

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

Neill K J Adhikari,¹ Karen E A Burns,¹ Jan O Friedrich,¹ John T Granton,¹ Deborah J Cook,² Maureen O Meade²

EDITORIAL by Ferguson

¹Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

²Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada

Correspondence to: N K J Adhikari neill.adhikari@sunnybrook.ca

BMJ 2007;334:779-82
doi: 10.1136/bmj.39139.716794.55

ABSTRACT

Objective To review the literature on the use of inhaled nitric oxide to treat acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and to summarise the effects of nitric oxide, compared with placebo or usual care without nitric oxide, in adults and children with ALI or ARDS.

Design Systematic review and meta-analysis.

Data sources Medline, CINAHL, Embase, and CENTRAL (to October 2006), proceedings from four conferences, and additional information from authors of 10 trials.

Review methods Two reviewers independently selected parallel group randomised controlled trials comparing nitric oxide with control and extracted data related to study methods, clinical and physiological outcomes, and adverse events.

Main outcome measures Mortality, duration of ventilation, oxygenation, pulmonary arterial pressure, adverse events.

Results 12 trials randomly assigning 1237 patients met inclusion criteria. Overall methodological quality was good. Using random effects models, we found no significant effect of nitric oxide on hospital mortality (risk ratio 1.10, 95% confidence interval 0.94 to 1.30), duration of ventilation, or ventilator-free days. On day one of treatment, nitric oxide increased the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂ ratio) (13%, 4% to 23%) and decreased the oxygenation index (14%, 2% to 25%). Some evidence suggested that improvements in oxygenation persisted until day four. There was no effect on mean pulmonary arterial pressure. Patients receiving nitric oxide had an increased risk of developing renal dysfunction (1.50, 1.11 to 2.02).

Conclusions Nitric oxide is associated with limited improvement in oxygenation in patients with ALI or ARDS but confers no mortality benefit and may cause harm. We do not recommend its routine use in these severely ill patients.

INTRODUCTION

Nitric oxide is a selective pulmonary vasodilator and has anti-inflammatory properties.^{1,2} Based on limited data on efficacy, clinicians have rapidly adopted it for use in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).³

A systematic review and meta-analysis of nitric oxide^{4,5} included five randomised controlled

trials^{w3-w7} and found no effect on mortality or ventilator-free days; one trial showed improved oxygenation.^{w3} Because confidence intervals were wide, it concluded that the effects of nitric oxide on morbidity and mortality were uncertain. We have incorporated data from new randomised controlled trials to evaluate the effects of nitric oxide on pulmonary physiology (oxygenation and pulmonary arterial pressure) and important clinical outcomes (mortality, duration of ventilation, and adverse effects) in patients with established ALI or ARDS.

METHODS

Search strategy—We searched Medline, CINAHL, Embase, and CENTRAL (to October 2006) for randomised controlled trials, searched proceedings of four conferences (1994-2006), screened bibliographies, recent review articles, and contacted content experts (see bmj.com for additional details of study methods).

Study selection—Two reviewers independently screened studies for inclusion. We selected parallel group trials that enrolled adults or children (excluding neonates), with ≥80% of patients or a separately reported subgroup having ALI or ARDS. Included trials compared nitric oxide with placebo or usual treatment (not prevention) for ALI or ARDS and reported mortality (at any time), duration of ventilation, ventilator-free days, or pulmonary physiological parameters on days one to four of treatment (PaO₂ (partial pressure of oxygen)/FiO₂ (fraction of inspired oxygen); oxygenation index, defined as 100 × mean airway pressure/(PaO₂/FiO₂); mean pulmonary arterial pressure). We included trials with cointerventions applied equally in both groups. We assessed agreement between reviewers for trial eligibility using Cohen's κ.

Data abstraction and validity assessment—Two reviewers independently abstracted data and methods from included trials and resolved disagreements by consensus. We attempted to contact authors for additional data if necessary.

Quantitative data synthesis—Our primary outcome was mortality in hospital (or, if not available, mortality in the intensive care unit or at 28 or 30 days). Secondary outcomes included duration of ventilation, ventilator-free days, and pulmonary physiology. We decided post hoc to combine data on renal dysfunction. We used random

This article is an abridged version of a paper that was published on bmj.com on 23 March 2007. Cite this version as: *BMJ* 2007; 334: 779-82, doi: 10.1136/bmj.39139.716794.55 (abridged text, in print: *BMJ* 2007; 334: 779-82).

