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RESEARCH

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

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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 (PaO_2/FiO_2 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

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), defined by acute hypoxaemia and bilateral lung infiltrates on radiography without left atrial hypertension,[1] are characterised by inflammation of the alveolar-capillary membrane triggered by various insults.[2] Because the pathophysiology involves mismatching of ventilation and perfusion and pulmonary hypertension, the possibility of using inhaled nitric oxide (NO) generated considerable interest.[3] Nitric oxide is a selective pulmonary vasodilator and has anti-inflammatory properties.[4 5] Based on limited data on efficacy, clinicians rapidly adopted this therapy; 63% of European intensive care specialists surveyed in 1997 reported using it, primarily for ALI or ARDS.[6] A more recent survey of specialists in Ontario, Canada, found that a substantial proportion (39%) reported using nitric oxide at least sometimes in selected patients with ARDS.[7]

A systematic review and meta-analysis of nitric oxide published in 2003[8 9] that included five randomised controlled trials[w3-w7] found no effect on mortality or ventilator-free days; one trial showed improved oxygenation.[w3] Because confidence intervals were wide, the authors 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

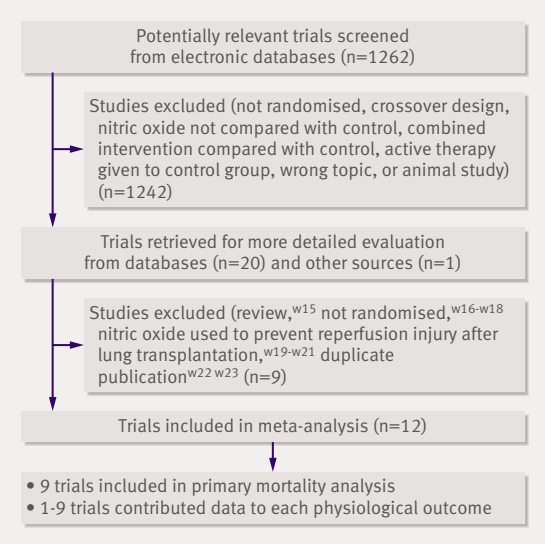

Fig 1 | Number of trials evaluated at each stage of the systematic review

(mortality, duration of ventilation, and adverse effects) in patients with established ALI or ARDS.

METHODS

Search strategy

We electronically searched Medline, CINAHL, Embase, and CENTRAL (to October 2006), limiting citations to randomised controlled trials. We also searched proceedings of four conferences (1994-2006), screened bibliographies of retrieved studies and recent review articles,[10-18] and contacted content experts to identify additional trials. There were no language restrictions. Further details of the search strategy and other aspects of study methods are on bmj.com.

Study selection

Two reviewers independently screened studies for inclusion, retrieved potentially relevant studies, and decided on study eligibility. 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 (using

