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Review Article

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The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane Systematic Review with trial sequential analysis

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Summary

Acute respiratory distress syndrome is associated with high mortality and morbidity. Inhaled nitric oxide has been used to improve oxygenation but its role remains controversial. Our primary objective in this systematic review was to examine the effects of inhaled nitric oxide administration on mortality in adults and children with acute respiratory distress syndrome. We included all randomised, controlled trials, irrespective of date of publication, blinding status, outcomes reported or language. Our primary outcome measure was all-cause mortality. We performed several subgroup and sensitivity analyses to assess the effect of inhaled nitric oxide. There was no statistically significant effect of inhaled nitric oxide on longest follow-up mortality (inhaled nitric oxide group 250/654 deaths (38.2%) vs. control group 221/589 deaths (37.5%; relative risk (95% CI) 1.04 (0.9–1.19)). We found a significant improvement in PaO_2/F_IO_2 ratio at 24 h (mean difference (95% CI) 15.91 (8.25–23.56)), but not at 48 h or 72 h, while four trials indicated improved oxygenation in the inhaled nitric oxide group at 96 h (mean difference (95% CI) 14.51 (3.64–25.38)). There were no statistically significant differences in ventilator-free days, duration of mechanical ventilation, resolution of multi-organ failure, quality of life, length of stay in intensive care unit or hospital, cost-benefit analysis and methaemoglobin and nitrogen dioxide levels. There was an increased risk of renal impairment (risk ratio (95% CI) 1.59 (1.17–2.16)) with inhaled nitric oxide. In conclusion, there is insufficient evidence to support inhaled nitric oxide in any category of critically ill patients with acute respiratory distress syndrome despite a transient improvement in oxygenation, since mortality is not reduced and it may induce renal impairment.

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Introduction

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) were initially defined by the American-European Consensus Conference (AECC) in 1994 [1]. In 2012, the ARDS definition task force developed the Berlin definition [2]. Acute respiratory distress syndrome is characterised by an inflammatory process of the alveolar–capillary membrane that may arise from a primary lung disease or be secondary to number of systemic disease processes [3]. It is mainly due to ventilation–perfusion mismatch, resulting in increased intrapulmonary shunting from pulmonary vasodilation in non-ventilated lung regions and vasoconstriction in ventilated areas, as well as pulmonary hypertension [4].

The incidence of ARDS is reported to be between 5 and 86 people per 100,000 per year in a general adult population [5–8]. Mortality among adults with ARDS ranges from 24% to 60% depending on age and the underlying general health of the patient [6, 9, 10]. Recent evidence indicates that the incidence of ARDS among children is 2–13 per 100,000 per year [11]. Paediatric in-hospital mortality was recently reported to be around 18–27%, with pneumonia, aspiration and sepsis as the primary causes of the condition [4, 11–14].

Nitric oxide is a potent endogenous vasodilator that can be exogenously administered via inhalation. It induces relaxation of vascular and bronchial smooth muscle and vasodilatation of blood vessels [15]. Inhaled nitric oxide has a half-life of 3–5 s, being rapidly inactivated on contact with haemoglobin. As a result, its vasodilatory effect may be limited to well-ventilated regions of the lung [16].

Inhaled nitric oxide has the ability to provide selective pulmonary vasodilatation in well-ventilated lung units, improve ventilation–perfusion mismatch and subsequently reduce the elevated pulmonary vascular resistance and pulmonary hypertension [17, 18]. Inhaled nitric oxide also increases right ventricular ejection fraction and decreases right endsystolic volume and thus prevents the decompensation of acute cor pulmonale [19]. However, nitric oxide also alters immune function [20–22] and inhibits platelet aggregation [23, 24].

Inhaled nitric oxide is used extensively worldwide as a rescue agent in severely hypoxaemic patients with ARDS [25]. Most patients with ARDS who receive inhaled nitric oxide respond with improved oxygenation, but the benefit appears to be transient [26, 27].

The primary objective of this review was to examine the effects of inhaled nitric oxide administration on mortality in adults and children with ARDS. We also planned to examine a number of secondary outcomes reflecting benefit and possible harm [28].

