NIH Consensus Development Conference

Inhaled Nitric Oxide Therapy for Premature Infants

Program and Abstracts

October 27–29, 2010

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Presented by

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
Office of Medical Applications of Research, NIH

Cosponsor

National Heart, Lung, and Blood Institute, NIH

The Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention provided additional conference development support.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available and what directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2-1/2 days. The first day and a half of the conference consists of plenary sessions, in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise its draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12 to 16 members, who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the U.S. Department of Health and Human Services.

- Must not hold financial or career (research) interests in the conference topic.
- May be knowledgeable about the general topic under consideration, but must not have published on or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
  - Practicing and academic health professionals
  - Biostatisticians and epidemiologists
  - Clinical trialists and researchers
  - Nonhealth professionals with expertise in fields relevant to the specific topic (ethicists, economists, attorneys, etc.)
  - Individuals representing public-centered values and concerns

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers: 3 present the information found in the Evidence-based Practice Center's systematic review of the literature; the other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs on the topic. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit its statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement is written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements have robust dissemination:

- A press briefing is held on the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at **consensus.nih.gov.**
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.
- The conference statement is published in a major peer-reviewed journal.

Contact Us

For conference schedules, past statements, and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

1–888–NIH–CONSENSUS (888–644–2667)
consensus.nih.gov

Upcoming Conferences

NIH State-of-the-Science Conference:	**Role of Active Surveillance in the Management of Men With Localized Prostate Cancer** *December 5–7, 2011*

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at **consensus.nih.gov/alerts.htm.**

Recent Conferences

NIH State-of-the-Science Conference	**Preventing Alzheimer's Disease and Cognitive Decline** *April 26–28, 2010*
NIH Consensus Development Conference:	**Vaginal Birth After Cesarean: New Insights** *March 8–10, 2010*
NIH Consensus Development Conference:	**Lactose Intolerance and Health** *February 22–24, 2010*
NIH State-of-the-Science Conference:	**Enhancing Use and Quality of Colorectal Cancer Screening** *February 2–4, 2010*
NIH State-of-the-Science Conference:	**Diagnosis and Management of Ductal Carcinoma In Situ (DCIS)** *September 22–24, 2009*
NIH State-of-the-Science Conference:	**Family History and Improving Health** *August 24–26, 2009*
NIH Consensus Development Conference:	**Management of Hepatitis B** *October 20–22, 2008*
NIH Consensus Development Conference:	**Hydroxyurea Treatment for Sickle Cell Disease** *February 25–27, 2008*
NIH State-of-the-Science Conference:	**Prevention of Fecal and Urinary Incontinence in Adults** *December 10–12, 2007*
NIH State-of-the-Science Conference:	**Tobacco Use: Prevention, Cessation, and Control** *June 12–14, 2006*
NIH State-of-the-Science Conference:	**Multivitamin/Mineral Supplements and Chronic Disease Prevention** *May 15–17, 2006*
NIH State-of-the-Science Conference:	**Cesarean Delivery on Maternal Request** *March 27–29, 2006*

To access previous conference statements, Webcasts, evidence reports, and other conference materials, please visit **consensus.nih.gov.**

General Information

Financial Disclosures

The Centers for Disease Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

Speakers	Company	Financial Relationship
Roberta A. Ballard, M.D.	IKARIA, Inc.	Unrestricted grant to study bronchopulmonary dysplasia (BPD). No salary support. Role of investigator
Keith J. Barrington, M.D., M.B.Ch.B.	IKARIA, Inc.	Research support for interstitial pulmonary disease meta-analysis. No income received of any kind. Role of co-investigator
Jean-Christophe Mercier, M.D., M.Sci.	IKARIA, Inc./INO Therapeutics	Minor fees and traveling support for advisory boards Research grant to study the effects of inhaled nitric oxide on rat pups
Michael D. Schreiber, M.D.	IKARIA, Inc.	Investigator-initiated research grant for role as principal investigator
Michele C. Walsh, M.D., M.S.	Watermark, Inc.	Salary received for role as Data and Safety Monitoring Board member for inhaled nitric oxide trial

Several presentations will include a discussion of the unlabeled use of a product or a product under investigational use. The nature of this conference discusses the use of inhaled nitric oxide in preterm infants, which is an off-label use of this product. Presentations of unlabeled use of inhaled nitric oxide include the following:

- Dr. Steven H. Abman's discussion on the use of inhaled nitric oxide in premature infants.
- Dr. Marilee C. Allen's discussion of the evidence of treatment of preterm infants born at or before 34 weeks gestation who require mechanical ventilation with inhaled nitric oxide.
- Dr. Roberta A. Ballard's discussion of a multicenter clinical trial of the use of inhaled nitric oxide in the preterm infant.
- Dr. Keith J. Barrington's discussion on the use of inhaled nitric oxide in premature infants.
- Dr. Elizabeth A. Cristofalo's discussion of studies in which inhaled nitric oxide has been used in premature infants (less than 34 weeks gestation).

- Dr. Maureen M. Gilmore's discussion of inhaled nitric oxide used off label for treatment of respiratory failure in premature infants. This use of the product is currently under clinical investigation.
- Dr. Susan R. Hintz's discussion of information pertaining to neurodevelopmental outcomes of the patients enrolled in the National Institute of Child Health and Human Development Neonatal Research Network trial of inhaled nitric oxide for premature infants with severe respiratory failure.
- Dr. Jean-Christophe Mercier's discussion on the use of inhaled nitric oxide in premature infants at risk of developing BPD.
- Dr. Michael D. Schreiber's discussion of the use of inhaled nitric oxide for premature infants.
- Dr. Philip W. Shaul's discussion of the investigational use of inhaled nitric oxide in animal models of BPD.
- Dr. Robin H. Steinhorn's discussion of inhaled nitric oxide for the prevention of BPD. She will discuss the evidence supporting its use in specific groups of the preterm infants based solely on published clinical trials.
- Dr. Krisa P. Van Meurs's discussion of the results of the Preemie Inhaled Nitric Oxide Trial performed by the National Institute of Child Health and Human Development Neonatal Research Network and published in the *New England Journal of Medicine* in 2005.
- Dr. Michele C. Walsh's discussion of inhaled nitric oxide to prevent BPD.

There is no commercial support for this activity.

Contents

Background

Infants born before the 37th week of pregnancy are said to be “premature” or “preterm” and face increased risk for a variety of complications. Babies born before the 28th week of pregnancy—more than 30,000 per year in the United States—are particularly vulnerable to breathing problems such as respiratory distress syndrome and respiratory failure due to their underdeveloped lungs. These infants often need respiratory support in the first days and weeks after birth. Those premature infants who still require supplemental oxygen 36 weeks after conception are diagnosed with bronchopulmonary dysplasia, which places them at greater risk for death or problems with long-term lung health, brain development, and brain function.

Nitric oxide is a chemical compound in gas form that is sometimes used to treat infants with severe breathing problems. Inhaled nitric oxide therapy was approved by the U.S. Food and Drug Administration in 2000 to treat term and near-term infants (born after the 33rd week of pregnancy) with respiratory failure. Inhaled nitric oxide therapy is typically administered in the neonatal intensive care unit using a device that delivers the drug in constant concentrations. It acts as a pulmonary vasodilator, widening the opening of blood vessels in the lungs. In term and near-term infants, use of this therapy may shorten the length of time respiratory support is required, thereby reducing progression to bronchopulmonary dysplasia, improving long-term lung health and brain development and function.

Since its approval, researchers have examined expanding the use of inhaled nitric oxide therapy to treat premature babies born at less than 34 weeks gestation. Studies to evaluate its safety and efficacy for these infants have had mixed results in terms of key outcomes. Thus, the potential benefits and harms of its use for premature infants with varying degrees of respiratory illness are not completely understood.

To better understand the benefits and risks of inhaled nitric oxide therapy for premature infants, the National Institutes of Health has convened a Consensus Development Conference October 27–29, 2010, to assess the available scientific evidence related to the following questions:

- Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?
- Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support?
- Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?
- Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia (BPD) and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?
- Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia (BPD) and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

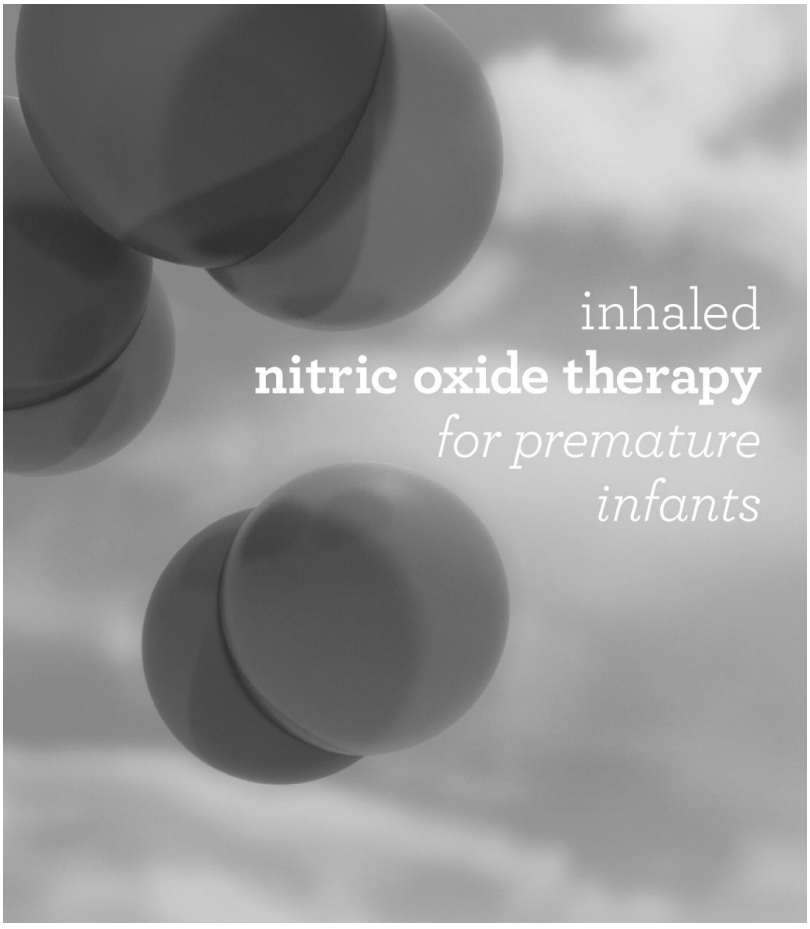
- What are the future research directions needed to better understand the risks, benefits, and alternatives to nitric oxide therapy for premature infants who receive respiratory support?

The conference is presented by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the Office of Medical Applications of Research, with additional support from the National Heart, Lung, and Blood Institute. Invited experts will present scientific evidence pertinent to the posed questions, and a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality will be summarized. Conference attendees will have opportunities to ask questions and provide comments during open discussion periods. After weighing the scientific evidence, an unbiased, independent panel will prepare and present a consensus statement addressing the key conference questions.

About the Artwork

The conference artwork depicts the two chemical elements, nitrogen and oxygen, that form the gaseous compound nitric oxide. The blue sky backdrop symbolizes an air of calm and easy breathing. When inhaled, nitric oxide signals blood vessels in the lungs to widen, increasing blood flow and promoting gas exchange. Inhaled nitric oxide is sometimes used to treat term and near-term infants (born after the 33rd week of pregnancy) with severe breathing problems. Expanding the use of inhaled nitric oxide for premature babies born before the 34th week of pregnancy is currently being explored.

The image was conceived and created by the National Institutes of Health's Division of Medical Arts and is in the public domain. No permission is required to use the image. Please credit "Bryan Ewsichek and Ethan Tyler/NIH Medical Arts."



Agenda

Wednesday, October 27, 2010

8:30 a.m. Opening Remarks
Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

8:40 a.m. Charge to the Panel
Jennifer M. Croswell, M.D., M.P.H.
Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
F. Sessions Cole, M.D.
Panel and Conference Chairperson
Park J. White, M.D. Professor of Pediatrics
Assistant Vice Chancellor for Children's Health
Vice Chairperson
Department of Pediatrics
Director
Division of Newborn Medicine
Washington University School of Medicine
Chief Medical Officer
St. Louis Children's Hospital

General Overview

9:00 a.m. Epidemiology of Bronchopulmonary Dysplasia (BPD): Burden of Disease and Current Practice
Roger F. Soll, M.D.
President
Vermont Oxford Network
Wallace Professor of Neonatology
Department of Pediatrics
University of Vermont College of Medicine

Wednesday, October 27, 2010 *(continued)*

General Overview *(continued)*

9:20 a.m. Biology of Bronchopulmonary Dysplasia (BPD) and Rationale for Inhaled Nitric Oxide Therapy
Philip W. Shaul, M.D.
Professor of Pediatrics
Director
Division of Pulmonary and Vascular Biology
Lowe Foundation Professor of Pediatric Critical Care Research
Department of Pediatrics
University of Texas Southwestern Medical Center at Dallas

9:40 a.m. **Discussion**
Participants with questions or comments for the speakers should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. Please be aware that all statements made at the microphone or submitted later are in the public domain.

I. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?

and

II. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support?

10:00 a.m. Trial: Nitric Oxide Therapy in Premature Infants With Respiratory Distress Syndrome
Michael D. Schreiber, M.D.
Professor and Executive Vice Chairperson
Department of Pediatrics
University of Chicago

Wednesday, October 27, 2010 *(continued)*

I. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support? *(continued)*

and

II. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support? *(continued)*

10:20 a.m. Inhaled Nitric Oxide for Premature Infants With Severe Respiratory Failure: Preemie Inhaled Nitric Oxide (PiNO) Trial Results
Krisa P. Van Meurs, M.D.
Professor of Pediatrics, Neonatology
Associate Chief, Clinical Programs
Division of Neonatal and Developmental Medicine
Associate Chairperson, Clinical Research
Department of Pediatrics
Stanford University School of Medicine
Lucile Packard Children's Hospital

10:40 a.m. Trial: Early Inhaled Nitric Oxide Therapy in Premature Newborns With Respiratory Failure
John P. Kinsella, M.D.
Professor of Pediatrics
Section of Neonatology
Medical Director
Newborn/Young Child Transport Service
Director of Clinical Research
Pediatric Heart Lung Center
Children's Hospital
University of Colorado, Denver

11:00 a.m. **Discussion**

11:30 a.m. **Lunch**
Panel Executive Session

Wednesday, October 27, 2010 *(continued)*

I. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support? *(continued)*

and

II. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support? *(continued)*

12:30 p.m. Inhaled Nitric Oxide for Prevention of Bronchopulmonary Dysplasia (BPD) in Premature Babies: The European Nitric Oxide (EUNO) Randomized Controlled Trial
Jean-Christophe Mercier, M.D., M.Sci.
Professor of Pediatrics
University of Paris 7 Denis Diderot
Chief
Department of Pediatric Emergency Care
Hôpital Robert-Debré

12:50 p.m. Trial: The Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) Trial
Roberta A. Ballard, M.D.
Professor of Pediatrics
Division of Neonatology
Department of Pediatrics
University of California, San Francisco
Emeritus Professor of Pediatrics
University of Pennsylvania

1:10 p.m. Evidence-based Practice Center Presentation I: A Systematic Review of Inhaled Nitric Oxide Therapy in Preterm Infants: Mortality, Bronchopulmonary Dysplasia (BPD), and Short-Term Risks
Marilee C. Allen, M.D.
Professor of Pediatrics
Johns Hopkins School of Medicine
Division of Neonatology
Johns Hopkins Children's Center
Neurodevelopmental Disabilities
Co-Director of Neonatal Intensive Care Unit Developmental Clinic
Kennedy Krieger Institute

1:30 p.m. **Discussion**

Wednesday, October 27, 2010 *(continued)*

III. Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?

2:00 p.m. Neurodevelopmental Outcomes of Premature Infants
Barbara K. Schmidt, M.D., M.Sc.
Kristine Sandberg Knisely Chair in Neonatology
Department of Pediatrics
University of Pennsylvania School of Medicine
Children's Hospital of Philadelphia

2:20 p.m. Pulmonary Physiologic Outcomes Among Premature Infants
Robert S. Tepper, M.D., Ph.D.
Mary Agnes Kennedy and Kathryn Kennedy Weinberger Professor
Pediatric Pulmonology and Critical Care Section
Department of Pediatrics
Herman B. Wells Center for Pediatric Research
Indiana University School of Medicine
James Whitcomb Riley Hospital for Children

2:40 p.m. Follow-Up of Trial: Inhaled Nitric Oxide Cohort Up to 5 Years of Age
Michael D. Schreiber, M.D.
Professor and Executive Vice Chairperson
Department of Pediatrics
University of Chicago

3:00 p.m. Neurodevelopmental Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network (NRN) Trial of Inhaled Nitric Oxide for Premature Infants With Severe Respiratory Failure (Preemie Inhaled Nitric Oxide [PiNO] Trial)
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal Medicine and Developmental Medicine
Stanford University School of Medicine
Director
Center for Comprehensive Fetal Health
Lucile Packard Children's Hospital

3:20 p.m. **Discussion**

4:00 p.m. **Adjournment**

Thursday, October 28, 2010

III. Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support? *(continued)*

8:30 a.m. Follow-Up of Trial: Inhaled Nitric Oxide in the Prevention of Chronic Lung Disease
John P. Kinsella, M.D.
Professor of Pediatrics
Section of Neonatology
Medical Director
Newborn/Young Child Transport Service
Director of Clinical Research
Pediatric Heart Lung Center
Children's Hospital
University of Colorado, Denver

8:50 a.m. The Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) Trial: Outcomes at 1 and 2 Years of Age
Michele C. Walsh, M.D., M.S.
Professor of Pediatrics
Case Western Reserve University
Medical Director
Neonatal Intensive Care Unit
Co-Chief
Division of Neonatology
Rainbow Babies & Children's Hospital
University Hospitals Case Medical Center

9:10 a.m. Inhaled Nitric Oxide for Preterm Infants: A Systematic Review
Keith J. Barrington, M.D., M.B.Ch.B.
Professor of Pediatrics
University of Montreal
Chief of Neonatology
University Hospital Center, Sainte-Justine

9:30 a.m. Evidence-based Practice Center Presentation II: Inhaled Nitric Oxide in Preterm Infants: Does This Therapy Influence Long-Term Pulmonary and/or Neurodevelopmental Outcomes When Used in Preterm Neonates Requiring Respiratory Support?
Elizabeth A. Cristofalo, M.D., M.P.H.
Assistant Professor of Pediatrics
Neonatal-Perinatal Medicine
Johns Hopkins Children's Center
Johns Hopkins Hospital

9:50 a.m. **Discussion**

Thursday, October 28, 2010 *(continued)*

IV. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia (BPD) and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?

10:30 a.m. Use and Misuse of Subgroup and Secondary Analyses in Clinical Trials
Kathleen A. Kennedy, M.D., M.P.H.
Richard W. Mithoff Professor of Pediatrics
Director
Division of Neonatal-Perinatal Medicine
Director
M.S. in Clinical Research Degree Program
University of Texas-Houston Medical School

10:50 a.m. Does the Effect of Inhaled Nitric Oxide Therapy on Bronchopulmonary Dysplasia (BPD), Death, or Neurodevelopmental Impairment Vary Across Subpopulations of Premature Infants?
Robin H. Steinhorn, M.D.
Raymond and Hazel Speck Berry Professor of Pediatrics
Vice Chairperson, Pediatrics
Chief
Division of Neonatology
Children's Memorial Hospital
Feinberg School of Medicine of Northwestern University

11:10 a.m. Evidence-based Practice Center Presentation III: Inhaled Nitric Oxide in Preterm Infants: A Systematic Review of Treatment in Subpopulations, and by Dosage, Timing, and Mode of Therapy Delivery
Maureen M. Gilmore, M.D.
Assistant Professor of Pediatrics
Neonatal-Perinatal Medicine
Johns Hopkins Children's Center
Johns Hopkins Hospital
Division of Neonatology
Johns Hopkins Bayview Medical Center

11:30 a.m. **Discussion**

Thursday, October 28, 2010 *(continued)*

V. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia (BPD) and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

Noon Knowns and Unknowns of Administering Inhaled Nitric Oxide
Steven H. Abman, M.D.
Professor
Department of Pediatrics
Director
Pediatric Heart Lung Center
Director
Ventilator Care Program
Co-Director
Pediatric Pulmonary Hypertension Program
University of Colorado School of Medicine
Children's Hospital

12:20 p.m. **Discussion**

12:30 p.m. **Adjournment**

Friday, October 29, 2010

9:00 a.m. **Presentation of the Draft Consensus Statement**
The panel chairperson will read the draft statement to the assembled audience.

9:30 a.m. **Discussion of Draft Consensus Statement**
The panel chairperson will call for questions and comments from the audience on the draft statement, beginning with the introduction and continuing through each subsequent section, in turn. Please confine your comments to the section under discussion. The chairperson will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Participants with comments should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. For participants viewing the remote Webcast, comments may be submitted online at ***consensus.nih.gov/comments.htm.*** *Comments will not be accepted after 11:30 a.m. Please be aware that all statements made at the microphone or submitted later are in the public domain.*

Friday, October 29, 2010 *(continued)*

11:00 a.m. **Adjournment**
Panel Meets in Executive Session
The public portion of the conference ends at 11:00 a.m. The panel meets in its last executive session to review public comments on the draft statement.

2:00 p.m. **Press Telebriefing**
The panel will provide a summary of its findings to the press and will answer questions from reporters via telebriefing. Only members of the press are permitted to ask questions of the panel during this time. Interested conference participants who are not members of the press may call in (from a remote location) to listen to the live telebriefing. Please go to ***consensus.nih.gov*** *for instructions on joining the call.*

The panel's draft statement will be posted to ***consensus.nih.gov*** *as soon as possible after the close of proceedings, and the final statement will be posted 4 to 6 weeks later.*

Panel

Panel Chairperson: **F. Sessions Cole, M.D.**
Panel and Conference Chairperson
Park J. White, M.D. Professor of Pediatrics
Assistant Vice Chancellor for Children's Health
Vice Chairperson
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Gainesville, Florida

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Harvard Medical School
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Division of Pediatric Allergy, Immunology, and Pulmonary Medicine
Associate Professor of Medical Ethics
Center for Biomedical Ethics and Society
Vanderbilt University School of Medicine
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Howard Hughes Medical Institute
Chief of Neonatology
University of California, San Francisco
San Francisco, California

Speakers

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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

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Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

Epidemiology of Bronchopulmonary Dysplasia (BPD): Burden of Disease and Current Practice

Roger F. Soll, M.D.

