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Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults (Review)

Gebistorf F, Karam O, Wetterslev J, Afshari A

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TABLE OF CONTENTS

[Intervention Review]

Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults

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ABSTRACT

Background

Acute hypoxaemic respiratory failure (AHRF) and mostly acute respiratory distress syndrome (ARDS) are critical conditions. AHRF results from several systemic conditions and is associated with high mortality and morbidity in individuals of all ages. Inhaled nitric oxide (INO) has been used to improve oxygenation, but its role remains controversial. This Cochrane review was originally published in 2003, and has been updated in 2010 and 2016.

Objectives

The primary objective was to examine the effects of administration of inhaled nitric oxide on mortality in adults and children with ARDS.

Secondary objectives were to examine secondary outcomes such as pulmonary bleeding events, duration of mechanical ventilation, length of stay, etc. We conducted subgroup and sensitivity analyses, examined the role of bias and applied trial sequential analyses (TSAs) to examine the level of evidence.

Search methods

In this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015 Issue 11); MEDLINE (Ovid SP, to 18 November 2015), EMBASE (Ovid SP, to 18 November 2015), CAB, BIOSIS and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We handsearched the reference lists of the newest reviews and cross-checked them with our search of MEDLINE. We contacted the main authors of included studies to request any missed, unreported or ongoing studies. The search was run from inception until 18 November 2015.

Selection criteria

We included all randomized controlled trials (RCTs), irrespective of publication status, date of publication, blinding status, outcomes published or language. We contacted trial investigators and study authors to retrieve relevant and missing data.

Data collection and analysis

Two review authors independently extracted data and resolved disagreements by discussion. Our primary outcome measure was all-cause mortality. We performed several subgroup and sensitivity analyses to assess the effects of INO in adults and children and on various clinical and physiological outcomes. We presented pooled estimates of the effects of interventions as risk ratios (RRs) with 95% confidence

intervals (CIs). We assessed risk of bias through assessment of trial methodological components and risk of random error through trial sequential analysis.

Main results

Our primary objective was to assess effects of INO on mortality. We found no statistically significant effects of INO on longest follow-up mortality: 250/654 deaths (38.2%) in the INO group compared with 221/589 deaths (37.5%) in the control group (RR 1.04, 95% CI 0.9 to 1.19; I^2 statistic = 0%; moderate quality of evidence). We found no statistically significant effects of INO on mortality at 28 days: 202/587 deaths (34.4%) in the INO group compared with 166/518 deaths (32.0%) in the control group (RR 1.08, 95% CI 0.92 to 1.27; I^2 statistic = 0%; moderate quality of evidence). In children, there was no statistically significant effects of INO on mortality: 25/89 deaths (28.1%) in the INO group compared with 34/96 deaths (35.4%) in the control group (RR 0.78, 95% CI 0.51 to 1.18; I^2 statistic = 22%; moderate quality of evidence).

Our secondary objective was to assess the benefits and harms of INO. For partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2), we found significant improvement at 24 hours (mean difference (MD) 15.91, 95% CI 8.25 to 23.56; I^2 statistic = 25%; 11 trials, 614 participants; moderate quality of evidence). For the oxygenation index, we noted significant improvement at 24 hours (MD -2.31, 95% CI -2.73 to -1.89; I^2 statistic = 0%; five trials, 368 participants; moderate quality of evidence). For ventilator-free days, the difference was not statistically significant (MD -0.57, 95% CI -1.82 to 0.69; I^2 statistic = 0%; five trials, 804 participants; high quality of evidence). There was a statistically significant increase in renal failure in the INO groups (RR 1.59, 95% CI 1.17 to 2.16; I^2 statistic = 0%; high quality of evidence).

Authors' conclusions

Evidence is insufficient to support INO in any category of critically ill patients with AHRF. Inhaled nitric oxide results in a transient improvement in oxygenation but does not reduce mortality and may be harmful, as it seems to increase renal impairment.

PLAIN LANGUAGE SUMMARY

Use of inhaled nitric oxide in patients with acute respiratory failure with low blood oxygen does not improve survival

Background

When a person has acute respiratory failure, some physicians administer nitric oxide (NO), which is a colourless gas that can dilate the pulmonary vasculature. This gas has been hypothesized to improve acute respiratory failure, as it could improve oxygenation by selectively improving blood flow to healthy lung segments.

Our objective was to evaluate whether this treatment improves outcomes of adults and children with acute respiratory failure.

Study characteristics

We included in this updated review 14 trials with 1275 participants. We found the overall quality of trials to be moderate, with little information provided on how experiments were carried out. Results were limited, and most included trials were small. In most trials, we identified risk of misleading information. Thus, results must be interpreted with caution. The evidence is up-to-date to 18 November 2015.

Key results

No strong evidence is available to support the use of INO to improve survival of adults and children with acute respiratory failure and low blood oxygen levels. In the present systematic review, we set out to assess the benefits and harms of its use in adults and children with acute respiratory failure. We identified 14 randomized trials comparing INO versus placebo or no intervention. We found no beneficial effects: despite signs of oxygenation and initial improvement, INO does not appear to improve survival and might be hazardous, as it may cause kidney function impairment.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. INO compared with control group for acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in children and adults

INO compared with control group for acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in children and adults

Patient or population: critically ill participants with ALI and ARDS

Setting: intensive care units, worldwide
Intervention: INO

Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	INO				
Overall mortality	**375 per 1000** (337 to 415)	**382 per 1000** (346 to 420)	**RR 1.04** (0.9 to 1.19)	1243 (13 studies[a])	⊕⊕⊕⊖ **moderate**[a,b]	TSA alfa-spending-adjusted analysis results in an RR of 1.04 (95% CI 0. to 1.23; I^2 = 0%, diversity D^2 = 0%). Only 41.92% of the required information size is actually available at this stage for rejection or acceptance of a 4% RRI for overall mortality. However, solid evidence may be obtained with fewer participants if eventually the cumulative meta-analysis z-curve crosses the trial sequential monitoring boundary constructed for a required information size of 3015 randomized participants (Figure 1)
Overall mortality at 28 days	**320 per 1000** (282 to 362)	**344 per 1000** (307 to 383)	**RR 1.08** (0.92 to 1.27)	1105 (9 studies)	⊕⊕⊕⊖ **moderate**[b]	
Mortality in paediatric population (subgroup)	**354 per 1000** (266 to 454)	**281 per 1000** (181 to 382)	**RR 0.78** (0.51 to 1.18)	185 (3 paediatric studies)	⊕⊕⊕⊖ **moderate**[b]	
PaO_2/FiO_2 up to 24 hours		Mean PaO_2/FiO_2 up to 24 hours was **higher**	**MD 15.91** (8.25 to 23.56)	614 (11 studies)	⊕⊕⊕⊖ **moderate**[b]	TSA-adjusted results with a mean difference of 15.91 with substantial heterogeneity and diversity (95% CI 8.25 to 23.56; I^2 = 25%, diversity D^2 = 49%)

		(**15.91,** 95% CI 8.25 to 23.56 higher) in the intervention group				TSA alfa-spending-adjusted confidence interval for the meta-analysis in a random-effects model results in an MD of 15.91 with substantial heterogeneity and diversity (95% CI 9.67 to 22.15; I^2 = 25%, diversity D^2 = 49%) with a required information size of 315 (Figure 2). However, the required information size based on the 2 trials with low risk of bias is 5137 participants (MD 14.94, TSA-adjusted 95% CI -73.70 to -103.58; I^2 = 87%, diversity D^2 = 91%)
Oxygenation index, 24 hours		Mean oxygenation index at 24 hours was **lower** (**2.31,** 95% CI 2.73 to 1.89) in the intervention group	**MD -2.31** (-2.73 to -1.89)	368 (5 studies)	⊕⊕⊕⊖ **moderate**	
Ventilation-free days, up to 30 days		**No statistically significant difference was noted** between control and intervention groups	**MD -0.57** (-1.82 to 0.69)	804 (5 studies)	⊕⊕⊕⊕ **high**[c]	
Renal impairment	**115 per 1000** (89 to 149)	**181 per 1000** (150 to 217)	**RR 1.59** (1.17 to 2.16)	945 (4 studies)	⊕⊕⊕⊕ **high**[c]	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **INO:** inhaled nitric oxide; **MD:** mean difference; **RR:** risk ratio; **RRI:** relative risk increase; **TSA:** trial sequential analysis; **vs:** versus

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Sensitivity analysis excluding trials published as abstracts did not change the overall mortality effect estimate
[b]The outcome was upgraded from low to moderate quality of evidence because most trials had moderate risk of bias
[c]The outcome was upgraded from moderate to high quality of evidence because most trials had low risk of bias

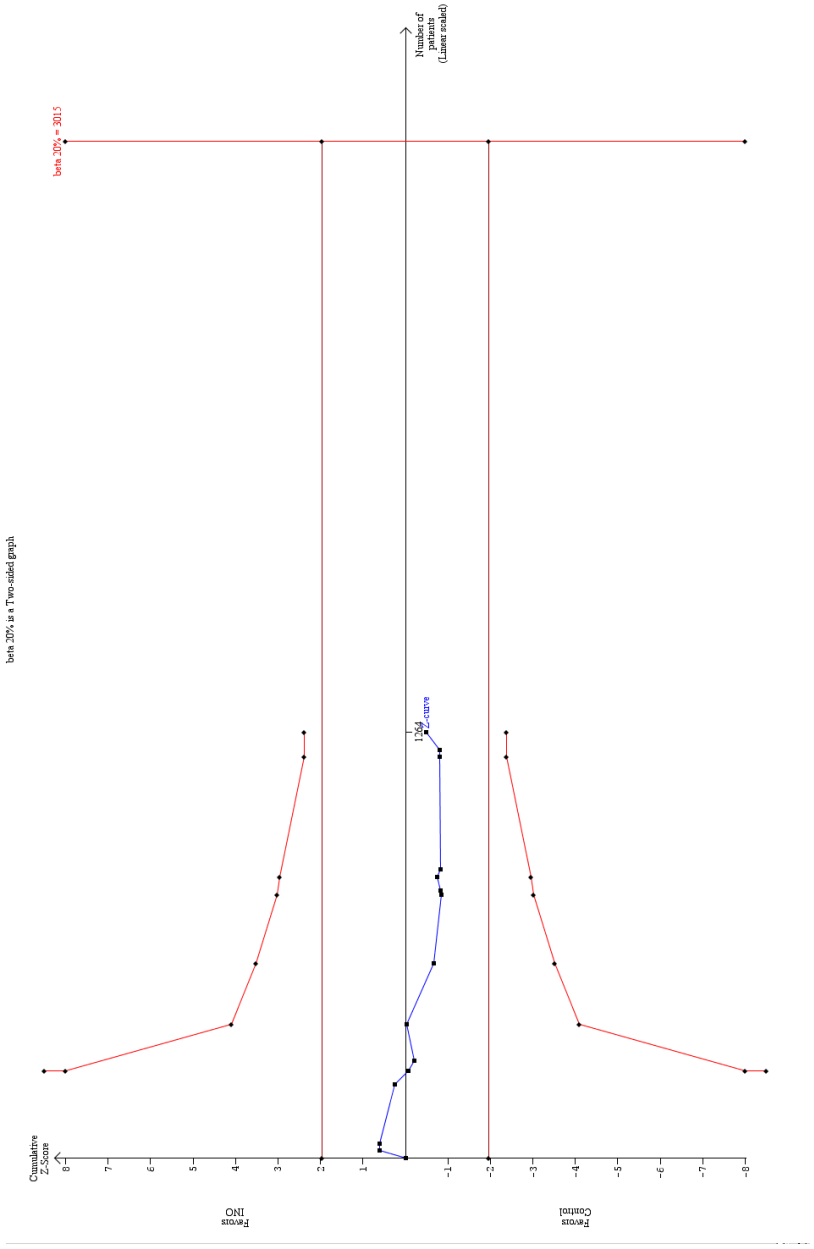


Figure 1. TSA of all trials of the effect of INO on mortality (longest follow-up). The TSA-adjusted confidence interval for the meta-analysis of the primary outcome with continuity correction for zero events trials (0.001 event in each arm) in a fixed-effect model results in an RR of 1.04 (95% CI 0.90 to 1.19; I^2 statistic = 0%, diversity D^2 = 0%). With an accrued information size of 1243 participants and no boundaries crossed so far, only 41.92% of the required information size is actually available at this stage for rejection or acceptance of a 4% RRI for overall mortality. However, solid evidence may be obtained with fewer participants if eventually the cumulative meta-analysis z-curve crosses the trial sequential monitoring boundary constructed for a required information size of 3015 randomized participants. However, regarding the TSA analysis for this outcome, it is important to bear in mind that only 4 out of the 14 included studies are classified as low risk of bias trials. Therefore, TSA is not able to directly adjust for the impact of bias.

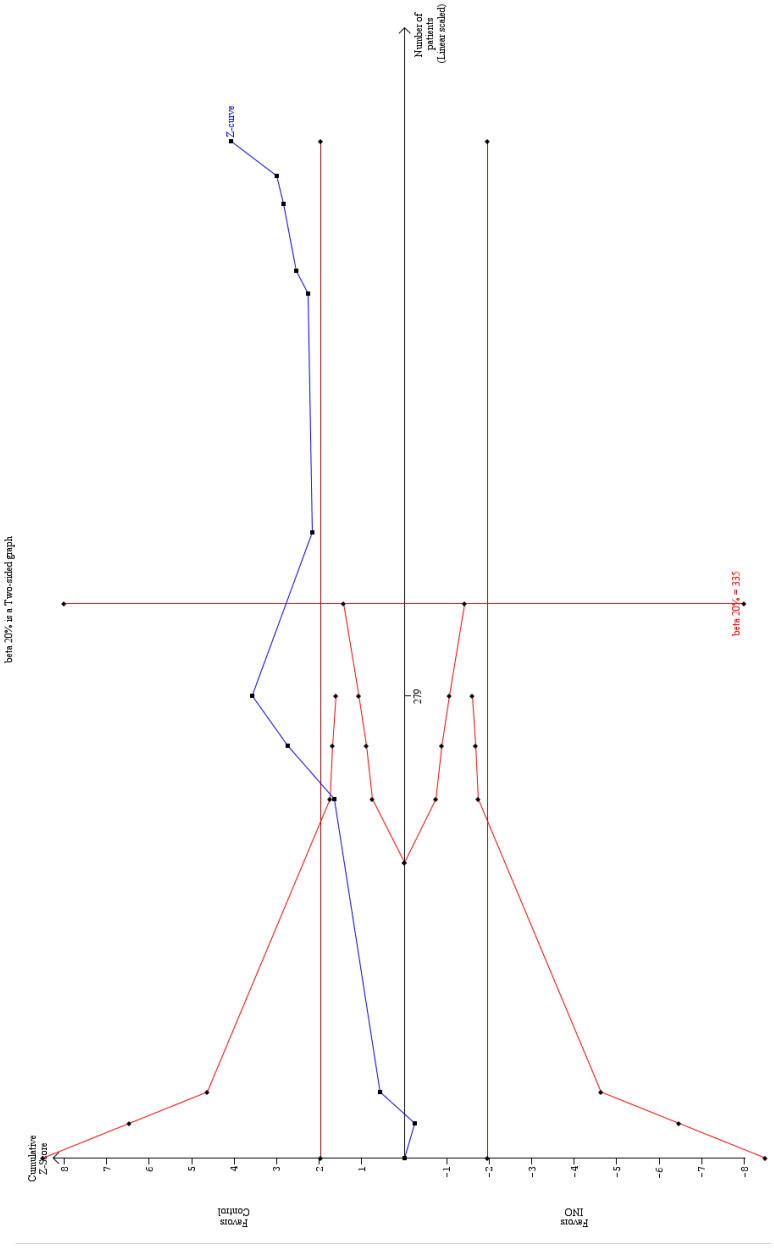


Figure 2. TSA of all trials of the effect of INO on PaO_2/FiO_2 ratio at 24 hours. Application of TSA to analysis of the PaO_2/FiO_2 ratio at 24 hours indicates statistical significance in favour of improved oxygenation, even with adjustment for repetitive testing on accumulating data in the cumulative meta-analysis, because the z-curve crossed the trial sequential monitoring boundary. The a priori information size (335 participants) is determined by a TSA-adjusted mean difference (MD) of 15.91. The cumulative z-curve (blue line with filled squares) at the current accrued information size of 614 participants crosses the boundary (red lines with open diamonds) (with 80% power and alpha 0.05, assuming a double-sided type 1 risk of 5% and type 2 risk of 20%). However, it is important to note that only two trials had low risk of bias and the TSA-adjusted confidence interval for the meta-analysis in a random-effects model results in an MD of 15.91 with substantial heterogeneity and diversity (95% CI 8.25 to 23.56; I^2 statistic = 25%, diversity D^2 = 49%).

BACKGROUND

Description of the condition

Since this review was first published (Sokol 2003a), the definition of acute respiratory failure has changed. Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in any adult or child older than one month of age were initially defined by the American-European Consensus Conference (AECC) in 1994 (Bernard 1994).. The ARDS definition task force produced the latest definition and has developed the Berlin definition (ARDS Definition Task Force 2012). Acute lung injury no longer exists and has been replaced by a gradation of ARDS that is based on the severity of hypoxaemia: mild (200 mm Hg < partial pressure of oxygen in arterial blood (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤ 300 mm Hg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O), moderate (100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O) or severe (PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O). The Berlin criteria also include onset within one week of a known clinical insult or worsening respiratory symptoms, bilateral opacities on chest x-ray not explained by effusion, collapse or nodule and no cardiac failure or fluid overload.

ARDS is characterized by an inflammatory process of the alveolar-capillary membrane that may arise from a primary lung disease or secondary to several systemic disease processes (Jain 2006). It is mainly due to a ventilation-perfusion mismatch, resulting in increased intrapulmonary shunting due to pulmonary vasodilatation in non-ventilated lung regions and vasoconstriction in ventilated areas, as well as pulmonary hypertension (Dahlem 2007).

The incidence of ARDS is reported to be between 14 and 86 persons per 100,000 per year in a general adult population (Luhr 1999; Rubenfeld 2005). However, a recent report from Finland indicates a smaller incidence of ARDS of five per 100,000 per year (Linko 2009). In Minnnesota, during an eight-year period of study between 2001 and 2008, the incidence decreased from 82.4 to 38.9 per 100,000 person-years (Li 2011). Mortality among adults with ARDS has been reported as 24% to 60%, depending on age and underlying health status of the patient (Anderson 2003; MacCallum 2005; Rubenfeld 2005). The worst prognosis is seen among patients with sepsis or multi-organ failure, those who are immunocompromised and those without improvement in oxygenation after six days (TenHoor 2001; Ware 2000).

Recent evidence indicates that the incidence of ARDS among children is 2.0 to 12.8 persons per 100,000 per year (Zimmerman 2009). Paediatric in-hospital mortality was recently reported at 18% to 27%, with pneumonia, aspiration and sepsis as primary causes of the condition (Dahlem 2003; Dahlem 2007; Flori 2005; López-Fernández 2012; Zimmerman 2009).

Description of the intervention

Nitric oxide (NO) is a potent endogenous vasodilator that can be exogenously administered via inhalation. It is synthesized by conversion of the terminal guanidine nitrogen atom of L-arginine via endothelial cell calcium-dependent enzyme nitric oxide synthetase, then diffuses across the cell membrane to activate the enzyme guanylate cyclase. This enzyme enhances the synthesis of cyclic guanosine monophosphate (cGMP), causing relaxation of vascular and bronchial smooth muscle and vasodilatation of blood vessels (Palmer 1998). Inhaled NO (INO) was first used in clinical practice in 1991 (Hsu 2008; Rossaint 1993).

Inhaled NO has the ability to provide selective pulmonary vasodilatation in well-ventilated lung units, to improve ventilation-perfusion mismatch and subsequently to reduce the elevated pulmonary vascular resistance and pulmonary hypertension seen in ARDS (Dellinger 1998; Sokol 2003b). A reduction in pulmonary arterial pressure and a decrease in intrapulmonary shunting occur within 40 minutes of INO treatment initiation (Rossaint 1993). Inhaled NO also increases the right ventricular ejection fraction and decreases right end-systolic volume, thus preventing decompensation of acute cor pulmonale (Fierobe 1995).

How the intervention might work

Inhaled NO has a half-life of three to five seconds and is rapidly inactivated on contact with haemoglobin. As a result, its vasodilatory effect may be limited to well-ventilated regions of the lung (Hsu 2008). Nitric oxide is involved in production of and protection from oxidative injury, regulates both immune and inflammatory responses, decreases neutrophil sequestration in the lung, decreases oedema formation and regulates its own production (McAndrew 1997; Prodhan 2004).

Inhaled NO is rapidly converted to active intermediates, including nitrogen dioxide, peroxy-nitrite and nitro-tyrosine, in the presence of superoxide (Pryor 1995). However, systemic exposure to INO, which is a cytotoxic free radical, or accumulation of its degradation products could result in deleterious side effects through formation of other free radicals, causing further lung tissue damage (Beckman 1990), impaired surfactant function (Haddad 1996) or aggravated circulatory failure (Köstler 2005).

Nitric oxide alters immune function by modifying the release of cytokines and other components of the inflammatory cascade from alveolar macrophages (Chollet-Martin 1996; Thomassen 1997); it inhibits active adhesion molecules and the neutrophil oxidative burst involved in neutrophil migration (Kubes 1991).

Inhaled NO rapidly binds to haemoglobin, with high affinity, to form methaemoglobin at doses of 40 ppm or greater (Sokol 2003a). This occurs after INO diffuses from alveoli to vascular smooth muscle cells adjacent to the alveoli.

Adenosine diphosphate (ADP) and collagen-induced platelet aggregation are significantly inhibited by INO via an increase in intraplatelet cGMP during passage of platelets through the lung, and bleeding time is significantly prolonged in a non-dose-related manner during inhalation (Barrington 2007; Gries 1998; Gries 2000).

Why it is important to do this review

Inhaled NO is still used extensively worldwide as a rescue agent in severely hypoxaemic patients with ARDS. A survey from Canada found that 39% of specialists still used INO in the treatment of ARDS (Meade 2004). Most patients with ARDS who receive INO respond with improved oxygenation, but the benefit appears to be transient, lasting less than 72 hours (Adhikari 2007; Calfee 2007). Furthermore, two systematic reviews found little evidence on clinical outcomes and increased risk of adverse effects, for example, renal dysfunction (Adhikari 2007; Sokol 2003a; Sokol 2003b). Thus INO application remains controversial, especially in the light of recent evidence. The aim of this review was to update

the best available evidence on this topic and to assess whether INO therapy has any role in the treatment of patients with ARDS.

We aimed to systematically review randomized controlled trials (RCTs) of INO administration in children and adults with ARDS. More compelling evidence is needed on this topic and on its potential benefits. This is an update of a review first published in 2003 (Sokol 2003a) and updated in 2010 (Afshari 2010).

OBJECTIVES

The primary objective was to examine the effects of administration of inhaled nitric oxide on mortality in adults and children with ARDS.

Secondary objectives were to examine secondary outcomes such as pulmonary bleeding events, duration of mechanical ventilation, length of stay, etc. We conducted subgroup and sensitivity analyses, examined the role of bias and applied trial sequential analyses (TSAs; Trial Sequential Analysis (TSA)) to examine the level of evidence.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of publication status, date of publication, blinding status, outcomes published or language. We contacted trial investigators and study authors to ask for relevant data. We included unpublished trials only if trial data and methodological descriptions were provided in written form or could be retrieved from the trial authors. We excluded cross-over trials. We identified no cluster-RCTs but planned to include these, if found, in future updates.

Types of participants

We included participants with a diagnosis of ARDS or ALI, according to the various definitions present in the literature. In the case of an intervention effect, we performed a subgroup analysis based on enrolment of participants to the ARDS groups. We chose to accept the terms 'standard treatment' of ARDS and critically ill patients as reported by many study authors, despite the ongoing controversy. We excluded neonates described as having 'bronchopulmonary dysplasia' or 'chronic lung disease' because of different pathophysiology, treatment, prognosis and progression of the disease.

Types of interventions

We included trials comparing INO versus placebo or no intervention in adults and children with ARDS. We included any type or dose of INO and any duration of administration. We permitted a co-intervention if it was administered in both groups. We excluded trials that compared only different INO treatment regimens and those in which INO was compared with interventions other than placebo or no intervention.

Types of outcome measures

Primary outcomes

1. Overall mortality (longest follow-up, regardless of the duration of follow-up).
2. Overall 28-day mortality (studies reporting mortality at 25 to 30 days were included in the same analysis).

Secondary outcomes

1. Bleeding events: defined as pulmonary bleeding or systemic bleeding requiring transfusion.
2. Complications during the in-patient stay (e.g. hypotensive episodes, direct irritation on administration, thrombosis, congestive cardiac failure, myocardial infarction, renal failure, cerebrovascular accident).
3. PaO_2/FiO_2 ratio.
4. Ventilator-free days.
5. Duration of mechanical ventilation.
6. Oxygenation index.
7. Improvement in mean pulmonary arterial pressure (mm Hg).
8. Methaemoglobin concentration > 5%.
9. Nitric oxide concentration > 3 ppm.
10. Resolution of multi-organ failure (according to different organ dysfunction scores).
11. Quality of life assessment, as defined by authors of included studies.
12. Length of stay in intensive care unit and in hospital.
13. Cost-benefit analyses.

Search methods for identification of studies

Electronic searches

For this review update, we performed a search update to 18 November 2015. Thus, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 11); SilverPlatter MEDLINE (WebSPIRSOvid SP, 1950 to 18 November 2015); SilverPlatter EMBASE (WebSPIRSOvid SP, 1980 to 18 November 2015); SilverPlatter BIOSIS Previews (WebSPIRS 1993 to 18 November 2015); International Institute for Scientific Information (ISI) Web of Science (1964 to 18 November 2015); Latin American Caribbean Health Sciences Literature (LILACS) (via BIREME) (1982 to 18 November 2015); the Chinese Biomedical Literature Database; advanced Google; and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO host) (1980 to 18 November 2015) (see Appendix 1).