Table 1 | Details of randomised trials of inhaled nitric oxide (NO) in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Author (funding*)	Population	Details of NO administration	Control group and crossovers
Day,[w1] 1997 (not for profit)	24 children, 1 centre. Acute bilateral CXR infiltrates, PEEP ›6 cm H_2O, FiO_2 ›0.5 for ›12 hours. Enrolment ≤48 h after meeting study criteria	10 ppm until oxygenation and PEEP criteria met	Usual care. All patients randomised to control received NO 10 ppm after 24 hours; no crossovers before 24 hours
Schwebel,[w2] 1997 (not for profit; industry supplied gas)	19 adults, 17 centres. Any CXR infiltrates, P/F ‹200 mm Hg, 10‹PAOP‹18 mm Hg, 6‹PEEP‹10 cm H_2O. Duration of ARDS ≤24 hours	10 ppm for 17 hours, then at clinician's discretion; mean 4.6 days (range 1.25 to 11)	Placebo gas (nitrogen). Crossovers mandated before 17 hours if P/F ≤100 mm Hg and permitted thereafter (at least 5/10 patients randomised to control received NO)
Dellinger,[w3] 1998 (industry)	177 adults, 30 centres. AECC criteria for ARDS and FiO_2 ≥0.5, PEEP ≥8 cm H_2O. Duration of ARDS ≤72 hours	1.25, 5, 20, 40 or 80 ppm until 28 days or oxygenation and PEEP criteria met. Protocol for weaning NO	Placebo gas (nitrogen). No crossovers
Michael,[w4] 1998 (not for profit)	40 patients, 1 centre; 37/40 ≥18 years. AECC criteria for ARDS except P/F ≤150 mm Hg and FiO_2 ≥0.8 for ≥12 hours or ≥0.65 for ≥24 hours	5, 10, 15, 20 ppm every 6 hours for 24 hours then clinically adjusted; mean dose 13 ppm, tapered if oxygenation not improved by 72 hours	Usual care. Patients with oxygenation failure received NO (2 patients before 72 hours and 7 patients after 72 hours, of 20 randomised to control)
Troncy,[w5] 1998 (not for profit)	30 adults, 1 centre. Lung injury score[30] ≥2.5	Initial titration (2.5, 5, 10, 20, 30, 40 ppm every 10 min) and daily re-titration; mean dose 5.3 ppm. Duration: until oxygenation and PEEP criteria met; mean 8 (SD 5) days	Usual care. No crossovers
Dobyns,[w6] 1999 (not for profit)	108 children (›1 month old, median age 2.5 years), 7 centres. Any CXR infiltrates, OI ≥15 on 2 arterial blood gases within 6 hours (mean duration of ventilation before randomisation 3.5 days in NO group, 3.7 days in control group)	10 ppm for 72 hours, then weaned if failure criteria not met	Usual care. Patients meeting failure criteria could receive NO (27/55 patients randomised to control met failure criteria and 2 other patients withdrawn from control group; 29 patients likely received NO)
Lundin,[w7] 1999 (not for profit and industry)	180 adults, 43 centres. Any CXR infiltrates, P/F ≤165 mm Hg, PEEP ≥5 cm H_2O, mean airway pressure ›10 cm H_2O. Duration of ventilation 0.75-4 days. NO responder†	1-40 ppm ("lowest effective dose"); mean dose 9 (SD 8) ppm, until end point met (reversal of ALI or severe respiratory failure), up to 30 days; mean 9 (SD 6) days	Usual care. Patients meeting severe respiratory failure criteria could receive NO (6/87 patients randomised to control received NO)
Payen,[w8] 1999 (not for profit; industry supplied gas)	203 adults, 23 centres. AECC criteria for ARDS, lung injury score[30] 2-3 after 24 hours of "therapeutic optimisation" (mean duration of ventilation before randomisation: 5.3 days in NO group, 5.9 days in control group)	10 ppm, until oxygenation and PEEP criteria met; median 5 days	Placebo gas (nitrogen). Patients meeting failure criteria crossed to other group (19/105 patients randomised to control and 12/98 patients randomised to NO crossed over)
Mehta,[w9] 2001 (not for profit and industry)	14 adults, 1 centre. Bilateral CXR infiltrates, P/F ‹200 mm Hg, PEEP ≥8 cm H_2O, PAOP ‹18 mm Hg. Duration of ARDS ≤5 days	Daily titration (5, 10, 20 ppm every 30 min) for 4 days. Most received 5-10 ppm on day 2-4; continued until oxygenation criteria met; mean 8 (SD 9) days	Usual care. No crossovers
Gerlach,[w10] 2003 (not for profit)	40 adults, 1 centre. Bilateral CXR infiltrates, P/F ≤150 mm Hg, PEEP ≥10 cm H_2O, PAOP ≤18 mm Hg. Duration of ventilation ≥48 hours with FiO_2 ≥0.6 (median duration of ventilation before randomisation: 14 days in NO group, 11.5 days in control group)	10 ppm (with daily dose response analysis) until weaning initiated	Usual care. No crossovers
Park,[w11] 2003 (not reported)	17 adults, 1 centre. AECC criteria for ARDS. Duration of ARDS ≤2 days	5 ppm for mean 3.5 (SD 1.5) days (stopping criteria not reported). Patients also received one lung recruitment manoeuvre (same as control group). Third group (n=6) received NO 5 ppm alone for 8.2 (SD 4.7) days	One lung recruitment manoeuvre (inflation pressure of 30-35 cm H_2O for 30 seconds). No crossovers
Taylor,[w12] 2004 (industry)	385 adults, 46 centres. AECC criteria for ALI except P/F ≤250 mm Hg, 0.5 ≤ FiO_2 ≤0.95 on PEEP ≥8 cm H_2O. Duration of ALI ≤3 days	5 ppm for 28 days or until oxygenation and PEEP criteria met	Placebo gas (nitrogen). No crossovers