Northway and colleagues first described bronchopulmonary dysplasia (BPD) as a condition characterized by chronic respiratory failure and characteristic radiographic changes in neonates after mechanical ventilation.[1] The lung damage seen in these infants was thought to be due to the effects of mechanical ventilation and the associated barotrauma as well as the toxic effects of high inspired oxygen concentrations. In subsequent decades, with the increased survival of less mature infants, different patterns and mechanisms of lung injury have emerged.[2,3] Infants with "new BPD" have a milder initial course of respiratory distress and require far less ventilator support and oxygen exposure. Nevertheless, these infants go on to show progressive deterioration in lung function, characterized by increasing ventilator and oxygen requirements and signs of ongoing respiratory failure.

Many factors have been implicated in contributing to BPD. Prematurity, oxygen toxicity, and exposure to positive pressure ventilation still have a significant role in causing BPD. The common pathway seems to be the creation of acute lung injury and inflammatory response. Other factors, such as infection or fluid overload, also may contribute to this injury and inflammatory response. Inflammation leads to airway damage, vascular injury, and interstitial damage.

Evolving patterns of disease have led to evolving definitions. BPD was first defined as "continued oxygen dependency during the first 28 days plus compatible clinical and radiographic changes." This definition, although useful in the initial categorization of BPD, fails when we consider the extremely low-birth-weight infant that is currently managed in the neonatal intensive care unit. If a definition of "oxygen requirement at 28 days" is used, well over 70% of extremely low-birth-weight infants would be categorized as having BPD. In 1988, Shennan and colleagues[4] suggested that oxygen requirement at 36 weeks postmenstrual age was a better predictor of long-term pulmonary outcome for very low-birth-weight infants. Using this definition, 32% of very low-birth-weight infants have BPD.[4] Newer definitions have tried to refine this approach.[5] The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development has demonstrated that they can decrease the variation in chronic lung disease reported by participating centers if they perform more rigorous physiologic testing.[6]

Can We Prevent Chronic Lung Disease?

Interventions to prevent chronic lung disease have been considered both before and after birth. At the root of the problem, any intervention that prevents preterm birth would be an important improvement in decreasing risk. Unfortunately, few therapies have been shown to prevent or postpone preterm labor. The only successful antenatal intervention is antenatal glucocorticosteroids for the promotion of lung maturity. Antenatal steroid treatment leads to a decrease in respiratory distress syndrome, chronic lung disease, and mortality and is used in well over 70% of all very low-birth-weight infants.

Postnatal Interventions

A wide variety of postnatal interventions to prevent BPD have been tested (Table 1),[7] but few have worked. Since ventilator-associated lung injury has always been thought to be a key contributor to BPD, research has been focused on innovative new devices or ventilation strategies that might minimize lung injury including patient-triggered ventilation, high-frequency ventilation, and permissive hypercarbia. These trials have not been able to demonstrate significant improvement in BPD. In fact, less invasive approaches to ventilation, including nasal continuous positive airway pressure ventilation and nasal intermittent positive pressure ventilation may well hold greater promise. Decreasing oxygen exposure by targeting lower saturation ranges may also decrease the risk of BPD.[8] Surfactant treatment leads to a greater number of survivors without BPD.

Other interventions have targeted various proposed pathways in the pathogenesis of BPD. Decreasing pulmonary edema (diuretics and treatment of patent ductus arteriosis), airway restriction (bronchodilators), and various anti-inflammatory agents (including alpha-1 protease inhibitor, superoxide dismutase, vitamin E) have all been tested with little or no effect. Of these medical interventions, only Vitamin A and caffeine offer some protection against the development of BPD.[9]

Postnatal steroid therapy has a significant impact on the oxygen requirement of treated infants. BPD defined at 28 days or at 36 weeks postmenstrual age is significantly reduced; however, concern has emerged regarding both short-term and long-term outcomes and the use of postnatal steroid therapy has been limited to only the sickest infants.[10,11]

Inhaled Nitric Oxide

Inhaled nitric oxide has been tested early in the course of respiratory distress and in infants with evolving chronic lung disease.[12] Only one study has demonstrated a small improvement in chronic lung disease in infants given a prolonged course of inhaled nitric oxide, beginning at around 1–2 weeks of life.[13]

Conclusion

Despite advances in neonatal intensive care, BPD remains a significant burden in the very low-birth-weight population. Infants with BPD are at greater risk of developmental complications, longer hospital stays, and greater costs. Therapeutic interventions that have positively impacted on BPD include antenatal corticosteroids, less invasive ventilatory support, surfactant therapy, vitamin A, and caffeine. Therapies, such as inhaled nitric oxide, hold some promise in this population but remain to be further tested.

Table 1. Prevention or Treatment of Bronchopulmonary Dysplasia (BPD): Common Postnatal Interventions—Evidence From Systematic Reviews or Large Randomized Controlled Trials

Intervention	Outcome			
	BPD at 28 Days	BPD or Death at 28 Days	BPD at 36 Weeks	BPD or Death at 36 Weeks
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Ventilator Support				
– Synchronized ventilation	0.91 (0.75, 1.12)	Not reported	0.90 (0.75, 1.08)	Not reported
– Permissive hypercapnia	0.67 (0.37, 1.21)	Not reported	1.05(0.16 6.77)	0.94 (0.78, 1.15)
– Elective HFOV	0.98 (0.88, 1.10)	0.94 (0.85, 1.04)	0.89 (0.81, 0.99)	0.90 (0.78, 1.03)
Noninvasive Support				
– Early CPAP	0.82 (0.71, 0.94)	0.83 (0.73, 0.96)	0.82 (0.65, 1.04)	0.87 (0.70, 1.07)
– NIPPV	Not reported	Not reported	0.73 (0.49, 1.07)	Not reported
Surfactant				
– Prophylactic administration	0.91 (0.79, 1.05)	0.80 (0.72, 0.88)	Not reported	Not reported
– Selective treatment	0.88 (0.69, 1.13)	0.73 (0.60, 0.88)	Not reported	Not reported
Postnatal Steroids				
– Inhaled	1.05 (0.84, 1.32)	0.96 (0.80, 1.14)	0.97 (0.62, 1.52)	0.86 (0.63, 1.17)
– Early systemic (<8 days)	0.87 (0.81, 0.93)	0.92 (0.88, 0.96)	0.79 (0.71, 0.88)	0.89 (0.84, 0.95)
– Late systemic (≥8 days)	0.87 (0.81, 0.94)	0.84 (0.78, 0.89)	0.72 (0.61, 0.85)	0.72 (0.63, 0.82)
Inhaled Nitric Oxide				
– Prophylaxis	Not reported	Not reported	0.96 (0.85, 1.08)	0.91 (0.84, 0.99)
– Rescue	Not reported	Not reported	0.89 (0.76, 1.05)	0.95 (0.88, 1.02)
– Late	Not reported	Not reported	0.89 (0.78, 1.05)	0.90 (0.80, 1.02)
Other Interventions				
Fluid Restriction	0.85 (0.63, 1.14)	Not reported	Not reported	Not reported
Oxygen Targeting	Not reported	Not reported	0.82 (0.72, 0.93)	Not reported
Diuretics	0.81 (0.41, 1.59)	0.95 (0.32, 2.76)	Not reported	Not reported
Bronchodilators	1.03 (0.78, 1.37)	Not reported	Not reported	Not reported
Caffeine	Not reported	Not reported	0.78 (0.70, 0.87)	Not reported
Vitamin A	0.93 (0.86, 1.01)	0.93 (0.88, 0.99)	0.87 (0.77, 0.98)	0.91 (0.82, 1.00)
Vitamin E	0.91 (0.73, 1.14)	Not reported	Not reported	Not reported
Superoxide Dismutase	0.80 (0.65, 0.98)	0.87 (0.73, 1.04)	0.79 (0.44, 1.41)	0.84 (0.53, 1.34)
α-1 Proteinase Inhibitor	0.80 (0.65, 0.98)	0.87 (0.73, 1.04)	0.83 (0.47, 1.47)	0.95 (0.61, 1.49)
Erythromycin	Not reported	Not reported	1.40 (0.72, 2.70)	1.06 (0.66, 1.69)
Indomethacin Prophylaxis	1.08 (0.92, 1.26)	Not reported	1.06 (0.92, 1.22)	Not reported

HFOV = high-frequency oscillatory ventilation; CPAP = continuous positive airway pressure; NIPPV = nasal intermittent positive pressure ventilation; RR = relative risk; CI = confidence interval.

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Biology of Bronchopulmonary Dysplasia (BPD) and Rationale for Inhaled Nitric Oxide Therapy

Philip W. Shaul, M.D.

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that primarily affects preterm infants who have required mechanical ventilation due to biochemical or structural lung immaturity or inadequate respiratory drive. The current primary form of BPD is characterized by a reduction in both lung vascularization and alveolar development, with alveoli that are reduced in number and larger than normal. The pathogenetic basis of BPD is multifactorial, and contributing processes include fetal and/or neonatal infection as well as other inflammatory mechanisms, oxygen therapy and reactive oxygen species, surfactant deficiency and ventilation-induced injury, nutritional deficiencies, and other factors.[1,2]

The signaling-molecule nitric oxide serves multiple functions in the developing lung. In animal models, the stimulation of nitric oxide production causes decreases in lung liquid production in late gestation, and the administration of nitric oxide or cyclic monophosphate, the second messenger for nitric oxide, into the fetal lung liquid has the same effect. Epithelium-derived nitric oxide is critical to the regulation of bronchomotor tone in the early newborn period, playing an important role in the opposition of airway contraction. Nitric oxide synthase (NOS) antagonism causes increased tissue resistance in the newborn lung, suggesting that endogenous nitric oxide also may regulate peripheral contractile elements. In addition, nitric oxide has a well-recognized role in mediating the pulmonary vasodilation that accompanies successful transition from the intrauterine to extrauterine environment. From the perspective of lung structural development, nitric oxide participates in lung-branching morphogenesis, promotes alveolarization and lung growth, and plays an important role in angiogenesis.[3]

Nitric oxide is produced by three isoforms of the enzyme NOS, which are referred to as neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) based on the initial cell types and conditions in which they were first characterized. Studies in the lungs of late-gestation primates revealed that all three NOS isoforms are primarily expressed in the airway epithelium; nNOS also is expressed in airway and vascular smooth muscle, and eNOS is predictably expressed in pulmonary endothelium.[3] In human lung in the latter half of gestation, all three NOS isoforms are similarly expressed in airway epithelium.[4] Further studies in the primate lung showed that total NOS enzymatic activity normally doubles in the early third trimester due to elevations in nNOS and eNOS expression, that this is associated with an elevation in airway nitric oxide production, and that total NOS activity remains elevated thereafter during gestation due to increases in iNOS expression that occur as nNOS and eNOS expression fall.[3]

Animal models of BPD have provided insights into possible changes in lung NOS expression and function during the pathogenesis of the disorder. In these models, lung nNOS and eNOS expression and enzymatic activity are markedly attenuated.[5,6] Consistent with the observations for eNOS, eNOS null mice display altered lung structure.[7,8] The findings regarding diminished lung NOS expression in BPD have not yet been replicated in humans, in which the timing and conditions under which sampling occurs are unavoidably complex.

In light of the multiple roles of nitric oxide in the developing lung and the available evidence suggesting nitric oxide deficiency during the genesis of BPD, the impact of inhaled nitric oxide

on animal models of BPD has been studied. In preterm primates placed on ventilatory support, inhaled nitric oxide improved early pulmonary function, enhanced lung growth, and blunted the exaggerated extracellular matrix deposition that is characteristic of BPD.[9] In preterm lambs, inhaled nitric oxide preserved the structure and function of airway smooth muscle and promoted alveolar development.[10] In neonatal rats, hyperoxia-induced lung vascular growth and impaired alveolarization were improved by inhaled nitric oxide,[11] and also improved pulmonary hypertension and lung structural abnormalities in bleomycin-induced BPD.[12] In newborn mice, inhaled nitric oxide prevented hyperoxia-induced recruitment of leukocytes into the lung and normalized alveolar number.[13] These collective observations indicate that multiple processes regulate nitric oxide production in the developing lung, that endogenous nitric oxide serves numerous functions of importance to both the structure and function of the developing lung, and that the provision of exogenous nitric oxide has potential benefits on the abnormalities characteristic of BPD.

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Trial: Nitric Oxide Therapy in Premature Infants With Respiratory Distress Syndrome

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Background

Endogenous nitric oxide contributes to lung development, including parenchymal growth, extracellular matrix deposition, modulation of surfactant, and inhibition of inflammation inhibition within the immature lung.[1] We hypothesized that delivery of nitric oxide by inhalation decreases the incidence of bronchopulmonary dysplasia (BPD) and death in premature infants with respiratory distress syndrome.[2]

Methods

We conducted a randomized, double-blind, placebo-controlled trial of inhaled nitric oxide in premature infants (less than 34 weeks gestation) who were undergoing mechanical ventilation for respiratory distress syndrome. The primary outcome was the combined incidence of BPD and death. During the first week of life, infants were randomly assigned to receive inhaled nitric oxide (10 ppm on day 1, followed by 5 ppm for 6 days) or placebo for 7 days. We further randomly assigned infants in each group to receive either intermittent mandatory or high-frequency oscillatory ventilation.

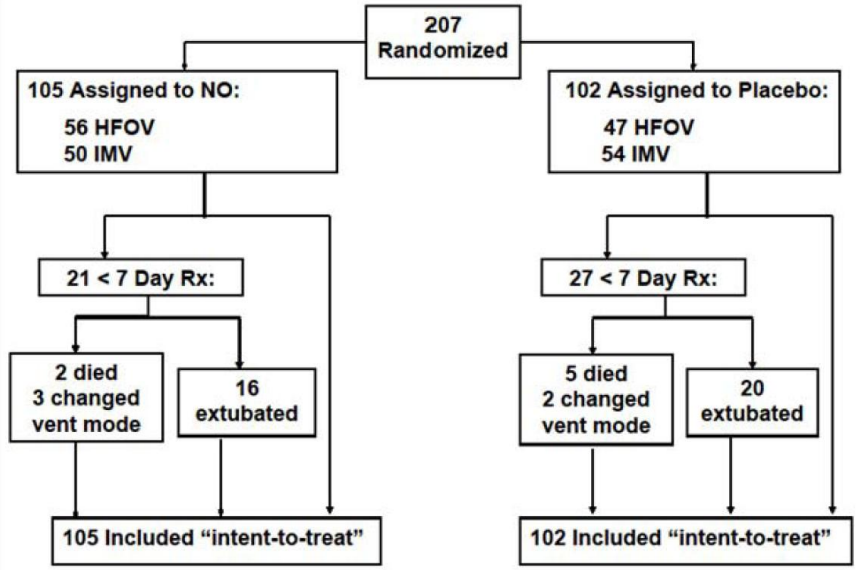
Results

The mean birth weight of enrolled infants (n=207) was 1 kg, and the mean gestational age was about 27 completed weeks. Figure 1 shows the flow of patients from randomization to analysis. Infants had moderate respiratory distress syndrome with a median oxygenation index of 7. Reflecting the patient population served by the University of Chicago, roughly 70% of the premature infants were black (Table 1). In the inhaled nitric oxide-treated group, 51 infants (48.6%) died or had BPD, as compared with 65 infants (63.7%) in the placebo group (relative risk, 0.76; 95% confidence interval, 0.60–0.97; p=0.03) (Table 2). Subgroup analysis revealed that improved pulmonary outcomes were restricted to infants having initial oxygen indices less than the median. There was no significant difference in the incidence of the primary outcome between infants treated with high-frequency oscillatory ventilation or intermittent mechanical ventilation. Neither was there a significant interaction between the type of study gas and the type of mechanical ventilation (p=0.11). Finally, there was no significant interaction between the type of study gas and birth-weight subgroups (p=0.36).

There was no significant difference between the inhaled nitric oxide and placebo groups in the overall incidence of intraventricular hemorrhage and periventricular leukomalacia (33.3% and 38.2%, respectively). However, the inhaled nitric oxide group had a lower incidence of severe (Papile Grade 3 and 4) intraventricular hemorrhage and periventricular leukomalacia (12.4% vs.

23.5%; relative risk, 0.53; 95% confidence interval, 0.28–0.98; *p*=0.040) (Table 3). The type of ventilation had no significant effect on any outcome. Treatment with inhaled nitric oxide did not alter the incidence of other complications of prematurity, such as air leak syndrome, pulmonary hemorrhage, necrotizing enterocolitis, late-onset sepsis, or retinopathy of prematurity. Three infants in the inhaled nitric oxide group had elevated methemoglobin concentrations. None exceeded 7%, and none was elevated on reevaluation. Nitrogen dioxide, which was continuously monitored throughout the study period, was never reported to be elevated (greater than 2 ppm).

Figure 1. Flow Diagram of Randomized Patients



NO = nitric oxide; HFOV = high-frequency oscillatory ventilation; IMV = intermittent mechanical ventilation; Rx = treatment.

Conclusions

In this randomized, controlled study, early treatment with inhaled nitric oxide improved pulmonary outcomes in premature infants with respiratory distress syndrome, decreasing the incidence of the combined end point of BPD and death. In addition, inhaled nitric oxide decreased the incidence of severe intraventricular hemorrhage and periventricular leukomalacia, the primary causes of serious, long-term neurologic disability in this population.

Table 1. Baseline Characteristics*

Characteristic	Inhaled Nitric Oxide (N=105)	Placebo (N=102)
Birth weight—grams	1,017±369	949±387
Gestational age—weeks	27.4±2.5	27.0±2.8
Age at study entry—hours		
Median	12.9	14.0
Interquartile range	7.0–25.2	7.6–28.5
Male sex—no. (%)	63 (60.0)	56 (54.9)
Mother's racial or ethnic group—no. (%)†		
Black	71 (67.6)	74 (72.6)
White	18 (17.1)	12 (11.8)
Other	16 (15.2)	16 (15.7)
Born at study hospital—no. (%)	80 (76.2)	80 (78.4)
Antenatal corticosteroids—no. (%)‡	58 (56.3)	52 (52.0)
Cesarean section—no. (%)	54 (51.4)	58 (56.9)
Apgar score at 1 minute		
Median	5	5
Interquartile range	3–6	3–6
Apgar score at 5 minutes		
Median	7	7
Interquartile range	6–8	6–8
Small for gestational age—no. (%)	6 (5.7)	9 (8.8)
Initial oxygenation index§		
Median	7.3	6.8
Interquartile rage	4.1–12.3	4.4–12.7
Early-onset sepsis—no. (%)¶	5 (4.8)	12 (11.8)
Surfactant no. of doses	2.3±0.9	2.2±1.0

*Plus–minus values are means ±SD.
†The racial or ethnic group was self-reported.
‡Data were missing for two infants in the nitric oxide group and two in the placebo group.
§The oxygenation index was calculated as (100 x the fractional inspiratory oxygen concentration x the mean airway pressure) ÷ the partial pressure of arterial oxygen.
¶Early-onset sepsis was defined as sepsis that occurred within 24 hours after birth.
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Table 2. Primary Outcome

Outcome	Inhaled Nitric Oxide (N=105)	Placebo (N=102)	*P* Value	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)*
	No. (%)				
Death or chronic lung disease	51 (48.6)	65 (63.7)	0.03	0.76 (0.60–0.97)	0.77 (0.60–0.98)
Death	16 (15.2)	23 (22.5)	0.18	0.68 (0.38–1.20)	0.68 (0.38–1.20)
Survival	89 (84.8)	79 (77.5)			
Survival without chronic lung disease	54 (60.7)	37 (46.8)			
Survival with chronic lung disease	35 (39.3)	42 (53.2)	0.07	0.74 (0.53–1.03)	0.75 (0.54–1.05)

CI = confidence interval.
*Values were adjusted for the type of ventilation.
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Table 3. Secondary Outcomes

Outcome	Inhaled Nitric Oxide (N=105)	Placebo (N=102)	Relative Risk (95% CI)	*P* Value*
	No. (%)			
Severe intraventricular hemorrhage and periventricular leukomalacia	13 (12.4)	24 (23.5)	0.53 (0.28–0.98)	0.04
Pneumothorax	11 (10.5)	16 (15.7)	0.67 (0.33–1.37)	0.27
Pulmonary interstitial emphysema	28 (26.7)	35 (34.3)	0.78 (0.51–1.18)	0.23
Pulmonary hemorrhage	4 (3.8)	7 (6.9)	0.56 (0.17–1.84)	0.37†
Symptomatic patent ductus arteriosus	20 (19.0)	26 (25.5)	0.75 (0.45–1.25)	0.27
Necrotizing enterocolitis‡	13 (12.4)	6 (5.9)	2.10 (0.83–5.32)	0.11
Late-onset sepsis§	54 (51.4)	50 (49.0)	1.05 (0.80–1.38)	0.73
Retinopathy of prematurity¶	6 (5.7)	10 (9.8)	0.58 (0.22–1.54)	0.27
Hydrocephalus	12 (11.4)	10 (9.8)	1.17 (0.53–2.58)	0.71

CI = confidence interval.
**P* values were calculated with the use of Pearson's chi-square test, except when otherwise specified.
†The *P* value was calculated with the use of Fisher's exact test.
‡Necrotizing enterocolitis was defined by a Bell's stage of 2 or greater.
§Late-onset sepsis was defined as sepsis that occurred after 24 hours of age.
¶Retinopathy of prematurity was defined by an international classification stage of 3 or greater.
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Inhaled Nitric Oxide for Premature Infants With Severe Respiratory Failure: Preemie Inhaled Nitric Oxide (PiNO) Trial Results

Krisa P. Van Meurs, M.D.

Inhaled nitric oxide initially demonstrated only short-term improvements in oxygenation in preterm infants until a single-center study reported a decrease in the incidence of bronchopulmonary dysplasia (BPD) or death in moderately ill preterm infants.[1] The objective of the Preemie Inhaled Nitric Oxide trial was to determine if inhaled nitric oxide use benefited the preterm infant with severe respiratory failure by reducing mortality or BPD.[2]

Hypotheses

The primary hypothesis was that inhaled nitric oxide use in neonates less than 34 weeks gestation with a birth weight of 401–1,500 grams and with severe respiratory failure would reduce the incidence of BPD or death. The secondary hypotheses were that inhaled nitric oxide would not increase the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, and that it would decrease the physiologic need for oxygen,[3] days of assisted ventilation and oxygen use, the length of hospitalization, and the incidence of threshold retinopathy.