Searching other resources

We handsearched the reference lists of reviews, randomized and non-randomized studies and editorials for additional studies. We contacted the main authors of included studies to ask about any missed, unreported or ongoing studies. We searched for ongoing clinical trials and unpublished studies on the following Internet sites.

1. http://www.controlled-trials.com
2. http://clinicaltrials.gov
3. http://www.centerwatch.com

We applied no language restriction to eligible reports and performed the latest search on 18 November 2015.

Data collection and analysis

Three review authors (FG, OK, AA) independently screened and classified all citations as potential primary studies, review articles or other. All review authors independently examined all potential primary studies and decided on their inclusion in the review (Figure 3). We evaluated all trials for major potential sources of bias (random sequence generation, allocation concealment, blinding, intention-to-treat analysis, funding and completeness of follow-up) (Figure 4; Figure 5). We assessed each trial quality factor separately and defined trials as having low risk of bias only if they adequately fulfilled all of the criteria. We independently extracted from each trial and evaluated data on methods and outcomes in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by reaching consensus among review authors.

Figure 3. INO search result.

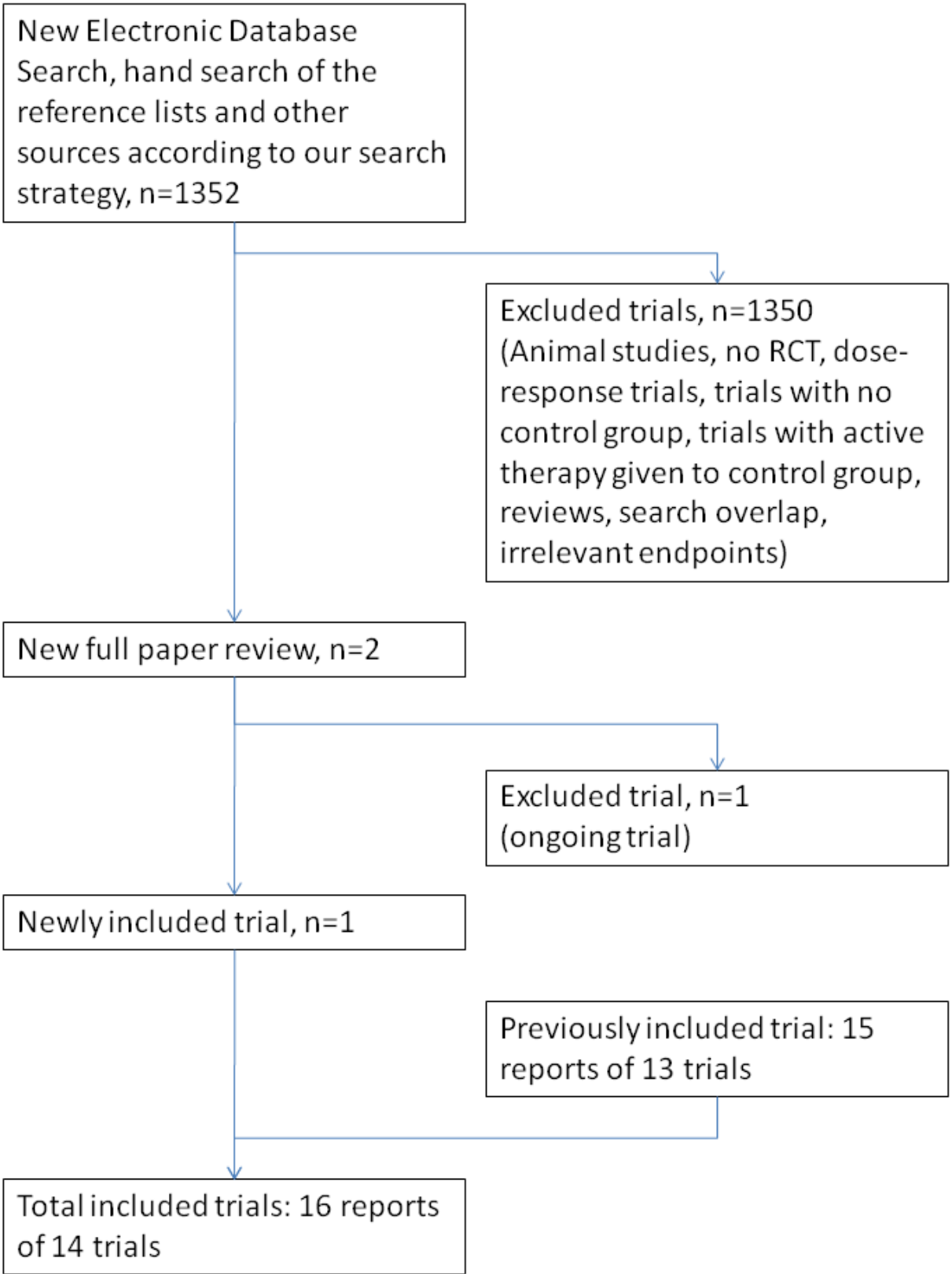


Figure 3. (Continued)

of 14 trials

Figure 4. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

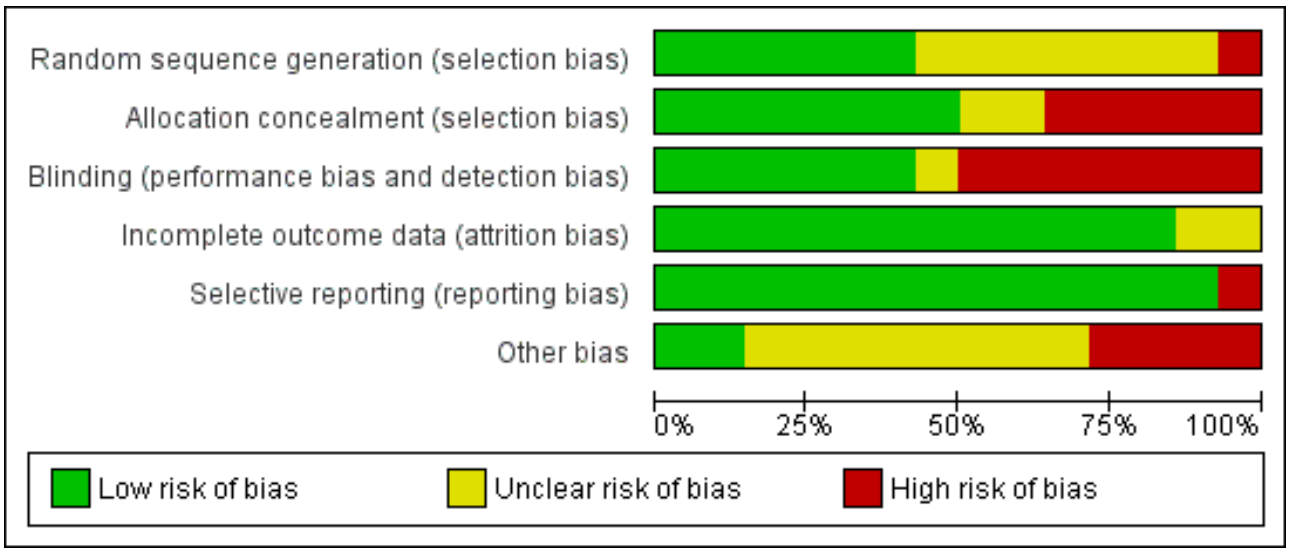
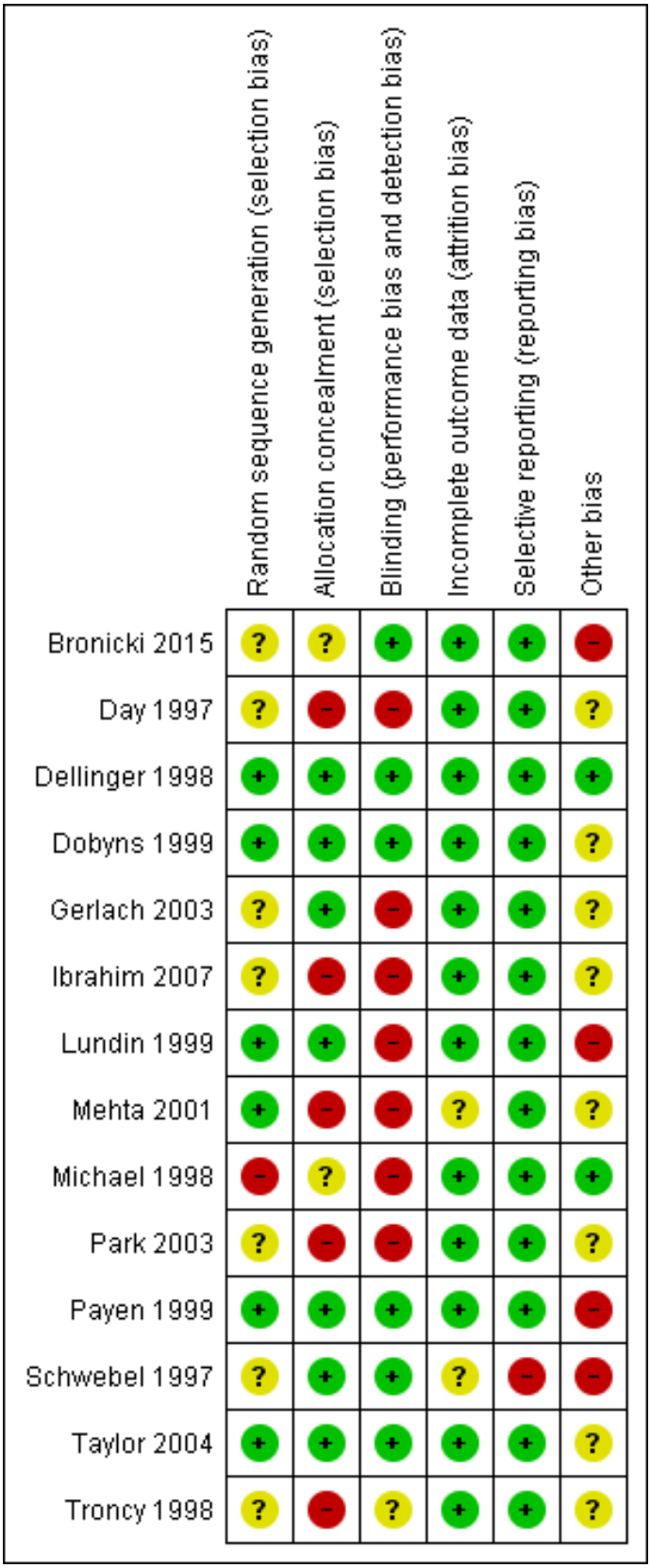


Figure 5. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Selection of studies

We assessed the articles identified via the described searches and excluded obviously irrelevant reports. Three review authors (FG, OK, AA) independently examined articles for eligibility and screened titles and abstracts to identify studies for eligibility (Figure 3; see Characteristics of included studies and Characteristics of excluded studies). We performed this process without blinding of study authors, institutions, journals of publication or results. We resolved disagreements by reaching consensus among review authors. We provide here a detailed description of the search and assessment.

Data extraction and management

We independently extracted and collected data without blinding to study authors, source institutions or publication source of trials. We resolved disagreements by discussion and approached all first authors of included trials for additional information on risks of bias. For more detailed information, please see Contributions of authors.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial.

We evaluated trials for major potential sources of bias (random sequence generation, allocation concealment, blinding, intention-to-treat (ITT) analysis and completeness of follow-up; see Appendix 2). We assessed each trial quality factor separately and defined trials as having low risk of bias only if they adequately fulfilled all of the criteria described below.

Measures of treatment effect

Dichotomous data

We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data (binary outcomes). These included the following:

Primary outcomes

1. Mortality by duration and overall mortality.

Secondary outcomes

1. Number of infectious complications.
2. Adverse events.

Continuous data

We used the mean difference (MD) or the RR if data were continuous and were measured in the same way between trials as follows:

1. Length of stay in an intensive care unit (ICU).
2. Number of days on a ventilator.
3. Length of hospital stay.

Unit of analysis issues

Cross-over trials

We excluded cross-over trials from our meta-analyses because of the potential risk for “carry-over” of treatment effect.

Studies with multiple intervention groups

In studies designed with multiple intervention groups, we combined groups to create a single pair-wise comparison in accordance with Higgins 2011. In trials with two or more groups receiving different doses, we combined data for primary and secondary outcomes.

Dealing with missing data

We contacted the authors of trials with missing data to retrieve the relevant information. For all included studies, we noted levels of attrition and any exclusion of participants. In cases of missing data, we chose ’complete-case analysis’ for our primary outcomes, thus excluding from the analysis all participants with missing outcomes. Selective outcome reporting, which occurs when non-significant results are selectively withheld from publication (Chan 2004), is defined as selection, on the basis of results, of a subset of the original variables recorded for inclusion in publication of trials (Hutton 2000). The most important types of selective outcome reporting are selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of different analyses using the same data; selective reporting of subsets of the data; and selective under-reporting of data (Higgins 2011).

Assessment of heterogeneity

We explored heterogeneity using the I^2 statistic and the Chi^2 test. An I^2 statistic higher than 50% represents substantial heterogeneity (Higgins 2011). In case of an I^2 statistic > 0%, we tried to determine the cause of heterogeneity by performing relevant subgroup analyses. We used the Chi^2 test to obtain an indication of heterogeneity between studies, with P value ≤ 0.1 considered significant.

Assessment of reporting biases

Funding bias is related to possible publication delay or discouragement of undesired results in trials sponsored by the industry (Higgins 2011). To explore the role of funding, we planned to conduct a sensitivity analysis based on our primary endpoint.

Data synthesis

We used Review Manager software (RevMan 5.3.5) and calculated RRs with 95% CIs for dichotomous variables and MDs with 95% CIs for continuous outcomes. We used the Chi^2 test to obtain an indication of heterogeneity between studies, with P value ≤ 0.1 considered significant. We quantified the degree of heterogeneity observed in the results by using the I^2 statistic, which can be interpreted as the proportion of total variation observed between studies that is attributable to differences between studies rather than to sampling error (Higgins 2011). An I^2 statistic value > 75% is considered very heterogeneous. We used both a random-effects model and a fixed-effect model. If the I^2 statistic value was 0%, we reported only results from the fixed-effect model, and with an I^2 statistic value > 0%, we reported only results from the random-effects model.

Trial sequential analysis

Risk of type 1 errors in meta-analyses due to sparse data and repeated significance testing following updates with new trials remains a serious concern (Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). As a result, spurious P values due to systematic errors from trials with high risk of bias, outcome reporting bias, publication bias, early stopping for benefit and small trial bias may result in false conclusions. In a single trial,

interim analysis increases the risk of type 1 errors. To avoid type 1 errors, group sequential monitoring boundaries (Lan 1983) are used to decide whether a trial could be terminated early because of a sufficiently small P value, thus the cumulative Z curve crosses the monitoring boundary.

Equally, sequential monitoring boundaries can be applied to meta-analyses and are labelled 'trial sequential monitoring boundaries'. In 'trial sequential analysis' (TSA), the addition of each new trial to a cumulative meta-analysis is viewed as an interim meta-analysis, which provides useful information on the need for additional trials (Wetterslev 2008).

It is appropriate and wise to adjust new meta-analyses for multiple testing on accumulating data to control overall type 1 error risk in cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008).

When TSA is performed, the cumulative Z curve crossing the boundary indicates that a sufficient level of evidence has been reached; as a consequence, one may conclude that no additional trials may be needed. However, evidence is insufficient to allow a conclusion if the Z curve does not cross the boundary or does not surpass the required information size.

To construct trial sequential monitoring boundaries (TSMBs), one needs a required information size, which is calculated as the least number of participants required in a well-powered single trial with low risk of bias (Brok 2009; Pogue 1998; Wetterslev 2008).

In this updated review, we adjusted the required information size for heterogeneity by using the diversity adjustment factor (Wetterslev 2009). We applied TSA, as it prevents an increase in the risk of type 1 errors (20%). If the actual accrued information size was too small, we provided the required information size in the light of actual diversity (Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses:

1. Benefits and harms of INO in participants with ALI or ARDS based on the cause (primary lung injury vs secondary lung injury).
2. Benefits and harms of INO in paediatric participants (paediatric participants (< 18 years) vs adult participants).
3. Benefits and harms of INO based on duration of drug administration (short-term vs long-term administration).

If analyses of various subgroups were significant, we performed a test of interaction (Altman 2003). We considered P values < 0.05 as indicating significant interaction between INO treatment and subgroup categories.

Sensitivity analysis

We decided to carry out a sensitivity analysis on the results by applying fixed-effect and random-effects models to assess the impact of heterogeneity on our results.

Summary of findings

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach to provide an overall assessment of evidence related to all of our outcomes. We constructed a 'Summary of findings' table using GRADEpro software. As outcomes of public interest, we chose to present overall mortality (regardless of the follow-up period), ICU length of stay, days on ventilator and length of hospital stay (see Summary of findings for the main comparison).

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

In this updated review, we identified two new trials via the search strategy; we included one of them (Bronicki 2015), and the second one is ongoing. A total of 1275 participants were included in this review update. We found one of the studies (Bronicki 2015) by handsearching. We have provided the flow chart for this updated review in Figure 3.

Included studies

All included trials except two (Day 1997; Taylor 2004) used the ARDS definition based on the European-American consensus statement as an entry criterion (Table 1). No currently included study used the Berlin ARDS definition, as patient enrolment for the most recent study took place from 2003 through 2005 (Bronicki 2015). One trial used the Murray Lung Injury Score > 2.5 (Troncy 1998), and another used oxygenation index (OI) criteria (Dobyns 1999). Two trials (Ibrahim 2007; Lundin 1999) used a definition of ALI that was modified from that used the consensus statement. Two studies were published in abstract form (Payen 1999; Schwebel 1997). We identified no duplicate reports. In Angus 2006, study authors described the 'activity of daily living scale' (ADL) and the 'quality of well being scale' (QWB), hospital costs and resource use, as well as long-term mortality, on the basis of Taylor 2004. All studies except one (Schwebel 1997) reported mortality. Analyses of the impact of INO on oxygenation were hindered as the result of application of different indicators of oxygenation, different time points for oxygenation measurement and demonstration of therapeutic effects in graphic form without adjacent numerical data in most publications. Investigators inconsistently reported other clinical outcome variables in line with our defined primary and secondary outcomes.

We classified four trials as paediatric trials (Bronicki 2015; Day 1997; Dobyns 1999; Ibrahim 2007); one trial included a few children (Michael 1998); and the remaining trials consisted of mixed populations of critically ill adults with ALI and ARDS. Sample size varied from 14 to 385 participants with ALI or ARDS (Table 1).

Intervention duration ranged from less than 24 hours to four weeks. The estimated median length of interventions was seven days. Follow-up ranged from 24 hours to one year. The comparison group received placebo in six trials (Bronicki 2015; Dellinger 1998; Dobyns 1999; Payen 1999; Schwebel 1997; Taylor 2004). Nitrogen was used as placebo, except in one trial, which used air (Dobyns 1999).

Nine trials applied a fixed dose of INO (median 10 ppm; range 5 to 10 ppm) (Bronicki 2015; Day 1997; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Park 2003; Payen 1999; Schwebel 1997; Taylor 2004). Four trials used the lowest dose to achieve an oxygenation response

(Lundin 1999; Mehta 2001; Michael 1998; Troncy 1998), and one trial used different doses of INO (Dellinger 1998). One trial enrolled only INO responders (Lundin 1999).

In five trials, a few participants allocated to the control group crossed over to INO as rescue therapy after randomization, according to predefined protocols (Dobyns 1999; Lundin 1999; Michael 1998; Payen 1999; Schwebel 1997). In one trial, all randomized participants (in control and INO groups) received INO after 24 hours (Day 1997). Thus, we chose to report only mortality data gathered before this cross-over took place (Day 1997). At the clinician's discretion, nitric oxide treatment was discontinued (Schwebel 1997) or was tapered after a pre-specified time period (Dobyns 1999; Ibrahim 2007; Michael 1998) or after pre-defined gas exchange endpoints were reached (Day 1997; Dellinger 1998; Lundin 1999; Mehta 2001; Michael 1998; Payen 1999). Only one trial did not provide information on INO discontinuation criteria (Park 2003). Investigators applied various co-interventions, such as the recruitment manoeuvre (Park 2003), the prone position (Bronicki 2015; Gerlach 2003; Ibrahim 2007; Taylor 2004)) and use of corticosteroids (Dellinger 1998).

Four unblinded trials (Gerlach 2003; Ibrahim 2007; Park 2003; Troncy 1998) and one blinded trial used pre-defined protocols for mechanical ventilation (Schwebel 1997); three unblinded trials adhered to guidelines (Dellinger 1998; Dobyns 1999; Taylor 2004).

Excluded studies

We excluded nine potentially relevant publications (Cuthbertson 2000; Johannigman 1997; Khan 2009; Meade 2003; Perrin 2006; Puybasset 1994; Puybasset 1995; Rossaint 1995; Tang 1998;) for reasons detailed in the Characteristics of excluded studies section.

Studies awaiting assessment

No studies are awaiting assessment.

Ongoing studies

We identified one ongoing study (Godinez). This study was reported to be completed in 2006 but no results have been published so far; for details, see the Characteristics of ongoing studies section.

Risk of bias in included studies

We classified four trials as having low risk of bias for the main outcome - overall mortality (Dellinger 1998; Dobyns 1999; Payen 1999; Taylor 2004) (see Analysis 2.1). For a more detailed description of individual trial qualities, see the table Characteristics of included studies. We have presented the various bias domains in the 'Risk of bias graph' and a 'Risk of bias summary' figure (Figure 4; Figure 5).

Allocation

Six trials (43%) adequately reported random sequence generation (Dellinger 1998; Dobyns 1999; Lundin 1999; Mehta 2001; Payen 1999; Taylor 2004), whereas seven trials (50%) reported allocation concealment (Dellinger 1998; Dobyns 1999; Gerlach 2003; Lundin 1999; Payen 1999; Schwebel 1997; Taylor 2004) (see Appendix 3).

Blinding

Six trials provided sufficient data to be categorized as double-blinded (46%) (Bronicki 2015; Dellinger 1998; Dobyns 1999; Payen 1999; Schwebel 1997; Taylor 2004). Remaining trials were open-label studies or did not provide sufficient data on how double-blinding was achieved (see Appendix 3).

Incomplete outcome data

All trials except two provided complete follow-up for the primary outcome (Angus 2006; Schwebel 1997) (see Appendix 3). The Angus 2006 publication is based on one-year follow-up of the same cohort of participants as were described in Taylor 2004, which presented complete follow-up. Study authors reported 90.2% follow-up at one year (Angus 2006). In Schwebel 1997, study authors did not provide data on mortality nor on length of follow-up. Six trials (43%) performed analysis according to the ITT method or provided sufficient data to permit ITT analyses (Dellinger 1998; Gerlach 2003; Lundin 1999; Payen 1999; Taylor 2004; Troncy 1998). Additionally, some trials did not provide explicit information on duration of the longest follow-up (Appendix 3). Many of our analyses were subject to limitations because most studies demonstrated therapeutic effects in graphic form, without providing numerical data.

We found one trial on Clinical Trial.gov (Godinez) and found that no other data had been published yet. We tried to contact study authors without success.

Selective reporting

Thirteen trials provided adequate information to be classified as low-risk trials (Bronicki 2015; Day 1997; Dellinger 1998; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Payen 1999; Taylor 2004; Troncy 1998). Supplementary information was often obtained through online registration, available protocols or clarifying responses to our questions as provided by study authors. One trial did not provide sufficient data on selective reporting (high-risk) (Schwebel 1997).

Other potential sources of bias

Seven trials reported a sample size calculation (Dellinger 1998; Gerlach 2003; Lundin 1999; Mehta 2001; Michael 1998; Payen 1999; Taylor 2004), but only two were powered to show statistically significant benefit for primary endpoints (Lundin 1999; Taylor 2004) (see Appendix 3). Lundin 1999 was stopped early for slow enrolment (at 45% of calculated sample size), Taylor 2004 enrolled only 75% of the planned sample size, for unknown reasons, and Bronicki 2015 was terminated prematurely because of slow enrolment (planned 338 participants, enrolled 55 participants).

The funnel plot of standard error versus risk ratio for overall longest follow-up mortality (Figure 6) and the funnel plot for 28-day to 30-day mortality (Figure 7) showed a symmetrical distribution that indicated no bias or publication bias. As we noted no asymmetry or heterogeneity in the funnel plot, we found no need to apply the arcsine-Thompson test, as proposed by Rücker (Rücker 2008). Additionally, we found no statistical significance (P value = 0.33) upon applying Egger's regression intercept test.

Figure 6. Funnel plot of comparison: 1 Mortality, outcome: 1.1 Longest follow-up, mortality.

