonary Dysplasia: Pilot Study

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Parklawn Building, Conference Room D
Rockville, Maryland

Presenter: Kristi L. Watterberg, M.D.
PROFESSOR OF PEDIATRICS, UNIVERSITY OF NEW MEXICO (FORMERLY AT PENNSYLVANIA STATE UNIVERSITY COLLEGE OF MEDICINE)

Reactors: Marilee C. Allen, M.D.
ASSOCIATE PROFESSOR OF PEDIATRICS
THE JOHNS HOPKINS UNIVERSITY

Michael C. Lambert, Ph.D.
ASSOCIATE PROFESSOR OF PSYCHOLOGY
MICHIGAN STATE UNIVERSITY

Moderator: Trina Anglin, M.D.
ACTING CHIEF, ADOLESCENT HEALTH BRANCH
MATERNAL AND CHILD HEALTH BUREAU

Bring your lunch, and enjoy the desserts and beverages provided.

Research Roundtable 31

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration
Maternal and Child Health Bureau

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Cosponsored by the Division of Research, Education and Training and the Division of Child, Adolescent and Family Health of the Maternal and Child Health Bureau

Research Roundtable

About the Presenter...

Kristi L. Watterberg, M.D., is currently professor of pediatrics at the University of New Mexico, having returned to New Mexico after 10 years at the Pennsylvania State University College of Medicine. Dr. Watterberg's research has focused primarily on the pathogenesis and prevention of bronchopulmonary dysplasia (BPD) in premature infants. Her investigations into the possible link between adrenal function and BPD led to the clinical intervention trial presented at this roundtable. Her work in this field has been published in *Pediatrics, Pediatric Research,* and *The Journal of Pediatrics.* Dr. Watterberg received her medical degree from the University of New Mexico, and was a member of the faculty there before moving to Pennsylvania.

About the Reactors...

Marilee C. Allen, M.D., is a board-certified neonatologist and a board-eligible neurodevelopmental pediatrician. She received her medical degree from The Johns Hopkins University School of Medicine, where she has been a member of the faculty since 1983, and is currently associate professor of pediatrics. In addition, Dr. Allen serves as associate director of neonatology at Johns Hopkins, director of the Maryland Regional Neonatal Transport Program, and co-director of the Neonatal Intensive Care Unit (NICU) Developmental Clinic at the Kennedy Krieger Institute. She has received numerous awards for her clinical research and presentations and has been active in a number of professional organizations.

Michael C. Lambert, Ph.D., is associate professor, Department of Psychology, and adjunct professor, David Walker Research Institute, College of Human Medicine, at Michigan State University. Dr. Lambert is also associate lecturer in the Department of Psychiatry and honorary lecturer in the Department of Child Health at the University of the West Indies, Mona, Jamaica. A graduate of Hahnemann Medical College and Bryn Mawr College, he received his Ph.D. in child clinical and general psychology from the University of North Carolina at Chapel Hill. Dr. Lambert's research interests include taxonomy and measurement of psychopathology in children and families internationally. His research also focuses on behavior and emotional strengths and problems in children and families of the African Diaspora, including children born with very low birthweight.

Early Cortisol Replacement to Prevent Bronchopulmonary Dysplasia: Pilot Study

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Kristi L. Watterberg, M.D.
University of New Mexico

Statement of the Problem

Bronchopulmonary dysplasia, or chronic lung disease (CLD) following neonatal lung injury, is a frequent complication of prematurity, and results in increased health care costs, prolonged hospital stays with frequent rehospitalizations, long-term pulmonary abnormalities, and subsequent compromise of growth and development. Because a very high percentage of extremely-low-birthweight infants (< 1,000 g birthweight) remain on supplemental oxygen and even mechanical ventilation at 1 month of life, the term

bronchopulmonary dysplasia applied to those infants at 28 days of life has lost much of its original connotation of severe disease. A new definition of chronic lung disease (CLD) as a continuing requirement for supplemental oxygen at 36 weeks postconceptional age may correlate better with adverse outcomes. When discussing outcomes, therefore, this final report refers to CLD at 36 weeks postconceptional age.

Therapies intended to reduce the incidence of CLD have met with little success thus far. New therapeutic concepts are urgently needed to address this difficult clinical problem.

Research Objectives

We have found that many very-low-birthweight (VLBW) infants show evidence of adrenal insufficiency early in life, and that such infants are more likely to develop CLD. The study hypotheses are as follows:

1. Early adrenal insufficiency leads to exaggerated inflammatory responses and/or other abnormalities in lung function, resulting in CLD; and
2. Cortisol replacement therapy during the first 12 days of life would prevent this deficiency, thereby decreasing the incidence of CLD.

