Meta-analysis of inhaled nitric oxide in premature infants: an update
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CRD summary
This review concluded that inhaled nitric oxide may decrease the incidence of chronic lung disease and combined mortality plus chronic lung disease in premature infants with hypoxemic respiratory failure, but that caution is required in infants at risk of intracranial haemorrhage. Multiple shortcomings in the review process and poor reporting make the reliability of these conclusions difficult to determine.

Authors' objectives
To assess the evidence for the use of inhaled nitric oxide in the treatment of respiratory failure and pulmonary hypertension in premature infants.

Searching
MEDLINE was searched. Search terms were reported but not search dates. A handsearch of the latest editions of paediatric and neonatal journals was conducted.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion. It appeared that the following inclusion criteria were also employed: the assessment of inhaled nitric oxide in the treatment of pre-term infants below 34 weeks gestation with respiratory failure and pulmonary hypertension. Primary outcomes were mortality, the development of chronic lung disease and major intracranial haemorrhage.

Included trials enrolled infants up to gestational ages that ranged from up to 32 to 34 weeks, except for the largest trial where the mean gestational age was 26.0 weeks; ages at randomisation ranged from four hours after surfactant replacement to 96 hours. A range of entry criteria and response definitions were used. Maximum inhaled nitric oxide doses ranged from 5 to 20ppm.

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted to permit the calculation of relative risks (RR) with 95% confidence intervals (CI).

The authors did not state how the data were extracted for the review.

Methods of synthesis
Pooled relative risks with 95% confidence intervals were calculated using meta-analyses. No details of the analytic methods were reported. Numbers need to treat (NNT) were calculated in the case of statistically significant benefits being found.

Results of the review
Five RCTs (n=808 infants) were included in the review. Sample sizes ranged from 21 to 415 infants.

There was a statistically significant benefit for use of nitric oxide for the outcome of chronic lung disease (RR 0.83, 95% CI 0.72 to 0.95; NNT=11). There was also a statistically significant benefit in the combined endpoint of chronic lung disease and mortality (RR 0.81, 95% CI 0.70 to 0.93; NNT=7).

There was no statistically significant difference in the rate of mortality (RR 1.03, 95% CI 0.87 to 1.22) or major intracranial haemorrhage (RR 0.72, 95% CI 0.50 to 1.02) between the nitric oxide and control groups.
Authors' conclusions
Use of inhaled nitric oxide may decrease the incidence of chronic lung disease and the combined endpoint of mortality and chronic lung disease in pre-term infants with hypoxemic respiratory failure, but the largest and most recent study was terminated due to an increase in the incidence of severe intracranial haemorrhage. Therefore, caution in the use of inhaled nitric oxide in pre-term infants at risk for intracranial haemorrhage is mandatory.

CRD commentary
The inclusion criteria were not clearly stated (with the exception of study design) and had to be inferred from the review question; this can increase the risk of errors and bias in the selection of studies for the review. Only one database was searched, which increased the chances that relevant studies were omitted from the review. It appeared that several relevant RCTs were in progress at the time of the review, therefore the reviews' conclusions may have been superseded. The authors did not report using methods designed to reduce reviewer bias and error at any stage of the review process.

A quality assessment of included trials was not reported. No details of the methods used in the statistical synthesis of the included trials were reported, which made it difficult to determine their appropriateness of the authors' approach. There was no attempt to assess or explore heterogeneity between trials.

Whilst the authors' conclusions reflected the result of the review, the poor reporting and shortcomings of the review process mean that it is difficult to determine their reliability.

Implications of the review for practice and research
Practice: The authors stated that caution should be employed in the use of inhaled nitric oxide in preterm infants at risk of intracranial haemorrhage.

Research: The authors stated that further studies with neurodevelopmental follow-up are required to determine if the reduction of chronic lung disease in very low birth weight infants is associated with differences in neurodevelopmental outcomes.

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