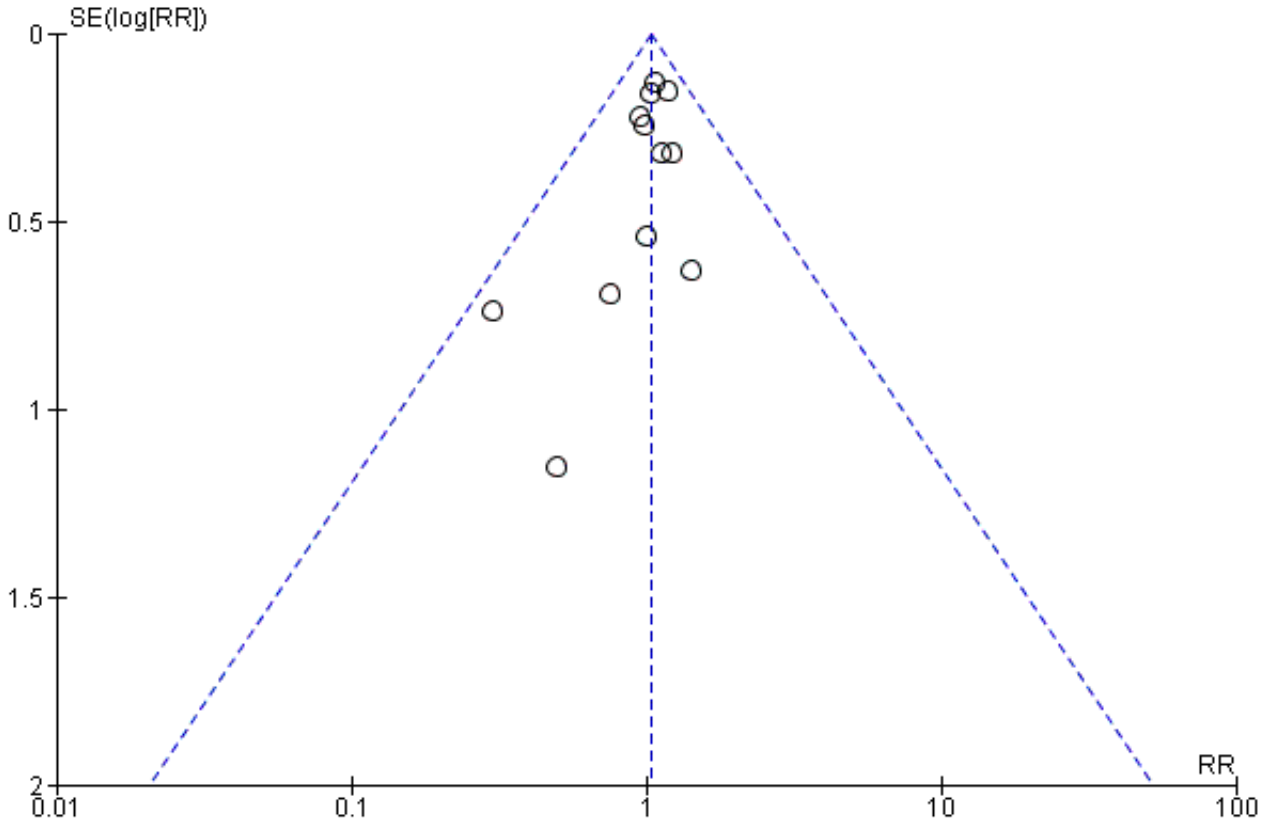
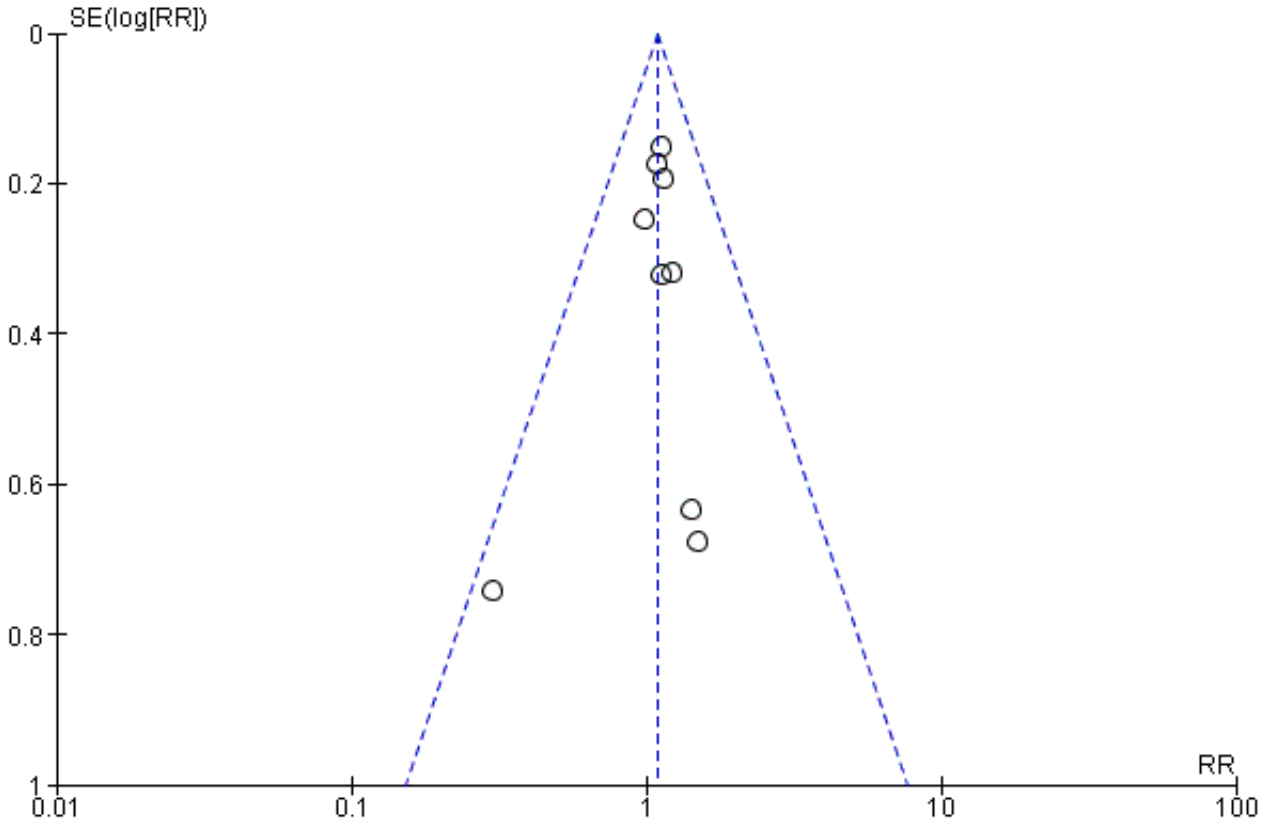


Figure 7. Funnel plot of comparison: 1 Mortality, outcome: 1.2 28- to 30-day mortality.



Effects of interventions

See: **Summary of findings for the main comparison** INO compared with control group for acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in children and adults

Primary outcomes

Overall mortality (longest follow-up, regardless of the duration of follow-up)

Combining data from the 13 included trials (1243 participants) and applying complete-case analysis revealed no statistically significant effects of INO on longest follow-up mortality: 250/654 deaths (38.2%) in the INO group compared with 221/589 deaths (37.5%) in the control group (RR 1.04, 95% CI 0.9 to 1.19; I^2 = 0%) (see Analysis 1.1). We upgraded the outcome from low to moderate quality of evidence because most trials had moderate risk of bias.

Overall 28-day mortality (studies reporting mortality as 25 to 30 days were included in the same analysis)

We combined nine trials (Bronicki 2015; Dellinger 1998; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Payen 1999; Taylor 2004; Troncy 1998) (1105 participants) in the 28-day mortality analysis and obtained the following results: 202/587 deaths (34.4%) in the INO group and 166/518 deaths (32%) in the control group (RR 1.08, 95% CI 0.92 to 1.27; I^2 = 0%) (see Analysis 1.2). We upgraded the outcome from low to moderate quality of evidence because most trials had moderate risk of bias.

We carried out a total of five subgroup and sensitivity analyses regarding our primary outcomes. We detected no statistically significant effects in any of these analyses.

Secondary outcomes

Bleeding events

Data from five trials (Dellinger 1998; Lundin 1999; Mehta 2001; Michael 1998; Payen 1999; 614 participants) show no statistically significant increase in bleeding events in the INO group compared with the control group (RR 0.88, 95% CI 0.43 to 1.79; I^2 = 0%) (see Analysis 3.1). We upgraded the outcome from low to moderate quality of evidence because most trials had moderate risk of bias.

Complications during the in-patient stay

Inhaled nitric oxide increased the risk of renal impairment, according to data from four adult trials (Dellinger 1998; Lundin 1999; Payen 1999; Taylor 2004, 945 participants; RR 1.59, 95% CI 1.17 to 2.16; I^2 = 0%) (see Analysis 4.1). However, the test of interaction for the RR of renal impairment from trials with low risk of bias (Dellinger 1998; Payen 1999; Taylor 2004; 765 participants) (see Analysis 4.1) versus the one trial with high risk of bias (Lundin 1999; 180 participants) (see Analysis 4.1) did not reach statistical significance (P value = 0.22). We accepted various definitions of renal impairment as proposed by study authors (see Appendix 4). We upgraded this outcome from moderate to high quality of evidence because most trials had low risk of bias.

One trial (Lundin 1999) involving 180 participants revealed that the rate of respiratory failure decreased in the INO group (RR 0.21, 95% CI 0.05 to 0.94) (see Analysis 4.3). One trial (Lundin 1999) involving 180 participants provided data on reversal of ALI, showing no statistically beneficial effects of INO (RR 1.13, 95% CI 0.88 to 1.46). No trial provided data on reversal of ARDS (see Analysis 10.1). The quality of evidence was moderate.

Other adverse events were variably reported, and events such as pneumothorax (see Analysis 4.2), circulatory failure and shock (see Analysis 4.4), pneumonia, sepsis, encephalopathy, myocardial infarction, liver impairment, myopathy, agitation and hypertension (Table 2) did not reach statistical significance. The quality of evidence was high for pneumothorax and circulatory failure but was moderate for the other adverse events.

Only one trial (Taylor 2004; 385 participants) provided data indicating increased risk of infection in the INO group (RR 1.62, 95% CI 1.16 to 2.26; $I^2 = 0$) (Table 2). The quality of evidence was high.

PaO_2/FiO_2 ratio

Eleven trials (Day 1997; Dellinger 1998; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Schwebel 1997; Troncy 1998 ; 614 participants) indicated an improved PaO_2/FiO_2 ratio at 24 hours (MD 15.91, 95% CI 8.25 to 23.56; $I^2 = 25\%$) (Analysis 5.1). An additional analysis of PaO_2/FiO_2 difference from baseline at 24 hours, based on data from three trials (Dobyns 1999; Park 2003; Troncy 1998; 155 participants), revealed a similar finding (MD 42.90, 95% CI 20.57 to 65.23; $I^2 = 58\%$) (see Analysis 5.5). The PaO_2/FiO_2 ratio at 48 and 72 hours no longer showed a statistically significant beneficial effect (see Analysis 5.2; Analysis 5.3), but the analysis at 96 hours, based on four trials (Dellinger 1998; Gerlach 2003; Lundin 1999; Mehta 2001; 334 participants), showed improved oxygenation in the INO group (MD 14.51, 95% CI 3.64 to 25.38; $I^2 = 0\%$) (see Analysis 5.4). We upgraded the outcome from low to moderate quality of evidence because most trials had moderate risk of bias.

Ventilator-free days

Data from five trials (Dellinger 1998; Park 2003; Payen 1999; Taylor 2004; Troncy 1998; 804 participants) show no statistically significant effect of INO on ventilator-free days up to day 28 or 30 (MD -0.57, 95% CI -1.82 to 0.69; $I^2 = 0\%$) (see Analysis 6.1). We upgraded the outcome from moderate to high quality of evidence because most trials had low risk of bias.

Duration of mechanical ventilation

Six trials (Day 1997; Dobyns 1999; Gerlach 2003; Lundin 1999; Park 2003; Troncy 1998; 390 participants) reported no effects of INO on duration of mechanical ventilation (MD 1.02, 95% CI -2.08 to 4.12; $I^2 = 76\%$) (see Analysis 7.1). The quality of evidence was moderate.

Oxygenation index

Five studies (Bronicki 2015; Day 1997; Dellinger 1998; Dobyns 1999; Ibrahim 2007; 368 patients) reported that the oxygenation index was significantly lower in the INO group at 24 hours (MD -2.31, 95% CI -2.73 to -1.89; $I^2 = 0\%$). Two studies (Day 1997; Dellinger 1998; 183 participants) noted no statistically significant differences at 48 hours (MD 1.99, 95% CI -10.40 to 14.38; $I^2 = 74\%$) but Dellinger 1998 and Dobyns 1999 (245 participants) reported statistically significant differences at 72 hours (MD -3.48, 95% CI -6.80 to -0.15; $I^2 = 0\%$) (see Analysis 8.3; Analysis 8.4; Analysis 8.5) (Table 3). We upgraded the outcome from low to moderate quality of evidence because most trials had moderate risk of bias.

Mean pulmonary arterial pressure (mm Hg)

Differences in mean pulmonary arterial pressure were significant at day one (MD -1.76, 95% CI -3.41 to -0.12; $I^2 = 1\%$) but were no longer significant on days two, three and four (see Analysis 9.1; Analysis 9.2; Analysis 9.3; Analysis 9.4; 1275 participants). The quality of evidence was moderate.

Methaemoglobin > 5%

All trials assessed methaemoglobin concentrations (1275 participants). Four participants in the INO group and three in the control group had methaemoglobin values > 5% (RR 0.88, 95% CI 0.20 to 3.79; $I^2 = 0\%$) (see Analysis 11.1). The quality of evidence was moderate.

NO_2 concentration > 3 ppm

Seven trials (Dellinger 1998; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Mehta 2001; Payen 1999; Taylor 2004; 959 participants) reported data on nitrogen dioxide, but only one trial reported three of 385 participants with raised concentrations; all had received 80 ppm INO (Taylor 2004). The quality of evidence was high.

Resolution of multi-organ failure (according to different organ dysfunction scores)

Only one trial (Taylor 2004; 385 participants) met our requirements in terms of trial intervention effects on resolution of multi-organ failure based on various illness scores, with no statistically beneficial effects reported (TISS score) (Table 4). The quality of evidence was high.

Quality of life assessment

One trial assessed quality of life (Taylor 2004; 385 participants) using the 'activities of daily living scale' (ADL) and the 'quality of well being scale' (QWB). Neither assessment supported intervention with INO. The ADL score at six months and at one year did not indicate an improvement (Table 5), and the QWB of survivors at six months and at one year showed similar improvements in INO and control groups, with slightly better scores in the control group, although this finding was not statistically significant (Table 5). The quality of evidence was high.

Length of stay in intensive care unit and in hospital

Length of stay in ICU and in hospital was provided by only one trial (Taylor 2004; 385 participants), which did not indicate reduced stay in ICU or hospital (Table 6). The quality of evidence was high.

Cost-benefit analyses

Only one trial (Taylor 2004; 385 participants) provided data for cost-benefit analysis.. Study authors described similar hospital costs in the INO group (48,500 USD) and in the control group (47,800 USD; P value = 0.8) (Table 7). The quality of evidence was high.

Sensitivity and subgroup analyses

Sensitivity analysis

Sensitivity analysis excluding data from articles published as abstracts did not change overall results regarding significance (see Analysis 1.5).

Benefits and harms of INO in participants with ALI or ARDS based on the cause (primary lung injury vs secondary lung injury)

Only one trial provided data for analysis of mortality based on origin of the lesion (primary vs secondary lung injury) without showing statistical significance (Troncy 1998) (Table 8).

Benefits and harms of INO in paediatrics (paediatric participants (age < 18 years) vs adult participants)

Three paediatric trials (Bronicki 2015; Day 1997; Dobyns 1999) with a total of 185 participants showed no statistically significant beneficial effects of INO (RR 0.78, 95% CI 0.51 to 1.18; I^2 = 22%), nor did the adult population subgroup (RR 1.08, 95% CI 0.93 to 1.25; I^2 = 0%) (Analysis 1.3). The quality of evidence was moderate.

Benefits and harms of INO based on duration of drug administration (short-term vs long-term administration)

A total of 12 trials (Day 1997; Dellinger 1998; Dobyns 1999; Gerlach 2003; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Payen 1999; Schwebel 1997; Taylor 2004; Troncy 1998) with a total of 1190 participants had a median duration of intervention longer than one week (see Analysis 1.4). Current evidence does not support a longer duration of intervention (RR 1.07, 95% CI 0.89 to 1.29; I^2 = 0%) nor a shorter duration of intervention (RR 1.04, 95% CI 0.84 to 1.29; I^2 = 0%). We did not conduct a subgroup analysis to assess the effects of different INO dosages as no evidence appears to support this and many reported trials did not use a fixed dose of INO but applied dose titration (Adhikari 2007; Sokol 2003a) (Table 1).

Definition of respiratory failure

Studies designed before 2012 used the AECC definition (Bernard 1994) of acute respiratory distress syndrome, whereas more recent studies use the 2012 definitions (ARDS Definition Task Force 2012). Sensitivity analysis performed to examine the role of inclusion by AECC criteria did not alter the overall result (see Analysis 1.6).

Bias assessment

Comparison of estimates of the pooled intervention effect based on random sequence generation, allocation concealment, blinding, follow-up, sample size calculation, early stopping and overall risk of bias revealed no statistically significant findings in any of the subgroups examined (see Analysis 2.1; Appendix 3). We identified four trials with low risk of bias (Dellinger 1998; Dobyns 1999; Payen 1999; Taylor 2004), which showed no statistically significant findings for our primary endpoint.

Trial sequential analysis (TSA)

We conducted trial sequential analysis (TSA) of INO versus control to examine longest follow-up mortality (see Analysis 1.1; Figure 1). The TSA alfa-spending-adjusted confidence interval for meta-analysis of the primary outcome with continuity correction for zero event trials (0.001 event in each arm) in a fixed-effect model resulted in an RR of 1.04 (95% CI 0.87 to 1.23; I^2 = 0%, diversity D^2 = 0%). However, for trials with low risk of bias, the TSA-adjusted RR was 1.02 with 95% CI of 0.79 to 1.33 (I^2 = 0%, diversity D^2 = 0%). With an accrued information size of 1243 participants (for all trials) and no boundaries crossed so far, only 41.92% of the required information size is actually available at this stage for rejection or acceptance of a 4% relative risk increase for overall mortality. However, solid evidence may be obtained with fewer participants if eventually the cumulative meta-analysis z-curve crosses the trial sequential monitoring boundary constructed for a required information size of 3015 randomized participants. However, when the TSA analysis for this outcome is examined, it is important to bear in mind that only four out of the 14 included studies are classified as trials with low risk of bias. Therefore, TSA is not able to directly adjust for the impact of bias.

Application of TSA to analysis of the PaO_2/FiO_2 ratio at 24 hours did indicate statistical significance in favour of improved oxygenation, even with adjustment for repetitive testing of accumulating data in the cumulative meta-analysis, as the z-curve crossed the trial sequential monitoring boundary (Figure 2). The a priori information size (335 participants) is determined by a TSA alfa-spending-adjusted mean difference (MD) of 15.91. The cumulative z-curve (blue line with filled squares) at the current accrued information size of 614 participants crosses the boundary (red lines with open diamonds) (with 80% power and alpha 0.05, assuming a double-sided type 1 risk of 5% and type 2 risk of 20%). However, it is important to note that only two trials were at low risk of bias, and the TSA alfa-spending-adjusted confidence interval for the meta-analysis in a random-effects model results in an MD of 15.91 with substantial heterogeneity and diversity (95% CI 9.67 to 22.15; I^2 = 25%, diversity D^2 = 49%). However, the required information size based on the two trials (Dellinger 1998; Dobyns 1999; 276 participants) with low risk of bias is 5137 participants (MD 14.94, TSA-adjusted 95% CI -73.70 to -103.58; I^2 = 87%, diversity D^2 = 91%).

DISCUSSION

In this systematic review of 14 trials with 1275 participants with acute hypoxaemic respiratory failure (AHRF), we found no benefits of inhaled nitric oxide (INO) for survival. The analysis on mortality showed no heterogeneity and was robust when different subgroup and sensitivity analyses were performed. Conversely, INO increased the risk of renal failure among an adult population and transiently improved oxygenation, only for the first 24 hours. Sparse data on mortality are not promising but do not provide evidence of the absence of a beneficial effect; the data suggest that a potentially beneficial effect of INO must be modest, and the actual point estimate suggests harm (see Analysis 1.1; Analysis 1.2). In addition, our mortality analysis on the longest follow-up may have been influenced by the fact that only one trial (Taylor 2004) provided long-term follow-up for more than six months (Angus 2006).

The point estimate of the potential intervention effect, as suggested by low-bias trials, shows a 2% relative risk increase (RRI) (Analysis 1.1). To demonstrate or reject an a priori anticipated beneficial effect on mortality in a single trial, assuming a relative risk reduction (RRR) of 10%, at least 3015 participants should be randomized (Figure 1) (with 80% power and alpha 0.05, assuming a double-sided type 1 risk of 5% and type 2 risk of 20%). However, solid evidence may be obtained with fewer participants if the RRR is higher than 10%, that is, if the cumulative meta-analysis z-curve crosses the trial sequential monitoring boundary before the required information size of 3015 randomized participants is reached.

We found no statistically significant differences when examining effects in subgroups according to duration of the intervention, looking at interventions among different populations (paediatric, adult) and performing sensitivity analyses, which excluded trials published only as abstracts. The three paediatric trials (Bronicki 2015; Day 1997; Dobyns 1999) that provided information on mortality had a combined total of 185 participants, which is insufficient to demonstrate any benefits or harms of INO therapy in paediatric acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Subgroup and sensitivity analyses assessing the impact of varied primary origins, reversal of ALI resolution of multi-organ failure and assessments of quality of life and bias did not result in statistically significant findings. Additional analyses, such as those involving adverse events, indicated increased risk of renal failure among adults with no signs of increased risk of bleeding, methaemoglobinaemia or increased nitrogen dioxide concentration, except possibly among participants receiving INO doses greater than 80 ppm. Outcomes such as duration of stay in both ICU and hospital and other clinically relevant outcomes were inconsistently reported. We did not perform a subgroup analysis of reversal of ARDS, as insufficient data were provided. We contacted study authors to request missing data. Few responded, and they did not provide much additional information beyond that originally published.

Despite evidence of initial but transient improved oxygenation in the INO group, these analyses were hampered by the fact that various trials described effects on oxygenation differently, thus preventing adequate pooling of data. Even though a beneficial effect may be noted, oxygenation may be only a surrogate outcome, and it is uncertain whether it predicts any clinical benefits. Additionally, many trials were conducted before the general recommendation of a lung protective, low tidal volume ventilation strategy was introduced (Petrucci 2013). The latter combined with oxygen toxicity, surfactant inhibition and ongoing fibrosis resulting from ARDS may have influenced the results of these trials. However, given that no differences in the mode of ventilation were noted between INO and control groups, this should not account for our findings of lack of benefit for survival and potential harm.

We suggest several possible explanations for why INO may not be beneficial. By reducing ventilation-perfusion mismatch in patients with ARDS, INO appears to initially improve oxygenation. However, theoretically, INO could worsen the clinical condition by reversing hypoxic pulmonary vasoconstriction, thereby causing vasodilatation of poorly ventilated areas, increasing the ventilation-perfusion mismatch and resulting in worsening oxygenation (Kass 1998). However, we found little evidence to support the latter based on both published data and our respiratory analyses (Adhikari 2007) (see Analysis 5.1).

Additonally, prolonged exposure to INO and its toxic metabolites could cause sensitization, over-riding the possible benefits of INO (Gerlach 2003). Improved oxygenation is not associated with increased survival because improved oxygenation does not necessarily indicate improved lung function, reduction of lung injury or resolution of the underlying cause of ARDS and often co-existing multi-organ failure (ARDS network 2000; Petrucci 2013). Nitric oxide (NO) is an important regulator of renal vascular tone and a modulator of glomerular function. At the same time, it has been suggested that changes in NO production could cause acute renal failure by altering the function of mitochondria, various enzymes, deoxyribonucleic acid and membranes (Adhikari 2007; Valdivielso 2002). The latter suggestion is consistent with our finding of a possible harmful effect of INO on renal function.

Summary of main results

Our systematic review showed that INO, despite transiently improving oxygenation, partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) and the oxygenation index, and despite providing signs of reducing the rate of severe respiratory failure, does not reduce mortality or length of stay in ICU or hospital. Conversely, it appears that INO results in impairment of renal function among adults. We conducted multiple subgroup and sensitivity analyses, and none indicated relevant benefits of INO. We classified only four trials as having low risk of bias. Current evidence does not support the routine use of INO for severe respiratory failure.

Overall completeness and applicability of evidence

The overall quantity of data on which robust conclusions can be based is limited to 14 trials with 1275 participants. Evidence indicating that INO was not beneficial for patients with acute respiratory failure is of moderate to high quality. The definition of acute respiratory failure was usually that provided by the American-European Consensus Conference (AECC) in 1994 (Bernard 1994), which allows for appropriate comparison between trials. Primary outcomes of mortality were generally well reported, and secondary outcomes were often reported as well.

Therefore, despite the limited number of studies and participants identified, available evidence seems to be applicable to intensive care patients.

Quality of the evidence

The randomized controlled trial (RCT) is considered the most rigorous method of determining whether a cause-effect relationship exists between an intervention and an outcome. The strength of the RCT lies in the process of randomization.

The quality of findings ranks from moderate to high across different outcomes. The main limiting factors that accounted for a decrease in quality included high risk of bias and small and poorly described trials.

Four trials were reported as having low risk of bias (Dellinger 1998; Dobyns 1999; Payen 1999; Taylor 2004). We applied several statistical methods to explore and reduce the extent of bias, such as complete case analysis, trial sequential analysis, overall methodological bias assessment and analyses of various relevant clinical and physiological outcomes.

Application of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach enables us to incorporate risk of bias, directness of evidence, heterogeneity, precision of effect estimate and risk of publication bias. On the basis of the criteria mentioned above, we deemed the quality of evidence in this review to be moderate to high.

Potential biases in the review process

Upon reading the systematic review (Adhikari 2007) and acknowledging that very few trials had been published subsequently, we became aware of some of the conclusions that we would reach. Addtitionally, we realized that retrieving data from the authors of included trials relatively close to the latest systematic review could be difficult because providing additional data is a time-consuming process for trial authors. This has been the case.