Methods

We included randomised, controlled trials (RCT) irrespective of publication status, date of publication, blinding status, outcomes reported or language of publication. We contacted the trial investigators and authors for relevant data. We included unpublished trials only if trial data and methodological descriptions were provided either in written form or could be retrieved from the trial authors. We excluded cross-over trials.

We included participants determined as having ARDS or acute lung injury according to the various definitions present in the literature. We did not study neonates described as having 'bronchopulmonary dysplasia' or 'chronic lung disease' as pathophysiology, treatment, prognosis and progression of disease are different.

We included trials comparing inhaled nitric oxide with placebo or no intervention in adults and children with ARDS. We included any type or dose of inhaled nitric oxide and any duration of administration. A co-intervention was allowed if administered to both groups. We excluded trials which only compared different inhaled nitric oxide treatment regimens, or if inhaled nitric oxide was compared with other interventions than placebo or no intervention.

Our primary outcomes were: (i) overall mortality (longest follow-up, regardless of the period of follow-up); and (ii) overall 28-day mortality. Our secondary outcomes were: (i) bleeding events; (ii) complications during the in-patient stay; (iii) PaO_2/F_IO_2 ratio; (iv) ventilator-free days; (v) duration of mechanical ventilation; (vi) oxygenation index; (vii) improvement in mean pulmonary arterial pressure; (viii) methaemoglobin concentration > 5%; (ix) nitrogen dioxide concentration > 3 ppm; (x) resolution of multi-organ failure;

(xi) quality of life assessment; (xii) length of stay in intensive care unit and in hospital; and (xiii) cost-benefit analyses.

We performed a search update up to 18 November 2015. We searched the Cochrane Central Register of Controlled Trials, SilverPlatter MEDLINE, SilverPlatter EMBASE, SilverPlatter BIOSIS Previews, International ISI Web of Science, Latin American Caribbean Health Sciences Literature (LILACS), Chinese Biomedical Literature Database; and advanced Google and Cumulative Index to Nursing and Allied Health Literature (CINAHL). We contacted the main authors of included studies to ask for any missed, unreported or ongoing studies. We searched for ongoing clinical trials and unpublished studies on the following Internet sites: (i) http://www.controlled-trials.com; (ii) http://clinicaltrials.gov; and (iii) http://www.centerwatch.com. No language restriction was applied to eligible reports.

Three review authors (FG, OK, AA) independently screened and classified all citations as potential primary studies, review articles or other. Also, the four review authors independently examined all potential primary studies and decided on their inclusion in the review (Fig. 1). All trials were evaluated for major potential sources of bias (random sequence generation, allocation concealment, blinding, intention-to-treat analysis, funding and completeness of follow up). We assessed each trial quality factor separately and defined the trials as having low risk of bias only if they adequately fulfilled all the criteria. We resolved any disagreements by consensus among the review authors.

We conducted the following subgroup analyses: (i) benefits and harms of inhaled nitric oxide in participants with ALI or ARDS based on the cause (primary lung injury vs. secondary lung injury); (ii) benefits and harms of inhaled nitric oxide in children (defined as aged less than 18 y) vs. adults; and (iii) benefits and harms of inhaled nitric oxide based on the duration of drug administration (short-term vs. long-term administration).

We calculated risk ratios (RR) with 95% confidence intervals (CI) for dichotomous data (binary outcomes) and used the mean difference (MD) or RR if data were continuous and measured in the same way between trials. We explored heterogeneity using the I^2 statistic and χ^2 test. An I^2 statistic above 50% represents substantial heterogeneity. In case of I^2 statistic $> 0\%$, we tried to determine the cause of heterogeneity by performing relevant subgroup analyses. We used the χ^2 test to provide an indication of heterogeneity between studies, with a $p \leq 0.1$ considered significant.

