Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis

CRD summary
The authors concluded that nitric oxide is associated with limited improvements in oxygenation in patients with acute lung injury and acute respiratory distress syndrome, but there is no improvement in mortality and it may cause adverse effects. This was a well-conducted and clearly reported review and the authors’ conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of inhaled nitric oxide for the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Searching
MEDLINE, CINAHL, EMBASE and the Cochrane CENTRAL Register were searched to October 2006; the search terms were reported. In addition, the proceedings of four specified conferences were searched from 1994 to 2006, the reference lists of retrieved studies and reviews were screened, and experts in the field were contacted for details of further studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Parallel-group, randomised controlled trials (RCTs) were eligible for inclusion. The review also included crossover trials.

Specific interventions included in the review
Studies that evaluated treatment with nitric oxide were eligible for inclusion. The included studies compared nitric oxide with placebo or usual treatment. Prevention studies were excluded. The studies could use similar cointerventions in both treatment groups. Most of the included studies evaluated a fixed dose of nitric oxide (median 10 ppm, range: 5 to 10); others used the lowest dose that achieved an oxygenation response, or evaluated different doses. The median duration of nitric oxide treatment was 6.5 days (range: 3.5 to 9; based on 5 studies). In some studies, controls meeting specified criteria received nitric oxide treatment as rescue therapy.

Participants included in the review
Studies of adults and children that included 80% or more (or separate subgroups) with ALI or ARDS (trial authors’ definition) were eligible for inclusion. Studies of neonates were excluded. In all but one of the included studies, patients met the American European Consensus Conference oxygenation criteria for ARDS; one trial included some patients with ALI. Most of the included studies enrolled only adults; a minority enrolled only children or a few children.

Outcomes assessed in the review
The main review outcomes were mortality (in hospital or in intensive care, or at 28 or 30 days), duration of ventilation, oxygenation, pulmonary arterial pressure and adverse events. The review also assessed ventilator-free days to 28 or 30 days, the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2), and the oxygenation index.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and inter-reviewer agreement was assessed.

Assessment of study quality
Two reviewers independently assessed validity using the following criteria: method of randomisation; allocation
concealment; blinding of the carers and outcome assessors; number of withdrawals after randomisation; and standardisation or equal treatment of intervention groups regarding mechanical ventilation, weaning and sedation. Any disagreements were resolved by consensus. Authors were contacted for clarification of data, where required.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements by consensus. Authors were contacted for clarification and additional data, where required. Intention-to-treat data were extracted and, where the studies evaluated more than one nitric oxide treatment regimen, the data were combined.

Methods of synthesis
How were the studies combined?
Studies in which less than 50% of the patients crossed over to nitric oxide were combined in meta-analyses of clinical outcomes. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes, while pooled weighted mean differences (WMDs) and ratios of means were calculated for continuous outcomes. Random-effects models were used. Data on other adverse effects were combined in a narrative. The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q and the I-squared statistics.

Results of the review
Twelve RCTs (n=1,237) were included.

All 12 studies were considered to be of a good quality. Ten studies reported concealment of randomisation and 7 studies reported a protocol or guidelines for mechanical ventilation. All studies had complete follow-up and analysed patients according to allocated groups.

Clinical outcomes.

There was no significant difference between nitric oxide treatment and control for mortality (RR 1.10, 95% CI: 0.94, 1.30; based on 9 studies), duration of ventilation (3.6 additional days, 95% CI: -4.0, 11.1; based on 3 studies), or ventilator-free days (0.6 fewer days, 95% CI: -1.8, 0.7; based on 5 studies). There was moderate to high heterogeneity for the analysis of ventilation duration (I-squared 63%).

The funnel plot based on mortality showed no evidence of publication bias.

Physiological outcomes.

On the first day of treatment, nitric oxide was associated with small improvements in the PaO2/FiO2 ratio (WMD 16 mmHg, 95% CI: 4, 27; based on 9 studies) and oxygenation index (WMD -3 cmH2O/mmHg, 95% CI: -5, -0.5; based on 3 studies) compared with control. The PaO2/FiO2 ratio was higher and the oxygenation index lower on some but not all subsequent days (to day 4). There were no significant differences between nitric oxide and control in pulmonary arterial pressure on any day.

Adverse effects.

Nitric oxide treatment was associated with an increased risk of renal dysfunction (RR 1.50, 95% CI: 1.11, 2.02; based on 4 studies). Four patients (of 651) randomised to nitric oxide and three controls (of 586) developed above 5% methaemoglobinaemia.

Authors' conclusions
Nitric oxide is associated with limited improvements in oxygenation in patients with ARDS and ALI, but there is no
improvement in mortality and it may cause adverse effects.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The authors searched several relevant sources for published and unpublished studies and made attempts to minimise language bias. They used methods to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. Validity was assessed using specified criteria and the results of this assessment reported. The studies were, in general, appropriately combined in a meta-analysis and statistical heterogeneity was assessed. Significant heterogeneity was found for duration of ventilation but potential reasons for this were not discussed. This was generally a well-conducted and clearly reported review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that they do not recommend the routine use of nitric oxide in patients with ARDS or ALI because of limited physiological benefits and potential adverse effects. Research: The authors did not state any implications for further research.

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