Our systematic review has several potential limitations, that is, our findings and interpretations are limited by the quality and quantity of available evidence. We assessed the risk of bias of included trials mainly by using published data, which ultimately may not reflect the truth. We contacted all study authors, but only a few responded and provided further information. We were not able to retrieve protocols of the published trials and thus could not compare published outcomes versus outcomes proposed in the protocols. The value of these analyses is limited by the fact that only a small number of trials contributed to our subgroup and sensitivity analyses. Further, two trials with 51 participants did not report mortality during the trial (Ibrahim 2007; Schwebel 1997).

We noted variation in participant populations; type, dose and duration of INO treatment; and length of follow-up, along with consistent lack of improved survival across trials; we found the most beneficial effect among the subgroup of trials with high risk of bias, although these findings did not reach statistical significance (see Analysis 2.1). This minimizes the possibility that some subgroups of patients may benefit from INO. No trial has used short-term INO among the subgroup of patients with critically low oxygenation to buy valuable time to instigate other treatments to improve lung function, and this issue remains controversial.

Although we noted minimal heterogeneity among trial results on mortality, we are aware that we pooled heterogeneous trials in terms of age, participants, settings and treatment regimens. Thus, the validity of our meta-analysis may be criticized. However, all trials included patients with acute respiratory failure with similar inflammatory pathways, providing in our opinion good biological reasons to perform a broad meta-analysis, which also considerably increases the generalizability and usefulness of the review. Further, a broad meta-analysis increases power, reduces the risk of erroneous conclusions and facilitates exploratory analyses that can generate hypotheses for future research (Gotzsche 2000).

Agreements and disagreements with other studies or reviews

In general, our review presents the same conclusions as were provided by Adhikari et al (Adhikari 2007) and by authors of previous versions of this Cochrane review. However, we included more trials and thus were able to determine more precise estimates of mortality. Furthermore, we applied several sensitivity and subgroup analyses, trial sequential analysis and GRADE, which supported the overall results. It is important to note that Dr. Neill Adhikari has provided us with valuable data on physiological and clinical outcomes, such as PaO_2/FiO_2, oxygenation index, mean pulmonary arterial pressure, duration of mechanical ventilation and number of ventilator-free days up to 30 days, on behalf of several authors of included trials.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is insufficient to support the use of INO in patients with any category of ARDS and ALI. Despite signs of improved oxygenation, we did not find a statistically significant effect of INO on mortality or other clinical outcomes. Additionally, INO appeared to increase the risk of renal failure. Subgroup analyses performed according to duration of intervention, length of follow-up and different patient groups did not show differences in the estimates of intervention effects. In terms of the paediatric population, data are insufficient to support or refute the routine use of INO. Therefore, it is important to emphasize that no evidence from randomized trials is available to support application of INO in the clinical setting among children or adults.

The GRADE approach only reaffirmed our interpretation of the level of evidence, and we are confident that at this stage, the quality of evidence related to our outcomes is moderate to high, despite the fact that many trials have some risk of bias.

Implications for research

Large randomized trials with low risk of bias with a sample size of up to several thousand participants are needed to evaluate INO for adults and children before this intervention can be definitively rejected or accepted for critically ill patients with ALI and ARDS. However, current results are not promising, and the potential for benefit seems modest, with the actual point estimate of the intervention effect on mortality suggesting harm. Despite the heterogeneity that might exist in the patient population of included trials, and despite the high mortality rate among patients with ARDS and ALI, we believe that INO should be used as only one part of randomized clinical trials. Additional trials need to focus on other relevant outcomes, such as long-term survival, duration of stay in the intensive care unit and hospital, number of ventilator-free days and assessment of quality of life.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bronicki 2015

Methods	Prospective, multi-centre (9), placebo-controlled RCT ITT: no Sample size calculation reported
Participants	53 children from 44 weeks post-conceptional age to 16 years of age with oxygenation index (OI) ≥ 12; chest radiograph with pulmonary infiltrates; mechanically ventilated ≤ 7 days; with signed institutional research board–approved informed consent Exclusion criteria: immunocompromised host, history of bone marrow transplantation, active oncological condition, long-term (> 30 days) or recent (< 72 hours) high-dose glucocorticoids, right to left cardiac shunt, cardiovascular surgery within the past 14 days, status asthmaticus, treatment with INO or other investigational medications within 24 hours before study initiation, chronically ventilated, and decision by primary care physician to not provide full support
Interventions	INO group: 24 participants, 5 ppm INO until death, ventilator-free or at day 28 after enrolment (whichever came first) Control group: 29 participants, 5 ppm nitrogen

Bronicki 2015 *(Continued)*

	Gas initiation and daily gas manipulation performed by study therapist. Ventilation strategy and weaning of INO standardized CMV management: low-volume tidal strategy (4 to 8 mL/kg and plateau pressure < 30 cm H_2O); PEEP based on serial chest radiographs (every 6 to 12 hours) with the goal of 8 ribs posteriorly. Target arterial blood gas values: SaO_2 88% to 95% with FiO_2 < 0.60; PaO_2 55 to 80 mm Hg; pH 7.25 to 7.40 HFOV settings: based on serial chest radiographs (as CMV); target FiO_2 and PaO_2 same as for CMV. FiO_2 weaned over mean airway pressure until FiO_2 < 0.60. Transfer to CMV before weaning Prone position ≥ 8 hours daily
Outcomes	Primary outcomes: ventilator-free days at 28 days after randomization Secondary outcomes: oxygen index at 4 and 12 hours, survival at 28 days, ECMO-free survival
Notes	Country: USA Participant enrolment from 2003 to 2005 Authors' conclusion: We found that INO led to a significant decrease in duration of ventilation and a significant increase in ECMO-free survival among paediatric patients with ARDS.Given the limitations of this study and of previous studies on children, the high mortality rate of ARDS among children and the findings of this trial, a larger, prospective, randomized controlled trial on the impact of INO on outcomes among children with ARDS is indicated Rate of ECMO-free survival: placebo group 51.7% vs intervention group 91.7%; 7 participants in the placebo group and 1 in the iNO group received ECMO Oxygenation index favoured INO at 4 and 12 hours, but findings became insignificant at 24 hours. Study authors provide no numbers in the manuscript Funded by industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization by central registry. Lack of information about sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Attending physician and care team blinded to study gas used and not allowed to manipulate blinded delivery system
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed until 28 days
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare versus protocol but appears to be free of selective reporting
Other bias	High risk	Study terminated prematurely owing to slow enrolment (planned 338 participants, enrolled 55 participants) Lack of explicit protocol for management of mechanical ventilation

Day 1997

Methods	Two-group parallel RCT, 1 centre ITT: no Overall study quality: high risk of bias
Participants	Twenty-four children with acute bilateral lung disease (chest x-ray infiltrates) requiring PEEP > 6 cm H_2O and FiO_2 > 0.5 for more than 12 hours. Enrolment ≤ 48 hours after meeting study criteria Exclusion criteria: unrepaired congenital heart defect or a poor neurological prognosis
Interventions	INO group: 12 participants, 10 ppm INO until ventilatory support was decreased to PEEP of 6 cm H_2O and FiO_2 of 0.5 Control group: 12 participants initially maintained on a regimen of conventional therapy alone. No placebo. After 24 hours, all participants received 10 ppm INO Ventilation at discretion of the clinician. No additional co-intervention described. No cross-over before 24 hours. INO therapy withdrawn in gradual decrements over a period of 6 hours
Outcomes	Primary outcomes: improved oxygenation (oxygenation index) or improved ratio of pulmonary vascular resistance to systemic vascular resistance (PVR/SVR) Secondary outcomes: mortality, adverse events, FiO_2, mean airway pressure (cm H_2O), pH, PCO_2 (mm Hg), PO_2 (mm Hg)
Notes	Country: USA Letter sent to study authors in June 2009. Reply received in June 2009 Length of follow-up: unclear. Mortality for longest follow-up was 6 in the INO group and 4 in the control group. As both groups received INO at the same concentration in the initial 24 hours, we have included only 24-hour mortality data in our analyses Study authors' conclusions: Pulmonary vascular resistance and systemic oxygenation are acutely improved by 10 ppm inhaled nitric oxide in some children with severe lung disease. However, sustained improvement in oxygenation may not occur during prolonged therapy. Thus, inhaled nitric oxide may have a limited therapeutic role in children with acute hypoxaemic respiratory failure Funding: not for profit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, no information provided
Allocation concealment (selection bias)	High risk	Blinded draw of 1 lot per participant
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting

Day 1997 *(Continued)*

Other bias	Unclear risk	No apparent other type of bias except that no sample size calculation was reported

Dellinger 1998

Methods	Prospective, phase 2, multi-centre, placebo-controlled RCT ITT: yes Overall study quality: low risk of bias despite funding bias Sample size calculation reported. Not powered to show statistically significant benefit for any outcome
Participants	Included: 177 adults from 30 centres with ARDS < 72 hours before randomization. ARDS defined by American-European Consensus Conference and minimal FiO_2 of 0.5 and minimal PEEP of 8 cm H_2O Exclusion criteria: pregnancy, < 18 years old, immunocompromised, sepsis-induced ARDS, > 20% body surface burns, persistent hypotension (inotropic support) and multi-system organ failure
Interventions	NO group: 120 participants at doses of 1.25, 5, 20, 40 or 80 ppm, for 28 days or until extubation Control group: 57 participants, placebo gas (nitrogen) Ventilation strategy and weaning of INO standardized (plateau airway pressure < 35 cm H_2O; PEEP to optimize compliance; FiO_2 minimized). No cross-over of treatment failures
Outcomes	Primary outcomes: duration of mechanical ventilation Secondary outcomes: changes in oxygenation (PaO_2, PaO_2/FiO_2, OI), percent responders, mortality, number of participants alive and off ventilator at 28 days, decrease in mean PA pressure, adverse events, methaemoglobin, hypotension, renal failure, pneumothorax
Notes	Country: USA Letter sent to study authors in June 2009. No reply received Follow-up: 28 days. Treatment stopped before oxygenation threshold criteria were reached in 56 participants. 20 participants in INO group received steroids after day 6, and only 6 in the control group received steroids. Only 8 participants received 80 ppm INO; 80 ppm INO dose was eliminated mid-study because international consensus suggests an unlikely advantage over lower concentrations. Data accounted for in analysis. Post hoc assessment for ventilator-free days. Not stratified for origin Data on ventilator-free days for the INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007) Study authors' conclusions: "Inhaled NO appears to be well tolerated in the population of ARDS patients studied. With mechanical ventilation held constant, inhaled NO is associated with a significant improvement in oxygenation compared with placebo over the first 4 hrs of treatment. An improvement in oxygenation index was observed over the first 4 days. Larger phase III studies are needed to ascertain if these acute physiologic improvements can lead to altered clinical outcome"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked for each site, unclear method. Considered adequate
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias)	Low risk	Clinicians and outcome assessors blinded during entire course of the trial. One unblinded investigator at each site, responsible for determining treatment al-

Dellinger 1998 *(Continued)*

All outcomes		location for each participant by using a supplied masked randomization code and daily recording of NO, NO_2 and methaemoglobin concentrations. These values were kept strictly confidential
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Low risk	No apparent bias except funding bias (industry)

Dobyns 1999

Methods	Prospective, multi-centre, placebo-controlled RCT ITT: not stated Overall study quality: low risk of bias despite no information on sample size calculation
Participants	108 children > 1 month old, from 7 centres, median age 2.5 years, with acute hypoxaemic respiratory failure and oxygenation index > 15, × 2 values within 6 hours and chest infiltrates Exclusion criteria: congenital heart disease, cardiac surgery within 14 days and treatment considered futile
Interventions	INO group: 53 children, 10 ppm for 3 days, then weaned if failure criteria not met. Maximum of 7 days after entry Control group: 55 children, placebo gas (air) Usual care in both groups. Ventilation strategy and weaning of gas standardized (peak airway pressure < 35 to 40 cm H_2O, tidal volume limitation, titrated PEEP, high-frequency oscillatory ventilation by clinician discretion). Cross-over of participants meeting treatment failure criteria Follow-up: 7 days
Outcomes	Primary outcome: acute effect on oxygen index and PaO_2/FiO_2 Secondary outcomes: rate of decline in oxygenation; oxygenation, PEEP, MAP, mortality, adverse event, methaemoglobin and NO_2 levels
Notes	Countries: USA and UK Letter sent to study authors in June 2009. Reply received in June 2009. No additional data supplied 27 participants from the control group received INO. Two dropouts from the control group Post hoc analysis of immunocompromised participants. Follow-up unclear, but ventilation data reported at day 108 Additonal data on PaO_2/FiO_2, duration of mechanical ventilation and oxygenation index provided in Dobyns 2002 based on mode of ventilation (high-frequency oscillatory ventilation (HFOV) and conventional mechanical ventilation (CMV)). Participants were divided into 4 groups (HFOV, HFOV + INO, CMV, CMV + INO). Data for our meta-analyses of PaO_2/FiO_2 up to 72 hours, duration of mechanical ventilation and oxygenation index at 72 hours provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007) Study not stratified for origins. According to data provided by Adhikari 2007, this trial fulfils the criteria set by American-European Consensus Conference for ARDS

Dobyns 1999 *(Continued)*

	Study authors' conclusions: "INO causes an acute improvement in oxygenation in children with severe AHRF. Two subgroups (immunocompromised and an entry oxygen index > 25) appear to have a more sustained improvement in oxygenation, and we speculate that these subgroups may benefit from prolonged therapy" Trial funded by industry Funding: not for profit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Appears adequate, randomization cards, type not stated
Allocation concealment (selection bias)	Low risk	Envelopes sealed, sequentially numbered and opaque
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinicians and outcome assessors blinded during entire course of the trial. One unblinded investigator (respiratory therapist or nurse) at each site determined treatment allocation for each participant and monitored INO and NO_2 concentrations
Incomplete outcome data (attrition bias) All outcomes	Low risk	Yes. Appears to have complete follow-up during trial period
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias, except that no sample size calculation reported

Gerlach 2003

Methods	Two-group parallel RCT, 1 centre Follow-up: adequate. No post-trial follow-up ITT: yes Overall study quality: high risk of bias
Participants	40 adults with ARDS according to American-European Consensus Conference: $FiO_2 \geq 0.6$, $PaO_2/FiO_2 \leq$ 150 mm Hg, PEEP ≥ 10 cm H_2O, PAOP ≤ 18 mm Hg No exclusion criteria defined specifically Median duration of ventilation before randomization: 5.3 vs 5.9 days (INO vs control)
Interventions	INO group: 20 participants, 10 ppm with daily dose response analysis until weaning initiated Control group: 20 participants, no placebo Standard care according to standardized protocols. No cross-overs. Protocols for prone position (4 to 6 hours), extracorporeal membrane oxygenation (ECMO), permissive hypercapnia and measures to reduce pulmonary oedema
Outcomes	Primary outcomes: PaO_2/FiO_2, mean pulmonary artery pressure, FiO_2 reduction

Gerlach 2003 *(Continued)*

	Secondary outcomes: duration of ventilation, intensive care unit stay, ECMO use, additional organ failure, mortality, cardiac index, central venous pressure, mean arterial pressure, various respiratory pressures, MPAP, PCWP
Notes	Country: Germany Letter sent to study authors in June 2009. No reply received Length of follow-up: unclear, but data for length of stay reported at day 91 Study authors' conclusion: "Long-term inhaled NO with constant doses of 10 ppm leads to enhanced sensitivity" Funding: not for profit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Low risk	Drawing a closed lot. Envelopes sealed and sequentially numbered and opaque
Blinding (performance bias and detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow up: adequate. No post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias except that no sample size calculation reported

Ibrahim 2007

Methods	Two-group parallel RCT, 1 centre ITT: no Overall study quality: high risk of bias
Participants	32 children 8 weeks to 10 years of age with the diagnosis of ARDS and on mechanical ventilation (PaO_2/FiO_2 ≤ 200 mm Hg, positive inspiratory pressure ≥ 30 cm H_2O, FiO_2 ≥ 0.5 for > 12 hours), divided into 3 groups. Study period of 24 hours Exclusion criteria: cardiac or neurological disease (cyanotic), chest or abdominal trauma, neurological surgeries, haemodynamic instability, extracorporeal membrane oxygenation
Interventions	INO group with children in supine position during 24-hour study period: 11 participants INO group with children in prone position during 24-hour study period: 11 participants INO used continuously for 20 hours (5 ppm for 18 hours, then decreased to 1 ppm in the last 2 hours) INO administered at 5 ppm for 18 hours, then decreased to 1 ppm

Ibrahim 2007 *(Continued)*

	Control group: 10 participants kept in prone position for 20 hours, then back to supine position for remaining 4 hours. No placebo. No cross-overs Standard care. Lung protective strategy (tidal volume 5 to 10 mL/kg), permissive hypercapnia ($PaCO_2$ > 50 mm Hg) as long as arterial pH > 7.2. Ventilation and weaning protocol for all participants
Outcomes	PaO_2/FiO_2, oxygenation index, methaemoglobin, NO_2, critical incidents related to prone position or repositioning
Notes	Country: Egypt Letter sent to study authors in June 2009. No reply received. Two children withdrawn from the trial and did not have oxygenation measured For PaO_2/FiO_2 and oxygenation index meta-analyses, we have chosen to include data from the control group (prone position) and INO with prone position group, thus having the same co-intervention (prone position). No mortality data provided. Although bilateral infiltrates are not explicitly mentioned as a criterion for inclusion, it does appear from reading the article that they have been used clinically to include participants. Thus this trial has been characterized as fulfilling the American-European Consensus Conference definition of ARDS Length of follow-up: 24 hours Study authors' conclusion: "The present study showed that in mechanically ventilated paediatric patients with ARDS, the combined use of prone position and INO is safe and has an additive effect, which causes a greater sustained improvement in oxygenation than either treatment strategy alone" Funding: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, no information provided
Allocation concealment (selection bias)	High risk	Alternate allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias except that no sample size calculation or funding reported

Lundin 1999

Methods	Prospective, multi-centre, open, phase 3 RCT ITT: yes Overall study quality: high risk of bias

Lundin 1999 *(Continued)*

	Sample size calculation reported
Participants	After a test response to INO, 180 adult INO responders with ALI (unilateral or bilateral lung infiltrates, ventilated for 18 to 96 hours with PaO_2/FiO_2 < 165 mm Hg, PEEP > 5 cm H_2O, MAP > 10 cm H_2O, pressure- or volume-controlled ventilation and I:E ratio between 1:2 and 2:1) were randomized. Duration of ventilation before randomization: 0.75 to 4 days Exclusion criteria: pregnancy, age < 18 years, mechanical ventilation > 10 days or ventilator treatment > 96 hours at FiO_2 > 0.5, independent lung ventilation, ongoing high-dose vasodilators, treatment with extracorporeal lung assist, malignancy, severe heart failure, ongoing intracranial haemorrhage, AIDS, immunocompromised, chronic renal, liver or pulmonary disease
Interventions	INO group: 93 participants randomized after INO test response with 2, 10, 40 ppm for 10 minutes daily until response, up to 30 days. Considered responders if positive PaO_2 increased by 25% (20% after protocol amendment). When randomized, participants received 1 to 40 ppm INO at the lowest effective dose for up to 30 days, or until endpoint was reached. Mean INO dose was 9 ppm, and mean number of days of INO was 9 Control group: 87 participants, no placebo gas Ventilation strategy and weaning of test gas was performed according to usual standards of care of each hospital. Cross-over of treatment failures allowed
Outcomes	Primary outcome: reversal of ALI Secondary outcomes: reduction of frequency of severe respiratory failure, mortality, ICU and hospitalisation status at 30 and 90 days, safety (methaemoglobinaemia, organ failure), reduction in days to reverse ALI
Notes	Country: multi-centre (43) European study, main country Sweden Letter sent to study authors in June 2009. No reply received Powered for 600 participants, stopped early because of slow recruitment. 268 patients were evaluated but only 67% were included on the basis of INO response. Protocol amendment after 140 participants randomized. Stratified per study centre and to APACHE II for 140 participants, then according to hypoxia score (PaO_2/FiO_2 ratio) for remaining participants. Post hoc analysis of reversal of ALI (participants alive and off ventilator over time). 6 participants in the control group received NO. Length of follow-up: 90 days Study authors defined severe respiratory failure (SRF) as follows: "FiO_2 > 0.9 with PaO_2 < 8 kPa in three blood gas analyses each 4 hours apart, with pressure controlled/limited ventilation, respiratory frequency between 5 and 30, a PEEP ≥ 10 cmH_2O and mean airway pressure ≥20 cmH_2O. SRF could also be defined as two arterial blood gases 2 hours apart at a FiO_2 ≥ 1.00 resulting in a PaO_2 < 6 kPa." Additionally, reversal of ALI was defined as participants on ventilator/mask CPAP system, PEEP ≤ 5 cm H_2O, PaO_2/FiO_2 > 31 kPa if < 60 years and PaO_2/FiO_2 > 29 kPa if > 60 years Additional data on duration of mechanical ventilation provided by Dr. Neill Adhikari, who extracted data from a Kaplan-Meier curve of participants alive and off mechanical ventilation over time (Adhikari 2007) Study authors' conclusion: "Improvement of oxygenation by INO did no increase the frequency of reversal of ALI. Use of inhaled NO in early ALI did not alter mortality although it did reduce the frequency of severe respiratory failure in patients developing severe hypoxaemia" Funding: funded in part by industry

Risk of bias

Bias	Authors' judgement	Support for judgement

Lundin 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	Central computer randomization
Allocation concealment (selection bias)	Low risk	Central computer allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, 90 days
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	High risk	Powered for 600 participants, stopped early because of slow recruitment. 268 patients evaluated, but only 67% included on the basis of INO response. Protocol amendment after 140 participants randomized

Mehta 2001

Methods	Two-group parallel RCT, 1 centre Follow-up: adequate. No post-trial follow-up ITT: no Overall study quality: high risk of bias Sample size calculation reported
Participants	14 adults with ARDS ≤ 5 days, bilateral chest infiltrates, PaO_2/FiO_2 < 200 mm Hg, PAOP < 18 cm H_2O, PEEP ≥ 8 cm H_2O Exclusion criteria: intravenous nitroglycerin or prostacyclin, high-dose corticosteroids (> 10 mg methylprednisolone per day), unconventional modes of mechanical ventilation (e.g. high-frequency ventilation, prone position), myocardial infarction < previous 72 hours, 2,3-DPG deficiency, entry criteria > 5 days
Interventions	INO group: 8 participants, daily titration for 4 days of INO at 5, 10 and 20 ppm for 30 minutes at each dose, with the dose resulting in use of the highest PaO_2/FiO_2 until the following day. INO continued until PaO_2/FiO_2 > 200 mm Hg on FiO_2 < 0.5. Mean duration of INO treatment 8 days Control group: 6 participants, no placebo gas, conventional therapy Usual care for all participants. No cross-overs
Outcomes	PaO_2/FiO_2, peak inspiratory pressure, PEEP, cardiac output, oxygen delivery index, mean arterial pressure, heart rate, PAOP, central venous pressure, systemic and pulmonary vascular resistances, arterial blood gas values, methaemoglobin, NO_2, mortality, adverse events
Notes	Country: USA Letter sent to study authors in June 2009. Reply received in June 2009 Additional data on ventilator-free days, duration of mechanical ventilation, PaO_2/FiO_2; oxygenation index for the INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007). Length of follow-up unclear, data on ARDS duration provided for day 25

Mehta 2001 *(Continued)*

Study authors' conclusion: "In patients with ARDS, NO reduces mean pulmonary artery pressure and improves oxygenation acutely but fails to improve these variables beyond 24 hours"

Funding: financed in part by industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence
Allocation concealment (selection bias)	High risk	At the time of randomization, investigator was granted access to entire randomization list
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor medical personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess degree of follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent bias except funding bias (financed in part by industry)

Michael 1998

Methods	Two-group parallel RCT, 1 centre ITT: no Overall study quality: high risk of bias Sample size calculation reported
Participants	40 adults and children 1 to 79 years of age. Only 3 participants younger than 18 years of age. ARDS defined by American-European Consensus Conference, except PaO2/FiO2 < 150 mm Hg and FiO_2 > 0.8 for ≥ 12 hours or 0.65 for ≥ 24 hours Exclusion criteria: pregnancy, patients not expected to survive hospitalisation because of underlying disease such as active malignancy, heart failure or left atrial hypertension Time period of study: January 1994 to June 1996
Interventions	INO group: 20 participants, increasing doses of INO each 6 hours (at 5, 10, 15, and 20 ppm) for 24 hours, then clinically adjusted. Mean dose of INO was 13 ppm. INO tapered if oxygenation did not improve by 72 hours Control group: 20 participants. No placebo gas All participants received conventional therapy. Mode of ventilation remained unchanged throughout the study period, with similar PEEP between groups for 72 hours. Cross-over in case of treatment failure, pre-defined criteria for clinical deterioration
Outcomes	Primary outcomes: improvement in oxygenation within 72 hours of treatment, correlation between changes in PaO_2/FiO_2 ratio acutely and after 72 hours

Michael 1998 *(Continued)*

	Secondary outcomes: PEEP, PaO_2, FiO_2, PaO_2/FiO_2, respiratory compliance, pulmonary artery pressure, central venous pressure, pulmonary and systemic vascular resistance and mortality, adverse events, methaemoglobin levels, bleeding diathesis
Notes	Country: USA Letter sent to study authors in June 2009. No reply received. Length of follow-up unclear, but data on ARDS duration were provided for day 25 Two participants in control group received INO before 72 hours, and seven received INO after 72 hours Powered to detect 35% to 40% difference in frequency of persistent decrease in $FiO_2 \geq 0.15$, not mortality Study authors' conclusion: "In patients with severe ARDS, our results indicate that INO does not lead to sustained improvement in oxygenation as compared with conventional therapy" Funding: not for profit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized within each ICU with balanced blocks of 14 participants
Allocation concealment (selection bias)	Unclear risk	Unclear, no information provided
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Low risk	Appears to be free of other types of bias