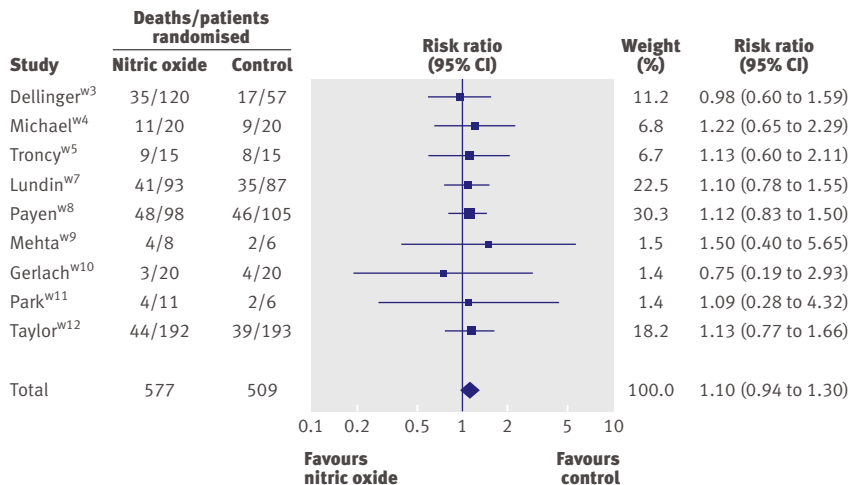


Fig 1 | Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with $\geq 50\%$ of control patients crossing over to nitric oxide also reported mortality data.^{w2,w6} Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27)

effects models for all analyses with $P \leq 0.05$ as significant. We report binary outcomes as risk ratios and continuous outcomes as weighted mean differences (measure of absolute change) and ratios of means (measure of relative change). We assessed homogeneity between studies for each outcome using the Cochran Q statistic and I^2 . We developed several a priori hypotheses to explain significant heterogeneity.

RESULTS

Electronic database searches yielded 1262 citations. After evaluation we included 12 parallel group randomised controlled trials which randomised 1237 patients (median 40; range 14-385) with ALI or ARDS.^{w1-w12} The two reviewers completely agreed ($\kappa=1$) on the selection. Seven trials used a fixed dose of nitric oxide (median 10

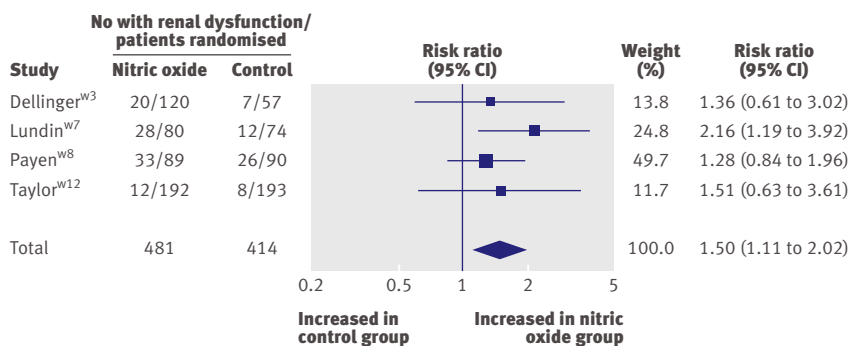


Fig 2 | Effect of nitric oxide on renal dysfunction (defined as new renal replacement therapy,^{w8} new renal replacement therapy or new raised creatinine concentration ($>300 \mu\text{mol/l}^{w9}$), or raised creatinine concentration ($>177 \mu\text{mol/l}^{w3}$ or $\geq 265 \mu\text{mol/l}^{w12}$)). The denominator includes only patients without baseline renal dysfunction,^{w7,w8,w12} except possibly for one trial.^{w3} Using a different definition of renal dysfunction (“adverse event”) in one trial^{w3} did not alter the summary estimate (risk ratio 1.49, 1.10 to 2.03). Weight is the relative contribution of each study to overall estimate of treatment effect on log scale assuming a random effects model

ppm; range 5-10 ppm),^{w1,w2,w6,w8,w10-w12} and five used the lowest dose to achieve an oxygenation response^{w4,w5,w7,w9} or randomised patients to different doses.^{w3} All trials had good scientific quality. Full details of study characteristics and methodological quality are on bmj.com. A funnel plot of standard error versus risk ratio for mortality did not suggest publication bias.