AECC=American-European Consensus Conference[1], CXR=chest radiograph, LIS=lung injury score,[30] OI=oxygenation index (100×mean airway pressure/(PaO_2/FiO_2)), PAOP=pulmonary artery occlusion pressure, PEEP=positive end expiratory pressure, P/F ratio=partial pressure of inspired oxygen (PaO_2)/fraction of inspired oxygen (FiO_2).
*Funding refers to data collection and analysis and supply of study gas (where information available).
†Patients given NO 0, 2, 10, 40 ppm every 10 min and response defined as relative increase in PaO_2 of 25% (n=140) or 20% (n=40). Responders were randomised.

authors' definitions). 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 (PaO_2 (partial pressure of oxygen)/FiO_2 (fraction of inspired oxygen); oxygenation index, defined as 100 × mean airway pressure/(PaO_2/FiO_2); 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.[19]

Data abstraction and validity assessment

Two reviewers independently abstracted data and methods from included trials. We resolved by consensus any disagreements that remained after contacting trial authors. From included studies we abstracted method of randomisation and allocation concealment, blinding of caregivers and outcomes assessors, and number of withdrawals after randomisation and determined whether mechanical ventilation, weaning, and sedation were standardised or applied equally in treatment groups.

We attempted to contact authors of all included trials to request additional data and clarify data and methods 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). We decided a priori to combine trials with less than half of patients crossing over from control to nitric oxide arms in analyses of clinical outcomes. Our analyses adhered to the intention to treat principle. In studies with two or more nitric oxide groups receiving different doses, we combined data to determine an overall effect for the nitric oxide group.

Secondary outcomes included duration of ventilation, ventilator-free days to 28 or 30 days, and pulmonary physiology. We decided post hoc to combine data on renal dysfunction after obtaining outcomes for most randomised patients, but we describe other adverse events qualitatively.

Table 2 | Scientific quality of trials of inhaled nitric oxide (NO) in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)*

Author	Allocation concealment	Blinding	Ventilation	Other cointerventions
Day,[w1] 1997	Blinded draw of 1 lot per eligible patient	None	Clinician discretion	Not described
Schwebel,[w2] 1997	Table of gas cylinder codes (revealed in sequence)	Clinicians, outcomes assessors	Protocol (no details) for 17 hours; clinician's discretion thereafter	Not described
Dellinger,[w3] 1998	Sealed, opaque envelopes	Clinicians†, outcomes assessors	Guideline (Pplat≤35 cm H_2O; PEEP to optimise compliance; FiO_2 minimised)	More patients in NO group received corticosteroids after day 6 (20/112 *v* 6/57)
Michael,[w4] 1998	Not reported	None	Clinician discretion; mode unchanged for 72 hours; mean PEEP similar between groups for 72 hours	Not described
Troncy, [w5] 1998	Envelopes‡	None	Protocol (V_T 10 ml/kg and goal $PaCO_2$ 35-45 mm Hg; maximum PEEP 15 cm H_2O and goal PaO_2 ›85 mm Hg)	Sedation, blood transfusion, and nutrition protocols. No prone ventilation in any patient
Dobyns,[w6] 1999	Envelopes‡	Clinicians†, outcomes assessors	Guideline ("open lung approach" with Ppk ≤35-40 cm H_2O, V_T limitation, titrated PEEP; HFOV by clinician discretion)	Not described
Lundin,[w7] 1999	Central	None	Clinician discretion	Not described
Payen,[w8] 1999	Central	Clinicians, outcomes assessors	Guideline before randomisation; unclear if applied afterwards (V_T, Pplat, Ppk limitation; various recruitment strategies)	Not described
Mehta,[w9] 2001	No§	None	Clinician discretion	No prone ventilation in any patient
Gerlach,[w10] 2003	Envelopes‡	None	Protocol (no details)	Protocol for prone ventilation and extracorporeal membrane oxygenation
Park,[w11] 2003	One random number generated when patient eligible	None	Protocol (V_T 6 ml/kg; Pplat ≤30 cm H_2O; PEEP to optimise PaO_2; FiO_2 minimised)	Weaning protocol. No prone ventilation in any patient
Taylor,[w12] 2004	Central	Clinicians†, outcomes assessors	Guideline (Pplat ≤ 35 cm H_2O; PEEP to optimise compliance; FiO_2 minimised)	Prone ventilation similar (NO: 10/192 and control: 14/193), weaning protocol