Park 2003

Methods	Three-group parallel RCT, 1 centre ITT: no Overall study quality: high risk of bias
Participants	23 adults with ARDS defined by American-European Consensus Conference Exclusion criteria: COPD, cardiac disease
Interventions	INO and lung recruitment manoeuvre (LRM) group: 11 participants, 5 ppm, and 1 LRM 2 hours after INO treatment initiation, twice daily; mean duration of INO treatment 3.5 days. No stopping criteria reported INO group: 6 participants received INO 5 ppm, mean duration of INO treatment 8.2 days

Park 2003 *(Continued)*

	Control group: 6 participants, LRM twice daily, no placebo gas Standard care for all participants. Weaning protocol. Ventilation protocol (LRM with inflation pressure of 30 to 35 cm H_2O for 30 seconds, volume control mode, tidal volume of 6 mL/kg ideal body weight, respiratory rate 20 to 25/min, plateau airway pressure ≤ 30 cm H_2O, PEEP to optimize PaO_2, FiO_2 minimized). No cross-overs. No prone position
Outcomes	Mechanical variables, mortality, blood pressure, heart rate, central venous pressure, mean pulmonary arterial pressure, pulmonary artery occlusion pressure, cardiac index. No data on distinction between primary vs secondary outcomes
Notes	Country: South Korea Letter sent to study authors in June 2009. Reply received in June 2009 Mortality data from groups 1 and 3 were combined, as we considered use of the recruitment maneuver as standard care. We have included data from INO + LRM group vs control group in meta-analyses of PaO_2/FiO_2. Length of follow up: 28 days Additional data on ventilator-free days, duration of mechanical ventilation, PaO_2/FiO_2; oxygenation index for the INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007) Study authors' conclusion: "the combined application of NO inhalation and recruitment maneuver could be beneficial and safe for patients with ARDS, showing an enhancing effect in improvement of oxygenation" Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, no information provided
Allocation concealment (selection bias)	High risk	Inadequte. One random number generated when patient eligible
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias except that no sample size calculation or funding reported

Payen 1999

Methods	Two-group parallel RCT, 23 centres ITT: yes Overall study quality: low risk of bias, despite publication bias (not published)

Payen 1999 *(Continued)*

	Sample size calculation reported
Participants	203 adults (> 15 years old) with ARDS according to American-European Consensus Conference and Murray Score, range 2 to 3 Exclusion criteria: pregnancy, chronic respiratory insufficiency, haemorrhagic disorder, malignancy, haematological disease
Interventions	INO: 98 participants, fixed INO of 10 ppm until oxygenation and PEEP criteria were met with median INO administration of 5 days Control group: 105 participants, placebo gas (nitrogen) Various ventilation guidelines were applied. Cross-overs when treatment failure
Outcomes	Primary outcome: participants alive and off mechanical ventilation at day 28 Secondary outcomes: 28-day mortality and at hospital discharge, duration of mechanical ventilation, proportion of participants weaned from adjunctive inhaled therapy, proportion of participants with a shift of inhaled gas before day 28, methaemoglobin, N_2O, haemodynamics, oxygenation variables, PEEP levels, length of stay in hospital
Notes	Country: France This trial was published only as an abstract. Letter sent to study authors in April and June 2009. Reply received in April and June 2009. Additional and valuable information received (unpublished manuscript). 19 participants in the control group and 12 in the INO group crossed over. Length of follow-up: 90 days Additional data on ventilator-free days, duration of mechanical ventilation, PaO_2/FiO_2, oxygenation index for the INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007) Study authors' conclusion: "In ARDS patients (Murray score 2-3), 10 ppm of NO did not alter either duration of mechanical ventilation, 28 day mortality, or clinical worsening of their ARDS" Funding: not for profit, industry supplied gas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer randomization
Allocation concealment (selection bias)	Low risk	Adequate, central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate, blinding of participants, caregivers, data collectors, assessors of outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	High risk	Publication bias. This trial was not published

Schwebel 1997

Methods	Two-group parallel RCT, multi-centre (17 centres) Overall study quality: high risk of bias Sample size calculation not reported
Participants	19 participants with ARDS defined by PaO_2/FiO_2 < 200, 6 < PEEP < 10, 10 < pulmonary capillary wedge pressure < 18 and ≥ 1 infiltrate on chest x-ray Exclusion criteria: COPD, haemodynamic instability
Interventions	INO group: 9 participants, 10 ppm INO for 17 hours, then at the clinician's discretion. Mean INO treatment 4.6 days Control group: 10 participants, placebo gas (nitrogen) Standard care. Fixed mechanical ventilation. If PaO_2/FiO_2 < 100 before 17 hours of treatment, crossover and thereafter clinician free to add NO, other technic, or to change respiratory variables
Outcomes	Haemodynamics, PaO_2/FiO_2, arterial oxygenation and other gas exchange variables, methaemoglobin
Notes	Country: France, 17 centres Published only as abstract. At least 5 participants in the control group received INO Letter sent to study authors in June 2009. Reply received in June 2009. No data on length of follow-up. No data on mortality Additional data on ventilator-free days, duration of mechanical ventilation, PaO_2/FiO_2; oxygenation index for the INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007) Study authors' conclusion: "Beneficial effects of inhaled NO on arterial oxygenation may be delayed, not necessary related to high baseline PVR level, as it has been previously suggested by uncontrolled studies. Delayed NO administration still improve gas exchanges. Finally this prospective trial is in favour of early clinical use of inhaled NO in ALI" Funding: not for profit, industry supplied gas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, no information provided
Allocation concealment (selection bias)	Low risk	Table of gas cylinder codes revealed in sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinicians and outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear follow-up
Selective reporting (reporting bias)	High risk	No data on mortality provided in the abstract although this was an outcome

Schwebel 1997 *(Continued)*

Other bias	High risk	Publication bias (published only as an abstract)

Taylor 2004

Methods	Prospective, phase 2, multi-centre (46 centres), placebo-controlled RCT ITT: yes Overall study quality: low risk of bias despite funding bias Sample size calculation reported
Participants	385 adults with moderately severe acute lung injury due to causes other than severe sepsis (modified American-European Consensus Conference definition): $PaO_2/FiO_2 \leq 250$, regardless of amount of PEEP, bilateral infiltrates on frontal chest radiograph, PAOP ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension, FiO_2 of 0.5 to 0.95 or set PEEP ≥ 8 cm H_2O Exclusion criteria: pregnancy, age ≤ 18 years, ALI > 72 hours, sepsis-induced ARDS, non-pulmonary organ system dysfunction at randomization, history of immunocompromise, persistent systemic hypotension and shock
Interventions	INO: 192 participants, INO at 5 ppm until end of trial (28 days) Control: 193 participants, placebo (nitrogen gas), until end of trial (28 days) or until oxygenation and PEEP criteria were met Standard care, ventilation and weaning protocol for both groups. No cross-overs
Outcomes	Primary outcome: days alive and off assisted breathing to day 28 Secondary outcomes: mortality, days alive and meeting oxygenation criteria for extubation, days alive following a successful unassisted ventilation test, adverse events, methaemoglobin, NO_2, oxygenation
Notes	Country: USA. 46 centres Letter sent to study authors in June 2009. No reply received One-year follow-up data published as Angus 2006. Letter sent to study authors in June 2009 and reply received in 2009. No additional data provided 10 participants in INO group and 14 in control group received prone position ventilation Study authors' conclusion: "Inhaled nitric oxide at a dose of 5 ppm in patients with acute lung injury not due to sepsis and without evidence of non-pulmonary organ system dysfunction results in short-term oxygenation improvements but has no substantial impact on the duration of ventilatory support or mortality" Funding: funded by industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer randomization
Allocation concealment (selection bias)	Low risk	Adequate, central allocation
Blinding (performance bias and detection bias)	Low risk	Blinding of participants, caregivers, data collectors, assessors of outcomes and data analysts (triple-blind)

Taylor 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up sufficient during the trial period. However, Angus 2006 describes 1-year follow-up of the same trial, and some participants were lost to follow-up. Despite this fact, this is the only trial with long-term follow-up, thus we have labelled it as having complete outcome data
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias except possible funding bias (industry)

Troncy 1998

Methods	Prospective, single-centre RCT ITT: yes Overall study quality: high risk of bias
Participants	Included: 30 participants with ARDS, between 18 and 75 years of age. Lung injury score minimum 2.5 Exclusion criteria: pregnancy, severe immunosuppression from end-stage neoplasia, pulmonary capillary wedge pressure > 18 mm Hg
Interventions	INO group: 15 participants, with increasing doses initially from 2.5, 5, 10, 20, 30 to 40 ppm every 10 minutes and daily re-titration until oxygenation and PEEP criteria were met Mean duration of INO treatment 8 days and mean dose 5.3 ppm Control group: 15 participants, no placebo gas Standard care and no cross-overs. Ventilation strategy and weaning of INO standardized (tidal volume of 10 mL/kg, goal $PaCO_2$ 35 to 45 mm Hg, maximum PEEP 15 cm H_2O, goal PaO_2 > 85 mm Hg, no prone position). Standardized protocols for sedation, curarization, intravenous perfusion, blood transfusion, parenteral or enteral feeding
Outcomes	Primary outcomes: therapeutic failure, death before 30 days, continued ventilation after 30 days, effects of INO on lung function Secondary outcomes: lung compliance, pulmonary arterial pressure, PaO_2, $PaCO_2$, pH, bicarbonate, volume dead space/tidal volume, alveolar-arterial oxygen difference, cardiac output, adverse events, methaemoglobin levels
Notes	Country: Canada Letter sent to study authors in June 2009. No reply received. Length of follow-up: 30 days Additional data on ventilator-free days, duration of mechanical ventilation, PaO_2/FiO_2; oxygenation index for INO group provided by Dr. Neill Adhikari on the basis of his work on his recent systematic review in BMJ (Adhikari 2007). Troncy et al reported duration of ventilation but assigned participants who died a duration of ventilation of 30 days. Adhikari et al assumed that all participants who died before day 30 were ventilated and derived the mean number of ventilator-free days to 30 days Study authors' conclusion: "This study shows that inhNO, in this population, may improve gas exchange but does not affect mortality" Funding: not for profit

Risk of bias

Troncy 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, no information provided
Allocation concealment (selection bias)	High risk	Inadequate, sealed envelopes sequentially numbered and opaque
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear, no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: adequate, no post-trial follow-up
Selective reporting (reporting bias)	Low risk	Yes. Unable to compare with protocol but appears to be free of selective reporting
Other bias	Unclear risk	No apparent other type of bias except no sample size calculation reported

AHRF: acute ischaemic heart failure; AIDS: acquired immune deficiency syndrome; ALI: acute lung injury; APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: acute respiratory distress syndrome; BMJ: British Medical Journal; cm: centimetre; CMV: continuous mandatory ventilation; COPD: chronic obstructive pulmonary disease; DPG: diphosphoglycerate; ECMO: extracorporeal membrane oxygenation; FiO_2: inspired fraction of oxygen; HFOV: high-frequency oscillatory ventilation; ICU: intensive care unit; INO: inhaled nitric oxide; ITT: intention-to-treat; kg: kilogram; kPa: kilopascal; LRM: lung recruitment manoeuvre; MAP: mean arterial pressure; mL: millilitres; mm Hg: millimetre of mercury; MPAP: mean pulmonary artery pressure; NO: nitric oxide; NO_2: nitrogen dioxide; OI: oxygen index; PA: pulmonary artery; PAOP: pulmonary artery occlusion pressure; PCO_2: partial pressure of carbon dioxide; PCWP: pulmonary capillary wedge pressure; PEEP: positive end-expiratory pressure; pH: potential hydrogen; PO_2: partial pressure of oxygen; ppm: parts per million; PVR: pulmonary vascular resistance; RCT: randomized controlled trial; SaO_2: peripheral capillary saturation; SRF: severe respiratory failure; SVR: systemic vascular resistance; vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cuthbertson 2000	Two-group parallel RCT, 1 centre. ITT: no evaluation of reversal of ALI in participant receiving INO compared with participant given no treatment other than conventional therapy. Study excluded because most participants (24 of 30 randomized) were included in a European multi-centre study (Lundin 1999) and therefore would be counted twice if both studies were included
Johannigman 1997	Prospective non-blinded RCT, evaluating clinical response to 4 randomly administered concentrations (1, 15, 30 and 60 ppm) of INO, each for a 3-hour period in 20 adults with ARDS. Study excluded because of short period of treatment and documentation of outcomes only up to 3 hours. Method of randomization and blinding to doses of administered gas unclear
Khan 2009	Prospective, randomized, cross-over pilot trial comparing nitric oxide and prostacyclin in the treatment of pulmonary hypertension, refractory hypoxaemia and right ventricular dysfunction in thoracic transplant recipients. Study excluded owing to inclusion of a different patient category
Meade 2003	Prospective placebo-controlled RCT enrolling 84 participants to evaluate effects of inhaled NO (20 ppm NO or nitrogen) initiated 10 minutes after reperfusion on outcomes after lung transplantation. Study excluded owing to different patient category, diagnosis and outcomes

Study	Reason for exclusion
Perrin 2006	Prospective RCT with 32 double-lung transplant recipients randomized to control or to 20 ppm INO at the time of reperfusion. Study excluded owing to different patient category, diagnosis and outcomes
Puybasset 1994	Prospective non-blinded RCT to determine the dose-response curve of inhaled INO in 6 adult participants with ARDS. 8 concentrations of inhaled NO administered at random: 100, 400, 700, 1000, 1300, 1600, 1900 and 5000 parts per billion (ppb), with measurements made after 20 minutes of exposure. Study excluded because of short-term administration of INO and assessment at 20 minutes post treatment only
Puybasset 1995	Prospective RCT examining effects of INO with and without PEEP in 21 adults with ARDS. Excluded because of short-term documentation of outcomes and short-term administration of INO at 30 minutes post stabilization only
Rossaint 1995	Prospective non-blinded RCT in which 10 adult participants with ARDS in random sequence inhaled NO at a concentration of 18 parts per million (ppm) followed by 36 ppm, and received an intravenous infusion of prostaglandin PGI2 (4 ng/kg/mn) compared with conventional therapy. Study excluded as intravenous prostacyclin was included in the treatment regimen, because it is an active intervention not provided to the control group
Tang 1998	Prospective non-blinded RCT examining effects of 3 concentrations of INO (1, 10 and 20 parts per million (ppm) in random order) for 12 children with ARDS. Study excluded because measurements were taken 1 hour after administration of study gas only

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; INO: inhaled nitric oxide; ITT: intention-to-treat; kg: kilogram; mn: minutes; NO: nitric oxide; PEEP: positive end-expiratory pressure; PGI: prostaglandin; ppb: parts per billion; ppm: parts per million; RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Godinez

Trial name or title	Nitric Oxide Administration for Acute Respiratory Distress Syndrome
Methods	Prospective, 1-centre, group-controlled RCT
Participants	52 children from 1 month to 18 years of age, mechanically ventilated with PaO_2/FiO_2 ratio ≤ 100, FiO_2 ≥ 0.60, PEEP ≥ 10 and Murray score ≥ 2.5 Exclusion criteria: neonates (1 week to 28 days) and/or patients on extracorporeal membrane oxygenation
Interventions	INO group: 28 participants; 10 ppm NO for 4 hours; initiation after 4 hours Control group: 24 participants; no intervention; initiation after administration of INO for 4 hours (then stop)
Outcomes	Primary outcome: mean PaO_2/FiO_2 ratio Secondary outcomes: duration of FiO_2 > 0.60, effect of early vs delayed onset of NO therapy, evaluation of characteristics of patients who respond to NO compared with those who do not
Starting date	October 14, 2005
Contact information	Richard Lin, The Children's Hospital of Philadelphia; e-mail: linr@email.chop.edu

Godinez *(Continued)*

Notes	According to the data available on ClinicalTrials.gov, the study was completed in February 2006. However, no results have been published so far. We tried to contact study authors but unsuccessfully.

FiO_2: fraction of inspired oxygen;
INO: inhaled;
NO: nitric oxide;
PaO_2: partial pressure of oxygen in arterial blood;
PEEP: positive end-expiratory pressure;
RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Mortality: INO versus control group

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall mortality: INO vs control	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
2 28- to 30-day mortality: INO vs control	9	1105	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
3 Mortality: subgroup analysis, paediatric vs adult population	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
3.1 Paediatric	3	185	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.51, 1.18]
3.2 Adult	10	1058	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.25]
4 Mortality: subgroup analysis based on duration of drug administration	12	1190	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.92, 1.22]
4.1 Shorter than median duration of INO	5	394	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
4.2 Longer than median duration of INO	7	796	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.29]
5 Sensitivity analysis: excluding abstracts, INO vs control	11	1021	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.21]
6 Sensitivity analysis: excluding trials not fulfilling AECC criteria, INO vs control	10	834	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]

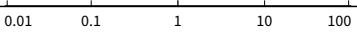
Analysis 1.1. Comparison 1 Mortality: INO versus control group, Outcome 1 Overall mortality: INO vs control.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bronicki 2015	2/24	8/29		3.2%	0.3[0.07,1.29]
Day 1997	1/12	2/12		0.88%	0.5[0.05,4.81]
Dellinger 1998	35/120	17/57		10.18%	0.98[0.6,1.59]
Dobyns 1999	22/53	24/55		10.41%	0.95[0.61,1.47]
Gerlach 2003	3/20	4/20		1.77%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		17.35%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		1.51%	1[0.35,2.88]
Michael 1998	11/20	9/20		3.98%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.31%	1.41[0.41,4.87]
Payen 1999	53/98	53/105		22.61%	1.07[0.82,1.39]
Schwebel 1997	0/9	0/10			Not estimable
Taylor 2004	54/165	53/167		23.27%	1.03[0.75,1.41]
Troncy 1998	9/15	8/15		3.53%	1.13[0.6,2.11]
Total (95% CI)	**654**	**589**		**100%**	**1.04[0.9,1.19]**
Total events: 250 (INO), 221 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.92, df=11(P=0.93); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					

Favours experimental — Favours control

Analysis 1.2. Comparison 1 Mortality: INO versus control group, Outcome 2 28- to 30-day mortality: INO vs control.

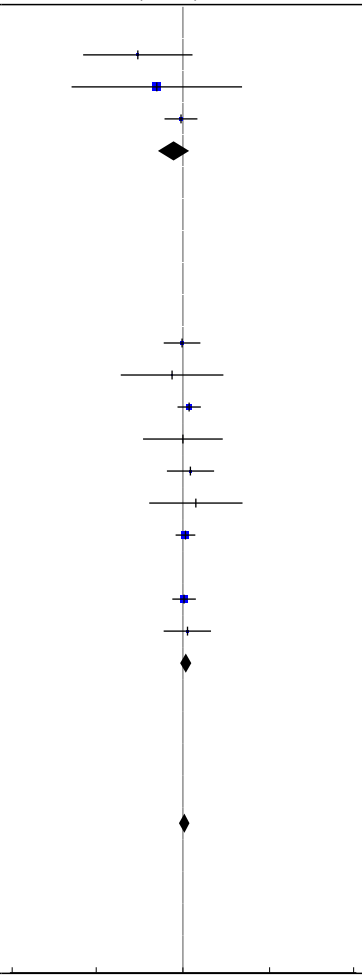
Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bronicki 2015	2/24	8/29		4.21%	0.3[0.07,1.29]
Dellinger 1998	35/120	17/57		13.4%	0.98[0.6,1.59]
Lundin 1999	41/93	35/87		21.02%	1.1[0.78,1.55]
Mehta 2001	4/8	2/6		1.33%	1.5[0.4,5.65]
Michael 1998	11/20	9/20		5.23%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.72%	1.41[0.41,4.87]
Payen 1999	48/98	46/105		25.82%	1.12[0.83,1.5]
Taylor 2004	44/192	39/193		22.61%	1.13[0.77,1.66]
Troncy 1998	9/15	8/15		4.65%	1.13[0.6,2.11]
Total (95% CI)	**587**	**518**		**100%**	**1.08[0.92,1.27]**
Total events: 202 (INO), 166 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.82, df=8(P=0.87); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					



Favours experimental — Favours control

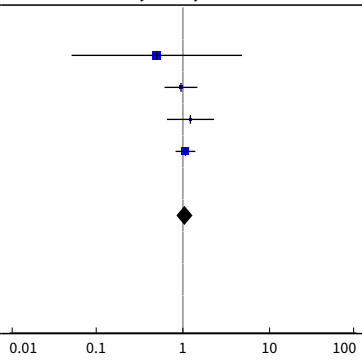
Analysis 1.3. Comparison 1 Mortality: INO versus control group, Outcome 3 Mortality: subgroup analysis, paediatric vs adult population.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Paediatric					
Bronicki 2015	2/24	8/29		3.2%	0.3[0.07,1.29]
Day 1997	1/12	2/12		0.88%	0.5[0.05,4.81]
Dobyns 1999	22/53	24/55		10.41%	0.95[0.61,1.47]
Subtotal (95% CI)	**89**	**96**		**14.49%**	**0.78[0.51,1.18]**
Total events: 25 (INO), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.57, df=2(P=0.28); I^2=22.27%					
Test for overall effect: Z=1.17(P=0.24)					
1.3.2 Adult					
Dellinger 1998	35/120	17/57		10.18%	0.98[0.6,1.59]
Gerlach 2003	3/20	4/20		1.77%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		17.35%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		1.51%	1[0.35,2.88]
Michael 1998	11/20	9/20		3.98%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.31%	1.41[0.41,4.87]
Payen 1999	53/98	53/105		22.61%	1.07[0.82,1.39]
Schwebel 1997	0/9	0/10			Not estimable
Taylor 2004	54/165	53/167		23.27%	1.03[0.75,1.41]
Troncy 1998	9/15	8/15		3.53%	1.13[0.6,2.11]
Subtotal (95% CI)	**565**	**493**		**85.51%**	**1.08[0.93,1.25]**
Total events: 225 (INO), 187 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.22, df=8(P=1); I^2=0%					
Test for overall effect: Z=0.99(P=0.32)					
Total (95% CI)	**654**	**589**		**100%**	**1.04[0.9,1.19]**
Total events: 250 (INO), 221 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.92, df=11(P=0.93); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
Test for subgroup differences: Chi^2=2.06, df=1 (P=0.15), I^2=51.44%					



Analysis 1.4. Comparison 1 Mortality: INO versus control group, Outcome 4 Mortality: subgroup analysis based on duration of drug administration.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Shorter than median duration of INO					
Day 1997	1/12	2/12		0.91%	0.5[0.05,4.81]
Dobyns 1999	22/53	24/55		10.75%	0.95[0.61,1.47]
Michael 1998	11/20	9/20		4.11%	1.22[0.65,2.29]
Payen 1999	53/98	53/105		23.35%	1.07[0.82,1.39]
Schwebel 1997	0/9	0/10			Not estimable
Subtotal (95% CI)	**192**	**202**		**39.13%**	**1.04[0.84,1.29]**
Total events: 87 (INO), 88 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=3(P=0.83); I^2=0%					
Test for overall effect: Z=0.37(P=0.71)					



Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.2 Longer than median duration of INO					
Dellinger 1998	35/120	17/57		10.52%	0.98[0.6,1.59]
Gerlach 2003	3/20	4/20		1.83%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		17.92%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		1.56%	1[0.35,2.88]
Park 2003	8/17	2/6		1.35%	1.41[0.41,4.87]
Taylor 2004	54/165	53/167		24.04%	1.03[0.75,1.41]
Troncy 1998	9/15	8/15		3.65%	1.13[0.6,2.11]
Subtotal (95% CI)	**438**	**358**		**60.87%**	**1.07[0.89,1.29]**
Total events: 161 (INO), 125 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.07, df=6(P=0.98); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
Total (95% CI)	**630**	**560**		**100%**	**1.06[0.92,1.22]**
Total events: 248 (INO), 213 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.97, df=10(P=1); I^2=0%					
Test for overall effect: Z=0.8(P=0.42)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					

Analysis 1.5. Comparison 1 Mortality: INO versus control group, Outcome 5 Sensitivity analysis: excluding abstracts, INO vs control.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bronicki 2015	2/24	8/29		4.14%	0.3[0.07,1.29]
Day 1997	1/12	2/12		1.14%	0.5[0.05,4.81]
Dellinger 1998	35/120	17/57		13.16%	0.98[0.6,1.59]
Dobyns 1999	22/53	24/55		13.45%	0.95[0.61,1.47]
Gerlach 2003	3/20	4/20		2.28%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		22.41%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		1.96%	1[0.35,2.88]
Michael 1998	11/20	9/20		5.14%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.69%	1.41[0.41,4.87]
Taylor 2004	54/165	53/167		30.07%	1.03[0.75,1.41]
Troncy 1998	9/15	8/15		4.57%	1.13[0.6,2.11]
Total (95% CI)	**547**	**474**		**100%**	**1.02[0.87,1.21]**
Total events: 197 (INO), 168 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.92, df=10(P=0.9); I^2=0%					
Test for overall effect: Z=0.29(P=0.77)					

Analysis 1.6. Comparison 1 Mortality: INO versus control group, Outcome 6 Sensitivity analysis: excluding trials not fulfilling AECC criteria, INO vs control.

