Inhaled nitric oxide in preterm infants


CRD summary
This review found that there was a small reduction in the composite outcome of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age, for infants treated with inhaled nitric oxide, compared with controls, but no reduction in death or bronchopulmonary dysplasia considered separately. These conclusions are clearly based on the evidence presented, and are likely to be reliable.

Authors' objectives
To review the evidence for inhaled nitric oxide therapy in pre-term infants (born at 34 weeks gestation or earlier), who were receiving respiratory support.

Searching
The following databases were searched to June 2010: MEDLINE, EMBASE, PsycINFO and Cochrane Central Register of Controlled Trials (CENTRAL). The proceedings of the Pediatric Academic Societies were searched (2009 and 2010) and reference lists were checked.

Study selection
Randomised controlled trials (RCTs) were eligible if they reported on deaths after neonatal intensive care unit discharge, the rates of bronchopulmonary dysplasia or short-term risks. The population of interest was infants born at or before 34 weeks gestation, who were receiving inhaled nitric oxide therapy and respiratory support. Other study designs were considered if they reported the long-term pulmonary or developmental outcomes, with factors such as initiation timing, dose, duration and mode of delivery.

The patients in included studies varied in their age (enrolled from birth through to 27 days); birth weight (401 to 2,000 grams); and clinical conditions. The dose of inhaled nitric oxide varied from five to 40 parts per million. Both RCTs and observational studies were included, depending on the specific question. Studies were conducted in Europe, North America or Asia.

Two reviewers independently selected studies for inclusion; disagreements were resolved by discussion or adjudication by a third reviewer.

Assessment of study quality
The Cochrane Risk of Bias tool was used to assess the quality of the RCTs. Cohort studies were assessed using an adapted version of the Newcastle-Ottawa Scale. The features assessed and how these were judged were described in the report. The body of evidence, for each outcome, was graded based on its quality, quantity and consistency, using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) working group guidelines.

Two reviewers independently assessed the studies and disagreements were resolved by discussion. Consensus on the grading of evidence was achieved within the entire research team.

Data extraction
A clinical expert and a research assistant independently extracted the data, as dichotomous outcomes, and calculated risk ratios for each study outcome; disagreements were resolved by discussion. The data were entered into evidence tables, according to the research question, and checked against the original publications.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to pool the risk ratios, for each outcome, and to calculate the associated 95% confidence intervals. Heterogeneity was evaluated using $I^2$. Sensitivity analyses were used to investigate the stability of the results.

Results of the review
A total of 14 RCTs and eight observational studies were included. Six of the RCTs were judged to be at a low risk of bias, three were at a fair risk, and the remaining five were at a high risk. None of the eight observational studies were rated at a low risk of bias, five were at a fair risk, and three were at a high risk.

Mortality did not significantly differ between infants treated with inhaled nitric oxide and controls, in neonatal intensive care units, across the 14 RCTs. Meta-analyses of mortality at 36 weeks postmenstrual age (gestation plus birth weeks), and 12 to 30 months and one to four or five years of age, all found no significant differences. Sensitivity analyses based on dosage and body weight also found no differences.

A small difference was found in favour of inhaled nitric oxide, compared with control treatment, for the composite outcome of death or bronchopulmonary dysplasia at 36 weeks (RR 0.93, 95% CI 0.87 to 0.99; 11 RCTs; I²=30%).

There was no evidence of significant differences in the incidence of any of the specified short or long-term pulmonary or neurodevelopmental outcomes.

Authors' conclusions
There was a seven percent reduction in risk of the composite outcome of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age, for infants treated with inhaled nitric oxide, compared with controls, but no reduction in death or bronchopulmonary dysplasia when considered separately.

CRD commentary
This review addressed a clear research question, with detailed inclusion criteria and reasonably broad searches. No restrictions were placed on publication date and status, and on language indicating that these were unlikely to be sources of bias. The review processes were clearly reported and steps were taken to reduce the impact of reviewer error and bias.

The included studies were quality assessed, with details provided, and appear to have been combined using appropriate statistical techniques. Clinical heterogeneity was explored, using sensitivity analyses, and these were described.

The authors' conclusions were clearly based on the evidence presented, and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the evidence did not support the use of inhaled nitric oxide for premature infants with respiratory failure.

Research: The authors stated that further research was needed into the use of inhaled nitric oxide, in pre-term infants, and they gave detailed recommendations.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.