Effect of nitric oxide on clinical outcomes—Meta-analyses (table) showed that nitric oxide did not affect mortality (fig 1), duration of ventilation or ventilator-free days. There was moderate to high heterogeneity between studies for duration of ventilation only.

Effect of nitric oxide on physiological outcomes—On the first day of therapy, nitric oxide was associated with small improvements in the $\text{PaO}_2/\text{FiO}_2$ ratio, and oxygenation index (table). Some evidence suggested that improvements in oxygenation in the nitric oxide group persisted beyond day one. Differences in mean pulmonary arterial pressure were not significant on any day. There was no evidence of important statistical heterogeneity in the physiological outcomes.

Adverse effects—Four nitric oxide patients (of 651 randomised) and three control patients (of 586 randomised) developed $>5\%$ methaemoglobinaemia.^{w3,w7,w12} One trial reported three patients developing raised nitrogen dioxide concentrations; all had received 80 ppm nitric oxide.^{w3} Nitric oxide increased the risk of renal dysfunction in one unblinded^{w7} and three blinded^{w3,w8,w12} trials that enrolled 72% of patients in all included trials (risk ratio 1.50, 1.11 to 2.02; fig 2). Other adverse events were variably reported, and we did not combine these data.

DISCUSSION

The routine use of inhaled nitric oxide is not beneficial for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Our meta-analysis found no benefit of nitric oxide on survival and an increased risk of renal dysfunction. Oxygenation improved over the first 24 hours, with some data suggesting improvements to 96 hours. Given the limited physiological improvements and possible harm, we cannot recommend routine use of nitric oxide in these patients.

The trend towards increased mortality in patients receiving nitric oxide was highly consistent across trials, with no trial dominating the meta-analysis. Given the strength and magnitude of this trend, consistency across trials, biological plausibility,^{8,w10} and the finding of other potential adverse effects of nitric oxide (for example, renal failure), our analysis raises concerns about its nitric oxide in this setting.

Adverse events

Descriptive analyses suggest that methemoglobinaemia and raised nitrogen dioxide concentration are not common or clinically important consequences, except possibly in patients receiving high doses (at least 80 ppm) of nitric oxide for several days. Data from four large trials representing nearly three

quarters of all randomised patients showed an increased risk of renal dysfunction in patients receiving nitric oxide. Cautious interpretation is warranted, as this result was a post hoc analysis and is potentially subject to publication bias. In addition, the potential physiological mechanisms linking administration of inhaled nitric oxide to acute renal dysfunction are controversial because of its simultaneous protective effects on renal blood flow and leucocyte adhesion.⁹

Why nitric oxide may not be beneficial

Firstly, short term physiological improvements in oxygenation seem to have no impact on patients' survival,¹⁰ possibly because oxygenation is not necessarily related to severity of lung injury. Secondly, as most patients with ARDS die of multiple organ failure rather than refractory hypoxaemia,¹¹ small changes in oxygenation might not lead to improvements in outcome. Thirdly, the prolonged fixed dosing regimen in most trials may have attenuated benefit over time because of increased sensitisation.^{8 w10} Fourthly, the benefits of nitric oxide may have been overwhelmed by a harmful mechanical ventilation strategy, which perpetuated multiple organ failure.¹² This, however, would not account for our finding of potential harm. Finally, trials restricting enrolment to patients with an acute oxygenation response to nitric oxide may have

found a positive effect on mortality, although not supported in one trial.^{w7}

Strengths and limitations

We used several methods to reduce bias and analysed a comprehensive set of clinical and physiological outcomes. We were unable to obtain any^{w4 w12} or complete^{w3} additional information from three trials. Considering secondary clinical outcomes, we expected to find variation between trials in duration of ventilation and ventilator-free days related to different populations of patients. We analysed these outcomes, while acknowledging the limited interpretability of this analysis. Finally, the tests for heterogeneity were underpowered.

Although our results do not exclude the possibility that some subgroups of patients may benefit from nitric oxide, the consistent lack of a mortality benefit across trials mitigates this possibility.

Previous research

A previous systematic review and meta-analysis of inhaled nitric oxide for acute hypoxaemic respiratory failure^{4,5} included fewer randomised controlled trials^{w3-w7} and found no effect on mortality (risk ratio 0.98, 95% confidence interval 0.66 to 1.44; two trials, 204 patients). Our report is consistent with this work and extends it by including more trials, thus narrowing the confidence limits around the estimate of mortality.