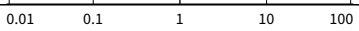
Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dellinger 1998	35/120	17/57		14.02%	0.98[0.6,1.59]
Dobyns 1999	22/53	24/55		14.33%	0.95[0.61,1.47]
Gerlach 2003	3/20	4/20		2.43%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		23.88%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		2.09%	1[0.35,2.88]
Michael 1998	11/20	9/20		5.47%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.8%	1.41[0.41,4.87]
Payen 1999	53/98	53/105		31.12%	1.07[0.82,1.39]
Schwebel 1997	0/9	0/10			Not estimable
Troncy 1998	9/15	8/15		4.87%	1.13[0.6,2.11]
Total (95% CI)	**453**	**381**		**100%**	**1.08[0.92,1.26]**
Total events: 193 (INO), 158 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=8(P=0.99); I^2=0%					
Test for overall effect: Z=0.91(P=0.37)					

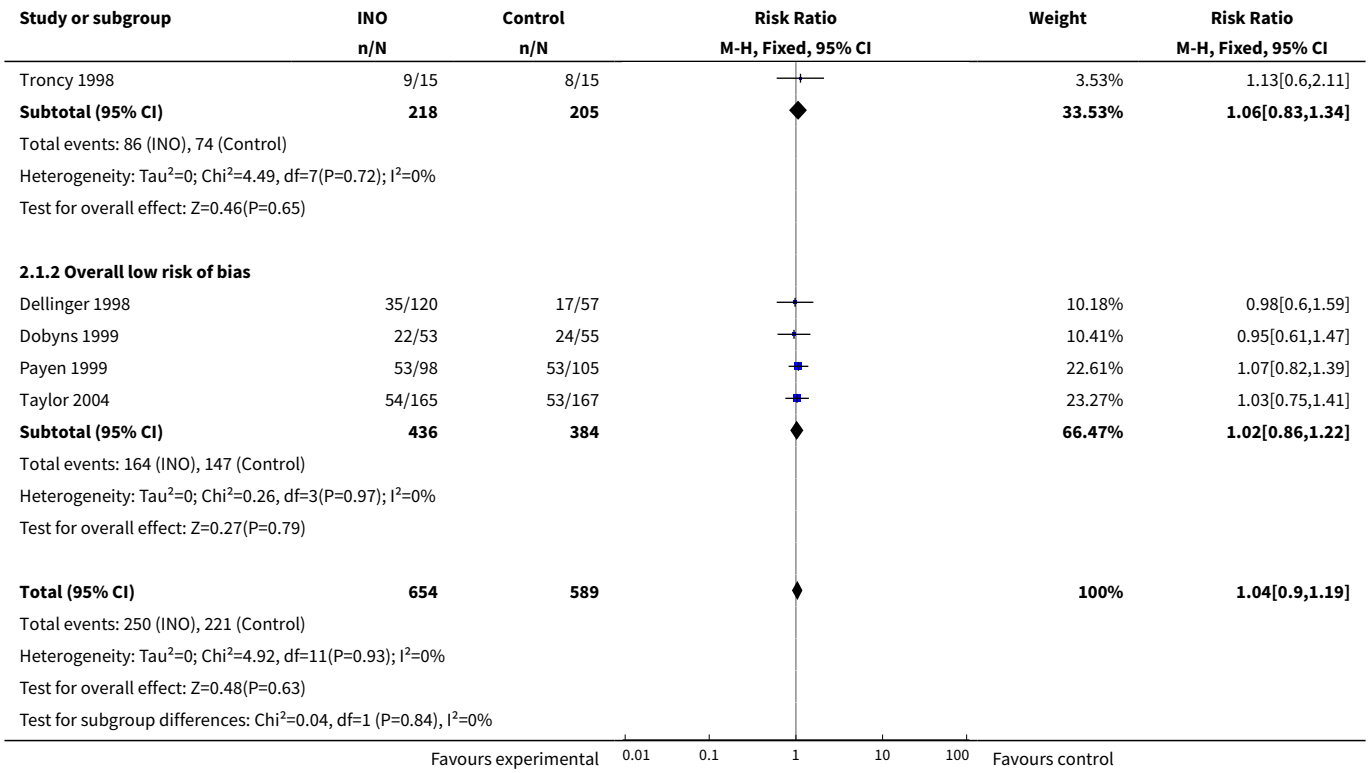
Comparison 2. Mortality: INO versus control (bias assessment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality: sensitivity analysis based on overall risk of bias	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
1.1 Overall high risk of bias	9	423	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.34]
1.2 Overall low risk of bias	4	820	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.86, 1.22]

Analysis 2.1. Comparison 2 Mortality: INO versus control (bias assessment), Outcome 1 Mortality: sensitivity analysis based on overall risk of bias.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Overall high risk of bias					
Bronicki 2015	2/24	8/29		3.2%	0.3[0.07,1.29]
Day 1997	1/12	2/12		0.88%	0.5[0.05,4.81]
Gerlach 2003	3/20	4/20		1.77%	0.75[0.19,2.93]
Lundin 1999	48/93	38/87		17.35%	1.18[0.87,1.61]
Mehta 2001	4/8	3/6		1.51%	1[0.35,2.88]
Michael 1998	11/20	9/20		3.98%	1.22[0.65,2.29]
Park 2003	8/17	2/6		1.31%	1.41[0.41,4.87]
Schwebel 1997	0/9	0/10			Not estimable

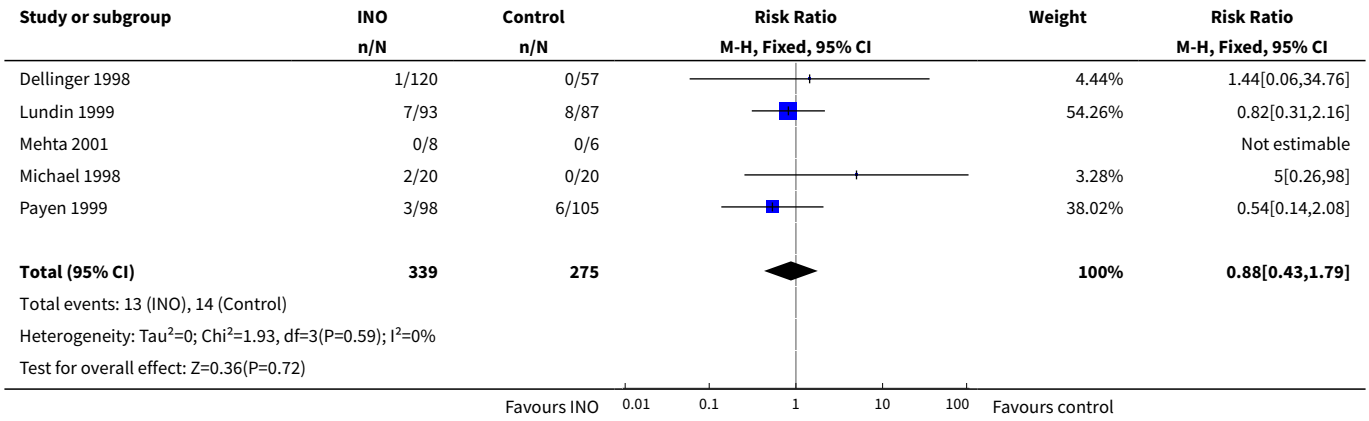




Comparison 3. Bleeding events: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding events: INO vs control	5	614	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.79]

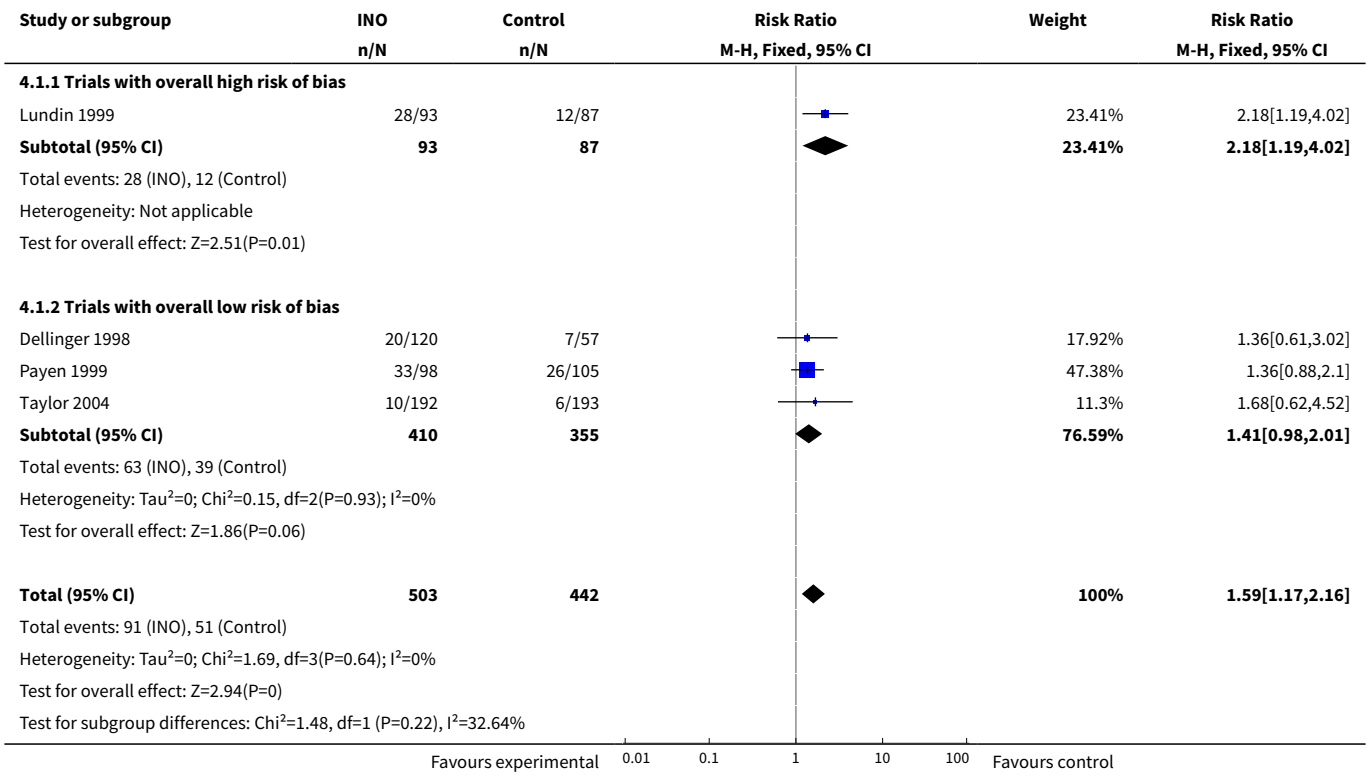
Analysis 3.1. Comparison 3 Bleeding events: INO versus control, Outcome 1 Bleeding events: INO vs control.



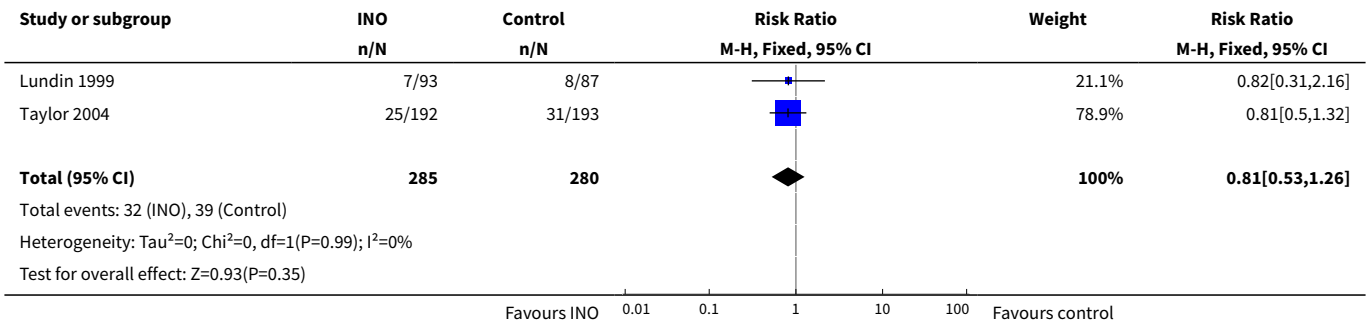
Comparison 4. Complications during the in-patient stay: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Renal impairment: INO vs control	4	945	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.17, 2.16]
1.1 Trials with overall high risk of bias	1	180	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.19, 4.02]
1.2 Trials with overall low risk of bias	3	765	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.98, 2.01]
2 Pneumothorax: INO vs control	2	565	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.26]
3 Severe respiratory failure: INO vs control	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.94]
4 Circulatory failure and shock: INO vs control	2	288	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.90, 2.47]

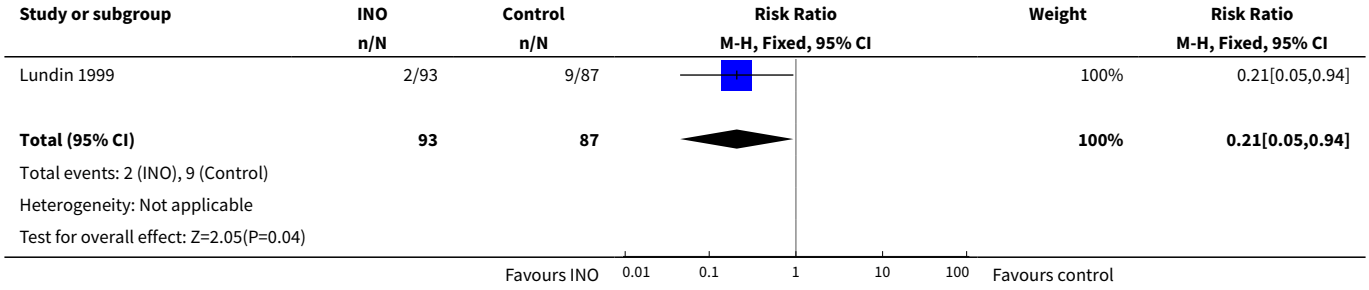
Analysis 4.1. Comparison 4 Complications during the in-patient stay: INO versus control, Outcome 1 Renal impairment: INO vs control.



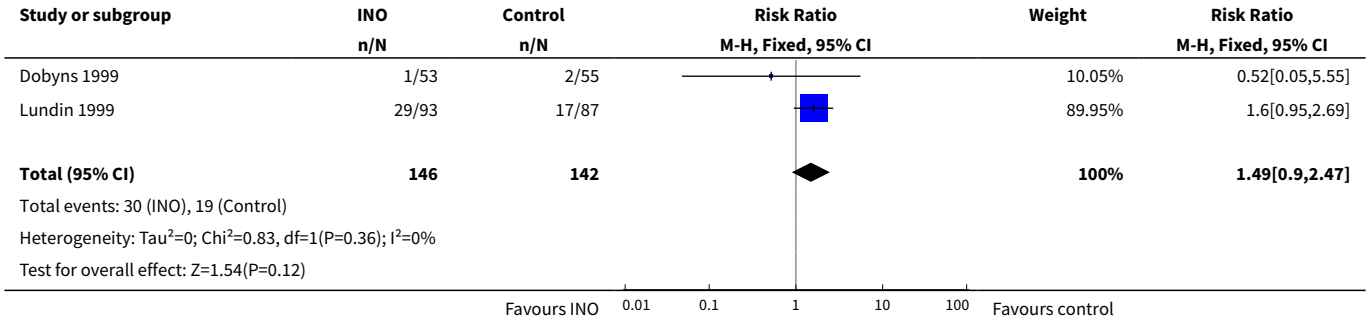
Analysis 4.2. Comparison 4 Complications during the in-patient stay: INO versus control, Outcome 2 Pneumothorax: INO vs control.



Analysis 4.3. Comparison 4 Complications during the in-patient stay: INO versus control, Outcome 3 Severe respiratory failure: INO vs control.



Analysis 4.4. Comparison 4 Complications during the in-patient stay: INO versus control, Outcome 4 Circulatory failure and shock: INO vs control.



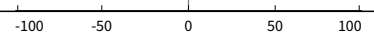
Comparison 5. PaO_2/FiO_2 (mm Hg): INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PaO_2/FiO_2 up to 24 hours	11	614	Mean Difference (IV, Random, 95% CI)	15.91 [8.25, 23.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 High risk of bias trials	9	338	Mean Difference (IV, Random, 95% CI)	14.27 [8.23, 20.30]
1.2 Low risk of bias trials	2	276	Mean Difference (IV, Random, 95% CI)	14.94 [-27.10, 56.98]
2 PaO_2/FiO_2 up to 48 hours	5	416	Mean Difference (IV, Random, 95% CI)	8.65 [-2.80, 20.11]
3 PaO_2/FiO_2 up to 72 hours	5	450	Mean Difference (IV, Fixed, 95% CI)	6.88 [-3.91, 17.68]
4 PaO_2/FiO_2 up to 96 hours	4	334	Mean Difference (IV, Fixed, 95% CI)	14.51 [3.64, 25.38]
5 PaO_2/FiO_2 difference from baseline up to 24 hours	3	155	Mean Difference (IV, Random, 95% CI)	42.90 [20.57, 65.23]

Analysis 5.1. Comparison 5 PaO_2/FiO_2 (mm Hg): INO versus control, Outcome 1 PaO_2/FiO_2 up to 24 hours.

Study or subgroup	INO N	INO Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.1.1 High risk of bias trials							
Day 1997	11	77.3 (35.7)	10	81.2 (37.7)		5.17%	-3.9[-35.38,27.58]
Gerlach 2003	20	142 (46)	20	129 (43)		6.48%	13[-14.6,40.6]
Ibrahim 2007	11	170 (9.5)	10	155 (8.5)		29.14%	15[7.3,22.7]
Lundin 1999	78	138 (48)	66	131 (53)		13.99%	7[-9.64,23.64]
Mehta 2001	8	115 (48)	6	96 (29.3)		3.26%	19[-21.69,59.69]
Michael 1998	16	92 (30)	16	72 (26)		11.26%	20[0.55,39.45]
Park 2003	11	254.2 (109.5)	6	247.8 (89.1)		0.62%	6.4[-89.88,102.68]
Schwebel 1997	9	213 (67)	10	177 (40)		2.19%	36[-14.31,86.31]
Troncy 1998	15	189.8 (40.1)	15	166.3 (53.2)		4.58%	23.5[-10.21,57.21]
Subtotal ***	**179**		**159**			**76.7%**	**14.27[8.23,20.3]**
Heterogeneity: Tau^2=0; Chi^2=3.47, df=8(P=0.9); I^2=0%							
Test for overall effect: Z=4.63(P<0.0001)							
5.1.2 Low risk of bias trials							
Dellinger 1998	120	166 (54)	57	131 (43)		16.28%	35[20.24,49.76]
Dobyns 1999	49	127 (59)	50	135 (74)		7.01%	-8[-34.34,18.34]
Subtotal ***	**169**		**107**			**23.3%**	**14.94[-27.1,56.98]**
Heterogeneity: Tau^2=805.85; Chi^2=7.79, df=1(P=0.01); I^2=87.17%							
Test for overall effect: Z=0.7(P=0.49)							
Total ***	**348**		**266**			**100%**	**15.91[8.25,23.56]**
Heterogeneity: Tau^2=36.89; Chi^2=13.34, df=10(P=0.21); I^2=25.02%							
Test for overall effect: Z=4.07(P<0.0001)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%							

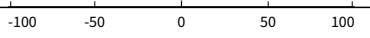


Analysis 5.2. Comparison 5 PaO_2/FiO_2 (mm Hg): INO versus control, Outcome 2 PaO_2/FiO_2 up to 48 hours.

Study or subgroup	INO N	INO Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dellinger 1998	114	156 (46)	52	157 (69)		19.93%	-1[-21.57,19.57]
Gerlach 2003	20	255 (23)	19	231 (26)		27.7%	24[8.56,39.44]
Lundin 1999	91	153 (56)	74	145 (54)		25.27%	8[-8.85,24.85]
Mehta 2001	8	100 (34)	6	117 (36.7)		7.94%	-17[-54.65,20.65]
Michael 1998	16	94 (24)	16	86 (36)		19.16%	8[-13.2,29.2]
Total ***	**249**		**167**			**100%**	**8.65[-2.8,20.11]**

Heterogeneity: Tau^2=61.28; Chi^2=6.32, df=4(P=0.18); I^2=36.72%

Test for overall effect: Z=1.48(P=0.14)

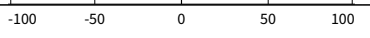


Analysis 5.3. Comparison 5 PaO_2/FiO_2 (mm Hg): INO versus control, Outcome 3 PaO_2/FiO_2 up to 72 hours.

Study or subgroup	INO N	INO Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dellinger 1998	102	155 (53)	46	143 (48)		39.06%	12[-5.27,29.27]
Dobyns 1999	49	168 (111)	50	175 (128)		5.24%	-7[-54.17,40.17]
Lundin 1999	89	167 (64)	71	155 (53)		35.43%	12[-6.13,30.13]
Mehta 2001	6	108 (34)	5	133 (35.8)		6.75%	-25[-66.53,16.53]
Michael 1998	16	101 (50)	16	101 (33)		13.52%	0[-29.35,29.35]
Total ***	**262**		**188**			**100%**	**6.88[-3.91,17.68]**

Heterogeneity: Tau^2=0; Chi^2=3.45, df=4(P=0.49); I^2=0%

Test for overall effect: Z=1.25(P=0.21)



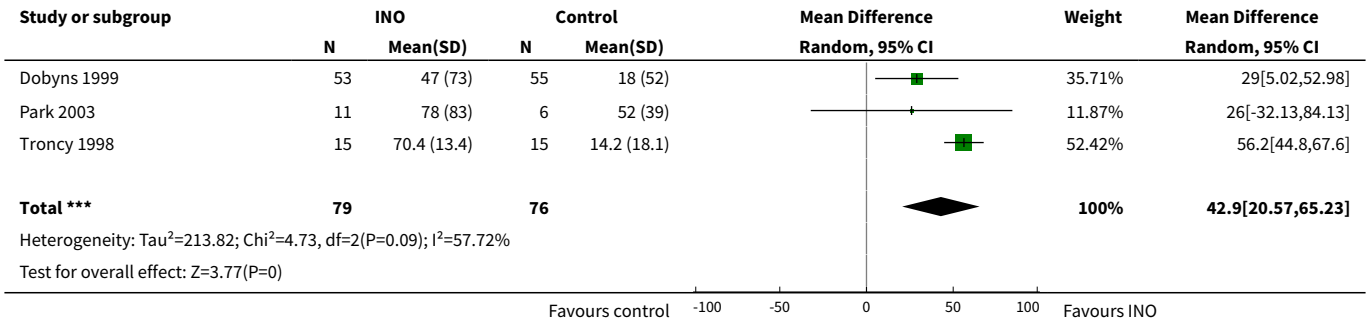
Analysis 5.4. Comparison 5 PaO_2/FiO_2 (mm Hg): INO versus control, Outcome 4 PaO_2/FiO_2 up to 96 hours.

Study or subgroup	INO N	INO Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dellinger 1998	95	155 (50)	40	143 (62)		25.12%	12[-9.69,33.69]
Gerlach 2003	18	281 (23)	18	266 (26)		45.94%	15[-1.04,31.04]
Lundin 1999	84	181 (74)	69	162 (64)		24.69%	19[-2.87,40.87]
Mehta 2001	6	126 (44)	4	128 (40)		4.26%	-2[-54.69,50.69]
Total ***	**203**		**131**			**100%**	**14.51[3.64,25.38]**

Heterogeneity: Tau^2=0; Chi^2=0.59, df=3(P=0.9); I^2=0%

Test for overall effect: Z=2.62(P=0.01)

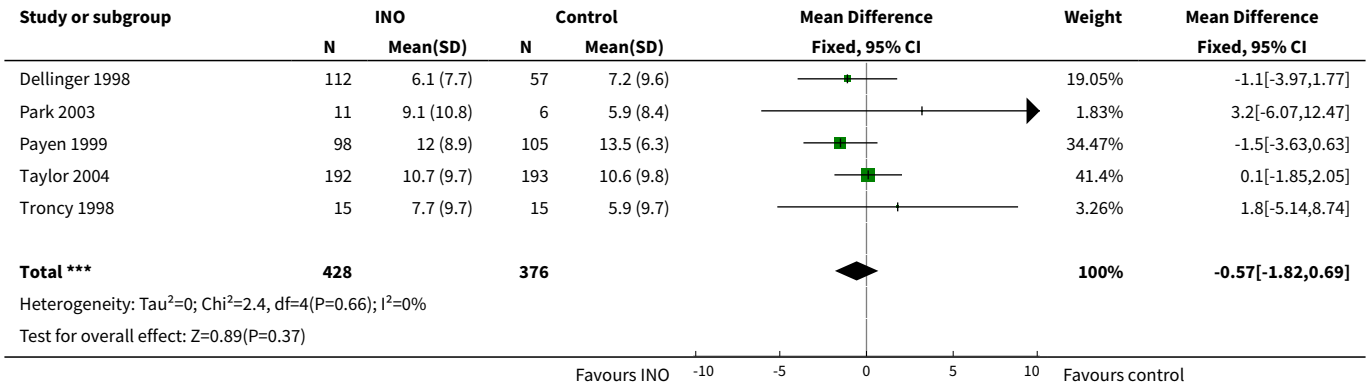
Analysis 5.5. Comparison 5 PaO_2/FiO_2 (mm Hg): INO versus control, Outcome 5 PaO_2/FiO_2 difference from baseline up to 24 hours.