FiO_2=fraction of inspired oxygen; HFOV=high frequency oscillatory ventilation; PaO_2=partial pressure of arterial oxygen; $PaCO_2$=partial pressure of arterial carbon dioxide; Pplat=plateau airway pressure; Ppk=peak airway pressure; PEEP=positive end expiratory pressure; V_T=tidal volume.
*No study reported withdrawals of patients or loss to follow-up for mortality; all patients analysed according to assigned group.
†Unblinded investigator at each site.
‡Envelopes sealed, sequentially numbered, and opaque.
§Computer generated random numbers. Investigator had access to entire randomisation list at time of randomisation.

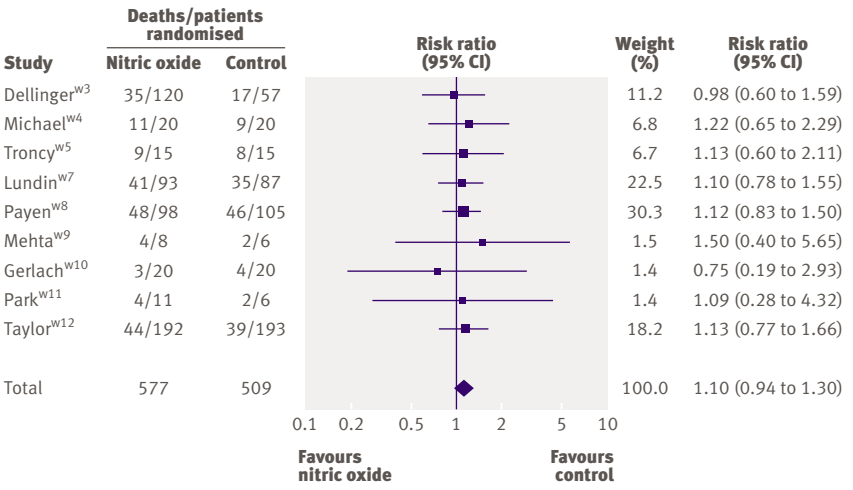

Fig 2 | Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with ≥50% of control patients crossing over to nitric oxide also reported mortality data.[w2 w6] Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27)

We used random effects models[20] implemented in Review Manager 4.2.7 (Cochrane Collaboration, Oxford) for all analyses and considered P≤0.05 (two sided) 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).[21] Summary effect estimates are presented with 95% confidence intervals.

We assessed homogeneity between studies for each outcome using the Cochran Q statistic,[22] with P≤0.10 indicating significant heterogeneity,[23] and I^2 [24 25] with suggested thresholds for low (25%-49%), moderate (50%-74%), and high (≥75%) values. We developed several a priori hypotheses to explain significant heterogeneity (excluding duration of ventilation and ventilator-free days), including dose and duration of nitric oxide therapy and whether therapy was restricted to patients whose oxygenation improved acutely ("nitric oxide responders") or to those with ARDS (the more hypoxaemic subset of ALI).

RESULTS

Trial flow

Electronic database searches yielded 1262 citations. After evaluating these citations, conference abstracts, review articles, and bibliographies of included trials, we included 12 parallel group randomised controlled trials[w1-w12] (fig 1). The two reviewers completely agreed (κ=1) on the selection of included studies. We obtained additional information from 10 authors (new clinical[w1 w2 w5 w7 w8 w11] or physiological data[w1 w2 w7 w11]; clarifications of data[w6 w9] or methods[w1-w3 w5-w11]).