Effects of inhaled nitric oxide (NO) on clinical and physiological outcomes in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Outcome	No of trials (patients)	Treatment effect (95% CI); P value		P value for homogeneity; I ²	
		Ratio of means	Weighted mean difference	Ratio of means	Weighted mean difference
Mortality*	9 (1086)	—	—	—	—
Duration of ventilation (days)	3 (237)	1.17 (0.80 to 1.70); 0.41	3.6 (-4.0 to 11.1); 0.36	0.02; 76%	0.07; 63%
Ventilator-free days†	5 (804)	0.94 (0.84 to 1.06); 0.33	-0.6 (-1.8 to 0.7); 0.37	0.71; 0%	0.66; 0%
PaO ₂ /FI _O ₂ (mm Hg):					
Day 1	9 (553)	1.13 (1.04 to 1.23); 0.003	16 (4 to 27); 0.007	0.19; 29%	0.11; 39%
Day 2	5 (416)	1.07 (1.02 to 1.13); 0.006	9 (-3 to 20); 0.14	0.43; 0%	0.18; 37%
Day 3	5 (450)	1.05 (0.98 to 1.13); 0.17	7 (-4 to 18); 0.21	0.54; 0%	0.49; 0%
Day 4	4 (334)	1.07 (1.02 to 1.12); 0.01	15 (4 to 25); 0.009	0.85; 0%	0.90; 0%
Oxygenation index (100)×mean airway pressure/(PaO ₂ /FI _O ₂) (cm H ₂ O/mm Hg):					
Day 1	3 (296)	0.86 (0.75 to 0.98); 0.02	-3 (-5 to -0.5); 0.02	0.46; 0%	0.72; 0%
Day 2	1 (164)	0.81 (0.67 to 0.98); 0.03	-3 (-6 to -0.04); 0.05‡	—	—
Day 3	2 (245)	0.82 (0.64 to 1.06); 0.13	-3 (-7 to -0.2); 0.04	0.28; 16%	0.34; 0%
Day 4	1 (134)	0.78 (0.63 to 0.96); 0.02	-4 (-8 to -0.3); 0.03‡	—	—
Mean pulmonary arterial pressure (mm Hg):					
Day 1	4 (165)	0.95 (0.88 to 1.03); 0.24	-2 (-4 to 1); 0.22	0.27; 23%	0.27; 23%
Day 2	3 (167)	0.96 (0.89 to 1.02); 0.19	-1 (-3 to 0.6); 0.18	0.64; 0%	0.68; 0%
Day 3	2 (111)	0.94 (0.87 to 1.02); 0.12	-2 (-4 to 0.5); 0.12	0.95; 0%	0.97; 0%
Day 4	3 (130)	0.94 (0.88 to 1.01); 0.08	-2 (-4 to 0.3); 0.10	0.81; 0%	0.72; 0%
Renal dysfunction§	4 (895)	—	—	—	—

PaO₂/FI_O₂=partial pressure of arterial oxygen/ fraction of inspired oxygen, ratio of means=nitric oxide relative to control. We used random effects models for all analyses and assessed heterogeneity using Cochran's Q test⁶ (P value for homogeneity shown) and I².⁷

*Risk ratio 1.10 (0.94 to 1.30); P=0.23, homogeneity P=1.00, I²=0%. Two trials with ≥50% of control patients crossing over to NO also reported mortality data.^{w2 w6} Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27).

†Combined trials reporting ventilator-free to day 28 and day 30.

‡Mean difference because only one trial contributed data.

§Risk ratio 1.50 (1.11 to 2.02); P=0.008; homogeneity P=0.57, I²=0%. Renal dysfunction defined as new renal replacement therapy,^{w8} new renal replacement therapy or new raised creatinine concentration (>300 μmol/l^{w7}), or raised creatinine concentration (>177 μmol/l^{w3} or ≥265 μmol/l^{w12}). Denominator includes only patients without baseline renal dysfunction,^{w7 w8 w12} except possibly for one trial.^{w3} Use of a different definition of renal dysfunction ("adverse event") in one trial^{w3} did not alter summary estimate (risk ratio 1.49, 1.10 to 2.03).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Inhaled nitric oxide continues to be used to improve oxygenation in patients with acute lung injury, despite no clear supporting evidence

A previous meta-analysis in 2003 included five randomised trials of nitric oxide; there are now 12 trials

WHAT THIS STUDY ADDS

Nitric oxide improves oxygenation temporarily but does not improve survival and may cause harm

We do not recommend routine use of nitric oxide in patients with acute lung injury

In conclusion, our systematic review and meta-analysis found that inhaled nitric oxide improved oxygenation in patients with ALI and ARDS with 24 hours of therapy, with some evidence for a more prolonged effect. Given that the best available evidence suggests no survival advantage and possible increased mortality and renal dysfunction with nitric oxide, we do not recommend its routine use.