Eligibility Criteria

Eligible infants were less than 34 weeks gestation with a birth weight of 401–1,500 grams, required mechanical ventilation, and had a diagnosis of respiratory distress syndrome, sepsis or pneumonia, aspiration syndrome, idiopathic persistent pulmonary hypertension, or suspected pulmonary hypoplasia. Infants were eligible between 4 and 120 hours of age, 4 hours after receiving surfactant and meeting the respiratory severity criteria, oxygenation index of 10 or greater on two consecutive blood gases between 30 minutes and 12 hours apart. Because the mortality rate was significantly higher in both treatment groups, these criteria were modified at the first interim analysis of the data safety and monitoring committee to an oxygenation index of 5 or greater followed by 7.5 or greater. Infants were ineligible if they had congenital heart disease other than ventricular septal defect, atrial-level shunt, or patent ductus arteriosus; any major congenital anomaly involving the respiratory system; thrombocytopenia or bleeding diathesis; or if a decision had been made to limit treatment.

Study Procedures

Infants were randomly assigned to inhaled nitric oxide or placebo according to center and three birth-weight strata (401–750 grams, 751–1,000 grams, 1,001–1,500 grams). A baseline blood gas was drawn, 5 ppm study gas administered for 30 minutes, and a repeat blood gas sent. If there was ≥20 mm Hg increase in PaO_2 (complete response), study gas was continued at 5 ppm. For less than a complete response, study gas was increased to 10 ppm and administered for 30 minutes. Infants with ≥10 mm Hg increase in PaO_2 (partial response) were maintained on 10 ppm of study gas. If there was <10 mm Hg increase in PaO_2 (no response), study gas was discontinued. Weaning from study gas followed a defined protocol. Safety monitoring included

blood methemoglobin levels at defined time points, continuous nitrogen dioxide monitoring, and cranial ultrasounds at 28±7 days.

Results

The trial was terminated on the recommendation of the data safety and monitoring committee at the second planned interim analysis with 66% of the target enrollment at a study end point. The incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia was significantly higher in the inhaled nitric oxide group, and there was no apparent benefit of the treatment on the primary outcome. At this point, 420 infants were enrolled instead of the planned enrollment of 440. There were no significant differences between treatment groups in baseline characteristics or status at randomization.

Primary and Secondary Outcomes

There was no difference in the primary outcome of BPD or death between the two treatment groups (see Table 1). There were no discernable differences in the age at death or cause of death between the two groups.

Table 1. Primary Outcome

	Inhaled Nitric Oxide (n=210)	Placebo (n=210)	Relative Risk (95% Confidence Interval)	*P* Value
Death or BPD	167 (80)	170 (82)	0.97 (0.86–1.06)	0.52
Death	109 (52)	93 (44)	1.16 (0.96–1.39)	0.11
BPD	65 (60)	86 (68)	0.90 (0.75–1.08)	0.26

BPD = bronchopulmonary dysplasia.

The rate of severe intraventricular hemorrhage or periventricular leukomalacia was not significantly different between the two groups according to concurrent local radiology readings (39% vs. 32%, p=0.11) or by central readings (37% vs. 39%, p=0.81). Both were based on the worst results of all ultrasounds performed during the hospitalization. There were no significant differences in the two treatment groups with respect to the other secondary outcomes including the physiologic need for oxygen.

Post-Hoc Analyses

Post-hoc analyses evaluated the relationship among birth weight, mode of ventilation, and severity of illness, as measured by oxygenation index, on the primary outcome and incidence of severe intraventricular hemorrhage or periventricular leukomalacia. The interaction between treatment assignment and birth weight had a significant effect on death (p=0.02) as well as on death or BPD (p=0.02). Infants more than 1,000 grams treated with inhaled nitric oxide had a lower rate of death or BPD, while those who were 1,000 grams or less and were treated with inhaled nitric oxide had a higher mortality and rate of severe intraventricular hemorrhage or periventricular leukomalacia (Table 2).

Table 2. Post-Hoc Analyses According to Birth Weight

	Inhaled Nitric Oxide n (%)	Placebo n (%)	Relative Risk (95% Confidence Interval)	*P* Value
≤1,000 grams	158	158		
Death/BPD	141 (89)	133 (85)	1.04 (0.96–1.13)	0.29
Death	98 (62)	76 (48)	1.28 (1.06–1.54)	0.01
BPD	49 (73)	65 (73)	1.02 (0.85–1.23)	0.84
Severe IVH/PVL	55 (43)	39 (33)	1.40 (1.03–1.88)	0.03
>1,000 grams	52	52		
Death/BPD	26 (50)	35 (69)	0.72 (0.54–0.96)	0.03
Death	11 (21)	17 (33)	0.65 (0.36–1.18)	0.16
BPD	16 (38)	21 (57)	0.68 (0.45–1.05)	0.08
Severe IVH/PVL	14 (27)	11 (30)	0.95 (0.53–1.69)	0.86

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage;
PVL = periventricular leukomalacia.

The interaction between treatment group and ventilation mode had a significant effect on mortality (p=0.03). Infants receiving inhaled nitric oxide on conventional mechanical ventilation had higher mortality compared to the placebo-treated group (62% vs. 40%, relative risk 1.46, confidence interval 1.10–1.92, p=0.01). The interaction between treatment group and oxygenation index was not significant.

Conclusion

The use of inhaled nitric oxide as performed in the PiNO trial in critically ill premature infants less than 1,500 grams and less than 34 weeks initiated early after birth did not decrease death or BPD. Post-hoc analysis suggests that infants 1,000 grams or less who are treated with inhaled nitric oxide have both higher mortality and higher rates of severe intraventricular hemorrhage and periventricular leukomalacia, while those more than 1,000 grams have reduced rates of death and BPD. Multicenter trials of inhaled nitric oxide therapy have used varying entry criteria, inhaled nitric oxide dose, and length of therapy.[2,4–9] No benefit has been found for the "rescue" use of inhaled nitric oxide in critically ill preterm infants[2,4–6] or for the routine early use of inhaled nitric oxide in preterm infants requiring mechanical ventilation in multicenter trials.[7,9] The only multicenter trial demonstrating an improvement in survival without BPD enrolled infants at 7–21 days of age requiring conventional mechanical ventilation or continuous positive airway pressure and administered a higher initial dose of 20 ppm of inhaled nitric oxide for a longer duration of therapy.[8] Post-hoc subgroup analysis found a significant interaction between age at study entry and treatment (p=0.006). There was significant benefit in infants treated between 7–14 days of age but not in those 15–21 days of age.

In summary, early use of inhaled nitric oxide has not been shown to benefit the preterm infant who is critically or mildly ill. However, the use of inhaled nitric oxide for evolving BPD started at a later postnatal age, at a higher initial dose, and continued for a longer time period appears to provide benefit by increasing survival without BPD and improving pulmonary medication use at 12 months of age.[10]

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Trial: Early Inhaled Nitric Oxide Therapy in Premature Newborns With Respiratory Failure

John P. Kinsella, M.D.

Early studies suggested that inhaled nitric oxide can improve gas exchange in premature newborns with hypoxemia due to respiratory distress syndrome or persistent pulmonary hypertension of the newborn.[1–4] In addition to effects on gas exchange and pulmonary hypertension, laboratory studies have shown inhaled nitric oxide can decrease early lung inflammation and oxidant stress,[5–7] sustain surfactant activity,[8] and improve lung structure in diverse models of bronchopulmonary dysplasia (BPD).[9–11] These findings suggested that inhaled nitric oxide may potentially reduce early lung injury leading to the development of BPD.[12]

Laboratory and clinical studies have suggested that high doses of inhaled nitric oxide may increase the risk of bleeding,[13,14] a paramount concern because of the predisposition of premature newborns to intracranial hemorrhage. Although an early multicenter, randomized, controlled trial of low-dose inhaled nitric oxide in premature newborns with severe hypoxemic respiratory failure showed no increased risk for intracranial hemorrhage,[4] two studies reported contradictory findings regarding the safety and efficacy of inhaled nitric oxide.[15,16]

We hypothesized that prolonged treatment with low-dose inhaled nitric oxide (5 ppm) would reduce a combined end point of mortality and BPD in premature newborns, without increasing incidence or progression of severe intracranial hemorrhage or periventricular leukomalacia. We also hypothesized that the impact of inhaled nitric oxide therapy may be dependent on the degree of prematurity.

We performed a multicenter trial that randomized 793 premature newborns of gestational age 34 weeks or less with respiratory failure, stratified by birth weight (500 to 1,250 grams). Newborns were randomized to inhaled nitric oxide (5 ppm) or placebo gas (controls) for 21 days or until extubation. The primary efficacy outcome was a composite of death or BPD at 36 weeks postmenstrual age. Secondary (safety) outcomes included severe intracranial hemorrhage, periventricular leukomalacia, and ventriculomegaly.

For the overall study population, the combined end point of death or BPD was not different between study groups (75.3% control, 71.6% inhaled nitric oxide; p=0.24) (Table 1). However, there was a significant interaction (p<0.001) between birth-weight strata and treatment. Prespecified subgroup analyses based on birth-weight stratification showed significant reductions in the combined primary outcome (p=0.0036) and in BPD alone (p<0.001) with inhaled nitric oxide therapy in the group with a birth weight of 1,000 to 1,250 grams.

Infants treated with low-dose inhaled nitric oxide had a lower incidence of periventricular leukomalacia (5.2% vs. 9%; p=0.048) (Figure 1). No interaction with birth-weight strata was found for periventricular leukomalacia. There was, however, a significant interaction between birth-weight strata and the combined outcome of intracranial hemorrhage/periventricular leukomalacia (p=0.044), with the largest reduction in this outcome with inhaled nitric oxide therapy found in the 750- to 999-gram stratum; (p=0.006).

Table 1. Death/Bronchopulmonary Dysplasia (BPD)

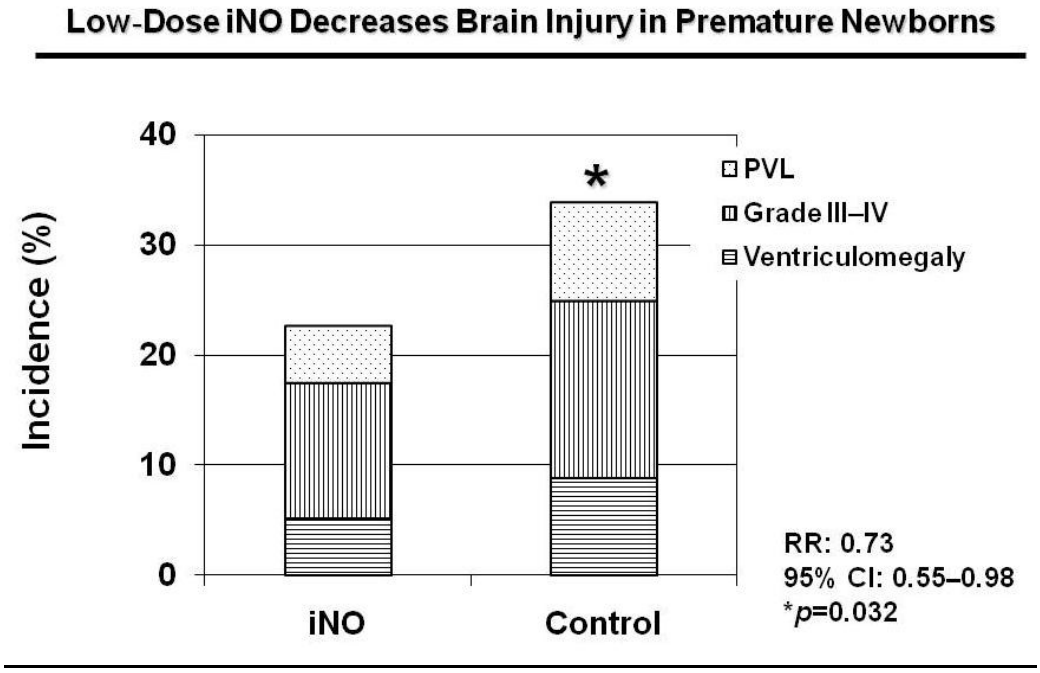
	Inhaled Nitric Oxide No. (%) (n=398)	Placebo No. (%) (n=395)	*P* Value	Relative Risk (95% Confidence Interval)
All patients				
Death	78 (19.8)	98 (25.0)	0.08	0.79 (0.61–1.03)
BPD	212 (65.0)	210 (68.0)	0.43	0.96 (0.86–1.09)
Death/BPD	282 (71.6)	295 (75.3)	0.24	0.95 (0.87–1.03)
Stratum 1: 500–749 grams				
Death	55 (28.8)	66 (34.9)	0.20	0.82 (0.61–1.11)
BPD	113 (78.5)	100 (75.8)	0.59	1.04 (0.91–1.18)
Death/BPD	162 (84.8)	159 (84.1)	0.85	1.01 (0.92–1.10)
Stratum 2: 750–999 grams				
Death	15 (10.9)	24 (17.3)	0.13	0.63 (0.35–1.15)
BPD	82 (65.6)	76 (63.3)	0.71	1.04 (0.86–1.25)
Death/BPD	95 (68.8)	95 (68.4)	0.93	1.01 (0.86–1.18)
Stratum 3: 1,000–1250 grams				
Death	8 (12.3)	8 (12.5)	0.97	0.98 (0.39–2.46)
BPD	17 (29.8)	34 (59.7)	0.001	0.50 (0.32–0.79)
Death/BPD	25 (38.5)	41 (64.1)	0.004	0.60 (0.42–0.86)

During the study period, there were no significant differences between the groups in the rates of serious adverse events, including air leak, pulmonary hemorrhage, need for medical or surgical treatment of patent ductus arteriosus, necrotizing enterocolitis, threshold retinopathy of prematurity, or sepsis. There also were no significant differences between groups in rates of postnatal corticosteroid use or treatment with respiratory medications at 36 weeks postmenstrual age, or in the durations of ventilator therapy or of hospitalization.

In this multicenter, randomized, controlled trial of inhaled nitric oxide therapy in premature newborns, we found that low-dose inhaled nitric oxide therapy (5 ppm) administered within 48 hours after birth for a median treatment period of 14 days did not decrease the incidence of a composite end point of death or BPD in infants with birth weights between 500 and 1,250 grams who required mechanical ventilation after birth. However, inhaled nitric oxide therapy significantly decreased the incidence of BPD, and the combined end points of death or BPD, by 50% and 40%, respectively, in premature newborns with birth weights 1,000 to 1,250 grams. Early, low-dose inhaled nitric oxide reduced the risk of brain injury in this population of premature newborns with respiratory failure and birth weight of 500 to 1,250 grams.

Serious adverse events were not increased with inhaled nitric oxide therapy in the population overall or within any of the birth-weight-related strata. These findings suggest that early treatment with low-dose inhaled nitric oxide therapy can safely and effectively improve neurologic and respiratory outcomes in premature infants.

Figure 1. Cranial Ultrasound Results



iNO = inhaled nitric oxide; PVL = periventricular leukomalacia; RR = relative risk; CI = confidence interval.

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Inhaled Nitric Oxide for Prevention of Bronchopulmonary Dysplasia (BPD) in Premature Babies: The European Nitric Oxide (EUNO) Randomized Controlled Trial

Jean-Christophe Mercier, M.D., M.Sci., on Behalf of the EUNO Study Group[1]

In animal models, inhaled nitric oxide improved gas exchange and lung structural development,[2,3] but its use in premature infants at risk of developing bronchopulmonary dysplasia (BPD) remains controversial. We therefore tested the hypothesis that inhaled nitric oxide at low concentration, started early and maintained for an extended period in babies with mild respiratory failure, might increase survival without BPD.

This study was done in 36 centers in 9 countries of the European Union between May 2005 and February 2008. The study was approved by the national health authority in each country and locally by the ethics committees. Written consent for participation was obtained from parents in accordance with local requirements. A steering committee designed and monitored the study, reviewed the data, and wrote the report. An independent data and safety monitoring committee reviewed unmasked safety data and did a scheduled interim analysis that was based on prospectively defined criteria.

Babies born less than 30 weeks of gestational age were screened for enrollment. They were eligible for randomization if they were inborn, had a gestational age at birth between 24 and 28 weeks plus 6 days (inclusive), weighed at least 500 grams, and required surfactant within 24 hours of birth (prophylactically or for signs of developing respiratory distress) or continuous positive airway pressure (FiO_2 >0.3 on mean airway pressure >4 cm H_2O) within 24 hours of birth to maintain a $SpO_2 \geq 85\%$.

Infants were excluded if they required FiO_2 >0.5 to maintain $SpO_2 \geq 85\%$ on a sufficient mean airway pressure (e.g., >8 cm H_20 on intermittent mandatory ventilation) to achieve lung expansion (i.e., more than 8–9 ribs on the chest x-ray) 2 hours after administration of exogenous surfactant; had substantial congenital heart disease, lung hypoplasia, or abnormal hemostasis; or had substantial congenital disorders such that full treatment was not indicated. A standardized management protocol for all other care was suggested for participating centers.

Patients were randomly assigned in a one-to-one ratio to inhaled nitric oxide or placebo. Randomization was stratified by study site and gestational age (i.e., 24–25 weeks plus 6 days and 26–28 weeks plus 6 days). Randomization was done centrally at INO Therapeutics in blocks of four. The study drug cylinders were labeled with random four-digit kit numbers and were assigned to patient use through an interactive Web site. Inhaled nitric oxide was provided as 400 ppm in nitrogen in 10-liter cylinders, while placebo gas was only nitrogen. Treatment was given by the use of a masked INOVent drug delivery system (Datex-Ohmeda, Madison, Wisconsin). Therefore, the care providers and investigators were unaware of the allocation of the study gas until the last baby reached 36 weeks postmenstrual age.

Baseline respiratory status, respiratory support, and methemoglobin were recorded. Infants were given 5 ppm inhaled nitric oxide or placebo nitrogen gas. This dose was chosen because it successfully prevented the development of BPD or brain injury with mild to moderate respiratory

distress in previous trials. Treatment was initiated within 2 hours of qualification and no later than 26 hours of life. Therapy was given for at least 7 days, up to a maximum of 21 days. If patients needed mechanical ventilation for less than 7 days, therapy was completed through nasal continuous positive airway pressure or nasal cannula.

The primary end point was survival without BPD at 36 weeks postmenstrual age, as defined by the physiological criteria of Walsh et al.[4]

Secondary end points included survival without substantial brain injury, which was defined as grade 3 or 4 intracranial hemorrhage, or periventricular leukomalacia according to the criteria of Deeg et al.[5] on the basis of head ultrasound images. Infants had a baseline head ultrasound within 72 hours of initiation of therapy, which was repeated at days 7 and 21 and week 36. Head ultrasounds were done locally in accordance with a standardized protocol, and were assessed for quality and read centrally by two independent readers, with a third reader adjudicating differences. Other secondary end points were days on ventilatory support and in the hospital.

Safety end points included overall survival, adverse events, including intracranial hemorrhage, periventricular leukomalacia, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, and sepsis. All neonates will be followed up for pulmonary and neurodevelopmental outcomes at ages 1, 2, and 7 years.

We assumed that 20% of enrolled infants would die and that 20% of survivors would have BPD (i.e., a success rate of 64% on the basis of survey outcomes from participating countries). A sample size of 800 babies was sufficient to detect a 20% improvement in survival without the development of BPD from 64% to 77% with 80% power for a type 1 error of 5%. An interim analysis was planned after the first 400 infants completed the trial, with prespecified rules for stopping for efficacy ($p>0.0015$) and futility ($p<0.1$ in favor of placebo).

Data were gathered on paper forms after onsite monitoring. All data management and statistical analyses were done at INO Therapeutics. All data were double-key entered into a validated database, and analyses were done with Statistical Analysis Software. The U.S. Food and Drug Administration reviewed the analysis plan before the data were unmasked. For the interim analysis and final safety review, all data were analyzed by the University of Glasgow Centre of Biostatistics, United Kingdom, and provided to the independent data safety monitoring committee. This study is registered with ClinicalTrials.gov, number NCT00551642.

The intention-to-treat population was all 800 babies who were entered into the study and randomly assigned to treatment (401 to placebo, 399 to inhaled nitric oxide). Of these, 792 (99%) were given the assigned treatment (397 to placebo, 395 to inhaled nitric oxide). BPD status was not available in 1 and 4, so 400 and 395 infants were analyzed on the intent-to-treat basis, respectively. The groups were well matched for baseline characteristics (Table 1).

Mean duration of therapy was 16.4 days (standard deviation [SD] 6.6) in infants given placebo and 16.3 days (SD 6.5) in those given inhaled nitric oxide. After exclusion of patients who died during therapy, mean duration of treatment was 17.4 days (SD 5.9) and 17.3 days (SD 5.9), respectively. The number of infants who were extubated and supported by nasal continuous positive airway pressure or nasal cannula during the 3-week treatment increased in both placebo and inhaled nitric oxide groups at day 7, 14, and 21, respectively; the difference between the groups was not significant (Table 2).

Table 1. Baseline Characteristics of Neonates

	Placebo (n=401)	Inhaled Nitric Oxide (n=399)
Gestational age (weeks)	26.6 (1.3)	26.4 (1.3)
Birth weight (grams)	864 (192)	851 (207)
Male sex	220 (55%)	207 (52%)
Mother's race or ethnic origin		
White	328 (82%)	329 (82%)
Black	48 (12%)	39 (10%)
Asian	2 (<1%)	4 (1%)
Other	23 (6%)	27 (7%)
Prenatal history		
Chorioamnionitis	94 (23%)	110 (28%)
Prenatal steroids	362 (90%)	357 (89%)
Spontaneous delivery	126 (31%)	136 (34%)
Multiple gestation	120 (30%)	116 (29%)
Postnatal surfactant	353 (88%)	356 (89%)
Oxygenation index	8.6 (12.7)	8.0 (10.7)
Continuous positive airway pressure	42 (10%)	41 (10%)
Intubated	359 (90%)	358 (90%)

Note: Data are number (%) or mean (standard deviation).