Study characteristics and methodological quality

Table 1 describes the included studies, two of which were published as abstracts only.[w2 w7] Data from one trial were distributed in two abstracts,[w8 w13] and data from another trial were distributed in two articles.[w6 w14] Trials randomised 1237 patients (median 40; range 14-385) with ALI or ARDS. Two trials enrolled only children,[w1 w6] one trial included a few children,[w4] and the remaining trials enrolled only adults. All patients met American-European Consensus Conference[1] oxygenation criteria for ARDS except for one trial that included some patients with ALI.[w12] Seven trials used a fixed dose of nitric oxide (median 10 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] One trial enrolled only patients whose oxygenation improved after a nitric oxide challenge ("nitric oxide responders"),[w7] and one used a cointervention (a recruitment manoeuvre) in both groups.[w11] Trials continued nitric oxide until prespecified gas exchange end points[w1 w3 w5 w7-w10 w12] or for a fixed period of time after which nitric oxide was tapered by using gas exchange criteria[w4 w6] or managed at clinicians' discretion.[w2] One trial did not report on criteria for stopping nitric oxide.[w11] The median duration of administration was 6.5 days (range 3.5-9.0 days; data available from five trials[w5 w7-w9 w11]). One trial randomised patients to nitric oxide or control for 24 hours, after which all patients received nitric oxide.[w1] In five other trials, control patients received nitric oxide as rescue therapy after randomisation if they met prespecified criteria (<50% of controls in three trials[w4 w7 w8] and ≥50% in two trials[w2 w6]). Not for profit agencies funded five trials,[w1 w4-w6 w10] industry funded two trials,[w3 w12] both sources funded or supported four trials,[w2 w7-w9] and one trial did not report this information.[w11]

The 12 trials had good scientific quality (table 2). Ten concealed randomisation,[w1-w3 w5-w8 w10-w12] and five blinded clinicians.[w2 w3 w6 w8 w12] Mechanical ventilation was delivered according to protocol in three unblinded trials[w5 w10 w11] and one blinded trial[w2] and according to guidelines in three blinded trials.[w3 w6 w12] Six trials described or standardised at least one other cointervention, such as corticosteroids,[w3] sedation,[w5] prone ventilation,[w5 w9-w12] and ventilator weaning.[w11 w12] All trials had complete follow-up, analysed patients by assigned group, and withdrew no one from clinical outcomes analyses. One trial stopped early because of slow enrolment (achieving 45% of the planned sample size[w7]), and another trial enrolled 75% of the planned sample, for unclear reasons.[w12]

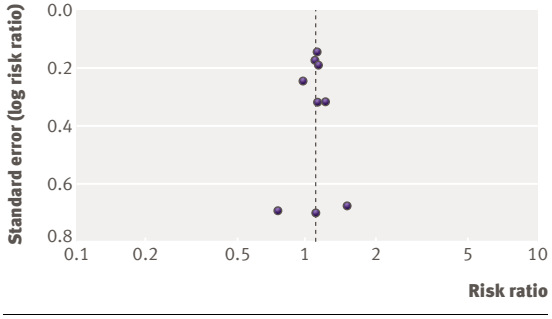

Fig 3 | Funnel plot for outcome of mortality in trials of nitric oxide. Each point represents one trial

Table 3 | 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/FiO_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/FiO_2) (cm H_2O/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)	—	—	—	—

PaO_2/FiO_2=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 test[22] (P value for homogeneity shown) and I^2.[24]
*Risk ratio 1.10 (0.94 to 1.30); P=0.23, homogeneity P=1.00, I^2=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 days 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, I^2=0%. Renal dysfunction was 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).