We thank Phil Dellinger, Emily Dobyms, Herwig Gerlach, and Sangeeta Mehta for providing additional information about their trials; Pascal Beuret, Gilbert Blaise, Ronald Day, Stefan Lundin, Kwang Joo Park, Didier Payen, and Benoît Vallet for providing additional outcomes data; Natasha Stankovic for assistance in translation; and Jim Julian for constructive comments on an earlier draft of the manuscript.

Contributors: See bmj.com.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

- Gries A, Bode C, Peter K, Herr A, Bohrer H, Motsch J, et al. Inhaled nitric oxide inhibits human platelet aggregation, P-selectin expression, and fibrinogen binding in vitro and in vivo. *Circulation* 1998;97:1481-7.
- Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci USA* 1991;88:4651-5.
- Beloucif S, Payen D. A European survey of the use of inhaled nitric oxide in the ICU. Working Group on Inhaled NO in the ICU of the European Society of Intensive Care Medicine. *Intensive Care Med* 1998;24:864-77.
- Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxic respiratory failure in children and adults: a meta-analysis. *Anesth Analg* 2003;97:989-98.
- Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. *Cochrane Database Syst Rev* 2003;(1):CD002787.
- Cochran W. The combination of estimates from different experiments. *Biometrics* 1954;10:101-29.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
- Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005;353:2683-95.
- Valdivielso JM, Blantz RC. Acute renal failure: is nitric oxide the bad guy? *Antioxid Redox Signal* 2002;4:925-34.
- Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
- Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985;132:485-9.
- Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;282:54-61.

Accepted: 23 January 2007

Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis

Thomas Clasen,¹ Wolf-Peter Schmidt,¹ Tamer Rabie,³ Ian Roberts,² Sandy Cairncross¹

EDITORIAL by Luby

¹Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT

²Department of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine

³World Bank, Washington, DC, USA

Correspondence to: T Clasen
thomas.clasen@lshtm.ac.uk

BMJ 2007;334:782-5

doi: 10.1136/bmj.39118.489931.BE

This article is an abridged version of a paper that was published on bmj.com on 12 March 2007. Cite this version as: *BMJ* 2007;334:782-5. doi: 10.1136/bmj.39118.489931.BE (abridged text, in print: *BMJ* 2007;334:782-5).

ABSTRACT

Objective To assess the effectiveness of interventions to improve the microbial quality of drinking water for preventing diarrhoea.

Design Systematic review.

Data sources Cochrane Infectious Diseases Group's trials register, CENTRAL, Medline, Embase, LILACS; hand searching; and correspondence with experts and relevant organisations.

Study selection Randomised and quasi-randomised controlled trials of interventions to improve the microbial quality of drinking water for preventing diarrhoea in adults and in children in settings with endemic disease.

Data extraction Allocation concealment, blinding, losses to follow-up, type of intervention, outcome measures, and measures of effect. Pooled effect estimates were calculated within the appropriate subgroups.

Data synthesis 33 reports from 21 countries documenting 42 comparisons were included. Variations in design, setting, and type and point of intervention, and variations in defining, assessing, calculating, and reporting outcomes limited the comparability of study results and pooling of

results by meta-analysis. In general, interventions to improve the microbial quality of drinking water are effective in preventing diarrhoea. Effectiveness was not conditioned on the presence of improved water supplies or sanitation in the study setting and was not enhanced by combining the intervention with instructions on basic hygiene, a water storage vessel, or improved sanitation or water supplies—other common environmental interventions intended to prevent diarrhoea.

Conclusion Interventions to improve water quality are generally effective for preventing diarrhoea in all ages and in under 5s. Significant heterogeneity among the trials suggests that the level of effectiveness may depend on a variety of conditions that research to date cannot fully explain.

INTRODUCTION

Reviews of environmental interventions to prevent diarrhoeal disease reported a 15-17% median reduction in diarrhoea from water quality interventions,^{1,2} yet the included studies concerned improvements at the water source and none at