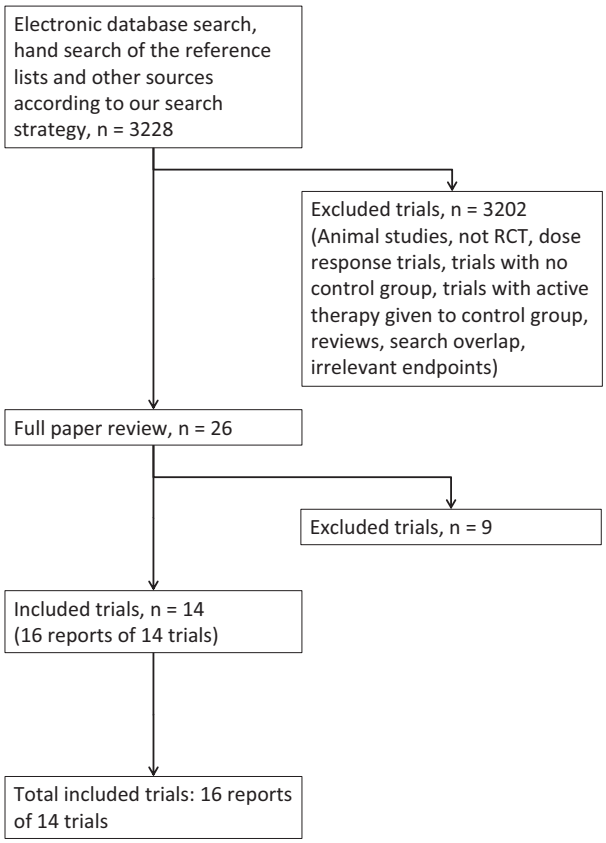

Figure 1 Flow diagram of inhaled nitric oxide search and study selection.

Trial sequential analysis is a methodology that combines the total accrued sample size of all included trials relative to the required information size (the cumulated meta-analytic sample size) with an adjusted threshold for statistical significance [29]. Trial sequential analysis is a tool for quantifying the statistical reliability of data in the cumulative meta-analysis, adjusting significance level for sparse data and repetitive testing on accumulating data. Thereby, we are able to adjust naïve 95% CI for sparse data and repetitive testing. For a more detailed description of this technique, see Supporting Information File S1 or visit ctu.dk/tsa.

We used the principles of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to provide an overall assessment of the evidence relating to all of our outcomes, evaluating within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. Furthermore, we used the Cochrane risk of bias tool in accordance with the Cochrane Handbook (see File S1).

Results

We found 3228 references that met our search strategy. Of these, only 16 reports of 14 trials were included. A total of 1275 participants were included in this review (Fig. 1). Full results are available in the Cochrane version [28].

The ARDS definition based on the European-American consensus statement was used for entry criteria in all included trials except two [30, 31]. Currently, no included study used the Berlin ARDS definition, as the most recent study's patient enrolment took place from 2003 to 2005 [32]. Acute lung injury with a modified definition from that of the consensus statement was used by two trials [33, 34]. Two studies were published in abstract form [35, 36]. There were no duplicate reports. Analyses of the impact of inhaled nitric oxide on oxygenation were hindered due to application of different indicators of oxygenation, different time points for oxygenation measurement, and demonstration of therapeutic effect in graphic form without adjacent numerical data in most publications. Other clinical outcome variables in line with our defined primary and secondary outcomes were inconsistently reported.

We classified four trials as paediatric trials [30, 32, 33, 37]; one further trial included a few children [38]; the remaining trials consisted of populations of critically ill adults. The sample size per study varied from 14 to 385 participants with ALI or ARDS.

The duration of intervention varied from less than 24 h to 4 weeks. An estimated median length of intervention was 7 days. Follow up ranged from 24 h to 1 year.

Nine trials applied a fixed dose of inhaled nitric oxide with a median (range) of 10 (5–10) ppm; [30–33, 35–37, 39, 40]. Four trials used the lowest dose to achieve an oxygenation response [34, 38, 41, 42], whereas one trial used different doses of inhaled nitric oxide [17]. One trial enrolled only patients who showed a response to inhaled nitric oxide [34].

Various co-interventions were applied, such as a recruitment manoeuvre [40], prone position [31–33, 39] and corticosteroids [17]. Five trials used pre-defined protocols for mechanical ventilation [33, 36, 39, 40, 42], whereas three unblinded trials adhered to guidelines [17, 31, 37].