Data synthesis

Effect of nitric oxide on clinical outcomes

We combined nine trials[w3-w5 w7-w12] in the mortality analysis (three were placebo controlled[w3 w8 w12]; five used "usual care" controls[w4 w5 w7 w9 w10]; one used recruitment manoeuvres in both arms[w11]). We combined three trials that reported duration of ventilation (including all patients[w10 w11] or only survivors[w7]) and five trials reporting ventilator-free days.[w3 w5 w8 w11 w12]

Meta-analyses (table 3) showed that nitric oxide did not affect mortality (risk ratio 1.10; 95% confidence interval 0.94 to 1.30; fig 2), duration of ventilation (17% increase, −20% to 70%; 3.6 additional days, −4.0 to 11.1 days), or ventilator-free days (6% decrease, −16% to 6%; 0.6 fewer days, −1.8 to 0.7 days). There was moderate to high heterogeneity between studies for duration of ventilation only.

A funnel plot of standard error versus risk ratio for mortality did not suggest publication bias (fig 3).

Effect of nitric oxide on physiological outcomes

On the first day of therapy, NO was associated with small improvements in the PaO_2/FiO_2 ratio (nine trials; 13% higher, 4% to 23%; 16 mm Hg higher, 4 mm Hg to 27 mm Hg; fig 4) and oxygenation index (three trials; 14% lower, 2% to 25%; 3 cm H_2O/mm Hg lower, 0.5 cm H_2O/mm Hg to 5 cm H_2O/mm Hg; fig 5). Some evidence suggested that improvements in oxygenation in the nitric oxide group persisted beyond day one. The PaO_2/FiO_2 ratio was higher on day two and four (but not on day three, and only in the ratio of means analysis on day two). The oxygenation index remained lower on days two, three, and four (only in the weighted mean difference analysis on day three), but only one[w3] (days two and four) or two[w3 w6] (day three) trials contributed data. 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

Table 4 gives details of adverse effects. All 12 trials gave information about methaemoglobin concentrations. 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 6). Other adverse events were variably reported, and we did not combine these data.

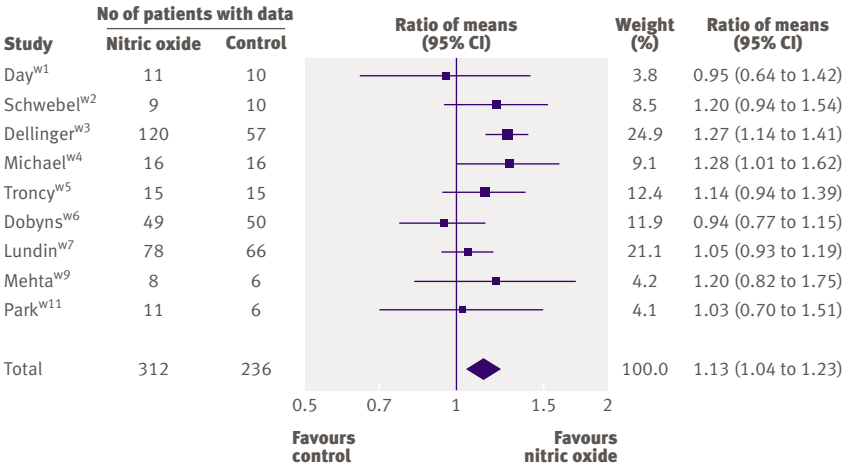

Fig 4 | Effect of nitric oxide on PaO_2/FiO_2 ratio at 24 hours. Weight is the relative contribution of each study to overall estimate of treatment effect (ratio of means, nitric oxide relative to control) on log scale assuming a random effects model. For some trials, number of patients with data is less than number randomised

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 included 12 trials that randomly assigned 1237 patients and investigated the effects of inhaled nitric oxide in such patients. We found no benefit of nitric oxide on survival and an increased risk of renal dysfunction. Oxygenation improved over the first 24 hours (13% relative increase in PaO_2/FiO_2 ratio; 14% decrease in oxygenation index), 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,[18 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.

