Inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn: a meta-analysis

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Authors' objectives
To evaluate the use of inhaled nitric oxide (NO) in the management of persistent pulmonary hypertension (PPHN) of the newborn.

Searching
MEDLINE, Current Contents and LILACS were searched from January 1990 to March 1998 by cross-referencing the following MeSH terms: 'nitric oxide and infant'; 'nitric oxide and newborn'; 'nitric oxide and pulmonary hypertension'; 'pulmonary hypertension and infant'; 'pulmonary hypertension and newborn'. The references lists of the retrieved articles and other reviews in the area were also searched. Only studies published in English, French, Spanish, and Portuguese were selected.

Study selection
Study designs of evaluations included in the review
Only randomised clinical trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies were included if the treated group received administration of inhaled NO by tracheal cannula, and the control group was managed with conventional treatment.

Participants included in the review
PPHN. Studies were included if the study population consisted of term (greater than 37 weeks of gestational age) or near term (greater than 34 but less than 37 weeks of gestational age) newborns (less than 28 days at the beginning of the study) with hypoxemia and a diagnosis of PPHN, as conducted by echocardiography. Infants with intracardiac shunting due to structural heart disease (except ductus arteriosus) were excluded.

Outcomes assessed in the review
Studies were eligible for inclusion if they examined the following outcomes: death; requirement for extracorporeal membrane oxygenation (ECMO); systemic oxygenation; disturbances of the central nervous system (haemorrhagic disorders and convulsions); and development of chronic pulmonary disease during hospitalisation.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of each study was assessed according to the scoring system of Heyland et al. (see Other Publications of Related Interest). The maximum score that could be achieved was 13 points. The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted were: author; year; single or multicentre design; the number of participants; gestational age; hypoxemia and mechanical ventilation; cointerventions, i.e. surfactant and/or high-frequency oscillatory ventilation;
study validity; and outcomes.

Methods of synthesis
How were the studies combined?
For categorical outcomes, the data were combined to estimate the typical odds ratio (OR), relative risk (RR), relative risk reduction, absolute risk reduction and number-needed-to-treat. For continuous measures, typical estimates for the weighted mean difference were calculated, along with their corresponding 95% confidence intervals (CIs). The RR, and not OR, was calculated if the outcome rate measured was higher than 0.2.

How were differences between studies investigated?
The heterogeneity of treatment effects across the studies was ascertained by a chi-squared analysis, using the null hypothesis that the results were similar. A p-value of greater than 0.05 for the homogeneity test was considered to be consistent with the assumption that differences in the study results were due to chance.

Results of the review
Eight RCTs (612 randomised newborns) fulfilled the inclusion criteria.

Three of the included RCTs scored 12 out of a maximum 13 points for methodological quality, the remaining 5 RCTs scored 11 points.

PPHN without congenital diaphragmatic hernia.

Death during hospitalisation: the meta-analysis included 5 studies (513 newborns). There were 31 (11%) deaths in the NO group and 26 (12%) in the control group. There was no difference in mortality between the groups (OR 1.04, 95% CI: 0.59, 1.82).

Requirements for ECMO (5 studies with 537 newborns): fewer patients from the NO group needed ECMO, 101 out of 305 (33%), compared with 115 of the 232 (50%) controls (RR 0.73, 95% CI: 0.6, 0.9).

Systemic oxygenation: in all but one of the 7 trials in which this outcome was analysed, it was concluded that NO improved oxygenation. The meta-analysis supported the superiority of NO for this outcome.

Disturbances of the central nervous system (3 studies with 420 newborns): there was no difference between the NO-treated and control groups (OR 0.83, 95% CI: 0.50, 1.37).

Development of chronic pulmonary disease during hospitalisation (2 trials with 378 infants): no difference between the NO-treated and control groups was found for this outcome (OR 1.3, 95% CI: 0.69, 2.46).

PPHN with congenital diaphragmatic hernia.

Death or ECMO requirement: one trial (53 infants) showed there was no significant difference between the groups (RR 1.17, 95% CI: 0.97, 1.41).

Systemic oxygenation: 2 trials examined this outcome, neither of which found NO to be superior to control.

Disturbances of the central nervous system: one study (53 newborns) showed no difference between the number of events in each group (OR 1.14, 95% CI: 0.26, 5.07).

Development of chronic pulmonary disease: one trial (53 newborns) found no benefit for inhaled NO (RR 0.62, 95% CI: 0.24, 1.61).

Authors' conclusions
Inhaled NO improves oxygenation and reduces the requirement for ECMO only in newborns with PPHN who do not


have diaphragmatic hernia. The risk of complications of the central nervous system and chronic pulmonary disease were not affected by inhaled NO.

CRD commentary
This was a reasonably well conducted and reported review of the research literature. The review question was clearly stated, with the papers being selected according to predefined criteria that related specifically to the study design, participants, interventions and outcomes. Details of electronic database searches were given, and attempts to identify literature through the reference lists of included trials and related reviews were reported.

The characteristics of the included trials were presented in reasonable detail, and these studies were synthesised using appropriate quantitative meta-analytic methods. However, it was unclear how many of the reviewers were involved in selecting the studies and extracting the data. If these processes were only carried out by a single author, potentially relevant studies may have been missed and errors in the data extraction may have gone undetected. Though the authors assessed the quality of the included studies, these data were not used in the synthesis. The overall quality scores were similar across studies, but there was variation on important characteristics, such as the presence or absence of crossovers.

Implications of the review for practice and research
Practice: The authors state 'Inhaled NO appears to improve the outcome in hypoxemic-term and near-term infants with PPHN. We do not consider it as the "magic bullet", but rather as part of a strategy addressing the complex cardiopulmonary interactions that characterise this syndrome. One of the possible co-interventions is a rescue treatment with high frequency ventilation and/or exogenous surfactant, allowing the NO to contact most pulmonary areas, improving the ventilation/perfusion rate. Adjunctive therapy of haemodynamic support is also useful in the maintenance of systemic arterial pressure, an essential condition to change the right to left intracardiac shunting. Patients selected for inhaled NO treatment cannot have high degrees of structural pulmonary abnormalities (hypoplasia or alveolar capillary dysplasia) that could prevent the action of the gas. An adequate concentration of inhaled NO (probably between 5 and 20 ppm) must be used to achieve the best response in each clinical situation and to prevent the cytotoxic effects. The treatment must therefore be initiated before structural pulmonary changes develop'.

Research: The authors state that more clinical trials should be performed with the above (see Implications for 'Practice') taken into consideration.

Bibliographic details

PubMedID
11082223

Original Paper URL

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Controlled Clinical Trials as Topic; Humans; Infant, Newborn; Nitric Oxide /therapeutic use; Persistent Fetal Circulation Syndrome /drug therapy; Randomized Controlled Trials as Topic; Treatment Outcome; Vasodilator Agents /therapeutic use

AccessionNumber
12001003712

Date bibliographic record published
31/12/2002

Date abstract record published
31/12/2002

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.