The risk of bias assessments are provided in Table 1.

Combining data from the 13 relevant trials (1243 participants) and applying complete case analysis showed no statistically significant effect of inhaled nitric oxide on longest follow-up mortality: 250/654 deaths (38.2%) in the inhaled nitric oxide group compared with 221/589 deaths (37.5%) in the control group (RR (95% CI) 1.04 (0.9–1.19)); $I^2 = 0\%$; quality of evidence: moderate; Fig. 2).

We conducted trial sequential analysis (TSA) of inhaled nitric oxide versus control on longest follow-up mortality (Fig. 3). The TSA-adjusted confidence interval for the meta-analysis of the primary outcome resulted in an RR of 1.04 with a TSA-adjusted CI of 0.87–1.23 ($I^2 = 0\%$, diversity $D^2 = 0\%$). However, for low risk of bias trials, the RR was 1.02 with a TSA-adjusted CI of 0.79–1.33 ($I^2 = 0\%$, diversity $D^2 = 0\%$). Currently, with 1243 participants, only 41.9% of the required information size to detect or reject a mean difference of 15.91 is actually available at this stage. The required information size (required meta-analytic sample size) would be 3015 randomised participants. More detail on the TSA results is available in File S1.

We combined nine trials (1105 participants) in the 28-day mortality analysis with 202/587 deaths (34.4%) in the inhaled nitric oxide group and 166/518 deaths (32%) in the control group (RR (95% CI) 1.08 (0.92–1.27); $I^2 = 0\%$; quality of evidence: moderate) [17, 31, 32, 34, 35, 38, 40–42]. A total of five subgroup and sensitivity analyses were carried out in regard to our primary outcomes. No statistically significant effect was detected in any of the analyses.

Based on data from five trials (614 participants), we observed no statistically significant increase in bleeding events in the inhaled nitric oxide group

Table 1 Results of the assessment of bias risk: review authors' judgements about each methodological quality item for each included study.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bronicki [32]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk
Day [30]	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk
Dellinger [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dobyns [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Gerlach [39]	Unclear risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Ibrahim [33]	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk
Lundin [34]	Low risk	Low risk	High risk	Low risk	Low risk	High risk
Mehta [41]	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk
Michael [38]	High risk	Possibly	High risk	Low risk	Low risk	Low risk
Park [40]	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk
Payen [35]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Schwebel [36]	Unclear risk	Low risk	Low risk	Unclear risk	High risk	High risk
Taylor [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Troncy [42]	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk

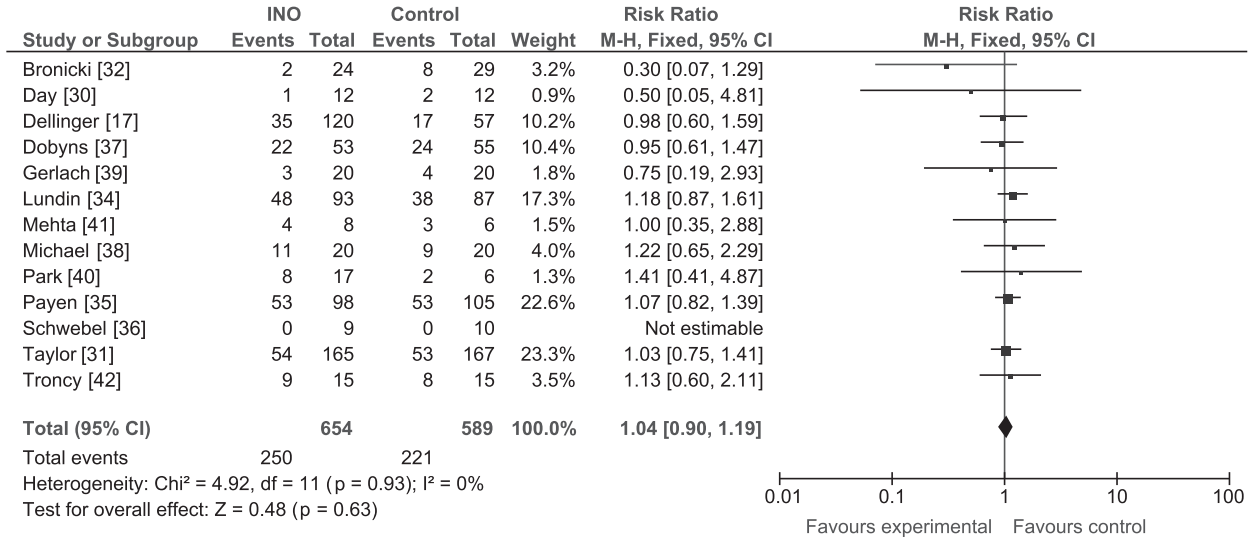

Figure 2 Forest plot for overall mortality. INO, inhaled nitric oxide; M–H, Mantel–Haentzel.

compared with the control group (RR (95% CI) 0.88 (0.43–1.79); I^2 = 0%; quality of evidence: moderate) [17, 34, 35, 38, 41].

Inhaled nitric oxide increased the risk of renal impairment based on data from four adult trials (945 participants, RR (95% CI) 1.59 (1.17–2.16); I^2 = 0%; Fig. 4; quality of evidence: high) [17, 31, 34, 35]. We accepted the various definitions of renal impairment as proposed by the authors.

The rate of severe respiratory failure decreased in the inhaled nitric oxide group based on data from one trial involving 180 participants (RR (95% CI) 0.21 (0.05–0.94); I^2 = 0%; quality of evidence: moderate) [34].

Other adverse events were variably reported, and differences in events such as pneumothorax, circulatory failure and shock, pneumonia, sepsis, encephalopathy, myocardial infarction, liver impairment, myopathy, agitation and hypertension did not reach statistical significance. Quality of evidence was high for pneumothorax and circulatory failure, but moderate for the other adverse events. Only one trial (385 participants) provided data indicating increased risk of infections in the inhaled nitric oxide group (RR

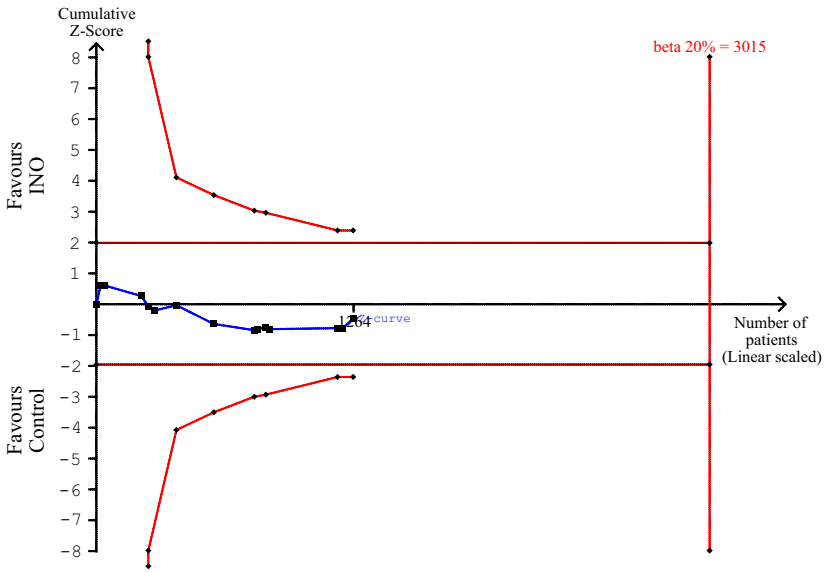

Figure 3 Trial sequential analysis of all trials of the effect of inhaled nitric oxide on mortality (longest follow up). INO, inhaled nitric oxide. Beta 20% is a two-sided graph.