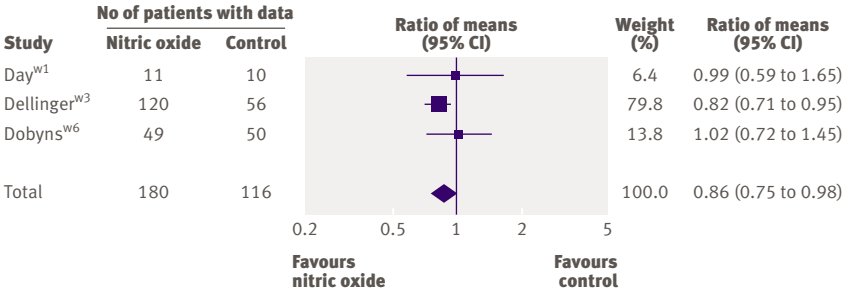

Fig 5 | Effect of nitric oxide on oxygenation index at 24 hours. Weight is the relative contribution of each study to overall estimate of treatment effect (ratio of means, nitric oxide relative to control) on log scale assuming a random effects model. For each trial, number of patients with data is less than number randomised

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, however, as this result was a post hoc analysis and is potentially subject to publication bias (we were unable to obtain explicit data on renal outcomes in eight of 12 smaller trials, in which this relation may not have been measured or observed). In addition, the potential physiological mechanisms linking administration of inhaled nitric oxide to acute renal dysfunction—inhibition of mitochondrial and enzymatic function and damage to deoxyribonucleic acid and membranes—are controversial because of its simultaneous protective effects on renal blood flow and leukocyte adhesion.[26]

Why nitric oxide may not be beneficial

There are several possible explanations for the lack of benefit of routine administration of nitric oxide in patients with ALI/ARDS. Firstly, short term physiological improvements in oxygenation seem to have no impact on patients' survival,[27] 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,[28] 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, dampening the oxygenation benefit while continuing to expose patients to toxic effects such as oxidative damage.[18 w10] Fourthly, the benefits of nitric oxide may have been overwhelmed by a harmful mechanical ventilation strategy, which perpetuated multiple organ failure.[29] 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 this hypothesis was not supported in one trial.[w7]

Strengths and limitations

We used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, prespecified criteria for methodological assessment and analysis) 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, given the small number of trials contributing to analyses of

Table 4 | Adverse effects of inhaled nitric oxide

Author, year	Methaemoglobin and nitrogen dioxide concentrations	Other adverse effects
Day,[w1] 1997	No known raised concentrations	None
Schwebel,[w2] 1997	No methaemoglobinaemia	None
Dellinger,[w3] 1998	Methaemoglobin concentration >5% (none >7%): NO 2.5% (3/120; 40 ppm, n=1; 80 ppm, n=2), control 2% (1/57); nitrogen dioxide level >3 ppm: NO 2.5% (3/120; all received 80 ppm), control: none	Renal function ("defined by adverse events"): NO 11% (13/120), control 9% (5/57); creatinine >177 μmol/l: NO 17% (20/120), control 13% (7/57). Adverse events "possibly" related to study gas: NO 3% (4/120: myopathy, agitation; abnormal liver enzymes; apnoea, lung haemorrhage, coagulopathy; renal dysfunction), control 2% (1/57: hypertension). All adverse events: no significant differences
Michael,[w4] 1998	No methaemoglobinaemia	Bleeding. Blood transfusion: NO 5% (1/20), control 0/20. Intracranial haemorrhage after thrombolytic therapy: NO 5% (1/20 after thrombolytic therapy) , control 0/20
Troncy,[w5] 1998	No methaemoglobinaemia	Not reported
Dobyns,[w6] 1999	Methaemoglobin concentration >5%: none; nitrogen dioxide concentration >2 ppm: none	No difference in "intensive care unit-dependent therapies"[31]
Lundin,[w7] 1999	Methaemoglobin concentration >5%: NO 1% (1/93), control 1% (1/87); median methaemoglobin concentrations over 30 days: NO 0.5%-1.2%, control 0.2%-1.0% ("overall lower" than in NO group)	Adverse events related to study gas: NO 1% (1/93: gastrointestinal bleeding), control 2% (2/87: coagulopathy, intracranial bleed). Renal function "abnormal": NO 13% (12/93), control 5% (4/87). Renal replacement (incident cases): NO 27% (23/84), control 13% (10/79); risk ratio 2.16, 1.10 to 4.25. Creatinine >300 μmol/l without renal replacement (incident cases): NO 6% (5/80), control 3% (2/74). Other serious adverse events more common in NO group: circulatory failure: NO 31% (29/93), control 20% (17/87); encephalopathy: NO 3% (3/93), control none; sepsis: NO 8% (7/93), control, 3% (3/87). Other adverse events: no difference in incidence of raised total bilirubin, pneumothorax, or platelet, bleeding or clotting disorders or haemodynamic failure (definitions of haemodynamic *v* circulatory failure not given)
Payen,[w8] 1999	Methaemoglobin concentrations reported as always acceptable and not different between groups	Renal replacement (incident cases): NO 37% (33/89), control 29% (26/90); risk ratio 1.28, 0.84 to 1.96. Bleeding: NO 6% (6/105), control 3% (3/98)
Mehta,[w9] 2001	Methaemoglobin concentration >3%: none (concentration in 1/8 NO patients was 3.8% before therapy); nitrogen dioxide concentration >2 ppm: none	None
Gerlach,[w10] 2003	No methaemoglobinaemia; no patients with increased nitrogen dioxide concentrations	No bleeding. No difference between groups in number of additional organ dysfunctions[32]
Park,[w11] 2003	No methaemoglobinaemia	None
Taylor,[w12] 2004	Methaemoglobin concentration >5%: NO 0/192, control 0.005% (1/193); nitrogen dioxide concentration >2 ppm: none	All adverse events: no difference (NO, 630 events; control, 666 events). No difference in cardiovascular, gastrointestinal, endocrine, haematological, metabolic and nutritional, and neurological adverse events. Adverse events with different frequencies. Infections: NO 66 infections, control 41 infections. Respiratory: NO 51% (98/192), control 61% (118/193); pneumonia, pneumothorax, apnoea more common in control group. Renal function: creatinine ≥265 μmol/l: NO 6% (12/192), control 4% (8/193); creatinine ≥309 μmol/l: NO 5% (10/192), control 3% (6/193)

