NICHD Neonatal Research Network

Early Inhaled Nitric Oxide Study

OBJECTIVE To evaluate whether the use of INO in term/near term infants with respiratory failure (an oxygenation index > 15 and < 25) will decrease the risk of ECMO/death before discharge in the early INO group

ORGANIZATION

Clinical centers:

Network: University of Alabama, Brown University, Case Western Reserve University, University of Cincinnati, Harvard University, Indiana University, University of Miami, University of New Mexico, Stanford University, University of Tennessee-Memphis, University of Texas-Dallas, University of Texas-Houston, Wayne State University, Yale University

Canadian: University of Alberta, University of Calgary, University of British Columbia, Baylor University, McGill University, University of Ottawa, McMaster University, University of Manitoba, UCSD Medical Center, The Hospital for Sick Children

Subcommittee chair: Ganesh Konduri, MD

DESIGN

Type:
- Randomized clinical trial

Major inclusion criteria:
- Require assisted ventilation for hypoxic respiratory failure
- > 34 weeks gestational age
- One of the following diagnoses:
  Primary PPHN
  Respiratory distress syndrome
  Perinatal aspiration syndrome
  Pneumonia/sepsis
  Suspected pulmonary hypoplasia
- An OI > 15 and < 25 on 2 arterial blood gases at least 15 minutes apart on FiO_2 > 80%
- Indwelling arterial line
- Parental consent

Treatment groups:
- Inhaled nitric oxide
- Control group (100% oxygen)

Level of masking:
- Double-masked

Stratification: Clinical center

Sample size:
- Goal = 400
- Assumptions:
  - Outcome event = death or initiation of ECMO
  - Reduction from 35% in control group to 20% in INO group
  - Confidence interval 95%
  - Power = 90%
  - Treatment noncompliance = 0%

SCHEDULED EVALUATIONS

Pre-randomization:
- Eligibility
- Baseline evaluation: neonatal, pulmonary, cardiac, therapies, bleeding

Post-randomization:
- Response to study gas, treatments, adverse events (air leak, CNS, bleeding), morbidities (CLD, tracheostomy, other)
- Outcome (death or initiation of ECMO)
- 18-24 month follow-up

MANAGEMENT PROTOCOLS

Study gas management:
- INO initiated at 5 ppm, increased to 20 ppm
- Weaning: Magnitude and schedule of all gas reductions defined.
- Maximum total time on study gas: 336 hours (after 240 hours, must be no more than 5 ppm)
- Regular monitoring of methemoglobin and NO_2 levels

OUTCOME MEASURES

Primary:
- Death before discharge/120 days or initiation of ECMO

Secondary:
- OI > 25 on 2 consecutive blood gases drawn at least 1 hr apart or OI > 30 on 2 consecutive ABGs 15 min apart
- OI > 40 on 2 consecutive arterial blood gases done at least 30 min apart
- Neurodevelopmental or hearing impairment evaluated at 18-24 mos corrected age

TIMETABLE

Randomization:
- 8/98 – 8/01 (Study halted 4/27/01)

Follow-up:
- Through 8/03

CONCLUSIONS

"Initiation of INO for term/ near-term infants in respiratory failure at OI of 15-25 improves oxygenation without increasing its toxicity but does not reduce incidence of ECMO/death significantly when compared to initiation at OI >25." (*Ped Res 2002; 2259*)

DATA CENTER

Cancer Trials Network (CTN) Services