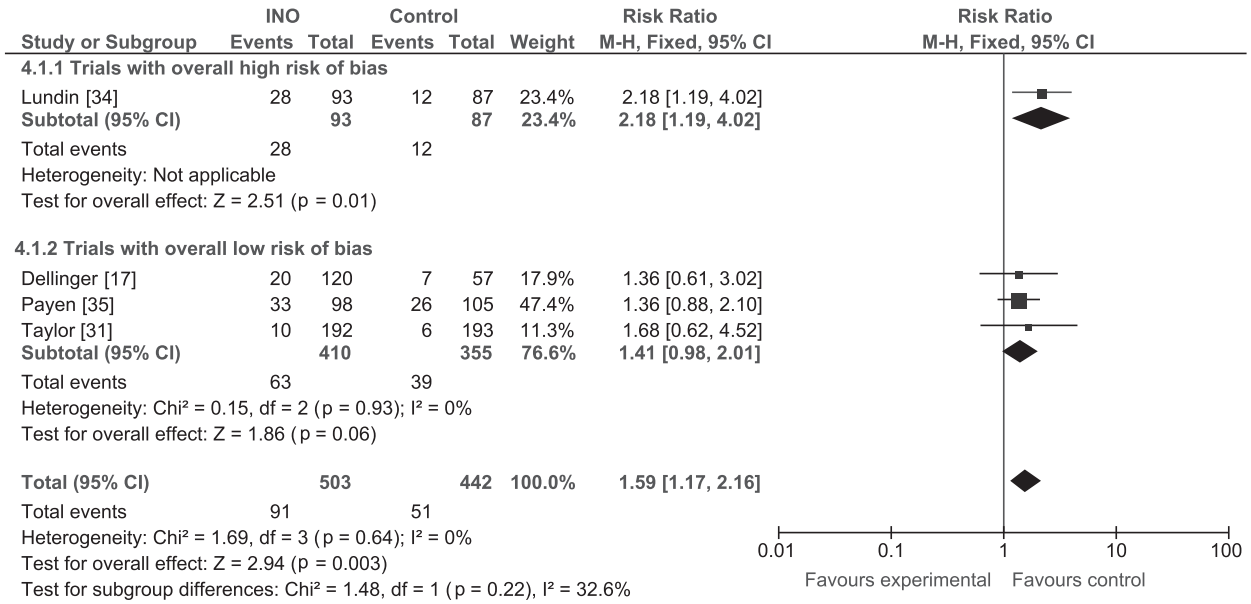

Figure 4 Forest plot for renal impairment. INO, inhaled nitric oxide; M–H, Mantel–Haentzel.

(95% CI) 1.62 (1.16–2.26); I^2 = 0%; quality of evidence: high) [31].

Eleven trials (614 participants) indicated an improved PaO_2/F_IO_2 ratio at 24 h (mean difference (95% CI) 15.91 (8.25–23.56); I^2 = 25%) [17, 30, 33, 34, 36–42]. An additional analysis of PaO_2/F_IO_2 difference from baseline at 24 h, based on data from three trials (155 participants), indicated a similar finding (MD (95% CI) 42.90 (20.57–65.23); I^2 = 58%) [37, 40, 42]. The PaO_2/F_IO_2 ratio at 48 h and 72 h no longer showed a statistically significant beneficial effect, while the analysis at 96 h, based on four trials (334 participants), indicated improved oxygenation in the inhaled nitric oxide group (MD (95% CI) 14.51 (3.64–25.38); I^2 = 0%; quality of evidence: moderate) [17, 34, 39, 41].

Application of TSA to the PaO_2/F_IO_2 ratio at 24 h did, however, indicate statistical significance in favour of improved oxygenation, since the z-curve crossed the

trial sequential monitoring boundary (Fig. 5). However, it is important to notice that only two trials were at low risk of bias. Based on the mean difference estimated from these two trials, the required information size would be 5137 randomised participants [17, 37]. More details on the TSA results are available in File S1.

There was no statistically significant effect of inhaled nitric oxide on ventilator-free days up to either day 28 or 30 (MD (95% CI) −0.57 (−1.82–0.69); I^2 = 0%; quality of evidence: high) based on five trials (804 participants) [17, 31, 35, 40, 42].

Six trials (390 participants) did not report any effect of inhaled nitric oxide on the duration of mechanical ventilation (MD (95% CI) 1.02 (−2.08–4.12); I^2 = 76%; quality of evidence: moderate) [30, 34, 37, 39, 40, 42].