Table 2. Ventilatory Support

	Placebo					Inhaled Nitric Oxide					*P* Value*
	n†	Off	Nasal cannula	CPAP	MV	n†	Off	Nasal cannula	CPAP	MV	
Baseline	401	0	0	42 (10%)	359 (90%)	399	0	0	41 (10%)	358 (90%)	—
Day 7	337	8 (2%)	0	184 (55%)	145 (43%)	342	3 (1%)	0	169 (49%)	170 (50%)	0.09
Day 14	291	34 (12%)	0	126 (43%)	131 (43%)	290	30 (10%)	0	127 (44%)	133 (46%)	0.889
Day 21	308	112 (36%)	20 (6%)	94 (31%)	82 (27%)	296	97 (33%)	21 (7%)	97 (33%)	81 (27%)	0.824

CPAP = continuous positive airway pressure; MV = mechanical ventilation; Off = off ventilatory support.
*Calculated by use of Fischer's exact test.
†Variations in total number at each time point are due to missing values.

There was no significant difference in survival without developing BPD between the two groups at 36 weeks postmenstrual age (Table 3). Although success was higher in girls than in boys, there was no treatment-related difference in relative risk. Infants born at a gestational age of 26 weeks or greater had a higher likelihood of survival without BPD than did younger infants. Neither stratum showed a benefit from inhaled nitric oxide. Although the difference in survival was not significant between infants given placebo or inhaled nitric oxide, a higher survival was noted in black infants given inhaled nitric oxide without developing BPD than in those who were not black. Gestational age also was a significant covariate for acute brain injury; infants born at 26 weeks or greater had a higher likelihood of survival without brain injury than did younger infants.

There were no significant differences in the two groups in the duration of mechanical ventilation (mean 45 days [SD 29] in the placebo group vs. 44 days [SD 26] in the inhaled nitric oxide

group; *p*=0.72) or time to hospital discharge (94 days [SD 36] vs. 93 [SD 35], respectively; *p*=0.68).

Table 3. Primary and Secondary Outcomes

	Placebo	Inhaled Nitric Oxide	Relative Risk (95% CI)	*P* Value
Primary end point				
Alive without BPD	262/400 (66%)	258/395 (65%)	1.05 (0.78–1.43)	0.73
Alive at 36 weeks postmenstrual age	359/401 (90%)	343/399 (86%)	0.74 (0.48–1.15)	0.21
BPD at 36 weeks postmenstrual age	96/358 (27%)	81/339 (24%)	0.83 (0.58–1.17)	0.29
Primary end point by gestational age (GA)				
Alive without BPD (GA <26 weeks)	67/134 (50%)	75/141 (53%)	1.14 (0.71–1.82)	0.60
Alive without BPD (GA ≥26 weeks)	195/266 (73%)	183/254 (72%)	0.94 (0.64–1.38)	0.75
Primary end point by race				
Alive without BPD (black)	28/48 (58%)	25/37 (68%)	1.49 (0.61–3.65)	0.38
Alive without BPD (nonblack)	234/352 (66%)	233/358 (65%)	0.94 (0.69–1.28)	0.70
Secondary end point				
Alive without brain injury at GA 36 weeks	188/249 (76%)	181/261 (69%)	0.78 (0.53–1.17)	0.23
Alive without brain injury with GA <26 weeks	62/91 (68%)	66/109 (61%)	0.72 (0.40–1.29)	0.27
Alive without brain injury with GA >26 weeks	126/158 (80%)	115/152 (76%)	0.79 (0.46–1.35)	0.39

BPD = bronchopulmonary dysplasia; CI = confidence interval.
Note: BPD assessed at mean postmenstrual age of 36 weeks (standard deviation 3 days).

Adverse events were common. Rates of adverse events suspected to be related to the study drug were similar in infants given inhaled nitric oxide and placebo. The stratum of neonates of gestational age 26 weeks or greater treated with inhaled nitric oxide had more adverse events than did those treated with placebo. However, between-group differences in serious adverse events were not significant.

Treatment with inhaled nitric oxide did not significantly increase survival of premature infants without development of BPD at 36 weeks postmenstrual age. Unlike Van Meurs et al.,[6] we targeted a population of babies with mild to moderate respiratory distress with FiO_2 less than 0.50, which corresponds to an oxygenation index between 5 and 10 on routinely used levels of mean airway pressure with intermittent mandatory ventilation or continuous positive airway pressure. Such an approach was in accord with a post-hoc analysis by Schreiber et al.,[7] who noted that inhaled nitric oxide was effective in reducing the number of infants who died or survived with BPD only in the infants with an oxygenation index of 6.94 or less at entry.

We targeted a specific subset of premature babies and were successful in enrolling that subset. Unlike the trial of Kinsella et al.,[8] we allowed newborn babies to enter and remain in the study on nasal continuous positive airway pressure, knowing that this would allow newborn babies with less severe respiratory failure to enter and all babies to remain on inhaled nitric oxide therapy for longer.

Inhaled nitric oxide showed a lack of treatment effect. There are several possible reasons for this result. The demographics of the study population differed from previous studies. Unlike most large studies of inhaled nitric oxide in premature infants, our study was done entirely in the European Union and all infants were born at investigator facilities. The proportion of infants reported as white was larger than in the trials in the United States. The results of Schreiber et al.[7] with a predominantly black population showed a clear benefit, whereas Kinsella et al.[8] and Ballard et al.[9] showed a small benefit. In our trial, black babies seemed to have a greater response to inhaled nitric oxide than did nonblack babies. Ethnic origin affects susceptibility to

chronic lung diseases.[10] Similarly, the treatment benefit from inhaled nitric oxide might be related to ethnic origin, and this should be investigated in a meta-analysis of relevant trials. We need to consider whether the dose was appropriate and adequately delivered. Schreiber et al.[7] and Kinsella et al.[8] used low-concentration inhaled nitric oxide, but all infants were intubated at study entry; Ballard et al.[9] allowed some babies to enter the study while on nasal continuous positive airway pressure, but the initial dose was 20 ppm for the first 48–72 hours. Unlike the Kinsella et al. trial,[8] we allowed newborn babies to enter and remain in the study on nasal continuous positive airway pressure, knowing that newborn babies with less severe respiratory failure would be allowed study entry and all babies could then remain on inhaled nitric oxide for longer. The optimum inhaled nitric oxide dose needed to promote angiogenesis is not known. Inhaled nitric oxide might not have been delivered in sufficient concentration in the alveoli to be effective; however, almost half of the babies in our trial were intubated for at least 2 weeks of treatment. We noted a substantial difference in the rate of successful outcome with placebo versus previous trials. The survival rate without BPD was high; mortality was low in our study. The selection of babies at low risk of BPD and the level of prenatal and postnatal care might have prevented inhaled nitric oxide from having any additional benefit in the improvement of survival without BPD.

The lower survival without brain injury in the infants given inhaled nitric oxide than in those given placebo is a cause for concern. Despite differences in the assessment of brain injury, the low incidence of severe intracranial hemorrhage in our trial in the infants given placebo and inhaled nitric oxide is striking when compared to other trials. In a systematic review of clinical studies of inhaled nitric oxide for preterm infants, an increased incidence of this adverse outcome was noted with the early rescue treatment. We excluded babies with severe respiratory failure, but they were enrolled on their first day of life in accordance with a strategy for prevention of BPD. Further analysis of a large number of patients, including those in our study, should clarify whether the incidence of severe intracranial hemorrhage becomes significant.[11]

Several clinical trials of the effects of inhaled nitric oxide in preterm infants had widely differing inclusion criteria, treatment regimens, and outcome measures, and their results were mixed.[6–9] Three distinct uses of inhaled nitric oxide in premature babies are prevention of BPD, treatment of BPD, and rescue therapy. Prevention implies a strategy to treat a large number of infants with mild respiratory distress early with a low dose to keep possible harm to a minimum. Treatments in Kinsella et al.[8] and our studies could be thought of as preventive, but, on the basis of the evidence, this approach is not useful. A treatment strategy implies management of established disease (i.e., newborns requiring mechanical ventilation days after birth), despite maximum medical management. This group might have been at increased potential to benefit from inhaled nitric oxide and would probably show benefit in controlled trials. This approach, used by Ballard et al.,[9] might be promising and deserves further investigation. Rescue therapy also should be considered. Inhaled nitric oxide is used nonspecifically to improve oxygenation in an infant with life-threatening respiratory failure. The goal of therapy is supportive, without expectation of long-term benefit on morbidity or mortality. Results of previous studies have shown that inhaled nitric oxide improves oxygenation in the short term, without much evidence for long-term benefit.[6] This use of inhaled nitric oxide might be helpful in specific circumstances, but substantial long-term benefit to the underlying disorder is unlikely.

Thus, early use of low-dose inhaled nitric oxide in very premature babies did not improve survival without BPD or brain injury, suggesting that such a preventive treatment strategy is unsuccessful.

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Trial: The Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) Trial

Roberta A. Ballard, M.D., and the NO CLD Investigators

Question I: Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?

The Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) Trial[1,2] was markedly different in hypothesis, population, dose of inhaled nitric oxide, and biostatistical analysis of multiples from other trials of inhaled nitric oxide in preterm infants.

Hypothesis

In this prophylactic trial, we hypothesized that inhaled nitric oxide would result in improved survival without BPD by decreasing airway muscularization and improving angiogenesis and alveolarization as in the animal model. (Discussed by Dr. Philip W. Shaul at this conference.)

Population

Preterm infants requiring mechanical ventilation between 7 and 21 days of age were selected because (1) infants who are still alive and require ventilation after 7 days of age have a high risk of death or BPD at 36 weeks (70%); (2) critically ill infants who die are most likely to expire during the first week of life; and (3) the first week is when hypotension and clinical instability make them susceptible to intraventricular hemorrhage with neurological damage (in 1998 there was concern that inhaled nitric oxide might increase the risk for intraventricular hemorrhage).

Dose

We administered inhaled nitric oxide at 20 ppm for 4 days with subsequent exposure for a week each at 10, 5, and 2 ppm for a total of 25 days treatment. Therapy was continued in those infants who were extubated to nasal continuous positive airway pressure or nasal cannula. We chose 20 ppm based on efficacy and apparent safety of this dose in our pilot study,[3] treating infants with established severe BPD. In addition, in our study of nitric oxide metabolites in both tracheal aspirate and plasma of NO CLD infants,[4] we found that 5 ppm of inhaled nitric oxide caused only a modest increase (50% or less) in levels compared with a several-fold increase at 10 and 20 ppm. Kinsella et al.[5] have evidence suggesting that the amount of inhaled nitric oxide received by infants on nasal cannula is about half the level delivered by endotracheal tube. Thus, the dose of inhaled nitric oxide and delivery to the lung in the NO CLD Trial was substantially different from the other trials using primarily 5 ppm.

Multiples

Parents of multiples prefer that their children receive the same treatment. We designed the study so that all infants in a given sibling group would receive the same treatment and prospectively planned the statistical analysis to address clustering.[6]

NO CLD Trial

Infants were enrolled between May 2000 and April 2005 in this investigator-initiated, National Heart, Lung, and Blood Institute-sponsored trial. At 21 U.S. participating hospitals, 5,129 infants with a birth weight between 500 and 1,250 grams were born with a 9% mortality rate prior to meeting the inclusion criteria of being ventilated for 7 to 21 days. In all, 1,555 infants were eligible and 587 (38%) were enrolled (5 were withdrawn). The dose and duration of prescribed inhaled nitric oxide is described above.

The primary outcome was to improve survival without BPD at 36 weeks. Secondary outcomes included decreasing the length of ventilation, hospitalization, and oxygen supplementation and improving outcome at 40 and 44 weeks. Safety addressed the comorbidities of prematurity, 1-year pulmonary[7] and 2-year neurodevelopmental outcome,[8] as well as biomarkers of safety in tracheal aspirate and plasma samples.

The data presented here were taken from the correction to the *New England Journal of Medicine* paper when we discovered that several multiples had been miscategorized and outcome was inappropriately assigned for one infant. There was no difference in the mean birth weight (766 grams vs. 759 grams for the inhaled nitric oxide vs. control group) with 67% and 68% of the infants less than 800 grams. The mean gestational age was 26±1.5 weeks in both groups and 53% versus 56% males in the inhaled nitric oxide versus the control group, respectively. Prior to enrollment, the incidence of common comorbidities of prematurity was comparable in the two groups. Bilateral grade 3–4 intraventricular hemorrhage was an exclusion criterion in this study. The primary outcome of survival without BPD for the entire group was 37% for placebo versus 44% for treated infants (p=0.027). For infants who were enrolled between 7 and 14 days, favorable outcome was 27% versus 49%, respectively, whereas there was no difference in outcome for those enrolled between 15 and 21 days. We also found a significant improvement in the number of infants who were either discharged or off all respiratory support by 40 weeks (p=0.004). Fewer of the infants in the inhaled nitric oxide group were discharged home on oxygen (36% vs. 46%); one of the treated infants versus five controls was discharged home on mechanical ventilation. On average, the treated infants enrolled between 7 and 14 days required 7 fewer days of ventilatory support and 9 fewer days of hospitalization, resulting in the cost-effectiveness of this therapy when the charge for inhaled nitric oxide is set at $12,000/28 days.[9]

Question II: Are there short-term risks of inhaled nitric therapy among premature infants who receive respiratory support?

Clinical Safety

There was no difference during treatment between groups in the incidence of clinical bleeding or thrombocytopenia nor the comorbidities of prematurity including sepsis, patent ductus arteriosus (18% of treated infants vs. 19% of the controls), necrotizing enterocolitis (8% vs. 7% with 3% in each group requiring surgery), and retinopathy of prematurity (84% vs. 82% with 24% in each group requiring surgery). There also was no difference in the number of infants in whom their head ultrasound findings evolved to a higher degree of cerebral pathology (5% vs. 4%).

Laboratory Findings

We examined surfactant content, composition, and function in samples of tracheal aspirate obtained from a subpopulation of 99 enrolled infants.[10] Over the first 4 days of treatment,

minimum surface tension increased in placebo infants and decreased in inhaled nitric oxide-treated infants (p=0.04 for change from baseline between groups). There was a trend toward increased surfactant protein B (p=0.08), but no change in surfactant proteins A and C, or total protein normalized to phospholipid. Thus, inhaled nitric oxide treatment does not alter surfactant recovery or protein composition and may transiently improve surfactant function.

Nitric oxide can have both proinflammatory and anti-inflammatory effects. Tracheal aspirate from the subset of infants was assayed for a panel of seven inflammatory biomarkers. Inhaled nitric oxide administration did not result in any time-matched significant change for any of the analytes compared to the controls. There also were no significant differences between control and treated infants for concentrations of plasma protein 3-nitrotyrosine and carbonylation as biomarkers of nitrative and oxidative stress, respectively.[11,12]

Summary

The NO CLD Trial addressed the potential of inhaled nitric oxide to modulate airway resistance and promote lung growth in preterm infants at very high risk of BPD who had survived the initial period but continued to require ventilation after 1 week of age. The infants were treated with a 3½-week course of exposure starting at 20 ppm inhaled nitric oxide, which represents a higher dose and longer exposure than in other trials. Infants enrolled between 7 and 14 days responded better (number needed to treat=4) than those enrolled between 15 and 21 days, and benefit extended to infants less than 800 grams birth weight. The outcome at 40 weeks also was significantly better for treated infants and, as Dr. Michele C. Walsh will discuss, treated infants also had improved pulmonary outcome at 1 year.[7] There were no short-term clinical or laboratory safety issues. At present, inhaled nitric oxide therapy by the NO CLD protocol is accepted care at many institutions.

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Evidence-based Practice Center Presentation I: A Systematic Review of Inhaled Nitric Oxide Therapy in Preterm Infants: Mortality, Bronchopulmonary Dysplasia (BPD), and Short-Term Risks

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Background

Prematurity and disorders related to respiratory distress are among the leading causes of infant mortality in the United States.[1] Although the U.S. Food and Drug Administration has approved inhaled nitric oxide, a specific pulmonary vasodilator, for the treatment of respiratory failure in term and near-term infants, its role and efficacy in preterm infants born before 34 weeks gestation is much less clear.

Objective

We systematically reviewed the literature on the impact of inhaled nitric oxide therapy for preterm infants less than 34 weeks gestation with respiratory failure. We describe the effects of inhaled nitric oxide on mortality, bronchopulmonary dysplasia (BPD), and the short-term risks of therapy.

Data Sources

We searched the following databases through June 23, 2010: MEDLINE®, Embase, the Cochrane Central Register of Controlled Studies (CENTRAL), and PsycINFO. In addition, we searched proceedings of the 2009 and 2010 Pediatric Academic Societies Annual Meetings and ClinicalTrials.gov. We identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts.

Eligibility Criteria

Studies were limited to randomized controlled trials (RCTs) of inhaled nitric oxide in infants born before 34 weeks gestation who required respiratory support.

Methods

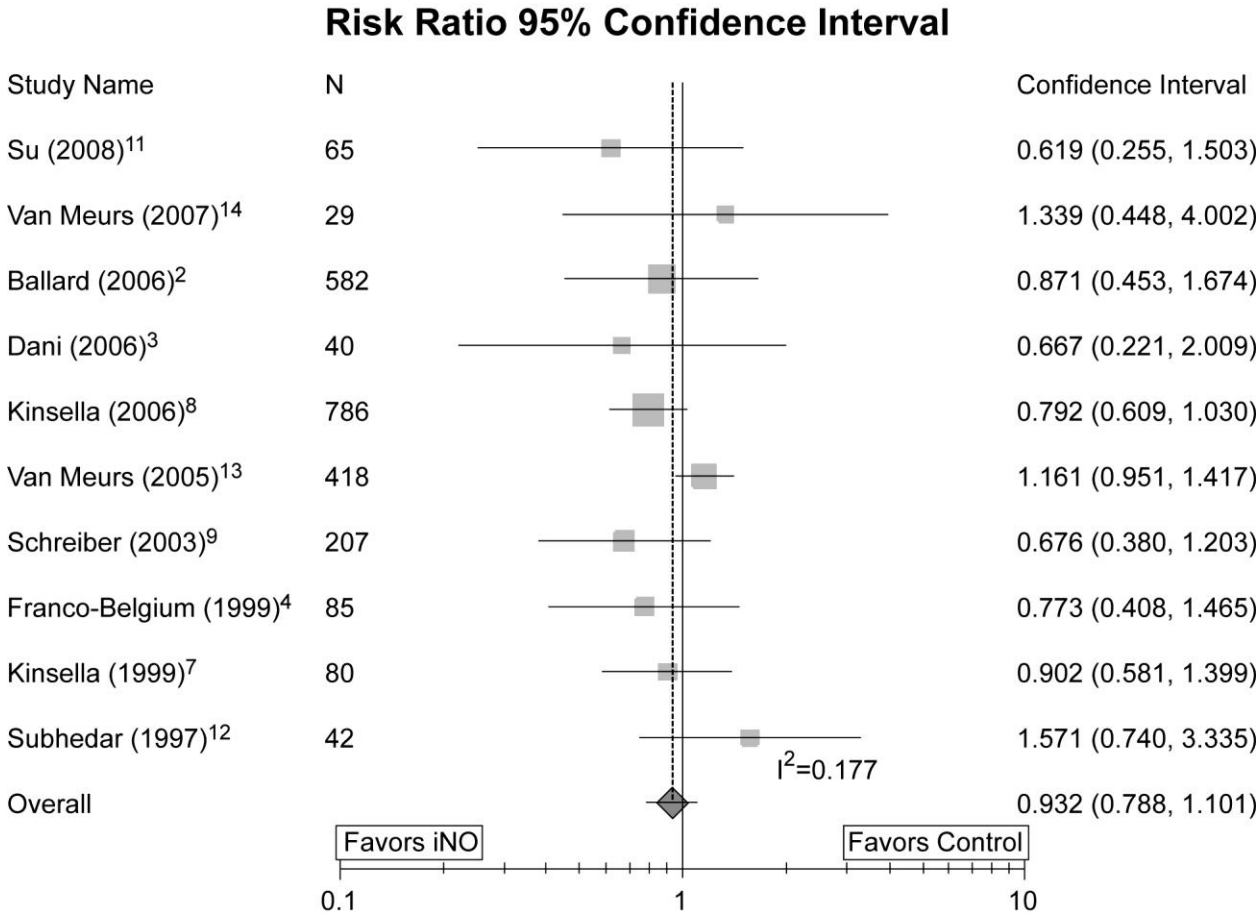
Two reviewers independently screened search results for eligibility. For eligible articles, reviewers abstracted information on general study characteristics, participant characteristics, and specific outcomes including mortality, BPD, and the short-term risks of therapy.

Results

We identified 13 RCTs[2–14] that compared inhaled nitric oxide therapy to standard treatment in preterm infants requiring mechanical ventilation, and these 13 reported no significant

differences in mortality at 7 or 28 days, 36 weeks postmenstrual age, or in the neonatal intensive care unit. Our meta-analysis of the 10 RCTs that reported death by 36 weeks postmenstrual age or in the neonatal intensive care unit also found no significant increase or decrease in death (or survival) rates (Figure 1). The relative risk was 0.932 (95% confidence interval 0.788, 1.101) (Figure 1).