Comparison 6. Ventilator-free days up to day 30: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ventilator-free days (28-30 days), INO vs control	5	804	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.82, 0.69]

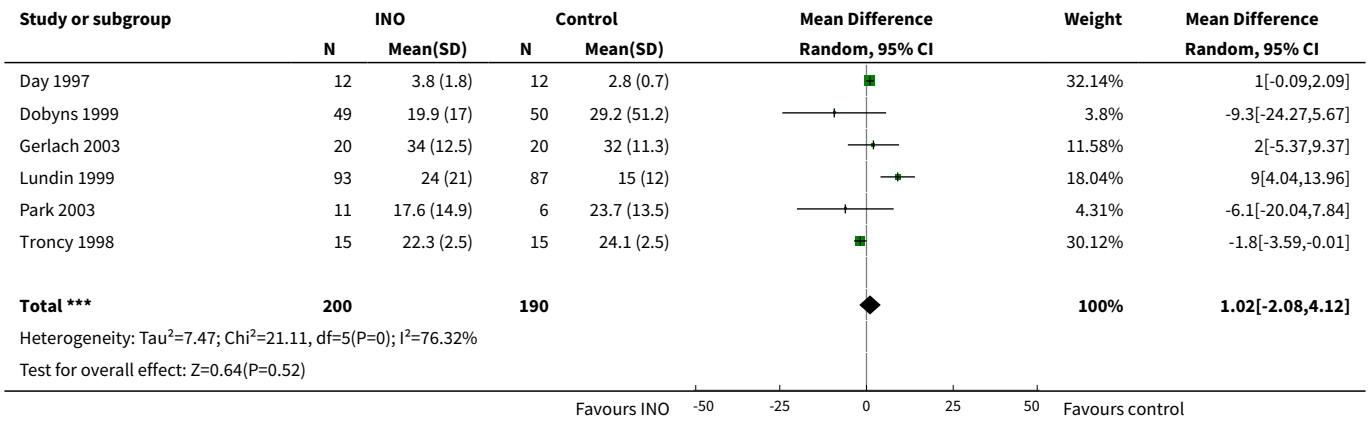
Analysis 6.1. Comparison 6 Ventilator-free days up to day 30: INO versus control, Outcome 1 Ventilator-free days (28-30 days), INO vs control.



Comparison 7. Duration of mechanical ventilation: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of mechanical ventilation	6	390	Mean Difference (IV, Random, 95% CI)	1.02 [-2.08, 4.12]

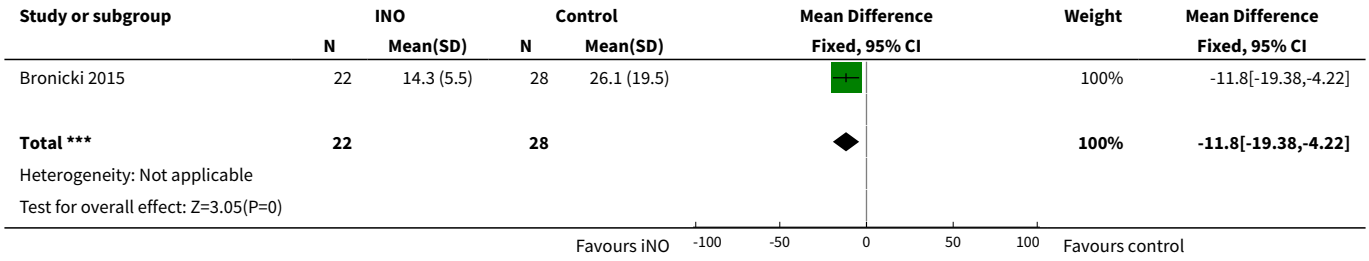
Analysis 7.1. Comparison 7 Duration of mechanical ventilation: INO versus control, Outcome 1 Duration of mechanical ventilation.



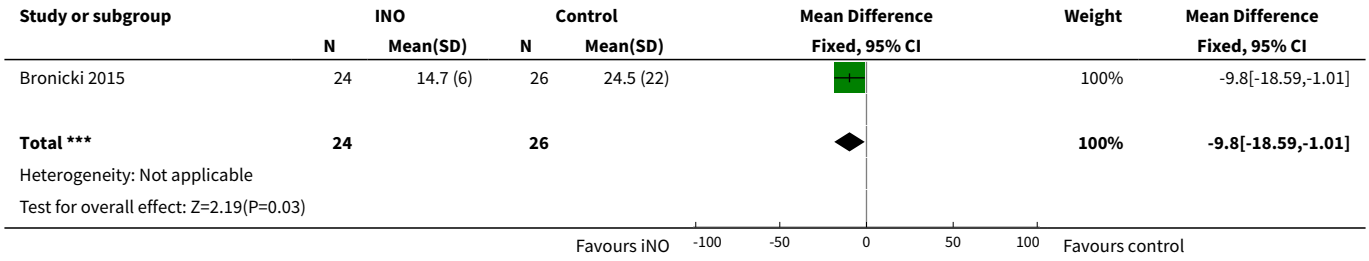
Comparison 8. Oxygenation index: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oxygenation index at 4 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	-11.8 [-19.38, -4.22]
2 Oxygenation index at 12 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	-9.8 [-18.59, -1.01]
3 Oxygenation index at 24 hours	5	368	Mean Difference (IV, Fixed, 95% CI)	-2.31 [-2.73, -1.89]
4 Oxygenation index at 48 hours	2	183	Mean Difference (IV, Random, 95% CI)	1.99 [-10.40, 14.38]
5 Oxygenation index at 72 hours	2	245	Mean Difference (IV, Fixed, 95% CI)	-3.48 [-6.80, -0.15]

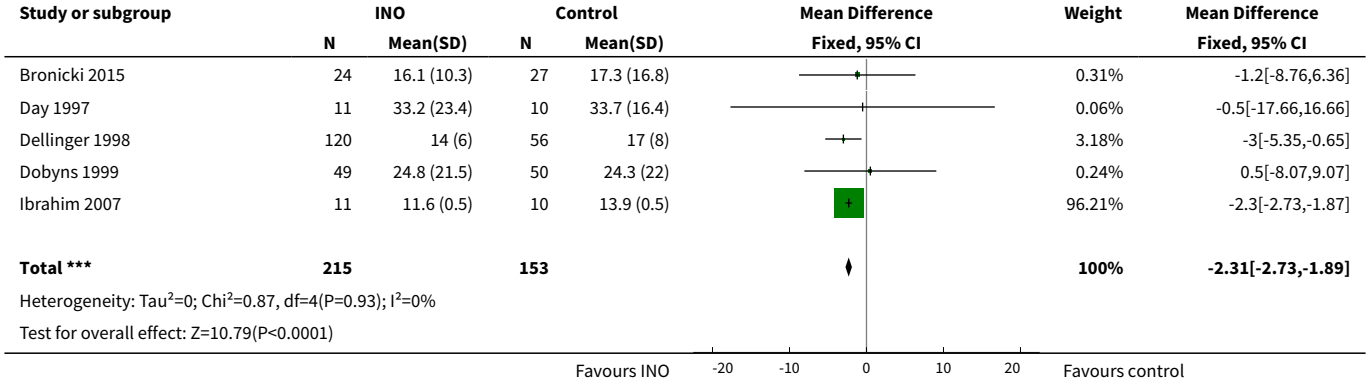
Analysis 8.1. Comparison 8 Oxygenation index: INO versus control, Outcome 1 Oxygenation index at 4 hours.



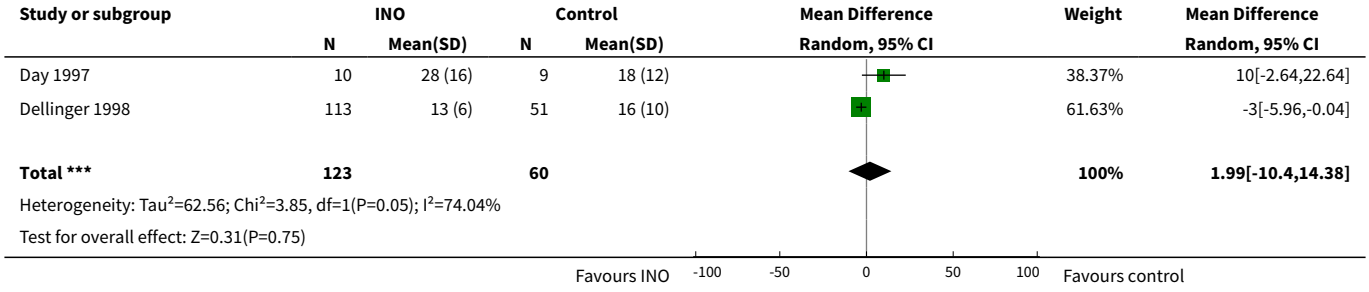
Analysis 8.2. Comparison 8 Oxygenation index: INO versus control, Outcome 2 Oxygenation index at 12 hours.



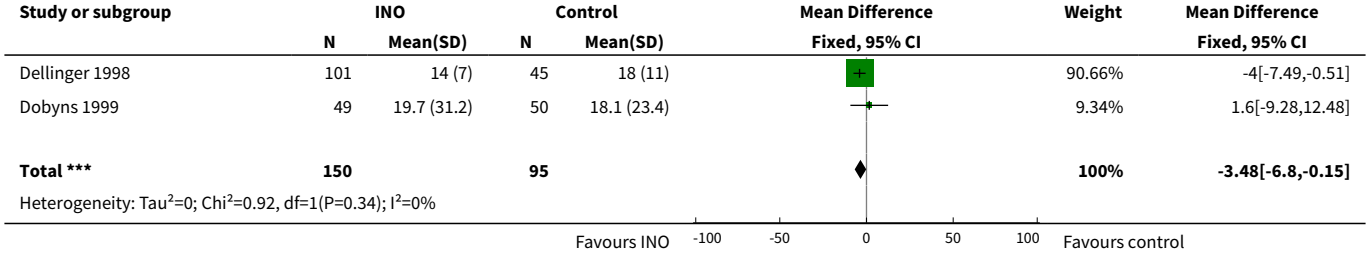
Analysis 8.3. Comparison 8 Oxygenation index: INO versus control, Outcome 3 Oxygenation index at 24 hours.

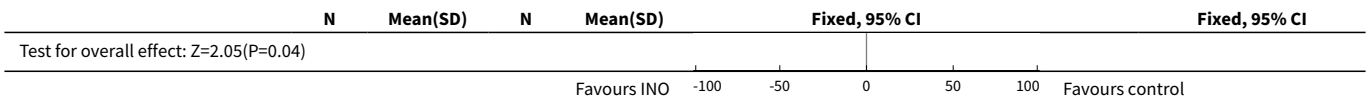


Analysis 8.4. Comparison 8 Oxygenation index: INO versus control, Outcome 4 Oxygenation index at 48 hours.



Analysis 8.5. Comparison 8 Oxygenation index: INO versus control, Outcome 5 Oxygenation index at 72 hours.

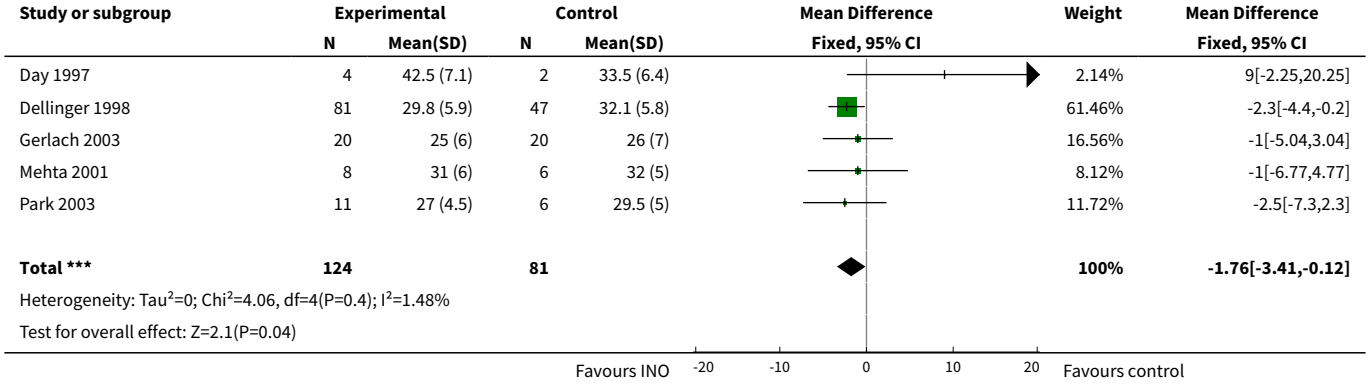




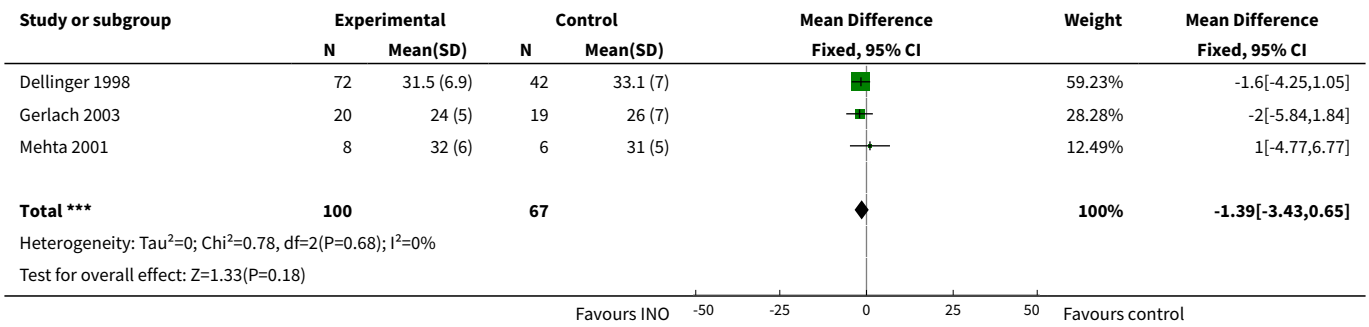
Comparison 9. Mean pulmonary arterial pressure (mm Hg): INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MPAP up to 24 hours	5	205	Mean Difference (IV, Fixed, 95% CI)	-1.76 [-3.41, -0.12]
2 MPAP up to 48 hours	3	167	Mean Difference (IV, Fixed, 95% CI)	-1.39 [-3.43, 0.65]
3 MPAP up to 72 hours	2	111	Mean Difference (IV, Fixed, 95% CI)	-1.92 [-4.36, 0.52]
4 MPAP up to 96 hours	3	130	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-3.77, 0.30]

Analysis 9.1. Comparison 9 Mean pulmonary arterial pressure (mm Hg): INO versus control, Outcome 1 MPAP up to 24 hours.

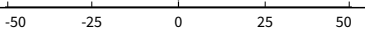


Analysis 9.2. Comparison 9 Mean pulmonary arterial pressure (mm Hg): INO versus control, Outcome 2 MPAP up to 48 hours.



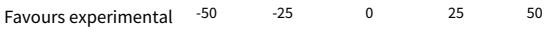
Analysis 9.3. Comparison 9 Mean pulmonary arterial pressure (mm Hg): INO versus control, Outcome 3 MPAP up to 72 hours.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dellinger 1998	63	31.6 (6.9)	37	33.5 (6.7)		78.91%	-1.9[-4.65,0.85]
Mehta 2001	6	30 (5)	5	32 (4)		21.09%	-2[-7.32,3.32]
Total ***	**69**		**42**			**100%**	**-1.92[-4.36,0.52]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%							
Test for overall effect: Z=1.54(P=0.12)							



Analysis 9.4. Comparison 9 Mean pulmonary arterial pressure (mm Hg): INO versus control, Outcome 4 MPAP up to 96 hours.

Study or subgroup	INO N	INO Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dellinger 1998	54	31 (5.8)	30	33.7 (7.5)		43.28%	-2.7[-5.8,0.4]
Gerlach 2003	18	22 (3)	18	23 (7)		33.55%	-1[-4.52,2.52]
Mehta 2001	6	30 (2)	4	31 (4)		23.17%	-1[-5.23,3.23]
Total ***	**78**		**52**			**100%**	**-1.74[-3.77,0.3]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=2(P=0.72); I^2=0%							
Test for overall effect: Z=1.67(P=0.1)							

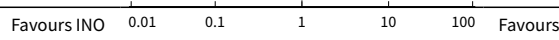


Comparison 10. Reversal of ALI: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reversal of ALI	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.88, 1.46]

Analysis 10.1. Comparison 10 Reversal of ALI: INO versus control, Outcome 1 Reversal of ALI.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lundin 1999	57/93	47/87		100%	1.13[0.88,1.46]
Total (95% CI)	**93**	**87**		**100%**	**1.13[0.88,1.46]**
Total events: 57 (INO), 47 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					



Comparison 11. Methaemoglobin concentration > 5%: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Methaemoglobin > 5%	13	1275	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.20, 3.79]

Analysis 11.1. Comparison 11 Methaemoglobin concentration > 5%: INO versus control, Outcome 1 Methaemoglobin > 5%.

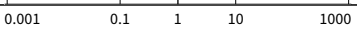
Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Day 1997	0/12	0/12			Not estimable
Dellinger 1998	3/120	1/57		34.9%	1.43[0.15,13.4]
Dobyns 1999	0/53	0/55			Not estimable
Gerlach 2003	0/20	0/20			Not estimable
Ibrahim 2007	0/22	0/10			Not estimable
Lundin 1999	1/93	1/87		26.6%	0.94[0.06,14.73]
Mehta 2001	0/8	0/6			Not estimable
Michael 1998	0/20	0/20			Not estimable
Park 2003	0/17	0/6			Not estimable
Payen 1999	0/98	0/105			Not estimable
Schwebel 1997	0/9	0/10			Not estimable
Taylor 2004	0/192	1/193		38.51%	0.34[0.01,8.17]
Troncy 1998	0/15	0/15			Not estimable
Total (95% CI)	**679**	**596**		**100%**	**0.88[0.2,3.79]**
Total events: 4 (INO), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=0.53, df=2(P=0.77); I²=0%					
Test for overall effect: Z=0.18(P=0.86)					

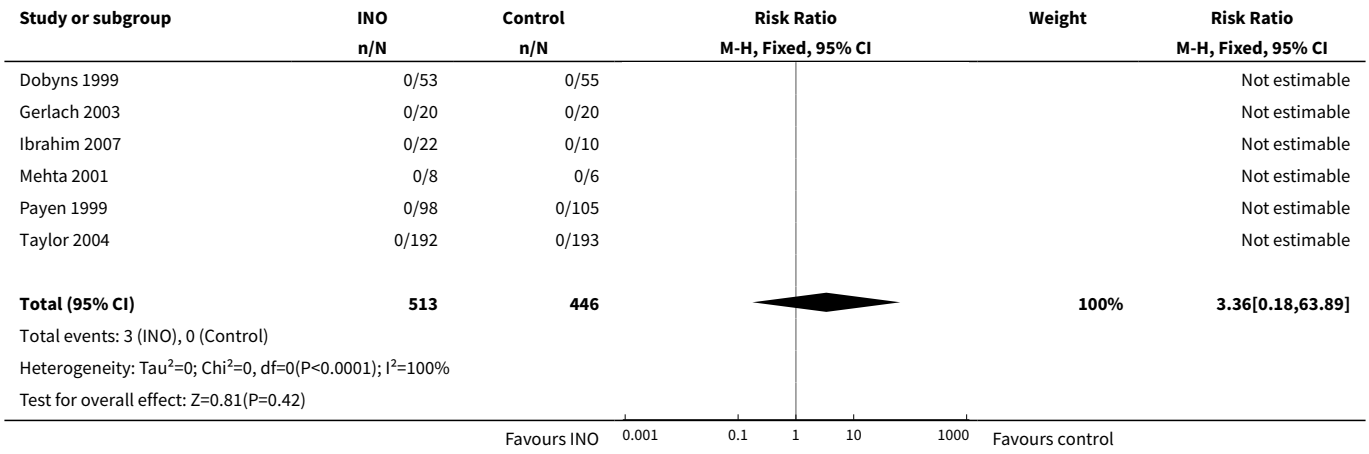
Comparison 12. NO_2 concentration > 3 ppm: INO versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NO_2 concentration > 3 ppm	7	959	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [0.18, 63.89]

Analysis 12.1. Comparison 12 NO_2 concentration > 3 ppm: INO versus control, Outcome 1 NO_2 concentration > 3 ppm.

Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dellinger 1998	3/120	0/57		100%	3.36[0.18,63.89]





ADDITIONAL TABLES

Table 1. Details of included studies

Study	Population and inclusion criteria	INO group characteristics and details of INO administration	Control group characteristics	Ventilation strategy	Duration of longest follow-up	Co-interventions
Bronicki 2015	53 children, 9 centres, oxygenation index (OI) ≥ 12; chest radiograph with pulmonary infiltrates; mechanically ventilated ≤ 7 days	24 participants, 5 ppm INO until death, ventilator-free or at day 28 after enrolment (whichever came first)	29 participants, 5 ppm nitrogen	CMV: low-volume tidal strategy (4-8 mL/kg and plateau pressure < 30 cm H_2O); PEEP based on serial chest radiographs. Target arterial blood gas values: SaO_2 88%-95% with FiO_2 < 0.60; PaO_2 55-80 mm Hg; pH 7.25-7.40 HFOV settings: based on serial chest radiographs (as CMV); target FiO_2 and PaO_2 same as for CMV. FiO_2 weaned over mean airway pressure until FiO_2 < 0.60. Transfer to CMV before weaning	28 days	Prone position
Day 1997	24 children, 1 centre, acute bilateral lung disease (chest x-ray infiltrates), PEEP > 6 cm H_2O, FiO_2 > 0.5 for > 12 hours. Enrolment ≤ 48 hours of meeting study criteria	INO group: 12 participants, 10 ppm INO until ventilatory support decreased to PEEP of 6 cm H_2O and FiO_2 of 0.5. INO withdrawn over 6 hours	12 participants, initially conventional therapy alone, no placebo. After 24 hours, all participants received 10	Ventilation at clinician discretion. INO therapy withdrawn in gradual decrements over a period of 6 hours	Unclear, only 24-hour data included because of cross-over	Not described

Table 1. Details of included studies *(Continued)*

			ppm INO. No cross-over before 24 hours			
Dellinger 1998	177 adults, 30 centres, ARDS < 72 hours before randomization, AECC criteria and $FiO_2 \geq 0.5$, PEEP > 8 cm H_2O	120 participants at doses of 1.25, 5, 20, 40 or 80 ppm, for 28 days or until extubation	57 participants, usual care, placebo gas (nitrogen), no cross-over of treatment failures	Ventilation strategy and weaning of INO standardized (plateau airway pressure < 35 cm H_2O; PEEP to optimize compliance, FiO_2 minimized)	28 days	Corticosteroids received by more participants in INO group after day 6 (20/112 vs 6/57)
Dobyns 1999; (Dobyns 2002)	108 children, 7 centres, oxygenation index > 15 on 2 arterial blood gases < 6 hours, chest infiltrates. Mean duration of ventilation before randomization: 3.5 vs 3.7 days (INO vs control)	53 children, 10 ppm for 3 days, then weaned if failure criteria not met. INO for maximum of 7 days after entry	55 children, usual care, placebo gas (air), cross-over of participants meeting treatment failure criteria (27 participants)	Ventilation strategy and weaning of gas standardized (peak airway pressure < 35-40 cm H_2O, tidal volume limitation, titrated PEEP, high-frequency oscillatory ventilation by clinician discretion)	Unclear, ventilation data reported for day 108	Not described
Gerlach 2003	40 adults with ARDS (AECC criteria), $FiO_2 \geq 0.6$, $PaO_2/FiO_2 \leq 150$ mm Hg, PEEP ≥ 10 cm H_2O, PAOP ≤ 18 mm Hg, median duration of ventilation before randomization: 5.3 vs 5.9 days (INO vs control)	20 participants, 10 ppm with daily dose response analysis until weaning initiated	20 participants, usual care, no placebo, no cross-overs	Ventilation protocols, unspecified	Unclear, length of stay in ICU reported for day 91	Standard care according to standardized protocols. Protocols for prone position (4-6 hours), extracorporeal membrane oxygenation (ECMO), permissive hypercapnia and measures to reduce pulmonary oedema
Ibrahim 2007	32 children, single-centre, ARDS ($PaO_2/FiO_2 \leq 200$ mm Hg, positive inspiratory pressure ≥ 30 cm H_2O, $FiO_2 \geq 0.5$ for > 12 hours)	22 children, INO + supine position (11 children) and INO + prone position (11 patients). INO at 5 ppm for 18 hours, then decreased to 1 ppm for 2 hours	10 participants kept in prone position for 20 hours, then back to supine position for remaining 4 hours. No placebo, usu-	Lung protective strategy (tidal volume 5-10 mL/kg), permissive hypercapnia ($PaCO_2$ > 50 mm Hg) as long as arterial pH > 7.2. Ventilation and weaning protocol	24 hours	Prone position (11/22 in INO group and 10/10 in control group)

Table 1. Details of included studies *(Continued)*

			al care. No cross-over			
Lundin 1999	80 adults, 43 centres, INO responders with ALI (lung infiltrates, ventilated for 18-96 hours, PaO_2/FiO_2 < 165 mm Hg, PEEP > 5 cm H_2O, MAP > 10 cm H_2O, pressure- or volume-controlled ventilation, I:E ratio between 1:2 and 2:1, duration of ventilation before randomization 0.75-4 days	93 participants, 1-40 ppm INO at lowest effective dose for up to 30 days or until end point reached. Mean INO dose: 9 ppm (SD 8), mean number of days of INO: 9 (SD 6)	87 participants, no placebo gas, cross-over of treatment failures allowed (6 participants)	Ventilation strategy and weaning test gas according to usual standards of care and at clinician discretion	90 days	Not described
Mehta 2001	14 adults, single-centre, ARDS ≤ 5 days, bilateral chest infiltrates, PaO_2/FiO_2 < 200 mm Hg, PAOP < 18 cm H_2O, PEEP ≥ 8 cm H_2O	8 participants, daily titration for 4 days (5,10, 20 ppm every 30 minutes), dose with highest PaO_2/FiO_2 used until next day. INO until PaO_2/FiO_2 > 200 mm Hg on FiO_2 < 0.5. Mean duration of INO: 8 days (SD 9). INO 5-10 ppm used for most participants on days 2-4	6 participants, no placebo, conventional therapy. No cross-overs	Clinician discretion	Unclear, mortality data provided at day 68	Not described. Prone position protocol but not used in any participant
Michael 1998	40 adults and children, single-centre. ARDS, AECC criteria except PaO_2/FiO_2 < 150 mm Hg and FiO_2 > 0.8 for ≥ 12 hours or 0.65 for ≥ 24 hours	20 participants, INO titration each 6 hours (5, 10, 15, 20 ppm) for 24 hours, then clinically adjusted, tapered if no oxygenation improvement by 72 hours. Mean INO dose: 13 ppm	20 participants, conventional therapy. No placebo gas. Cross-over: 2 participants received INO before and 7 participants after 72 hours	Mode of ventilation unchanged throughout study period with similar PEEP between groups for 72 hours. Pre-defined criteria for clinical deterioration, clinician discretion	Unclear, data on ARDS duration provided for day 25	Not described
Park 2003	23 adults, single-centre, ARDS (AECC criteria)	6 participants received INO 5 ppm. Mean duration of INO treatment: 8.2 days	6 participants, conventional therapy, lung recruitment manoeuvre (LRM) twice daily, no placebo gas. No cross-overs	Ventilation protocol (LRM + inflation pressure of 30-35 cm H_2O for 30 seconds, volume control mode, tidal volume 6 mL/kg/ideal body weight, respiratory rate 20-25/min, plateau airway pressure ≤ 30 cm H_2O, PEEP to optimize PaO_2, FiO_2 mini-	28 days	Not described. Prone position protocol but not used in any participant