It was also postulated that cortisol replacement therapy would prevent symptoms of acute adrenal insufficiency, specifically hypotension, hyponatremia, hyperkalemia, and delayed weight loss.

The research objectives of this study were to

1. Estimate the efficacy of cortisol replacement therapy during the first 12 days of life for prevention of CLD;
2. Estimate the effect of this therapy on the signs of acute adrenal insufficiency listed above; and
3. Evaluate the effects of such therapy on adrenal hormone concentrations and on the ability of the adrenal glands to respond to adrenocorticotropic hormone (ACTH).

Study Design and Methods

This study was a randomized, double-blind, placebo-controlled clinical trial of 40 infants weighing between 500 and 999 g at birth. The study was conducted at two sites: Children's Hospital of Pennsylvania State University, Hershey, PA (June 1996–May 1998), and Pennsylvania Hospital of the University of Pennsylvania, Philadelphia (June 1997–May 1998). Infants were eligible for the study if they were mechanically ventilated beyond 12 hours of life, could be enrolled before 48 hours of life, had no apparent major congenital anomaly or congenital sepsis, were considered appropriate for their gestational age, and had no history of maternal diabetes.

Infants in the study received either placebo or hydrocortisone therapy for 12 days. Blood samples were obtained at baseline, at day 6, and 3 days after the end of therapy. Response to ACTH stimulation was also determined at the last timepoint.

The primary outcome variable was "success," defined as survival without CLD. Analysis of this primary outcome variable was by stepwise logistic regression, which included study center and other baseline population characteristics. Secondary endpoints included other measures of respiratory disease and clinical outcomes, and indicators of daily physiologic stability. Because chorioamnionitis is associated with increased cortisol concentrations, increased lung inflammation, and adverse outcomes, this subset of patients was also examined separately.

Findings

A total of 40 infants were enrolled (20 in the treatment group and 20 in the placebo group); 17 in each group survived. Birthweight and gestation were similar for treatment (hydrocortisone therapy) and placebo groups.

Following are the findings for each of the three stated research objectives:

Objective 1 (to estimate the efficacy of cortisol replacement therapy during the first 12 days of life for prevention of CLD): More infants treated with hydrocortisone achieved study success, defined as survival without CLD. Lower birthweight, chorioamnionitis, and preeclampsia were significant risk factors in this regression, whereas study center, prenatal steroids, sex, and ethnicity were not. Hydrocortisone therapy also reduced the number of days on oxygen, days on mechanical ventilation, and oxygen at discharge. No significant differences were detected in adverse outcomes.

Objective 2 (to estimate the effect of this therapy on signs of acute adrenal insufficiency): During the treatment period, infants who received hydrocortisone therapy had significantly less hyponatremia and showed a trend toward lower fluid requirements. Although the direction of effect for blood pressure and inotropic therapy for hypotension favored the treatment group, no significant differences were seen between groups. Within the subset of infants exposed

to chorioamnionitis, those infants treated with hydrocortisone received significantly more enteral nutrition during the first month of life, and weighed more at outcome.

Objective 3 (to evaluate the effect on adrenal hormone concentrations and response to ACTH stimulation): Infants treated with hydrocortisone had no suppression of either basal or stimulated cortisol values when tested 3 days after the end of therapy. Additionally, hydrocortisone therapy had no significant effect on the concentrations of cortisol precursors.

We analyzed the differences in hormone concentrations between those infants who developed CLD and those who did not. At study entry, infants who subsequently developed CLD had significantly higher concentrations of 17OH progesterone, suggesting an impaired ability to synthesize cortisol. After the study, infants who developed CLD had lower basal cortisol concentrations and a reduced response to ACTH stimulation. These infants continued to have significantly higher concentrations of 17OH progesterone and increased ratios of precursor hormones to cortisol, indicating a continuing limitation of ability to synthesize cortisol, resulting in accumulation of these precursors.

Recommendations

We found that hydrocortisone therapy significantly improved the likelihood of survival without CLD. The results of this pilot study now justify a larger multicenter randomized trial to confirm the benefits and further assess the risks of low-dose hydrocortisone therapy for prevention of CLD in extremely premature infants.

Publications

Watterberg KL, Gerdes JS, Gifford KL, Lin HM. 1999. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. *Pediatrics* 104(6):1258–1263.

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