Figure 1. Meta-Analysis of Death

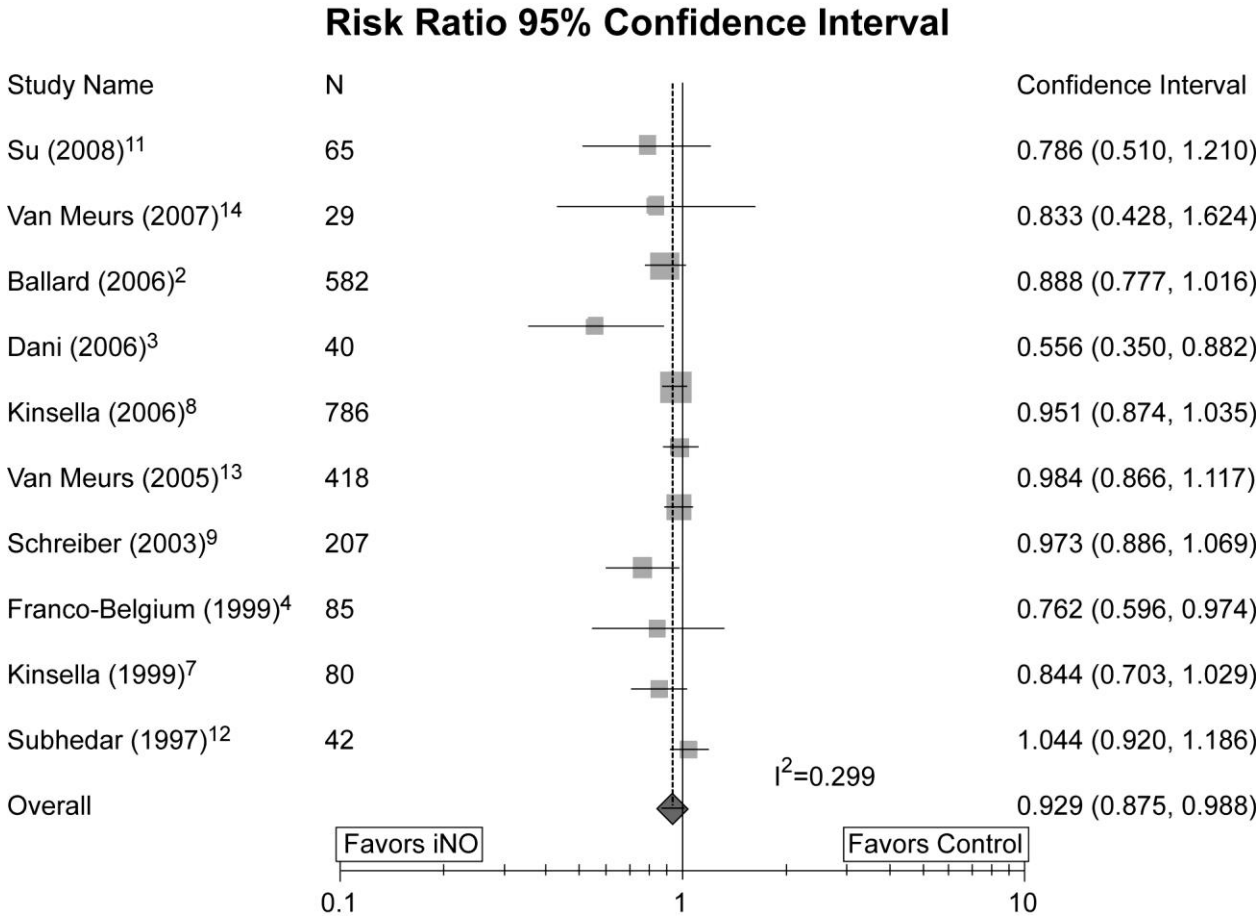


iNO = inhaled nitric oxide.

BPD has been variously defined in terms of persistent respiratory symptoms, radiographic features, and treatments, reflecting changes in neonatal intensive care and our understanding of BPD. Despite some variation in BPD definitions used, RCTs have found no significant differences in rates of BPD at 36 weeks postmenstrual age in inhaled nitric oxide and control groups. We found no significant differences between groups in our meta-analysis of all 11 RCTs that reported BPD at 36 weeks postmenstrual age; the relative risk was 0.909 (0.823, 1.003).

The composite variable of death or BPD at 36 weeks postmenstrual age (or survival without BPD at 36 weeks postmenstrual age) was the primary outcome variable in 7 randomized controlled trials and reported in 11 RCTs. Three RCTs found a significantly lower rate of death or BPD at 36 weeks postmenstrual age.[2,3,9] All 11 RCTs that reported this composite outcome variable were included in our meta-analysis, which found a statistically significant difference in favor of inhaled nitric oxide. The relative risk for death or BPD at 36 weeks postmenstrual age (or survival without BPD at 36 weeks postmenstrual age) was 0.929 (0.875, 0.988) (Figure 2).

Figure 2. Meta-Analysis of Death or Bronchopulmonary Dysplasia (BPD) at 36 Weeks Postmenstrual Age



iNO = inhaled nitric oxide.

All 13 RCTs that compared treatment with inhaled nitric oxide to standard treatment in preterm infants on respiratory support reported data regarding short-term risks including methemoglobinemia and complications of prematurity. Eleven RCTs measured methemoglobin levels and noted rare or no elevations, but most did not provide data regarding specific levels of methemoglobinemia. No RCT found a significant difference between inhaled nitric oxide-treated infants and controls in the incidence of patent ductus arteriosus, sepsis, necrotizing enterocolitis, retinopathy of prematurity, pulmonary hemorrhage, or air leak.

One of the most worrisome short-term outcome variables is evidence of brain injury on serial head ultrasounds; these signs include intraventricular hemorrhage, intraparenchymal hemorrhage, periventricular leukomalacia and other signs of white matter injury, ventriculomegaly, and hydrocephalus. Twelve RCTs compared rates of one or more of these signs of brain injury in their inhaled nitric oxide and control groups. One large multicenter RCT (n=420) and one large single-center RCT (n=207) found a lower rate of brain injury (grade 3 intraventricular hemorrhage, intraparenchymal hemorrhage, periventricular leukomalacia, $\pm$ventriculomegaly) in infants treated during the first week after birth with inhaled nitric oxide compared to controls.[8,9] Another large multicenter RCT was terminated early for concern that the inhaled nitric oxide group had a higher rate of grade 3 intraventricular hemorrhage, intraparenchymal hemorrhage, or periventricular leukomalacia than controls, but on final

analysis, there were no significant differences between the inhaled nitric oxide and control groups.[13] All the other RCTs found no significant differences between the inhaled nitric oxide and control groups. Most RCTs did not determine whether evidence of brain injury preceded study entry. Four RCTs obtained head ultrasounds before treatment[2,7,8,12]; one of these found a significantly lower incidence of grade 3 intraventricular hemorrhage, intraparenchymal hemorrhage, periventricular leukomalacia, or ventriculomegaly in the group treated with inhaled nitric oxide as compared with controls.[8]

Conclusion

Although none of the 13 RCTs reported any significant differences between inhaled nitric oxide and control groups in rates of mortality in the neonatal intensive care unit, BPD at 36 weeks postmenstrual age, short-term risks, or methemoglobinemia, three RCTs and our meta-analysis found a significant reduction in the composite variable of death or BPD at 36 weeks postmenstrual age in infants treated with inhaled nitric oxide. The finding of a reduction in rates of a composite brain injury variable in two of the four large RCTs (with n more than 200) raises the prospect of neuroprotective effects. These findings warrant further study of the effect of inhaled nitric oxide on subgroups of preterm infants, administration of inhaled nitric oxide, and longer term health and neurodevelopmental outcomes. They do not constitute sufficient evidence for use of inhaled nitric oxide as a standard treatment for preterm infants on respiratory support.

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Neurodevelopmental Outcomes of Premature Infants

Barbara K. Schmidt, M.D., M.Sc.

Premature infants face an increased risk of adverse neurodevelopmental outcomes.[1] The smallest and least mature infants have the highest rates of neurodevelopmental impairments, because they are most likely to acquire multiple and serious medical complications during their stay in the neonatal intensive care unit.[2] These prognostically important complications include brain injury, severe retinopathy of prematurity, and bronchopulmonary dysplasia (BPD).[2,3] In most clinical and epidemiologic studies to date, BPD has been described as the need for supplemental oxygen at a postmenstrual age of 36 weeks.[4]

Several teams of investigators have followed single-center, multicenter, and national cohorts of preterm infants to school age and beyond. However, the most commonly reported time point at the last follow-up has been 18 to 24 months, corrected for the degree of prematurity. At this age, neurodevelopmental impairment is typically defined as survival with one or more of the following: cerebral palsy, cognitive delay, blindness, and deafness (Table 1).

Table 1. Neurodevelopmental Outcomes at 18–24 Months Corrected for Prematurity

Outcome	Measure	Strengths	Limitations
Cerebral palsy	Clinical Exam	Detects motor impairments based on abnormalities of tone, reflexes, and posture.	Mild impairments may not be detectable before the age of 3 to 5 years.
	Gross Motor Function Classification System	Standardized system to describe different levels of gross motor function.	Interrater reliability for children less than 2 years of age is worse than for older children.[5]
Cognitive delay	Bayley Scales of Infant Development Griffiths Mental Development Scales	Both tests are standardized assessments of early childhood development. Both use "structured observation, appropriate toys, and prompts."[6]	Results of these tests may not be predictive of school age IQ and academic performance.[7] Results are influenced by sociodemo-graphic and environmental effects. Reference values may not be generalizable to populations in other cultural, geographic, or social settings.[8]
Hearing impairment	Screening tests: otoacoustic emissions; auditory brainstem response	Easy to perform and widely available in neonatal intensive care units.	Screening at term-corrected age or first discharge home may fail to detect delayed-onset hearing loss and underestimate progressive hearing loss.[9,10]
	Definitive test: audiometry	Accurate; identifies type and quantitates degree of hearing impairment.	Audiometry is unpopular with many parents of young infants and children.
Vision impairment	Ophthalmologic exam	Screening for retinopathy of prematurity during the stay in the neonatal intensive care unit is well established.	Postdischarge screening for other eye problems such as myopia, strabismus, and cortical visual impairment before 2 years of age is more haphazard.[11,12]

Cerebral palsy is a nonprogressive neurologic disorder that permanently affects body movement and muscle coordination. Two population-based studies in Europe and Canada reported a recent decline in the prevalence of cerebral palsy after very preterm birth.[13,14] Cognitive delay is the most common impairment in this population, but the reported rates vary a great deal between different studies and are heavily influenced by sociodemographic and other environmental effects.[1,6] Bilateral blindness and deafness are relatively rare, although milder vision and hearing impairments are more common and likely underestimated in this high-risk population of children.[15]

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Pulmonary Physiologic Outcomes Among Premature Infants

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The lung is composed of the alveolar volume, where gas exchange occurs, and the airway tree, which conducts air between the environment and the distal lung for gas exchange. Premature birth has the potential to interfere with the subsequent development of each of these two interconnected components, which undergo dysanaptic growth early in life. In addition, infants and children who were born prematurely may exhibit additional respiratory dysfunction, that is, secondary superimposed injury resulting from the oxygen and ventilator support required by the premature lung.

More than 25 years ago, investigators demonstrated the presence of obstructive airway disease, as evidenced by increased airway resistance, as well as decreased forced expiratory flows, even in relatively healthy-appearing infants with bronchopulmonary dysplasia (BPD).[1,2] Clinical symptoms of recurrent episodes of airway disease are frequent among infants, children, and adults who were born prematurely, and multiple studies have demonstrated persistently decreased forced expiratory flows in follow-up studies.[3–7] Infants who were born prematurely and develop BPD or chronic lung disease of infancy have an increased incidence of airway reactivity and often exhibit improved lung function following a bronchodilator; however, these subjects usually do not have normal postbronchodilator spirometry.[6,8,9] The physiologic mechanisms contributing to airway obstruction remain poorly defined and could relate to smaller sized airway, thickened airway walls that narrow the airway lumen, more collapsible airway, and/or decreased pulmonary elastic recoil pressure.

The earliest measurements of lung volumes in infants with BPD reported markedly decreased functional residual capacity in early infancy, which normalized with growth early in life.[2,10] However, more recent studies report very small differences in functional residual capacity,[11,12] and follow-up studies of older children born prematurely have reported normal total lung capacity.[7,13] Several studies of older children and adults with chronic lung disease of infancy have found decreased pulmonary diffusing capacity, as well as decreased exercise performance.[7,13,14] Recent measurements in infants and toddlers with chronic lung disease of infancy found normal alveolar volumes but decreased pulmonary diffusing capacity.[15] These findings support the limited morphometric data suggesting fewer, but larger, alveoli following extremely premature birth.[16]

Although evaluation of older children born prematurely can be performed with standard assessments of pulmonary function used for cooperative subjects, the primary limitation is maintaining a long-term cohort with appropriate control subjects. Assessment of pulmonary outcomes of infants and toddlers born prematurely has significant additional limitations. The underlying pathophysiology of this disease early in life has not been adequately defined. State-of-the-art methodology is available in a limited number of academic centers, and there are limited reference data, because assessment of healthy control subjects remains difficult. There is a potential to compare outcomes of controlled intervention studies, even with limited normative data; however, obtaining measurements for management of individual subjects should be performed with great caution.

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Follow-Up of Trial: Inhaled Nitric Oxide Cohort Up to 5 Years of Age

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Background

Bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage, and periventricular leukomalacia increase the risks of abnormal neurodevelopmental outcomes in children born prematurely. We previously found that administration of inhaled nitric oxide during the first week of life to premature infants with moderate respiratory distress syndrome decreased the combined risk of BPD and death, as well as the risks of severe intraventricular hemorrhage and periventricular leukomalacia.[1] Accordingly, we hypothesized that inhaled nitric oxide-treated infants from this trial would have improved neurodevelopmental outcomes compared with placebo-treated infants from the same trial.

Methods

We conducted a prospective, longitudinal follow-up study of premature infants treated with inhaled nitric oxide or placebo to investigate outcomes at 2 years corrected age and at 5 years.[2–4]

2-Year Follow-Up

Patients were evaluated at the University of Chicago Neonatal High-Risk Follow-Up Clinic. Medical records, including visual and hearing examinations, were reviewed. Self-reported maternal race or ethnic group was obtained from the maternal medical record. Socioeconomic status was determined by interviewing the mothers at follow-up. The children's height, weight, and head circumference were measured. A physical examination was performed by a pediatrician, a neurologic examination by a pediatric neurologist, and an infant development assessment by a certified neonatal occupational therapist. Infant development was assessed with the Bayley Scales of Infant Development II, Mental and Psychomotor Developmental Indexes, adjusted for prematurity. Examiners and parents were unaware of the patients' assignments to inhaled nitric oxide or placebo in the initial study. The primary outcome—abnormal neurodevelopmental—was defined as either disability (cerebral palsy, bilateral blindness, or bilateral hearing loss) or delay (no disability, but 1 Bayley score of less than 70).

School-Age Follow-Up

At age 5, medical outcomes, including somatic growth, hospitalizations, and ongoing morbidities, were obtained from a physical exam and parental questionnaire. To obtain a multifaceted assessment of neurodevelopment, the authors constructed a four-level school-readiness score[5] using standardized scores on assessments of basic concepts (Bracken School Readiness Assessment), perceptual skills (Visual-Motor Integration Test), receptive vocabulary (Peabody Picture Vocabulary Test, 3rd Edition), daily living functional skills (WeeFIM®), and presence of sensory impairments or autism.

Results

2-Year Follow-Up

At 2-year follow-up, 138 children (82% of survivors; Table 1) were evaluated. Across treatment groups, smaller birth weight, male gender, BPD, and severe intraventricular hemorrhage or periventricular leukomalacia significantly increased the risk for abnormal neurodevelopmental outcome (Table 2). In the inhaled nitric oxide group, 17 of 70 children (24%) had abnormal neurodevelopmental outcomes compared with 31 of 68 children (46%) in the placebo group (relative risk, 0.53; 95% confidence interval, 0.33 to 0.87; *p*=0.01; Table 2). This decreased risk in inhaled nitric oxide-treated children persisted after adjustment for birth weight and sex. Most importantly, this decreased risk also persisted after combined adjustment for the presence or absence of BPD and severe intraventricular hemorrhage or periventricular leukomalacia (Table 3), indicating a neuroprotective effect unrelated to a decrease in comorbidities known to be associated with worse neurodevelopmental outcomes in this population. In fact, the improvement in neurodevelopmental outcome in the group given inhaled nitric oxide was primarily due to a 47% decrease in the risk of cognitive impairment (defined by a score of less than 70 on the Bayley Mental Developmental Index) (*p*=0.03).

Table 1. Characteristics of the Follow-Up Cohort and Their Mothers*

Characteristic	Inhaled Nitric Oxide (N=70)	Placebo (N=68)	*P* Value
Infants			
Birth weight—grams	1,026±366	958±356	0.27
Gestational age—weeks	27.5±2.4	27.2±2.6	0.50
Corrected age at follow-up—months	24.9±7.9	25.2±8.4	0.84
Male sex—no. (%)	39 (56)	33 (49)	0.50
Initial oxygenation index†			
Median	6.6	7.2	0.37
Interquartile range	4.0–11.5	4.5–14.3	
Antenatal corticosteroids—no./total no. (%)	40/69 (58)	38/67 (57)	1.0
Surfactant—no. of doses	2.2±0.9	2.3±1.0	0.44
Prolonged postnatal exposure to corticosteroids—no. (%)‡	6 (9)	6 (9)	1.0
At end of original study—no. (%)‡			
Chronic lung disease§	27 (39)	37 (54)	0.09
Severe intraventricular hemorrhage or periventricular leukomalacia¶	6 (9)	16 (24)	0.02

*Plus–minus values are means ±SD.
†The initial oxygenation index was calculated by means of the following equation: 100 x the fractional inspiratory oxygen concentration x mean airway pressure (in centimeters of water) ÷ partial pressure of arterial oxygen in millimeters of mercury).
‡Prolonged exposure was defined as more than 7 days.
§Chronic lung disease was defined as the need for supplemental oxygen at 36 weeks postmenstrual age plus abnormal findings on chest radiography.
¶Severe intraventricular hemorrhage or periventricular leukomalacia was defined by a Papile grade of III or IV.
Adapted from Mestan et al., 2005.[2]

School-Age Follow-Up

At school-age follow-up, 135 children were evaluated. Compared with placebo (n=65), inhaled nitric oxide-treated children (n=70) had no difference in the number of standard deviations from the mean *z*-score in weight (*z*-score, *p*=0.11), head circumference (*p*=0.27), or height (*p*=0.30). Children in the inhaled nitric oxide group did not differ from the placebo group in the number of hospitalizations (*p*=0.94), nor were they more likely to require subsequent hospitalization. Levels of school readiness were similar between the two groups (*p*=0.87).

Table 2. Risk Factors for the Primary Outcome of Abnormal Neurodevelopment at 2 Years of Age

Risk Factor	Neurodevelopmental Outcome		Relative Risk (95% CI)	*P* Value
	Normal (N=90)	Abnormal (N=48)		
Birth weight				
Mean—grams	1,047±374	891±316		
Per 100-gram increment			0.91 (0.85–0.99)	0.02
Sex—no./total no. (%)				
Male	39/72 (54)	33/72 (46)	2.02 (1.21–3.36)	0.007
Female	51/66 (77)	15/66 (23)	1.00	
Maternal education—no./total no. (%)				
Less than high school	15/20 (75)	5/20 (25)	0.73 (0.33–1.63)	0.61
High school or higher	71/108 (66)	37/108 (34)	1.00	
Household without an employed person—no./total no. (%)				
Yes	19/30 (63)	11/30 (37)	1.17 (0.50–2.74)	0.83
No	69/103 (67)	34/103 (33)	1.00	
Type of ventilation—no./total no.%				
High-frequency oscillatory	44/66 (67)	22/66 (33)	0.92 (0.58–1.46)	0.86
Intermittent mechanical	46/74 (62)	26/74 (35)	1.00	
Prolonged postnatal exposure to corticosteroids—no./total no. (%)				
Yes	8/12 (67)	4/12 (33)	0.94 (0.41–2.16)	1.0
No	80/124 (65)	44/124 (35)	1.00	
Chronic lung disease—no./total no. (%)				
Yes	33/64 (52)	31/64 (48)	2.11 (1.29–3.43)	0.002
No	57/74 (77)	17/74 (23)	1.00	
Severe intraventricular hemorrhage or periventricular leukomalacia—no./total no. (%)				
Yes	10/22 (45)	12/22 (55)	1.76 (1.10–2.81)	0.05
No	80/116 (69)	36/116 (31)	1.00	

CI = confidence interval.

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Children treated with inhaled nitric oxide as infants were significantly less likely to have multiple chronic ongoing morbidities or technology dependence compared with children who had received placebo (p=0.03; Figure 1). Furthermore, children who received inhaled nitric oxide also had less functional disability than children who received placebo (p=0.03; Table 4).

Table 3. Primary Outcome Adjusted for Potential Confounders and Intermediate Variables

Potential Confounders and Intermediate Variables	Relative Risk of Abnormal Neurodevelopmental Outcome (95% CI)	*P* Value
None	0.53 (0.33–0.87)	0.01
Potential confounders		
Birth weight	0.57 (0.35–0.93)	0.02
Sex	0.52 (0.32–0.82)	0.006
Mother's graduation from high school	0.48 (0.28–0.82)	0.007
Household without an employed person	0.49 (0.29–0.82)	0.006
Type of ventilation	0.53 (0.33–0.87)	0.01
Prolonged postnatal exposure to corticosteroids	0.53 (0.33–0.87)	0.01
Simultaneous adjustment for birth weight and sex	0.55 (0.35–0.88)	0.01
Potential intermediate variables		
Severe intraventricular hemorrhage or periventricular leukomalacia	0.55 (0.34–0.89)	0.01
Chronic lung disease	0.59 (0.36–0.95)	0.03
Simultaneous adjustment for chronic lung disease and severe intraventricular hemorrhage or periventricular leukomalacia	0.60 (0.38–0.96)	0.03

CI = confidence interval.
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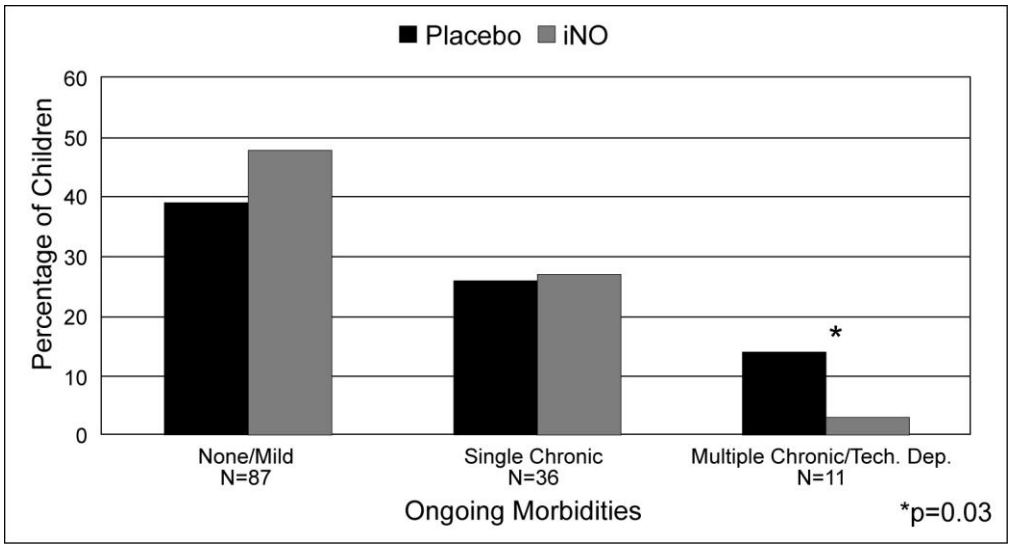
Conclusions

These results demonstrate that inhaled nitric oxide treatment during prematurity improves neurodevelopmental outcomes at age 2 and that this improvement is still apparent at school age, a time when socioeconomic circumstance and the quality of family interactions play an increasingly greater role in neurodevelopment compared with the initial biologic burden of prematurity. In addition, the absence of a detrimental effect on growth, overall health, and school readiness at early school age provides convincing evidence that inhaled nitric oxide treatment during infancy confers no health risks.