many physiological outcomes, 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. The included trials did not specifically study the issue of nitric oxide as rescue therapy for patients with critically low oxygenation. With nitric oxide, short term improved oxygenation in these patients may create a window for other strategies to improve lung function, such as treatment of the underlying cause of ARDS.

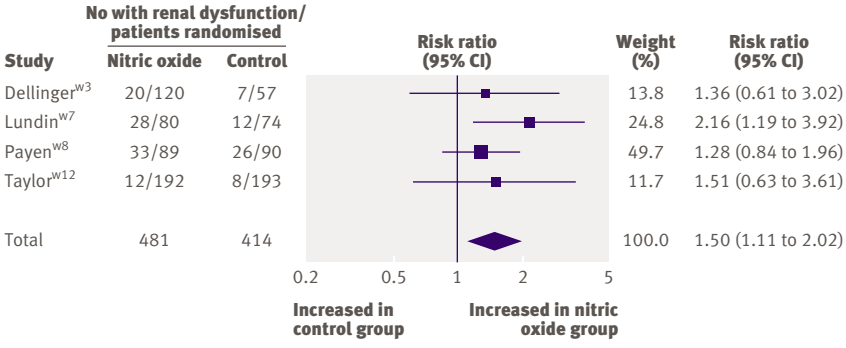

Fig 6 | Effect of nitric oxide on renal dysfunction (defined as new renal replacement therapy,[w8] new renal replacement therapy or new raised creatinine concentration (>300 μmol/l[w7]), or raised creatinine concentration (>177 μmol/l[w3] or ≥265 μmol/l[w12])). The denominator includes only patients 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 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

Previous research

A previous systematic review and meta-analysis of inhaled nitric oxide for acute hypoxaemic respiratory failure[8 9] 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. We also provide new estimates of the impact of nitric oxide on other clinical and physiological end points and raise the possibility of harm induced by nitric oxide.

In conclusion, our systematic review and meta-analysis found that inhaled nitric oxide improved oxygenation in patients with ALI and ARDS at 24 hours of

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

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. Despite a lack of evidence for benefit, some clinicians may still consider nitric oxide for life threatening hypoxaemia, in conjunction with other supportive therapies. Given the challenges of enrolling such severely ill patients into large trials, definitive data supporting or refuting a role for nitric oxide in such desperate situations may not be forthcoming, leaving clinicians to rely on their judgment and the current evidence.

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