Table 1. Details of included studies *(Continued)*

				mized), weaning protocol		
Payen 1999	203 adults, 23 centres, > 15 years, ARDS (AECC criteria and Murray lung injury score: 2-3 after 24-hour optimization period), mean duration of ventilation before randomization: 5.3 vs 5.9 days (INO vs control)	98 participants, fixed INO of 10 ppm until oxygenation and PEEP criteria met with median INO administration of 5 days. 12 participants crossed over to control group owing to treatment failure	105 participants, placebo gas (nitrogen), conventional therapy. 19 participants crossed over to INO group owing to treatment failure	Various ventilation guidelines (e.g. recruitment manoeuvres, prone position, limited tidal volume, peak and plateau inspiratory pressures) applied before randomization. No information after randomization	90 days	Not described
Schwebel 1997	19 participants, 17 centres, ARDS ≤ 24 hours, PaO_2/FiO_2 < 200, PEEP 6-10 cm H_2O, PAOP 10-18 cm H_2O, chest x-ray infiltrates	9 participants, 10 ppm INO for 17 hours followed by clinician discretion. Mean INO treatment: 4.6 days	10 participants, placebo gas (nitrogen), conventional therapy. At least 5 participants crossed over to INO	Fixed mechanical ventilation. If PaO_2/FiO_2 < 100 before 17 hours of treatment, cross-over, thereafter INO or other technic or change in respiratory parameters	Unclear	Not described
Taylor 2004; (Angus 2006)	385 adults, 46 centres, ALI ≤ 3 days of duration, modified AECC criteria: PaO_2/FiO_2 ≤ 250, bilateral infiltrates on x-ray, PAOP ≤ 18 mm Hg or no signs of left atrial hypertension, FiO_2 0.5-0.95 or PEEP ≥ 8 cm H_2O	192 participants, 5 ppm INO until oxygenation and PEEP criteria met or until end of trial (28 days)	193 participants, placebo (nitrogen gas), until end of trial (28 days), no cross-overs, conventional therapy	Ventilation protocol (FiO_2 minimized, PEEP to optimize compliance and prevent shear force injury, plateau pressure ≤ 35 cm H_2O). Weaning protocol	1 year	Prone position (INO 10/192 vs control 14/193)
Troncy 1998	30 participants, single-centre, ARDS, Murray lung injury score ≥ 2.5	15 participants, dose titration (2.5, 5, 10, 20, 30, 40 ppm every 10 minutes), daily re-titration. Mean duration of INO: 8 days (SD 5), mean dose: 5.3 ppm	15 participants, no placebo gas, conventional therapy, no cross-overs	Ventilation protocol (tidal volume: 10 mL/kg, $PaCO_2$ ≤ 35-45 mm Hg, PEEP ≤ 15 cm H_2O, PaO_2 > 85 mm Hg, no prone position). Weaning protocol	30 days	Protocols for sedation, curarization, intravenous perfusion, blood transfusion, parenteral or enteral feeding. Prone position protocol but not used in any participant

AECC: American-European Consensus Conference; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; cm: centimetre; cm H_2O: centimetre of water; CMV: continuous mandatory ventilation; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired

oxygen; HFOV: high-frequency oscillatory ventilation; ICU: intensive care unit; I:E: ventilator inspiratory-to-expiratory time ratio; INO: inhaled nitric oxide; LRM: lung recruitment manoeuvre; MAP: mean arterial pressure; min: minutes; mL/kg: millilitres per kilogram; mm Hg: millimetre of mercury; OI: oxygen index; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAOP: pulmonary artery occlusion pressure; PEEP: positive end-expiratory pressure; pH: potential hydrogen; ppm: parts per million; SaO_2: arterial oxygen saturation; SD: standard deviation; vs: versus; x-ray: chest radiography

Table 2. Complications during in-patient stay: INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
Hypertension	Dellinger 1998	177	Risk ratio (M-H, fixed, 95% CI)	0.16 [0.01, 3.86]
Myopathy/Agitation	Dellinger 1998	177	Risk ratio (M-H, fixed, 95% CI)	1.44 [0.06, 34.76]
Liver impairment	Dellinger 1998	177	Risk ratio (M-H, fixed, 95% CI)	1.44 [0.06, 34.76]
Encephalopathy	Lundin 1999	180	Risk ratio (M-H, fixed, 95% CI)	6.55 [0.34, 125.07]
Sepsis	Lundin 1999	180	Risk ratio (M-H, fixed, 95% CI)	2.18 [0.58, 8.18]
Myocardial infarction	Michael 1998	40	Risk ratio (M-H, fixed, 95% CI)	3.00 [0.13, 69.52]
Infection	Taylor 2004	385	Risk ratio (M-H, fixed, 95% CI)	1.62 [1.16, 2.26]
Pneumonia	Taylor 2004	385	Risk ratio (M-H, fixed, 95% CI)	0.80 [0.52, 1.22]

Table 3. Oxygenation index: INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
Oxygenation index at 72 hours	Dellinger 1998	134	Mean difference (IV, fixed, 95% CI)	-4.00 [-7.69, -0.31]
Oxygenation index change from baseline up to 24 hours	Dobyns 1999	108	Mean difference (IV, fixed, 95% CI)	5.00 [-1.21, 11.21]

Table 4. Resolution of multi-organ failure, INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
TISS score	Taylor 2004	385	Mean difference (IV, fixed, 95% CI)	4.60 [-57.24, 66.44]

TISS score: Therapeutic Intervention Scoring System

Table 5. Quality of life assessment: INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
ADL score at 6 months: INO vs control	Taylor 2004	368	Mean difference (IV, fixed, 95% CI)	-1.00 [-5.09, 3.09]

Table 5. Quality of life assessment: INO versus control, single-study analyses *(Continued)*

ADL score at 12 months: INO vs control	Taylor 2004	368	Mean difference (IV, fixed, 95% CI)	-2.00 [-5.07, 1.07]

ADL = activity of daily living

Table 6. Length of stay in ICU and hospital: INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
Number of days in hospital	Taylor 2004	368	Mean difference (IV, fixed, 95% CI)	0.10 [-4.51, 4.71]
Mean length of stay in ICU	Taylor 2004	368	Mean difference (IV, fixed, 95% CI)	1.40 [-1.99, 4.79]

ICU: intensive care unit

Table 7. Cost-benefit analysis: INO versus control, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
Total hospital cost in US$	Taylor 2004	312	Mean difference (IV, fixed, 95% CI)	700.00 [-9595.70, 10995.70]

Table 8. Mortality: INO versus control group, single-study analyses

Subgroup analysis	Study	Participants	Statistical method	Effect estimate
Mortality, primary lung injury	Troncy 1998	10	Risk ratio (M-H, fixed, 95% CI)	1.00 [0.58, 1.72]
Mortality, secondary lung injury	Troncy 1998	20	Risk ratio (M-H, fixed, 95% CI)	1.14 [0.69, 1.90]
Mortality	Bronicki 2015	53	Relative risk (95% CI)	0.28 [0.06,1.19]

Table 9. Abbreviations

Abbreviations
ADL: activity of daily living; AECC: American-European Consensus Conference; AHRF: acute hypoxaemic respiratory failure; ALI: acute lung injury; APACHE score: Acute Physiology and Chronic Health Evaluation score; APHIS: a priori heterogeneity adjusted information size; ARDS: acute respiratory distress syndrome; BMJ: British Medical Journal; CI: confidence interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; cm: centimetre; CMV: conventional mechanical ventilation; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; HFOV: high-frequency oscillatory ventilation; ICU: intensive care unit; I:E ratio: inspiratory:expiratory ratio; INO: inhaled nitric oxide; ITT: intention-to-treat analysis; LBHIS: low bias heterogeneity adjusted information size; LILACS: Latin American Caribbean Health Sciences Literature; LRM: lung recruitment manoeuvre; MAP: mean arterial pressure; min: minutes; mL/kg: millilitres per kilogram; MPAP: mean arterial pulmonary pressure; ng: nanogram; NO: nitric oxide; NO_2: nitrogen dioxide; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAOP: pulmonary artery occlusion pressure; PEEP: positive end-expiratory pressure; P/F ratio: PaO_2/FiO_2; ppm: parts per million; PVR: pulmonary vascular resistance; QWB: quality of well being scale; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio; RRI: relative risk increase; RRR: relative risk reduction; SVR: systemic vascular resistance; TSA: trial sequential analysis; WMD: weighted mean difference

Abbreviations: Table 9

APPENDICES

Appendix 1. Search strategy

Database	Search strategy
CENTRAL	#1 MeSH descriptor Anoxia explode all trees #2 MeSH descriptor Respiratory Paralysis explode all trees #3 MeSH descriptor Respiratory Insufficiency explode all trees #4 MeSH descriptor Respiratory Distress Syndrome, Adult explode all trees #5 MeSH descriptor Respiratory Distress Syndrome, Newborn explode all trees #6 (Acute near (hypox* or respiratory)):ti,ab #7 (respirat* near (distress or failure)):ti,ab #8 lung injury #9 (hypoxia or hypoxemia):ti #10 AHRF or ARDS or ALI #11 (#1 OR #2 OR #3 OR # OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) #12 MeSH descriptor Nitric Oxide explode all trees #13 MeSH descriptor Endothelium-Dependent Relaxing Factors explode all trees #14 Nitric near oxide #15 (#12 OR #13 OR #14) #16 (#11 AND #15)
EMBASE (Ovid SP)	1. exp respiratory-distress/ 2. exp acute-respiratory-tract-disease/ 3. exp acute-respiratory-failure/ 4. exp adult-respiratory-distress-syndrome/ 5. exp neonatal-respiratory-distress-syndrome/ 6. exp acute-lung-injury/ 7. exp idiopathic-respiratory-distress-syndrome/ 8. exp transfusion-related-acute-lung-injury/ 9. exp hypoxemia/ or hypoxia/ 10. (Acute adj3 (hypox* or respirator*)).mp. 11. (respirat* adj3 (distress or failure)).mp. 12. lung injury.mp. 13. (hypoxia or hypoxemia).ti. 14. (AHRF or ARDS or AL).mp. 15. or/1-14 16. nitric-oxide/ 17. endothelial?derived relax*.mp. 18. Endothelium?Dependent Relax*.mp. 19. Nitric oxide.ti,ab. 20. or/16-19 21. 20 and 15 22. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) and human*.ec,hw,fs. 23. 22 and 21
ISI Web of Science and BIOSIS Previews	#1TS=(Respirat* SAME Insufficiency) or TS=(Respirat* SAME Paralysis) or TS=(Respirat* SAME Distress*) or TS=(Respirat* SAME failure) or TS=(Anoxemia or Anoxia) or TS=(Acute SAME hypox*) or TS=(Acute SAME respiratory) or TS=(lung injur*) OR TS=(AHRF or ARDS or ALI) #2 TS=(nitric oxide) or TS=(Endothel* SAME Depend* SAME Relaxi*) #3#2 AND #1 #4 TS=random* or TS=placebo or TS=(controlled trial*) #5 #4 AND #3

(Continued)

LILACS (via BIREME)	("RESPIRATORY DISTRESS" or "RESPIRATORY INSUFFIENCY" or ((lesion$ or ferimento) and pulm $) or ((insuficiência or escasez) and respirat$) or (síndrome de distress respiratorio agudo) or (distress and sindrome) or (SDRA or VAFO or ARDS) or (alta frecuencia oscilatoria) or (lung and injury) or (Anox$) or (Acute and (hypox$ or respirator$))) and (nitric$ and oxid$)
MEDLINE (Ovid SP)	1. Anoxia/ or Anoxemia/ or exp Respiratory-Paralysis/ or exp Respiratory-Insufficiency/ or exp Respiratory-Distress-Syndrome-Newborn/ or exp Respiratory-Distress-Syndrome-Adult/ or (Acute adj3 (hypox* or respiratory)).mp. or (respirat* adj3 (distress or failure)).mp. or lung injury.mp. or (hypoxia or hypoxemia).ti,ab. or (AHRF or ARDS or ALI).mp. 2. exp nitric-oxide/ or exp Endothelium-Dependent-Relaxing-Factors/ or (Nitric adj3 oxide).mp. 3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh. 4. 1 and 2 and 3
CINAHL (EBSCO host)	S1 MW Anoxia S2 MW Anoxemia S3 (MH "Respiratory Failure+") S4 (MH "Respiratory Distress Syndrome+") or (MM "Respiratory Distress Syndrome, Acute") S5 Acute and (hypox* or respiratory) S6 respirat* and (distress or failure) S7 TX lung injury S8 TI hypoxia or hypoxemia S9 TX AHRF or ARDS or ALI S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 S11 (MM "Nitric Oxide") S12 TX Nitric oxide S13 S11 or S12 S14 S10 and S13 S15 ("random") or (MH "Random Assignment") or (MM "Random Sample+") or (MM "Clinical Trials+") S16 (MM "Double-Blind Studies") or (MM "Single-Blind Studies") or (MM "Triple-Blind Studies") or (MM "Concurrent Prospective Studies") S17 (MM "Placebos") S18 TX placebo* or random* S19 TI trail* S20 S15 or S16 or S17 or S18 or S19 S21 S14 and S20

Appendix 2. Assessment of risk of bias in included studies

1. Random sequence generation

Assessment of randomization: sufficiency of the method in producing two comparable groups before intervention.

Grade: 'low risk': a truly random process (e.g. random computer number generator, coin tossing, throwing dice); 'high risk': any non-random process (e.g. date of birth, date of admission by hospital or clinic record number or by availability of the intervention); or 'unclear risk': insufficient information.

2. Allocation concealment

Allocation method prevented investigators or participants from foreseeing assignment.

Grade: 'low risk': central allocation or sealed opaque envelopes; 'high risk': use of open allocation schedule or other unconcealed procedure; or 'unclear risk': insufficient information.

3. Blinding

Assessment of appropriate blinding of the team of investigators and participants: person responsible for participant care, participants and outcome assessors.

Grade: 'low risk': blinding considered adequate if participants and personnel were kept unaware of intervention allocations after inclusion of participants into the study, and if the method of blinding involved a placebo indistinguishable from the intervention, as mortality is an objective outcome; 'high risk': not double-blinded, categorized as an open-label study, or without use of a placebo indistinguishable from the intervention; 'unclear risk': blinding not described.

4. Incomplete outcome data

Completeness of outcome data, including attrition and exclusions.

Grade: 'low risk': numbers and reasons for dropouts and withdrawals in the intervention groups described, or no dropouts or withdrawals specified; 'high risk': no description of dropouts and withdrawals provided; 'unclear risk': report gave the impression of no dropouts or withdrawals, but this was not specifically stated.

5. Selective reporting

The possibility of selective outcome reporting.

Grade: 'low risk': reported outcomes are pre-specified in an available study protocol, or, if this is not available, published report includes all expected outcomes; 'high risk': not all pre-specified outcomes reported, reported using non-pre-specified subscales, reported incompletely or report fails to include a key outcome that would have been expected for such a study; 'unclear risk': insufficient information.

6. Funding bias

Assessment of any possible funding bias:

Grade: 'low risk': reported no funding, funding from universities or public institutions; 'high risk': funding from private investors,

pharmaceutical companies or trial investigator employed by the pharmaceutical company; 'unclear risk': insufficient information.

7. Other bias

Assessment of any possible sources of bias not addressed in domains 1 to 6.

Grade: 'low risk': report appears to be free of such biases; 'high risk': at least one important bias is present that is related to study design, early stopping because of some data-dependent process, extreme baseline imbalance, academic bias, claimed fraudulence or other problems; or 'unclear risk': insufficient information, or evidence that an identified problem will introduce bias.

Appendix 3. Bias assessment of mortality: INO versus control (sensitivity analysis)

Outcome	Studies	Participants	Statistical Method	Effect Estimate
Sensitivity analysis based on random sequence generation	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
- Adequate	6	1014	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.23]
- Inadequate or unclear	7	229	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.35]
Sensitivity analysis based on allocation concealment	12	911	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
- Adequate	6	727	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.25]
- Inadequate or unclear	6	184	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.65, 1.38]
Sensitivity analysis based on blinding	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
- Adequate	6	892	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]

(Continued)

- Inadequate or unclear	7	351	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.89, 1.44]
Sensitivity analysis based on degree of follow-up	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
- Adequate	11	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.21]
- Inadequate or unclear	2	127	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
Sensitivity analysis based on sample size calculation and early stopping	13	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.19]
- Adequate	5	766	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.25]
- Inadequate or unclear	8	477	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.27]

Appendix 4. Definition of variables and outcome measures and abbreviations in included studies

Outcome measure/ variable/ abbreviation	Definition	Studies
Oxygenation index	100 × mean airway pressure/(PaO_2/FiO_2) or (mean airway pressure × FiO_2 × 100)/systemic arterial oxygen tension	Bronicki 2015; Day 1997; Dellinger 1998; Dobyns 1999; Ibrahim 2007
PaO_2/FiO_2	Partial pressure of arterial oxygen/fraction of inspired oxygen	Day 1997; Dellinger 1998; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Schwebel 1997; Troncy 1998
Reversal of ALI	Ability to maintain PaO_2 ≥11 kPa if < 60 years and PaO_2 ≥ 10 kPa if > 60 with FiO_2 ≤ 0.35 and PEEP ≤ 5 cm H_2O; On ventilator/mask CPAP system, PEEP ≤ 5 cm H_2O, PaO_2/FiO_2 > 31 kPa if < 60 years and PaO_2/FiO_2 > 29 kPa if > 60 years	Lundin 1999
Severe respiratory failure	Defined as FiO_2 1.0 with PaO_2 < 8 kPa for at least 8 hours, pressure-controlled ventilation (rate 5 to 30 beats/min), peak airway pressure ≥ 20 cm H_2O, mean airway pressure >10 cm H_2O; or as FiO_2 > 0.9 with PaO_2 < 8 kPa in 3 blood gas analyses (4 hours apart), pressure-controlled/limited ventilation (rate 5-30), PEEP ≥ 10 cm H_2O, mean airway pressure ≥ 20 cm H_2O; or 2 arterial blood gases 2 hours apart at FiO_2 ≥ 1.00, resulting in PaO_2 < 6 kPa	Lundin 1999
Renal dysfunction	New renal replacement therapy ± new raised creatinine concentration (> 300 µmol/L) or creatinine concentration > 177 µmol/L or ≧ 265 µmol/L	Dellinger 1998; Lundin 1999; Payen 1999; Taylor 2004

(Continued)

Liver impairment	Bilirubin ≧ 0.4 mg/dL, platelets ≤ 50 × 10^3/mm^3 and prothrombin time ≧ 1.5 times normal	Dellinger 1998
ADL score	Activity of daily living scale	Angus 2006 (Taylor 2004)
TISS score	Therapeutic Intervention Scoring System	Angus 2006 (Taylor 2004)
AECC criteria	American-European Consensus Conference criteria for ALI and ARDS ARDS: acute non-cardiogenic pulmonary oedema, acute severe hypoxaemia (PaO_2 to FiO_2 ratio (P/F ratio) < 200, bilateral infiltrates on chest radiography, pulmonary artery occlusion pressure (PAOP) ≤ 18. ALI = hypoxia score 200-300 mm Hg + ARDS criteria	Dellinger 1998; Dobyns 1999; Gerlach 2003; Ibrahim 2007; Lundin 1999; Mehta 2001; Michael 1998; Park 2003; Payen 1999; Schwebel 1997; Troncy 1998

WHAT'S NEW

Date	Event	Description
12 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 2, 2001

Date	Event	Description
5 January 2017	Amended	Co-published in Anaesthesia (Karam 2017)
18 November 2015	New search has been performed	A new lead author (Fabienne Gebistorf) together with a new co-author (Oliver Karam) has updated this review in collaboration with 2 of the original review authors (AA and JW). We have updated the Methods section and have included full risk of bias tables and summary of findings tables. We have applied trial sequential analysis (TSA) We searched the databases until 2015 November 18. We included one new trial in this updated review (Bronicki 2015). We excluded from this review one randomized controlled trial (Cuthbertson 2000) that had been included in the previous version (Afshari 2010), because new information provided to us indicated that most of these patients had been included in Lundin 1999. Furthermore, mortality data for Ibrahim 2007 have been revised since we became aware of a mistake in the last version of the review (Afshari 2010) This review now has 14 included studies in total (1275 participants) The overall conclusion remains unchanged

Date	Event	Description
18 November 2015	New citation required but conclusions have not changed	Our conclusion remains the same Two review authors - Jesper Brok and Ann Meret Møller - have left the team, and two new review authors - FG and OK - have joined the team
17 April 2012	Amended	Contact details updated
12 October 2010	Amended	Contact details updated
30 June 2010	Amended	Typo corrected
8 June 2010	New citation required and conclusions have changed	This review is an update of the previous Cochrane systematic review (Sokol 2003a), which included five randomized controlled trials (RCTs) Previous review authors Sokol J, Jacobs SE and Bohn D decided they would not update the review (Sokol 2003a); new review authors Afshari A, Brok J, Møller AM and Wetterslev J have updated this version This review was previously known as 'Inhaled nitric oxide for acute hypoxaemic respiratory failure in children and adults' (Sokol 2003a) We found 10 new trials and chose to include 8 of them because they met our inclusion criteria (Cuthbertson 2000; Gerlach 2003; Ibrahim 2007; Mehta 2001; Michael 1998; Park 2003; Payen 1999; Taylor 2004). Two RCTs excluded from Sokol 2003a because they were published only as abstracts were included in our analyses (Day 1997; Schwebel 1997). We excluded 2 other trials (Meade 2003; Perrin 2006) In general, our review presents the same conclusions as were presented in Sokol 2003a. However, we included more trials and thus have provided more precise estimates on, for example, mortality. Furthermore, we applied several additional sensitivity and subgroup analyses that support the overall results
8 June 2010	New search has been performed	In the previous version (Sokol 2003a), databases were searched until 2002. We reran the searches until 31 January 2010. We have included risk of bias tables
8 June 2010	New search has been performed	In this updated systematic review, we have applied several new statistical methods to explore and reduce the size of bias, such as complete case analysis, test of interaction, trial sequential analysis, overall methodological bias assessment and analyses of various relevant clinical and physiological outcomes that were not addressed in Sokol 2003a. We have extended our search strategy to include additional electronic databases
25 July 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Fabienne Gebistorf (FG), Oliver Karam (OK), Jørn Wetterslev (JW), Arash Afshari (AA).

Conceiving of the review: AA, JW.

Co-ordinating the review: AA.
Undertaking manual searches: AA.
Screening search results: AA, FG, OK.
Organizing retrieval of papers: AA.
Screening retrieved papers against inclusion criteria: AA, FG, OK.
Appraising the quality of papers: AA, FG, OK.
Abstracting data from papers: AA, FG, OK.
Writing to authors of papers to ask for additional information: AA, OK.
Providing additional data about papers: AA.
Obtaining and screening data from unpublished studies: AA, FG, OK.
Managing data for the review: AA, JW, FG, OK.
Entering data into Review Manager (RevMan 5.3.5): AA, JW, FG, OK.
Analysing RevMan statistical data: JW, AA, FG, OK.
Performing other statistical analysis not using RevMan: JW, AA.
Performing double entry of data: data entered by person one: AA; data entered by person two: OK.
Interpreting data: AA, JW, FG, OK.
Performing statistical analysis: JW, AA, FG, OK.
Writing the review: AA, JW, FG, OK.

Performing previous work that was the foundation of the present study: Dr. Sokol, AA.
Serving as guarantor for the review (one review author): AA.
Taking responsibility for reading and checking the review before submission: OK.

Defining abbreviations (Table 9): FG, AA, OK.

DECLARATIONS OF INTEREST

Fabienne Gebistorf: none.

Oliver Karam: none.

Jørn Wetterslev is a member of the Copenhagen Trial Unit (CTU) task force. The CTU develop the theory and software for Trial Sequential Analysis (TSA) which is available free of charge at: www.ctu/tsa.

Arash Afshari: none.

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Internal sources

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External sources

- No external support, Other.

  No external support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2016

Title of the review changed. Acute lung injury is no longer mentioned in the title of the review. This is because as the Description of the condition section states, acute lung injury no longer exists and has instead been replaced by a gradation of ARDS that is based on the severity of hypoxaemia; the title of the updated review reflects this change.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Acute Lung Injury [*drug therapy] [mortality]; Administration, Inhalation; Hypoxia [*drug therapy] [mortality]; Length of Stay; Nitric Oxide [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome [drug therapy] [mortality]; Respiratory Insufficiency [*drug therapy] [mortality]; Vasodilator Agents [adverse effects] [*therapeutic use]

MeSH check words

Adult; Child; Humans