Figure 1. Ongoing Morbidities of Study Patients at School Age



iNO = inhaled nitric oxide; Tech. Dep. = technology dependence.

Table 4. Functional Disability at School Age

WeeFIM® % Score	Placebo (n=58)			Inhaled Nitric Oxide (n=60)		
	School Readiness			School Readiness		
	Level 2 n=14	Level 3 n=11	Level 4 n=33	Level 2 n=14	Level 3 n=8	Level 4 n=38
≥80	11	10	32	14	8	38
<80	3	1	1	0	0	0

WeeFIM® = the Functional Independence Measure for Children.

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Neurodevelopmental Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network (NRN) Trial of Inhaled Nitric Oxide for Premature Infants With Severe Respiratory Failure (Preemie Inhaled Nitric Oxide [PiNO] Trial)

Susan R. Hintz, M.D., M.S. Epi

Trials of inhaled nitric oxide for premature infants have included patients at varying gestational ages, age at enrollment, severity of illness, and length of exposure to inhaled nitric oxide and have yielded differing short-term and long-term results.[1–7] The National Institute of Child Health and Human Development Neonatal Research Network (NRN) conducted a multicenter trial (Preemie Inhaled Nitric Oxide [PiNO] trial) of critically ill preterm infants and found no overall reduction in death or bronchopulmonary dysplasia (BPD) with inhaled nitric oxide treatment, although post-hoc analysis demonstrated benefit for infants greater than 1,000 grams birth weight.[6] Survivors from the PiNO trial cohort were followed at 18–22 months corrected age.

Infants were eligible for the PiNO trial if they were less than 34 weeks of gestation, 4–120 hours of age at enrollment, 401–1,500 grams birth weight, mechanically ventilated, and had severe respiratory failure as defined by specific oxygenation index criteria. The duration of study gas exposure was 76±73 hours for the inhaled nitric oxide group and 39±65 hours for the placebo group; maximum exposure was 14 days.[6] A total of 210 infants were randomized to inhaled nitric oxide and 210 to placebo.

The primary outcome for the follow-up component of the PiNO trial was death or neurodevelopmental impairment at 18–22 months of age corrected for prematurity.[7] Neurodevelopmental impairment was defined as moderate to severe cerebral palsy, bilateral blindness or deafness, or Bayley Scales of Infant Development II Mental Developmental Index or Psychomotor Developmental Index less than 70. Adjusted relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a regression model that included birth-weight category, center, and treatment group as covariates.

Of the 420 patients enrolled, 109 inhaled nitric oxide (52%) and 98 placebo (47%) died before 18–22 months corrected age (p=0.11), and 10 in each group were lost to follow-up. The primary outcome could be determined for 198 inhaled nitric oxide (95%) and 200 placebo patients (95%). In this extremely ill cohort, oxygenation index at randomization was high (median oxygenation index=17), as was the proportion of those on high-frequency ventilation (59%). Primary and secondary outcomes are shown in Table 1.

The rate of death or neurodevelopmental impairment was high and was not significantly different between the treatment groups; nor was the rate of death or moderate to severe cerebral palsy significantly different between the treatment groups. Among those surviving to follow-up, there was an increased risk for moderate to severe cerebral palsy for the inhaled nitric oxide group associated with borderline significance.

At the 18- to 22-month corrected age visit, medical or surgical outpatient subspecialty care had been received by 70% (59/84) of inhaled nitric oxide and 77% (77/100) of placebo groups (p=0.30). At least one rehospitalization had occurred for 58% (51/88) of inhaled nitric oxide and

Table 1. Primary and Secondary Outcomes at 18–22 Months Corrected Age

	iNO n (%)	Placebo n (%)	RR (95% CI) Unadjusted	*P* Value	RR (95% CI) Adjusted	*P* Value
N=died or followed	198	200				
Death or NDI	**154 (78%)**	**146 (73%)**	**1.07 (0.95–1.19)**	**0.32**	**1.06 (0.95–1.17)**	**0.29**
Death or moderate to severe CP	127 (64%)	109 (54%)	1.17 (0.99–1.38)	0.07	1.15 (0.99–1.34)	0.07
N=follow-up group only	91	102				
NDI	**45/89 (51%)**	**48 (47%)**	**1.07 (0.80–1.44**	**0.74**	**1.07 (0.82–1.39)**	**0.64**
Moderate to severe CP	18/90 (20%)	11 (11%)	1.85 (0.93–3.71)	0.11	2.01 (1.03–3.94)	0.04
MDI <70	37/86 (43%)	35/98 (36%)	1.20 (0.84–1.73)	0.39	1.18 (0.85–1.64	0.33
Unimpaired	21/90 (23%)	26 (25%)	0.92 (0.56–1.51)	0.86	0.89 (0.56–1.42)	0.64
Head circumference (cm)	46.8±1.7	46.7±1.9		0.64		
Weight (kg)	10.6±1.4	10.6±1.7		0.72		

iNO = inhaled nitric oxide; NDI = neurodevelopmental impairment; CP = cerebral palsy; MDI = Mental Developmental Index; RR = relative risk; CI = confidence interval.

50% (51/102) of placebo groups (p=0.27); approximately 50% of the hospitalizations in both treatment groups were due to respiratory causes. Bronchodilators were being used by 50% (44/88) of inhaled nitric oxide and 44% (45/102) of placebo groups (p=0.42).

We also performed post-hoc analyses, including exploration of the potential effects of birth weight on outcomes. Infants with a birth weight less than or equal to 1,000 grams given inhaled nitric oxide had a significantly higher risk for death (64% vs. 52%; RR 1.22, 95% CI 1.01–1.46), and death or moderate to severe cerebral palsy (74% vs. 59%; RR 1.22, 95% CI 1.05–1.43). The interaction between birth weight and treatment group on death was significant (p=0.02) but was not significant (p=0.12) on death or moderate to severe cerebral palsy.

In summary, we found that treatment with inhaled nitric oxide was not associated with a reduction in death or neurodevelopmental impairment, or improved neurodevelopmental outcomes among survivors at 18–22 months. This may appear inconsistent with the outcomes of Mestan et al.,[2] which showed a significant reduction in neurodevelopmental impairment with the inhaled nitric oxide group (24%) compared with placebo (46%). However, the two trials were quite different. Eligibility for the single-center Schreiber et al.[1] trial was open to infants who were less than 34 weeks gestation and less than 72 hours of age, had received surfactant, and were mechanically ventilated. There were no oxygenation index entry criteria, and treatment was continued for 7 days. This approach, providing a longer exposure in a less severely ill group, may have played a role in the observed reduction in severe short-term morbidities and adverse neurodevelopmental outcomes. Of note, Mestan et al.[2] demonstrated that inhaled nitric oxide was significantly associated with improved neurodevelopmental outcomes *independent* of intermediate variables such as severe intraventricular hemorrhage and BPD. This finding may

implicate extrapulmonary nitric oxide-related mechanisms involving tolerance to cerebral ischemia and neuronal maturation.[8,9] Such protective processes could attenuate subtle brain injury not easily demonstrated by cranial ultrasound.

Similar to our findings, the multicenter Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) trial follow-up[5] found that no benefit of inhaled nitric oxide on neurodevelopmental impairment was demonstrated at 2 years, despite an improvement in survival without BPD.[4] In that trial, infants of less than 1,250 grams birth weight were eligible for randomization if they remained ventilated at 7–21 days of age; treatment continued for a minimum of 24 days. Lack of early childhood benefit both underscores the complex, multifactorial nature of neurodevelopmental outcomes and may suggest that earlier initiation of inhaled nitric oxide may be required to impact neurologic protection.

Our observed increased adjusted risk for moderate to severe cerebral palsy with inhaled nitric oxide is concerning, although it was but one of several secondary outcomes examined and patient numbers were small. Nonetheless, our findings indicate that inhaled nitric oxide as administered in the PiNO trial certainly does not *reduce* the risk for moderate to severe cerebral palsy and suggest the need for considerable circumspection before administration of inhaled nitric oxide to the smallest and sickest preterm infants. The results of our post-hoc analysis should be approached with caution but are consistent with the main trial finding of significant interactions of treatment group with both birth weight and mode of ventilation on death.[6] Conversely, inhaled nitric oxide was not associated with neurodevelopmental outcome benefit among survivors of more than 1,000 grams birth weight, despite the observed benefit on BPD in this weight group.

In conclusion, our findings demonstrate no benefit from inhaled nitric oxide exposure on death or neurodevelopmental impairment, or neurodevelopmental outcomes in early childhood among the severely ill premature infants in the PiNO trial. If future trials of inhaled nitric oxide in preterm infants are to be undertaken, they will likely target less critically ill infants with a longer required period of exposure. In planning such trials, consideration should be given to more extended neurodevelopmental follow-up. Early childhood outcomes do not necessarily predict later challenges; many subtle but significant cognitive, behavioral, and executive function impairments cannot be delineated until school age. In addition, future trials would ideally include advanced neuroimaging including MRI and diffusion tensor imaging to investigate potential treatment-associated macro- and microstructural white matter injury.

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Follow-Up of Trial: Inhaled Nitric Oxide in the Prevention of Chronic Lung Disease

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We studied the safety and efficacy of early, low-dose, prolonged inhaled nitric oxide therapy in 793 premature newborns with respiratory failure and found that inhaled nitric oxide reduced the incidence of brain injury in the newborn period.[1] We subsequently measured neurodevelopmental impairment at 1- and 2-year follow-up visits using Bayley Scales of Infant Development II. A total of 611 infants survived to discharge (77%); 468 (77%) were evaluated at 1 year of age, and 458 (75%) were evaluated at 2 years of age. There were no significant differences in growth parameters or neurodevelopmental outcomes between the inhaled nitric oxide and control groups at 1- and 2-year follow-up (Tables 1 and 2).

Table 1. Year 1 Outcomes

Measurements	Nitric Oxide Group	Control Group	*P* Value
Weight	8.81 kg	8.85 kg	*P*=0.74
Length	72.2 cm	72.7 cm	*P*=0.34
Occipital frontal circumference	45.4	45.3	*P*=0.62
Bayley Psychomotor Developmental Index	80.2	82.8	*P*=0.18
Bayley Mental Developmental Index	88.8	88.2	*P*=0.77
Disabling palsy	14 (5.9%)	13 (6.1%)	*P*=0.96
Sits without support	206 (88.4%)	199 (90.9%)	*P*=0.39
Walks independently	65 (27.7%)	67 (30.6%)	*P*=0.49
Hearing loss	29 (7.3%)	24 (6.1%)	*P*=0.49

Table 2. Year 2 Outcomes

Measurements	Nitric Oxide Group	Control Group	*P* Value
Weight	10.8 kg	11.0 kg	*P*=0.35
Length	81.6 cm	82.7 cm	*P*=0.06
Occipital frontal circumference	49.1	46.8	*P*=0.24
Bayley Psychomotor Developmental Index	80.7	81.7	*P*=0.65
Bayley Mental Developmental Index	80.5	79.8	*P*=0.73
Disabling palsy	14 (6.1%)	16 (7.4%)	*P*=0.59
Sits without support	220 (96.1%)	204 (94.9%)	*P*=0.55
Walks independently	193 (84.7%)	190 (88.4%)	*P*=0.27

As used in this trial, long-term outcomes suggest that inhaled nitric oxide at a dose of 5 ppm is safe in the first week after birth in premature newborns with a birth weight of 500–1,250 grams. However, the early reduction in brain injury did not translate into improved late neurodevelopmental outcomes.

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The Nitric Oxide To Prevent Chronic Lung Disease (NO CLD) Trial: Outcomes at 1 and 2 Years of Age

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for the NO CLD Study Investigators

Background

Bronchopulmonary dysplasia (BPD) in premature infants is associated with prolonged hospitalization as well as abnormal pulmonary and neurodevelopmental outcomes. In a double-blind, placebo-controlled, randomized multicenter trial conducted at 21 centers, we demonstrated that inhaled nitric oxide significantly increased survival without BPD in ventilated premature infants (birth weight 500–1,250 grams) who were treated for 25 days beginning between 7 and 21 days of age.[1,2] We sought to evaluate longer term outcomes at 1 and 2 years of age to assess both the efficacy and safety of inhaled nitric oxide treatment.

Methods

At 1 year of age, 456 infants (85%) of 535 survivors were evaluated for growth and healthcare utilization including hospital, emergency room, and medications. At 2 years, we prospectively evaluated neurodevelopmental and growth outcomes in 477 (89%) of 535 surviving infants enrolled in the trial with a structured questionnaire, neurologic exam, hearing tests, and Bayley Scales of Infant Development II. In the main trial, BPD was evaluated with a structured room air challenge to rigorously define BPD.[3] Infants from multiple births were randomized to the same treatment arm. To account for known clustering of BPD among siblings,[4,5] all results were adjusted for such effects using generalized estimating equations.

Results

At 1 year, compared with control infants, infants randomized to inhaled nitric oxide received significantly less bronchodilators, inhaled steroids, systemic steroids, diuretics, and supplemental oxygen after discharge from the neonatal intensive care unit. There were no significant differences between parental report of rehospitalizations or wheezing or whistling in the chest[6] (Table 1). At 2 years of age in the treated group, 109 of 243 children (44.9%) had abnormal neurodevelopmental outcomes, defined as either disability (moderate or severe cerebral palsy, bilateral blindness, or bilateral hearing loss) or delay (1 score of less than 70 on the Bayley Scales of Infant Development II), compared with 114 of 234 (48.7%) in the placebo group (relative risk, 0.92; 95% confidence interval, 0.75–1.12; p=0.39) (Table 2). No statistically significant differences on any subcomponent of the neurodevelopmental outcome assessment or growth parameters were found between those receiving inhaled nitric oxide or placebo.[7]

Conclusions

High-risk premature infants treated with inhaled nitric oxide for 25 days had improved survival free of BPD and improved pulmonary health at 1 year of age. Neither benefit nor adverse neurodevelopmental effects were seen at 2 years of age.

Table 1. Pulmonary Morbidity From Hospital Discharge to Age 1 Year

	Nitric Oxide (%)	Placebo (%)	Odds Ratio (95% CI)	Number Needed To Treat
Wheezing or whistling in the chest	49.6	56.4	0.70 (0.48–1.03)	—
Bronchodilator use	40.1	54.1	0.53 (0.36–0.78)	6.3 (4.0–15.6)
Inhaled steroid use	19.8	32.4	0.50 (0.32–0.77)	7.5 (4.6–19.6)
Systemic steroid use	11.0	17.7	0.56 (0.32–0.97)	14.1 (7.3–25.0)
Diuretic use	18.6	28.4	0.54 (0.34–0.85)	9.0 (5.2–33.3)
Any home oxygen use	38.4	49.5	0.65 (0.44–0.95)	9.4 (5.0–76.9)
Persistent oxygen use at follow-up	3.0	9.4	0.30 (0.13–0.73)	15.9 (9.4–52.6)
Any hospitalization	46.5	50.4	0.83 (0.57–1.21)	—

CI = confidence interval.

Table 2. Neurodevelopmental and Growth Outcomes at Age 2 Years

	Nitric Oxide (%)	Placebo (%)	*P* Value, or Relative Risk and 95% Confidence Intervals
Neurodevelopmental impairment*	45	49	0.92 (0.75–1.12)
Died (n, %)	8	8	1.02 (0.59–1.77)
Mental Developmental Index†	(n=210) 81±20	(n=214) 79±22	0.35
Psychomotor Developmental Index†	(n=207) 76±20	(n=212) 77±21	0.87
Unable to crawl or walk‡	6	5	1.23 (0.59–2.55)
Bilateral deafness§	3	1	2.56 (0.68–9.52)
Bilateral blindness	4	4	0.97 (0.40–2.40)
Head circumference (cm)	(n=217) 47.6±2.1	(n=205) 47.8±1.9	0.22
Weight (kg)	(n=222) 11.4±1.7	(n=204) 11.5±1.7	0.65
Length (cm)	(n=216) 85.2±5.2	(n=204) 85.3±6.0	0.99

*Neurodevelopmental impairment is defined as one or more of the following at 2 years of age: Mental Developmental Index less than 70, Psychomotor Developmental Index less than 70, unable to crawl/walk as defined by a Palisano gross motor level 2 or more, bilateral blindness, or bilateral deafness with amplification.
†Bayley Scales of Infant Development II. Values are mean ±1 standard deviation. Eighty-two children with severe neurodevelopmental impairment could not be tested and were assigned a score of 49.
‡Palisano examination score of 2 or more.
§Bilateral deafness requiring amplification.

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Inhaled Nitric Oxide for Preterm Infants: A Systematic Review

Keith J. Barrington, M.D., M.B.Ch.B.

Inhaled nitric oxide is effective in term infants with hypoxic respiratory failure, reducing the need for extracorporeal membrane oxygenation among newborns with hypoxic respiratory failure with a number needed to treat of five.[1] The pathophysiology of respiratory failure and the potential risks differ substantially in preterm infants. Therefore, analysis of the efficacy and toxicities of inhaled nitric oxide in infants born before 35 weeks is necessary. This is an update to the published version of the Cochrane review,[2] including data from the recent European Nitric Oxide (EUNO) Trial.

Objectives

The objectives were to determine the effect of treatment with inhaled nitric oxide on the rates of death, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, or neurodevelopmental disability in preterm newborn infants (less than 35 weeks gestation) with respiratory disease.

Search Methods

Standard methods of the Cochrane Neonatal Review Group were used, last updated in June 2010**;** search terms included nitric oxide, clinical trial, and newborn.

Selection Criteria

Randomized and quasi-randomized studies in preterm infants with respiratory disease that investigated the effects of administration of inhaled nitric oxide gas compared to control infants, with or without placebo, are included in this review.

Data Collection and Analysis

Data regarding clinical outcomes including death, BPD (defined as oxygen dependence at 36 weeks postmenstrual age), intraventricular hemorrhage, periventricular leukomalacia, long-term neurodevelopmental outcome, and short-term effects on oxygenation were excerpted from the trial reports by the investigators. As noted, standard methods of the Cochrane Neonatal Review Group were used. Two investigators extracted, assessed, and coded separately all data for each study. Any disagreement was resolved by discussion.

Results

Fourteen randomized controlled trials of inhaled nitric oxide therapy in preterm infants were found. The trials were grouped post hoc into three categories depending on the entry criteria: entry in the first 3 days of life based on oxygenation criteria,[3–11] routine use in preterm babies with pulmonary disease,[12–14] and later enrollment based on an increased risk of BPD.[15,16] The usefulness of the overall analysis was considered limited by the differing characteristics of the studies, and only subgroup analyses were performed.

Trials of early rescue treatment of infants based on oxygenation criteria demonstrated no significant effect of inhaled nitric oxide on mortality or BPD. The subgroup of studies with routine

use of inhaled nitric oxide in preterm infants with pulmonary disease also demonstrated no significant reduction in the combined outcome of death or BPD (typical relative risk [RR] 0.96, 95% confidence interval [CI] 0.86, 1.01), although this small effect approached significance. Later treatment with inhaled nitric oxide based on the risk of BPD demonstrated no significant benefit for this outcome in our analysis, which includes summary data for all randomized infants as reported in the original publications. The substantial paper in this group, Ballard et al.,[16] randomized eligible infants from multiple gestations as a cluster and used a cluster analysis technique, multiple outputation, to analyze the results, which cannot be replicated using summary data.

Studies of early rescue treatment with inhaled nitric oxide demonstrated a trend toward increased risk of severe intraventricular hemorrhage (typical RR 1.2, 95% CI 0.94, 1.52); the subgroup of studies with routine use in preterm infants with pulmonary disease also seems to show no reduction in the risk of having either a severe intraventricular hemorrhage or periventricular leukomalacia (typical RR 0.90, 95% CI 0.73, 1.12). Later inhaled nitric oxide treatment of infants at risk of BPD is given after the major risk period for intraventricular hemorrhage and does not appear to lead to progression of old lesions. Several studies have now presented data on long-term neurodevelopmental outcome.[5,6,10,12,16] There appears to be no overall effect of inhaled nitric oxide on the incidence of neurodevelopmental impairment.

Conclusions

Inhaled nitric oxide as rescue therapy for the very ill, ventilated preterm infant does not appear to be effective and may increase the risk of severe intraventricular hemorrhage. Early routine use of inhaled nitric oxide in mildly sick preterm infants does not effect serious brain injury or improve survival without BPD. Later use of inhaled nitric oxide to prevent BPD also does not appear to be effective from this form of analysis; however, we are unable to repeat the cluster analyses of the Ballard et al. trial,[16] which, as reported in the original manuscript, shows a benefit in terms of increasing survival without BPD. Further studies examining the effects of inhaled nitric oxide in preterm infants who remain intubated between 7 and 14 days are warranted.

As a result of these findings (and, in view of the importance of this issue—that is, the potential reduction in brain injury in some of the early routine treatment studies, the apparent increase in brain injury in some of the rescue treatment studies, and the reported reduction in BPD in the Ballard et al. trial[16]), we developed a collaborative group, the Meta-Analysis of Preterm Patients on inhaled Nitric Oxide (MAPPiNO) Collaboration,* to perform an individual patient data meta-analysis, for which the protocol has been published.[17] The preliminary overall results are below.

MAPPiNO Collaboration

Design/Methods

Individual patient data meta-analysis included randomized controlled trials of preterm infants (less than 37 weeks). Dichotomous outcomes were analyzed using log-binomial regression

*The MAPPiNO Collaboration included the following members: Lisa M. Askie, Roberta A. Ballard, Keith Barrington, Gary Cutter, Carlo Dani, Richard A. Ehrenkranz, Diana Elbourne, David Field, Neil Finer, Jean-Michel Hascoet, Anna Maria Hibbs, John P. Kinsella, Jean-Christophe Mercier, Wade Rich, Michael D. Schreiber, Pimol Srisuparp, Nim V. Subhedar, Krisa P. Van Meurs, Merryn Voysey.

models adjusting for trial differences. Correlation in outcomes from multiple births was accounted for using multiple outputations.

Results

Major and important differences between trials in terms of timing, duration, dose, and indications for treatment limit the applicability of the overall analyses. Nevertheless, based on 3,298 babies from 11 trials (96% data), death or chronic lung disease occurred in 59% of inhaled nitric oxide-treated versus 61% placebo infants (RR, 95% CI 0.96 [0.92, 1.01], *p*=0.11). Death occurred in 23% of inhaled nitric oxide-treated and 23% of controls (RR 1.05, 95% CI 0.93, 1.18). Chronic lung disease occurred in 49% of the survivors of inhaled nitric oxide treatment, and 52% of the survivors in the control group (RR 0.93, 95% CI 0.87, 1.00, *p*=0.060).

Severe neurological events on imaging occurred in 25% of the inhaled nitric oxide group compared to 23% of the placebo group (RR 1.12 [0.98, 1.28], *p*=0.09). Secondary outcomes are shown in Table 1.

There were no statistically significant differences in inhaled nitric oxide effect by any of the patient-level characteristics tested as shown in Table 2. In trials using a starting inhaled nitric oxide dose more than 5 ppm versus less than 5 ppm, there was evidence of improved outcome (interaction test *p*=0.02); however, these differences were not observed using other cutpoints for dose or levels of exposure to inhaled nitric oxide.

Table 1. Secondary Outcomes

Outcome	Trials	Inhaled Nitric Oxide	Control	Relative Risk (95% Confidence Interval)	*P* Value
Death by 36 weeks	11	350/1,649 (21%)	336/1,649 (20%)	1.05 (0.93, 1.20)	0.421[†]
Death by discharge	11	383/1,649 (23%)	366/1,649 (22%)	1.06 (0.94, 1.20)	0.313
Severe intraventricular hemorrhage	9	234/1,221 (19%)	221/1,165 (19%)	1.02 (0.86, 1.21)	0.804
Postnatal steroids	10	664/1,633 (41%)	624/1,631 (38%)	1.05 (0.97, 1.15)	0.203
Gross air leak	7	136/1,119 (12%)	128/1,140 (11%)	1.16 (0.93, 1.46)	0.193
Pulmonary hemorrhage	9	107/1,613 (7%)	118/1,611 (7%)	0.94 (0.73, 1.22)	0.654
Severe retinopathy of prematurity	6	203/1,383 (15%)	207/1,363 (15%)	0.93 (0.78, 1.10)	0.405

[†]Chi-square test for heterogeneity, *p*=0.04; all other *p*>0.05.
Note: Relative risks, confidence intervals, and *p* values derived from n=1,000 iterations of log-binomial model using multiple outputation method.

Table 2. Death or Chronic Lung Disease by Subgroups

Subgroup		Inhaled Nitric Oxide	Placebo	Relative Risk (95% Confidence Interval)
Gestational Age	≤26 weeks	596/869 (69%)	649/908 (71%)	0.96 (0.91, 1.02)
	>26 weeks	360/760 (47%)	344/719 (48%)	0.96 (0.87, 1.07)
Birth Weight	≤750 grams	472/674 (70%)	511/706 (72%)	0.97 (0.91, 1.04)
	>750 grams	483/954 (51%)	482/919 (52%)	0.95 (0.87, 1.03)
Multiple Birth	Singleton	725/1,226 (59%)	746/1230 (61%)	0.97 (0.91, 1.03)
	Multiple	231/403 (57%)	247/397 (62%)	0.88 (0.79, 0.98)
Race	Other/Unknown	428/692 (62%)	497/751 (66%)	0.93 (0.86, 1.00)
	White	518/901 (57%)	484/838 (58%)	0.99 (0.91, 1.06)
Antenatal Steroids	No	212/338 (63%)	255/375 (68%)	0.87 (0.79, 0.96)
	Yes	690/1,216 (57%)	690/1,185 (58%)	0.96 (0.90, 1.03)
Age at Randomization	≤3 days	744/1,274 (58%)	766/1,283 (60%)	0.98 (0.92, 1.04)
	>3 days	209/344 (61%)	219/331 (66%)	0.89 (0.79, 1.00)
	≤7 days	777/1,318 (59%)	792/1,318 (60%)	0.98 (0.92, 1.04)
	>7 days	176/300 (59%)	193/296 (65%)	0.87 (0.76, 0.99)
Oxygenation Index	≤5	266/506 (53%)	260/470 (55%)	0.95 (0.85, 1.06)
	>5	585/857 (68%)	617/866 (71%)	0.96 (0.90, 1.02)
Pulmonary Hypertension	No	211/275 (77%)	220/278 (79%)	0.98 (0.90, 1.07)
	Yes	57/81 (70%)	45/61 (74%)	0.88 (0.72, 1.06)
Ventilation Type	Conventional	564/1,014 (56%)	600/1,014 (59%)	0.91 (0.84, 0.98)
	High frequency	358/495 (72%)	354/495 (72%)	1.00 (0.92, 1.08)
Overall				**0.96 (0.92, 1.01)**

Note: Subgroup by treatment interaction effect: all $p>0.05$. Estimates derived from n=1,000 iterations of a Poisson regression model with robust error variance using multiple outputation method.

Conclusions

Routine use of inhaled nitric oxide for treatment of respiratory failure in preterm infants cannot be recommended. The use of a higher inhaled nitric oxide starting dose may be associated with improved outcome, but this requires further examination.

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Evidence-based Practice Center Presentation II: Inhaled Nitric Oxide in Preterm Infants: Does This Therapy Influence Long-Term Pulmonary and/or Neurodevelopmental Outcomes When Used in Preterm Neonates Requiring Respiratory Support?

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Background

Nitric oxide is an endogenously produced smooth muscle vasodilator. When inhaled, it acts specifically on the smooth muscle of the pulmonary arterial system and can improve oxygenation in neonates. Clinical trials support the efficacy of inhaled nitric oxide in term and late preterm neonates with pulmonary hypertension, and it was approved by the U.S. Food and Drug Administration for this group in 1999. Shortly thereafter, the American Academy of Pediatrics issued a policy statement with specific recommendations for inhaled nitric oxide use in neonates greater than 34 weeks gestation and acknowledged the paucity of data to support use in premature infants.[1] Since then, there have been several studies of inhaled nitric oxide use in premature infants. Despite mixed results of these studies, and recent reaffirmation of the American Academy of Pediatrics Policy Statement,[2] use of this therapy for premature infants with hypoxic respiratory failure has been increasing.

Objective

The objective was to systematically evaluate and summarize the evidence that is currently published in the medical literature regarding the short- and long-term effects of inhaled nitric oxide when used in premature infants less than 34 weeks gestation requiring respiratory support. Here we evaluate long-term pulmonary and neurodevelopmental effects of inhaled nitric oxide in this population.

Data Sources

We searched the following databases through June 23, 2010: MEDLINE®, Embase, the Cochrane Central Register of Controlled Studies (CENTRAL), and PsycINFO. In addition, we searched proceedings of the 2009 and 2010 Pediatric Academic Societies Annual Meetings and ClinicalTrials.gov. We identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts.

Eligibility Criteria

Studies included preterm infants less than 34 weeks gestational age who required respiratory support. Eligibility was not limited by study design except for the exclusion of case reports and case series.

Methods

Two reviewers independently screened search results for eligibility. For all articles, reviewers abstracted information on general study characteristics, participant characteristics, and specific outcomes including any that included long-term pulmonary and/or neurodevelopmental outcomes.

Results

Three cohort studies[3–5] and 7 randomized controlled trials[6–12] provided the reference population for the 10 follow-up studies[6,9,13–20] (Table 1) in which long-term neurodevelopment, respiratory status, and other health indicators were evaluated. Follow-up time varied among these studies, ranging from 10 months corrected age[4] to 4–5 years of age.[14]

There was no significant difference in survival/death at time of later follow-up when comparing infants who received inhaled nitric oxide to controls in any of the six studies reporting this outcome.[9,10,16,17,19,20]

Several facets of neurodevelopment were evaluated, including cerebral palsy,[3,4,6,14,15,17,19,20] cognitive function,[6,14,17,19,20] sensory impairment,[6,14,16,19,20] and neurodevelopmental impairment.[6,14–17,19,20] For the majority of these parameters, there were no differences in the incidence of these outcomes between the inhaled nitric oxide and control groups.

One of the six studies that compared the incidence of cerebral palsy in non-subgroup inhaled nitric oxide recipients and controls showed a difference. Hintz et al.[17] demonstrated an increased incidence of cerebral palsy at 18–22 months in participants who had received inhaled nitric oxide but only after adjusting for several variables (unadjusted relative risk [RR] 1.85 [0.93, 3.71]; adjusted RR 2.41 [1.01, 5.75]). We performed a meta-analysis including these six studies and found no difference (RR 1.29 [0.837, 1.98]).

Of the five studies comparing cognition in inhaled nitric oxide recipients and nonrecipients, only the Mestan et al. follow-up[19] of the Schreiber randomized controlled trial[12] revealed a difference in the Bayley Mental Developmental Index at 2 years of age corrected for prematurity, favoring those who received inhaled nitric oxide (19% vs. 35% with the Mental Developmental Index less than 2 standard deviation below mean, p=0.03). Similarly, of seven studies in which neurodevelopmental impairment was assessed at follow-up, only Mestan et al.[19] reported a difference between groups; inhaled nitric oxide recipients had a lower incidence of neurodevelopmental impairment when compared with controls (24% vs. 46%, RR 0.53 [0.33, 0.87], p=0.01). Our meta-analysis of these studies revealed no difference in neurodevelopmental impairment between groups (RR 0.92 [0.68, 1.23]).

Sensory impairment was evaluated in six studies. The incidence of hearing and visual impairment in the inhaled nitric oxide and control groups was 7% or lower in every study; there was no difference between those treated with inhaled nitric oxide when compared with controls.

Growth parameters at time of follow-up were reported in five randomized controlled trials and one cohort study. There were no differences in measure of head circumference or length in any of these studies. Mestan et al.[19] reported that infants who received inhaled nitric oxide were heavier at 2 years of age than controls; the others reported no difference. Various indicators of respiratory health were reported in one or more of four randomized controlled trials and two cohort studies. Different follow-up evaluations included information about respiratory diagnoses

and symptoms, the need for pulmonary medications or supplemental oxygen after discharge, and rehospitalizations. Hibbs et al.[18] reported on infants at 12 months corrected age and found that a greater percentage of controls had respiratory symptoms, and required respiratory medications and supplemental oxygen at home. However, Watson et al.[16] found that among the infants with a birth weight less than 750 grams, a greater proportion who had received inhaled nitric oxide needed supplemental oxygen at 1 year of age when compared with controls (11.7% vs. 4%, $p<0.04$).

Table 1. Study Design and Long-Term Outcomes of Inhaled Nitric Oxide-Treated Preterm Infants

Study Design	Author, Year	Death/ Survival	Cerebral Palsy	Cognitive Outcomes	NDI	Growth	Pulmonary Outcomes
Randomized controlled trial	Huddy et al., 2008[14]*	X	X	X	X	X	X
	Van Meurs et al., 2007[6]		X	X	X		
	Field et al., 2005[9]	X				X	X
	Bennett et al., 2001[15]†	X	X		X		
	Watson et al., 2009[16]‡	X			X		X
	Hintz et al., 2007[17]	X	X	X	X	X	
	Hibbs et al., 2008[18]§						X
	Mestan et al., 2005[19]¶	X	X	X	X	X	
	Walsh et al., 2010[20]§	X		X	X	X	
Observational	Cheung et al., 1998[4]	X	X			X	X
	Tanaka et al., 2007[3]	X	X				
	Clark et al., 2002[5]						X

NDI = neurodevelopmental impairment.
*Follow-up study of Field et al., 2005.[9]
†Follow-up study of Subhedar et al., 1997.[10]
‡Follow-up study of Kinsella et al., 2006.[7]
§Follow-up study of Ballard et al., 2006.[11]
¶Follow-up study of Schreiber et al., 2003.[12]

Conclusion

In our systematic review of the current literature, the evidence regarding the association between inhaled nitric oxide use in premature neonates with infant and early childhood outcomes is limited. The results of studies that reveal risks or benefits are conflicting. Further investigation into inhaled nitric oxide use in subgroups of premature infants at different times may clarify and provide direction for inhaled nitric oxide use in the neonatal intensive care unit.

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Use and Misuse of Subgroup and Secondary Analyses in Clinical Trials

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This presentation will focus on the methodologic issues involved in conducting and interpreting subgroup analyses and analyses of secondary outcomes. It will serve as a background for the subsequent discussion of subgroup analyses in trials of inhaled nitric oxide therapy.

Notwithstanding the common cautions against the misuse of findings from subgroup analyses, many clinical research experts recommend that subgroup analyses be planned, considered, and executed along with clinical trials for the following reasons: (1) We should get the most information that we can from our investment in clinical trials, and we should provide as much information as feasible to clinicians about the application of clinical trial findings to individual patients.[1,2] (2) There may be real differences in how certain subgroups of patients with different baseline characteristics (e.g., age or illness severity) respond to a given treatment.[3] These differences in treatment effect may be qualitative (treatment is beneficial in one group and harmful in another) or quantitative (more effective in one subgroup than another).[4] This difference in treatment effect, or effect modification, is termed an interaction in statistical terminology.

A number of problems or reasons for skepticism have been raised about subgroup analyses. First, when subgroups are not planned in advance, with randomization stratified by subgroup, or if the subgroups are small, there are often imbalances between the subgroups in other measured or unmeasured baseline variables that affect outcomes and confound the attribution of outcome differences to differential treatment effects between the subgroups.[5] Second, clinical trials are rarely sufficiently powered to identify clinically meaningful treatment effects within subgroups or to evaluate for interaction between subgroups.[4] The potential for beta error (false finding of no difference) will be greater for the subgroups than for the overall trial. The potential for alpha error (false finding of a difference) increases according to the number of subgroups evaluated (whether or not all of the subgroups considered are reported).[6] These problems have often led to misleading interpretation of subgroup findings.[4]

The rationale for examining and reporting secondary outcomes in clinical trials includes the following: (1) If the primary outcome was chosen to allow for a smaller sample size, secondary outcomes may be more clinically important than the primary outcome. (2) Clinical trials rarely evaluate adverse effects as a primary outcome, and clinical decisions need to incorporate a balance between all of the beneficial and harmful effects of a given treatment strategy. Criticisms of analyses of secondary outcomes are largely directed at treatment recommendations that are made on the basis of a benefit that was identified in one of many secondary outcomes when no benefit was observed for the primary outcome.[7] As with subgroup analyses, the opportunity for alpha error increases according to the number of secondary outcomes that are considered. There also is a greater opportunity for beta error if, as is often the case, the prevalence of the secondary outcome is lower than the prevalence of the primary outcome.

The story of antenatal steroids illustrates these principles well because much was made of subgroup analyses in the early studies, and we now have sufficient additional data to determine when these subgroup analyses were misleading and when they were informative. In the

U.S. Collaborative Trial of Antenatal Dexamethasone, the results were interpreted to demonstrate that the effects were "mainly attributable to … differences among singleton female infants" with "no treatment effect … observed in male infants," and "non-Caucasians were improved, whereas Caucasians showed little benefit."[8] Subsequent meta-analyses summarizing the findings from 18 trials including 3,438 fetuses have clearly shown that the relative risk for respiratory distress syndrome is comparable for males and females and for Caucasians and non-Caucasians.[9] The relative risk of respiratory distress syndrome also is comparable for gestational age subgroups. That said, the relative risk is not as meaningful as the absolute risk difference in defining a clinically important benefit for the patient.[2] Because the prevalence of respiratory distress syndrome decreases with increasing gestational age at birth, the absolute risk difference decreases, and the number needed to treat to prevent one case of respiratory distress syndrome increases, with increasing gestational age.[10] Basing decisions about antenatal steroid treatment on sex or race would have been an inappropriate application of subgroup findings to clinical practice, whereas the findings from gestational age subgroups allow clinicians and patients to make better informed decisions about the risk and benefits of treatment for the individual patient.

How can clinical researchers and clinicians make the best use of information from subgroups and secondary outcomes in clinical trials? Focus should first be placed on prespecified subgroups for which there was a compelling rationale for differential treatment effect, ideally with stratified randomization by subgroup.[3,11,12] Formal statistical tests of interaction should be used to evaluate for heterogeneity in treatment effects.[4] Subgroup analyses should be viewed with skepticism and viewed as hypothesis generating, particularly if there is inadequate power to identify clinically important interaction.[5,7,12,13] It should be recognized that interaction may be present or not depending on how the outcome is expressed (relative risk vs. risk difference) and whether the definition of no interaction is based on an additive versus multiplicative scale.[14] Treatment effects should be expressed as point estimates and confidence intervals rather than *p* values.[15,16] The total number of subgroup analyses performed or considered should be explicitly acknowledged.[4,11]

If the problems with publication bias (for specific findings within studies as well as entire studies) can be overcome, meta-analysis can be a powerful tool to address the alpha- and beta-error problems encountered with subgroup and secondary analyses.[3] The power to identify or exclude clinically important differences will be much greater if multiple similar trials categorize and report outcomes in the same way. If multiple studies report comparable effects (as expressed by point estimates and confidence intervals, not *p* values) for the same subgroups or outcomes, it becomes unlikely that an observed difference was a spurious finding in a single study.[17] Bayesian approaches also can be used to express findings in terms that are more meaningful to clinicians who apply subgroup and secondary analyses to decisions in clinical practice.[5] In contrast to the frequentist approach, which expresses each analysis in a binary fashion (the null hypothesis was or was not rejected; there is or is not a difference), the Bayesian approach gives the clinician a probability, based on the data and pre-existing information, that there is a difference of a given magnitude for each subgroup and outcome considered.[18,19]

How does this relate to the published trials of inhaled nitric oxide? Is there a consistent pattern of differential effectiveness, depending on illness severity or postnatal age at enrollment, within and among trials? Is it consistent and convincing enough to drive treatment decisions, or does it require further study? If there is a treatment benefit within a subgroup of patients, is the benefit of sufficient clinical importance to justify the risks and expense?[20]

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Does the Effect of Inhaled Nitric Oxide Therapy on Bronchopulmonary Dysplasia (BPD), Death, or Neurodevelopmental Impairment Vary Across Subpopulations of Premature Infants?

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Introduction

In the United States, more than 10,000 babies develop bronchopulmonary dysplasia (BPD), placing them at risk for significant long-term pulmonary disease, rehospitalization, and neurodevelopmental sequelae. Preclinical studies indicating that nitric oxide plays an important role in promoting normal lung development sparked interest in a potential role for inhaled nitric oxide in the management of respiratory failure of preterm infants. To date, a dozen or more randomized trials have been published comparing inhaled nitric oxide with placebo for the treatment of preterm infants with respiratory failure. Of these, five large randomized, masked clinical trials have completed patient enrollment of more than 2,800 babies, representing a wide range of patient populations, disease severity, and potential treatment approaches (Table 1). Although the caveats of both predefined and post-hoc subgroup analysis must be considered,[1] these studies provide interesting insights into whether the effects of inhaled nitric oxide therapy on BPD, death, or neurodevelopmental impairment vary across subpopulations of premature infants.

Table 1. Treatment Strategies for Large Trials of Inhaled Nitric Oxide Preterm Infants

	Year	Number of Patients Enrolled	Gestational Age (Week)	Treatment Strategy
Schreiber et al.[2]	2003	207	27.0	Early intervention (single center)
Van Meurs et al.[3]	2005	420	27.2	Early “rescue”; sickest babies only
Kinsella et al.[4]	2006	793	26.0	Early intervention
Mercier et al.[5]	2010	800	25.6	Early intervention; excluded smallest, babies sickest
Ballard et al.[6]	2006	582	26.0	Intervention at 7–21 days for evolving chronic lung disease

Severity of Respiratory Failure

The extremely low-birth-weight infant with severe respiratory failure is likely to die or survive with significant morbidity, which may lead clinicians to consider inhaled nitric oxide for early intervention in the sickest babies. The Van Meurs et al. trial[3] addressed this question by delivering inhaled nitric oxide as “rescue” therapy to infants with especially severe respiratory failure (mean oxygenation index of 22–23). Although short-term improvements in oxygenation were observed, there was no effect on the rate of death or BPD. Post-hoc analysis revealed that nitric oxide use was associated with significant increases in mortality and brain injury in babies less than 1,000 grams. Interpretation and comparison of these data have been

somewhat difficult because this study did not require a screening head ultrasound, enrolled only infants with severe respiratory failure, and provided the shortest duration of inhaled nitric oxide treatment.

The other trials enrolled infants with less severe respiratory failure and used inhaled nitric oxide as a longer term preventative strategy. A post-hoc analysis performed by Schreiber et al.[2] suggested a severity-specific interaction, showing that nitric oxide significantly improved survival without BPD in infants with the mildest disease (oxygenation index below 6.94, the median for the study population). The Kinsella et al.[4] and Mercier et al.[5] trials had populations with a mean oxygenation index of 5.6 and 8.3, respectively, but did not report a similar interaction. No trial had sufficient numbers of babies receiving continuous positive airway pressure to draw conclusions about this important population.

Gestational Age or Birth Weight

Three trials prospectively stratified randomization by weight or gestational age (Kinsella et al.,[4] Mercier et al.,[5] and Ballard et al.[6]), and other trials examined this relationship by post-hoc analysis. The four randomized trials of early intervention reported no specific benefit in the smallest babies (defined variably, but generally less than 750 grams or 26 weeks gestation) treated with inhaled nitric oxide, although the Ballard et al. trial[6] found that small babies shared in the beneficial effects of later inhaled nitric oxide administration. As noted above, in the Van Meurs et al. trial,[3] post-hoc analysis revealed significantly higher rates of death and brain injury (defined as severe intraventricular hemorrhage or periventricular leukomalacia) in babies less than 1,000 grams treated with inhaled nitric oxide. Analysis of these smaller babies at follow-up[7] indicated that 74% of the inhaled nitric oxide group died or had moderate to severe cerebral palsy, compared with 59% of the placebo group (p=0.01).

In contrast, in some trials, inhaled nitric oxide appeared to benefit larger preterm infants presenting with early respiratory failure. The Kinsella et al. trial[4] suggested a 50% reduction in brain injury (severe intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly) in the 750- to 1,000-gram subgroup, and showed a substantial reduction in death or BPD in the 1,000- to 1,250-gram subgroup (relative risk reduction 40%, p=0.004). This latter finding was supported by the post-hoc analysis performed by Van Meurs et al.[3] (relative risk reduction 28%, p=0.03). It also is interesting to note that the mean birth weight of the infants enrolled in the Schreiber et al. study[2] was 983 grams, indicating that the reported pulmonary and neuroprotective benefits may have been partly due to enrollment of larger and more mature infants. Importantly, no increases in short-term adverse outcomes were identified in babies greater than 1,000 grams in any trial. Furthermore, follow-up trials to date indicate that when observed, short-term neuroprotective benefits of inhaled nitric oxide appear to be reflected in improved neurodevelopmental outcomes at 12–18 months.[8,9]

Age at Initiation of Therapy

Ballard et al.[6] studied the effects of inhaled nitric oxide on in-hospital mortality and respiratory morbidity at a later time point, and after a high risk of BPD was established. This trial enrolled ventilated infants between 7 and 21 days of age and treated them with higher initial doses of inhaled nitric oxide (20 ppm) for longer durations (24 days). In this very different population, treatment with inhaled nitric oxide led to improved pulmonary outcomes: a 23% increase in survival without chronic lung disease was observed at 36 weeks postmenstrual age, and reduced need for supplemental oxygen also was observed at 40 and 44 weeks postmenstrual age. These improvements were sustained, as evidenced by a reduced need for medications

and home oxygen during the first year of life.[10] There were no differences in any complications of prematurity, including brain injury or long-term neurodevelopmental impairment.[11] Post-hoc analysis showed a striking effect of age at study entry. Inhaled nitric oxide started between 7 and 14 days resulted in a 77% increase in survival without chronic lung disease, while there was no benefit if inhaled nitric oxide was started after 15 days. The findings of Ballard et al.[6] raise important questions about the timing and potential reversibility of lung injury, as well as whether higher doses or longer exposures to inhaled nitric oxide are significant factors.

Gender

No trial to date has reported a significant interaction between gender and outcomes after treatment with inhaled nitric oxide.

Ethnicity

As trial reports emerged, differences in their racial composition were noted. This was particularly true for the Schreiber et al. study,[2] which enrolled a population of infants that was 70% black and showed a significant benefit of inhaled nitric oxide. Three subsequent studies[4–6] performed post-hoc analyses to determine the relationship between race and treatment. The Kinsella et al.[4] and Mercier et al.[5] studies did not find a significant interaction between race and outcomes after treatment with inhaled nitric oxide. In contrast, the Ballard et al. study,[6] which enrolled 237 black and Hispanic infants, found a significant beneficial interaction in these groups (relative benefit 1.7, p=0.05).

Conclusions

The results of these large randomized, masked clinical trials have begun to clarify a potential role for inhaled nitric oxide in specific subgroups of preterm infants. The probable benefits for older infants (greater than 7 days) at high risk for BPD are particularly encouraging and indicate a benefit at least as robust as vitamin A.[12] Larger preterm infants and those with milder disease also may benefit from early administration of inhaled nitric oxide. However, the Van Meurs et al. data[3] suggest that inhaled nitric oxide use should be avoided in the smallest infants with severe respiratory failure until more is known.

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Evidence-based Practice Center Presentation III: Inhaled Nitric Oxide in Preterm Infants: A Systematic Review of Treatment in Subpopulations, and by Dosage, Timing, and Mode of Delivery

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Background

Prematurity and disorders related to respiratory distress are among the leading causes of infant mortality in the United States.[1] Inhaled nitric oxide, a selective pulmonary vasodilator, is approved by the U.S. Food and Drug Administration for treatment of respiratory failure in term and near-term infants greater than 34 weeks gestation. However, for preterm infants less than 34 weeks gestation, the role and efficacy of inhaled nitric oxide is much less clear.

Objective

We systematically reviewed the literature on the impact of inhaled nitric oxide therapy for preterm infants less than 34 weeks gestation with respiratory failure. We describe here our findings on the effects of inhaled nitric oxide across subpopulations of preterm infants and variations of effect of inhaled nitric oxide by timing, dose, mode of delivery, and with concurrent therapies.

Data Sources

We searched the following databases through June 23, 2010: MEDLINE®, Embase, the Cochrane Central Register of Controlled Studies (CENTRAL), and PsycINFO. In addition, we searched proceedings of the 2009 and 2010 Pediatric Academic Societies Meetings and ClinicalTrials.gov. We identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts.

Eligibility Criteria

Studies included preterm infants less than 34 weeks gestational age who required respiratory support. Eligibility was not limited by study design except for the exclusion of case reports and case series.

Methods

Two reviewers independently screened search results for eligibility. For all articles, reviewers abstracted information on general study characteristics, participant characteristics, and specific outcomes including survival, death, bronchopulmonary dysplasia (BPD), neurodevelopmental outcomes, and/or composites of these outcomes.

Results

The effects of inhaled nitric oxide across subpopulations of preterm infants were addressed in 14 articles (9 randomized controlled trials and 5 cohort studies); 19 articles (13 randomized controlled trials and 6 follow-up studies) addressed variations of effect of inhaled nitric oxide by timing, dose, mode of delivery, and with concurrent therapies. Most studies were not powered to find differences between subgroups or by the various characteristics of inhaled nitric oxide therapy.

Birth Weight

The effect of inhaled nitric oxide therapy for birth-weight subgroups is shown in Table 1.

Severity of Illness

Three randomized controlled trials used the oxygenation index (OI) as a surrogate measure of severity of illness. No significant differences were seen between infants treated with inhaled nitric oxide and controls when groups were stratified by median OI ≤17 or OI >17,[4] or OI <30 or OI ≥30[7] at the time of randomization. In a third randomized controlled trial,[3] inhaled nitric oxide-treated infants with an OI <6.94 had a lower rate of death or survival with chronic lung disease (36%) than controls (67.4%). No differences were seen between the groups for those with an OI >6.94[3] except in follow-up at age 2 years, where the risk of abnormal neurodevelopmental outcome was diminished for those receiving inhaled nitric oxide (relative risk [RR] 0.38 [0.16–0.93]).[8]

Cause of Respiratory Failure

No difference was reported between inhaled nitric oxide-treated and control infants when respiratory failure was the result of respiratory distress syndrome[7] or pulmonary hypoplasia.[9,10] For pulmonary hypertension, inhaled nitric oxide-treated infants had a lower rate of cerebral palsy at age 3 years than controls (22% vs. 64%) in one small study.[11]

Timing of Therapy

In post-hoc analyses, two randomized controlled trials considered the timing of initiation of inhaled nitric oxide therapy on outcomes. Field et al.[7] reported no difference in death, BPD, or disability for inhaled nitric oxide-treated infants whether inhaled nitric oxide was initiated at less than 3 days old or at 4–28 days. Ballard et al.[12] studied infants with developing BPD, administering inhaled nitric oxide at 7–14 days or 15–21 days of age. Risk of death at 36 weeks was similar in inhaled nitric oxide-treated and control infants, but survival without BPD was increased if treatment was initiated during the second week from birth (RR 1.91 [1.31–2.78]).

Mode of Therapy

Two randomized controlled trials examined outcomes for infants treated with inhaled nitric oxide and conventional ventilation or high-frequency ventilation. One study found no difference between inhaled nitric oxide-treated infants delivered by conventional ventilation or high-frequency ventilation and controls in the combined outcome of death or BPD at 36 weeks,[3] or the risk of developmental delay or disability in survivors.[8] By post-hoc analysis, Van Meurs et al.[4] reported an increased risk for death during infancy for those receiving inhaled nitric oxide

Table 1. Birth-Weight Categories and Outcomes for Inhaled Nitric Oxide-Treated Infants Compared With Controls

Birth Weight	Author, Year	Survival Without BPD	Death (Time)	BPD	Neuro-Develop-ment	Composite Outcomes
Less than 750 grams	Kinsella et al., 2006[2]	—	NS	NS	—	NS: death or BPD
	Schreiber et al., 2003[3]	NS	—	—	—	NS: death or BPD
	Van Meurs et al., 2005[4]			NS		
	Hintz et al., 2007[5]*	—	73% vs. 56%, *p* value=0.01[†]	—	NS	81% vs. 62%, death or cerebral palsy, *p* value=0.0039[†]
	Watson et al., 2009[6‡]	—	NS	11.7% vs. 4% on oxygen at 1 year, *p* value=0.04	NS	NS: death or oxygen NS: death, oxygen, or NDI
750–999 grams	Kinsella et al., 2006[2]	—	NS	NS	__	NS: death or BPD
	Hintz et al., 2007[5]*	—	NS	—	NS	NS: death or cerebral palsy
	Schreiber et al., 2003[3]	NS	—	—	—	
	Watson et al., 2009[6‡]	—	NS	—	NS	32.1% vs. 44.4%, death or NDI, *p* value=0.04[§]; 32.9% vs. 45.1%, death, oxygen, or NDI, *p* value= 0.04[§]
Less than 1,000 grams	Van Meurs et al., 2005[4]	—	62% vs. 48%, *p* value=0.01	NS	—	NS: death or BPD
	Hintz et al., 2007[5]*	—	64% vs. 52%, *p* value= 0.04[†]	—	—	74% vs. 59%, death or cerebral palsy, *p* value=0.01[†]
1,000–1,250 grams	Kinsella et al., 2006[2]	—	NS	29.8% vs. 59.6 %, *p* value= 0.001	—	38.5 vs. 64.1%, death or BPD, *p* value=0.004
	Watson et al., 2009[6‡]	—	NS	—	NS	NS: death or oxygen NS: death, oxygen, or NDI
	Schreiber et al., 2003[3]	NS	—	—	—	NS: death or BPD
More than 1,250 grams	Schreiber et al., 2003[3]	NS	—	—	—	NS: death or BPD

NS = no statistically significant difference; BPD = bronchopulmonary dysplasia; NDI = neurodevelopmental impairment.

*Follow-up study of Van Meurs et al., 2005.[4]

†Findings at age 18–22 months.

‡Follow-up study of Kinsella at al., 2006.[2]

§Findings at age 1 year.

delivered by conventional ventilation (RR 1.46 [1.10–1.92]), a difference which persisted at age 18 to 22 months (RR 1.37 [1.05–1.79]), and an increase in motor impairment (RR 1.29 [1.03–1.60]).[5] No increase in mortality at any point was seen with inhaled nitric oxide delivered by high-frequency ventilation, and a similar risk for BPD at 36 weeks was reported for either mode of inhaled nitric oxide delivery.[4]

Dose

The initial dose of inhaled nitric oxide varied from 5 to 20 ppm among 13 randomized controlled trials. The concern for adverse side effects in preterm infants, particularly bleeding and intraventricular hemorrhage, was the basis for limitation of inhaled nitric oxide dosage and exposure in most studies. There was no difference in mortality or BPD between inhaled nitric oxide-treated infants and controls regardless of whether the initial dose was 5 ppm,[2,13] 10 ppm,[3,4,14–16] 20 ppm, or titrated to response.[7,12,17–20] Two studies of 10 ppm reported a reduction in the composite outcome of death or BPD among inhaled nitric oxide-treated infants compared with controls.[3,15] Cognitive impairment was decreased among infants treated with 10 ppm inhaled nitric oxide compared with controls in one follow-up study (RR 0.53 [0.29–0.94]),[8] and moderate to severe cerebral palsy was significantly increased in the inhaled nitric oxide group in a multivariate model (RR 2.01 [1.01–3.98])[5] in another follow-up study with similar dosing. No other differences in neurodevelopmental impairment were reported.[6,21–23]

Concurrent Therapies

One study directly addressed the effect of inhaled nitric oxide with concurrent therapies. Subhedar et al.[17] reported no difference between infants treated with inhaled nitric oxide and dexamethasone compared with dexamethasone alone in mortality, BPD, or the composite outcome of death and BPD.

Conclusion

Based on review of the published literature, there is limited evidence to suggest that some subgroups of preterm infants less than 34 weeks gestation with respiratory failure may benefit from inhaled nitric oxide therapy more than others. Interpretation of studies is limited by variable definitions of subgroups, differing times and doses of inhaled nitric oxide therapy, and post-hoc analyses.

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Knowns and Unknowns of Administering Inhaled Nitric Oxide

Steven H. Abman, M.D.

Although inhaled nitric oxide is approved for the treatment of term and near-term neonates with severe hypoxemic respiratory failure and pulmonary hypertension, its potential efficacy in the management of preterm infants remains controversial. Inhaled nitric oxide can improve gas exchange and lower pulmonary artery pressure in preterm infants with severe hypoxemia or in the setting of established bronchopulmonary dysplasia (BPD),[1–6] but whether early treatment reduces the risk for BPD or its severity is uncertain. Randomized trials have provided much helpful information, but findings from these studies have not consistently demonstrated that inhaled nitric oxide therapy improves survival or respiratory and neurodevelopmental outcomes in premature infants.[1,7–10] Variability in findings between these studies most likely reflects multiple factors related to study design, including differences in patient populations, such as disease severity and gestational and postnatal ages; the dose, duration, and timing of initiation of therapy; mode of inhaled nitric oxide delivery; and concurrent therapies.[11]

Differences in study design and findings partly reflect differences regarding specific therapeutic targets and end points for inhaled nitric oxide therapy in premature infants[1,7–10] (Table 1). Laboratory studies have shown that inhaled nitric oxide has several direct and indirect beneficial effects on the developing lung including improved oxygenation due to pulmonary vasodilation or increased ventilation-perfusion matching, anti-inflammatory properties, antioxidant effects, enhanced alveolar type II cell function and growth, epithelial fluid transport, and enhanced lung vascular and alveolar growth. The effects of inhaled nitric oxide on diverse biochemical and physiologic targets likely vary according to dose, duration, and timing of therapy. Understanding mechanisms that contribute to the failure to respond to nitric oxide experimentally may lead to greater insights into alternate strategies or concurrent therapies that may augment nitric responsiveness in the clinical setting.

Table 1. Inhaled Nitric Oxide for the Prevention of BPD

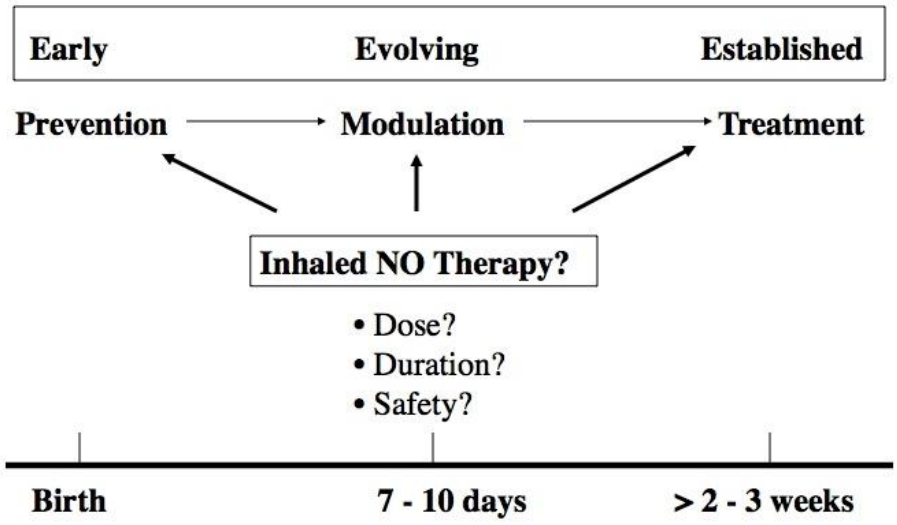
- Potential therapeutic targets:
  - — Improve gas exchange, reduce FiO_2.
  - — Lower pulmonary artery pressure.
  - — Provide anti-inflammatory effects.
  - — Povide antioxidant effects.
  - — Sustain surfactant function/production.
  - — Preserve or stimulate angiogenesis and alveolarization in the developing lung.

FiO_2 = fraction of inspired oxygen.

Therapeutic efficacy is further dependent on treatment strategies and goals including prophylaxis, modulation of evolving disease, or treating established BPD (Figure 1). Past clinical trials suggest that gestational age, postnatal age, dose, and duration of therapy are likely determinants of efficacy in reducing the risk for BPD.[7–11] For example, the study by Ballard et al., which applied the highest doses of inhaled nitric oxide for more sustained periods of treatment, had the greatest efficacy[8] (Figure 2). However, success in this study was exclusively

limited to earlier onset of treatment (less than 15 days). Whether higher doses (20 ppm) can be safely delivered during the first week of life, when the risk for intraventricular hemorrhage is greatest, is uncertain. Other studies consistently suggest that inhaled nitric oxide more effectively lowers the risk for BPD in neonates with birth weights greater than 1,000 grams.[1,7,9] These findings may reflect a key influence of lung maturation and the fact that inhaled nitric oxide is most effective when applied beyond the canalicular stage of lung development (Figure 3). These observations suggest that the duration of inhaled nitric oxide therapy should parallel the severity of prematurity, and that treatment should extend throughout the canalicular and saccular periods of lung development.

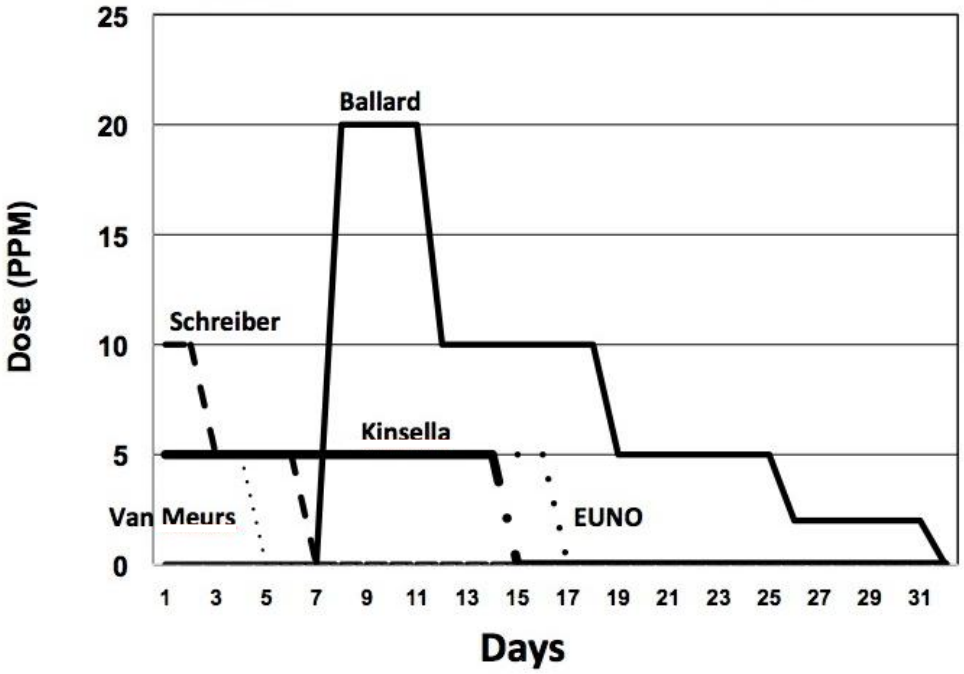
Figure 1. Treatment Strategies for BPD



NO = nitric oxide.

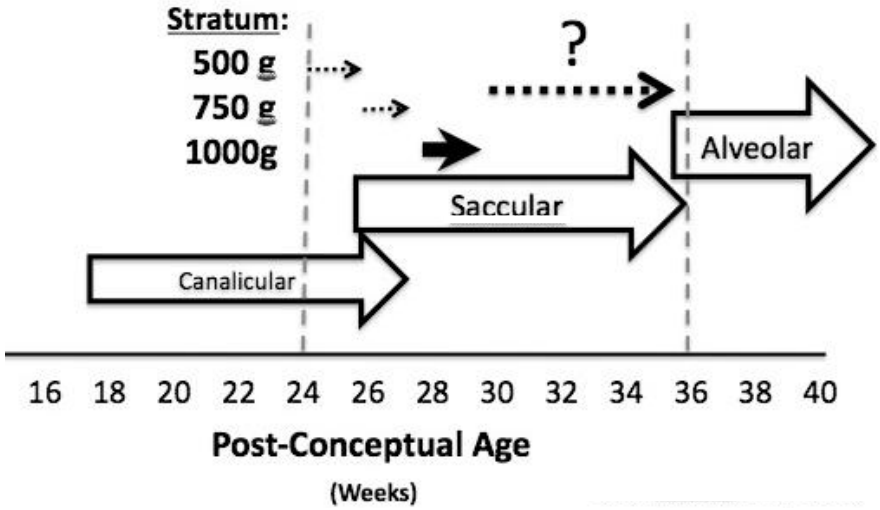
Past studies of term newborns suggest that ventilator strategies that maintain adequate lung volumes (functional residual capacity) may more effectively deliver inhaled nitric oxide to the distal lung. Although inhaled nitric oxide therapy can be successfully applied when delivered by nasal cannula or during nasal continuous positive airway pressure in some settings,[12–14] little is known about how consistent and effective nasal inhaled nitric oxide delivery can be in preterm infants with variable degrees of lung disease. Nasopharyngeal nitric oxide concentrations were measured at roughly half of the inhaled nitric oxide delivered, suggesting the need to increase inhaled nitric oxide dose during noninvasive therapy. Success may depend on how effectively nasal continuous positive airway pressure maintains lung volumes and ventilation in preterm infants with significant lung disease. Data are currently lacking on the relative effects of nitric oxide delivery during low- or high-flow nasal cannula therapy or continuous versus pulsed nitric oxide delivery. Plasma or urinary nitric oxide metabolite levels may provide a useful strategy to assess nitric oxide delivery in this setting.[15]

Figure 2. Inhaled Nitric Oxide Dose and Duration of Therapy



EUNO = European Nitric Oxide Trial.

Figure 3. Duration of Inhaled Nitric Oxide Therapy: Potential Impact of Stage of Lung Development



Note: Schematic based on data from Kinsella et al., 2006.[9]

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