The oxygenation index was significantly lower in the inhaled nitric oxide group at 24 h (MD (95% CI) −2.31 (−2.73 to −1.89); I^2 = 0%), based on five studies (368 patients) [17, 30, 32, 33, 37]. There was no statistically significant difference at 48 h (MD (95% CI) 1.99 (−10.40–14.38); I^2 = 74%) based on two studies (183 participants) [17, 30], but the difference was again statistically significant at 72 h (245 participants, MD (95% CI) −3.48 (−6.80 to −0.15); I^2 = 0%; quality of evidence: moderate) [17, 37].

All trials assessed mean pulmonary arterial pressure (1275 participants). Differences in mean pulmonary arterial pressure were initially significant at day one (MD (95% CI) −1.76 (−3.41 to −0.12); I^2 = 1%; quality of evidence: moderate) but no longer significant on days two, three or four.

All trials assessed methaemoglobin concentrations (1275 participants). Four participants in the inhaled nitric oxide group and three participants in the control group had methaemoglobin values > 5% (RR (95% CI) 0.88 (0.20–3.79); I^2 = 0%; quality of evidence: moderate).

Seven trials (959 participants) reported data on nitrogen dioxide [17, 31, 33, 35, 37, 39, 41], but only one trial reported 3/385 participants with concentrations exceeding 3 ppm, all of whom had received 80 ppm of inhaled nitric oxide (quality of evidence: high) [31].

Only one trial (385 participants) met our requirements in terms of trial intervention effect on resolution of multi-organ failure based on various illness scores, with no statistically beneficial effect (quality of evidence: high) [31].

One trial assessed quality of life (385 participants) as 'activities of daily living scale' and on the 'quality of well-being scale' [31]. Neither assessment supported intervention with inhaled nitric oxide. The 'activities of

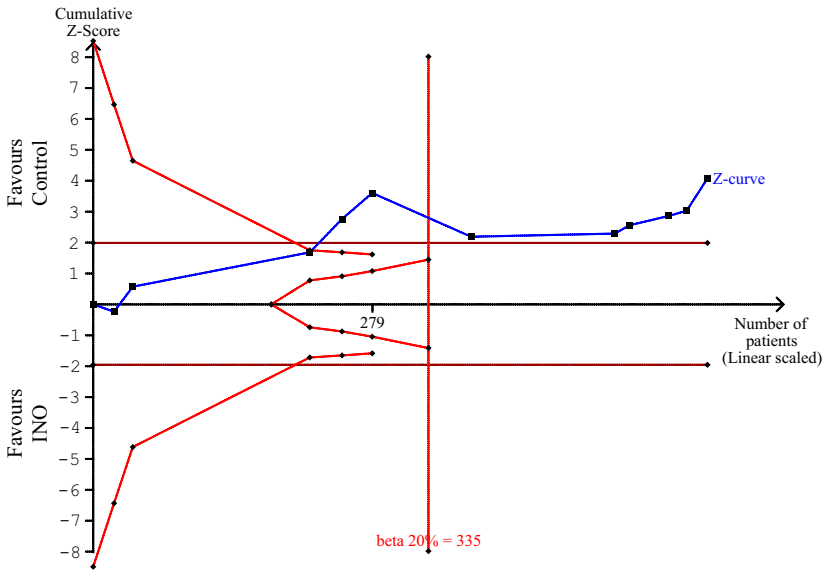

Figure 5 Trial sequential analysis of all trials of the effect of inhaled nitric oxide on PaO_2/F_IO_2 ratio at 24 h. Beta 20% is a two-sided graph.

daily living' scores at 6 months and 1 year did not indicate an improvement, while the 'quality of well-being' of survivors at 6 months and 1 year showed similar improvements in the inhaled nitric oxide and control groups, with slightly better scores in the control group – although this was not statistically significant (quality of evidence: high).

Data on length of stay in hospital were only provided by one trial (385 participants), with no indication of reduced stay in ICU or hospital (quality of evidence: high) [31].

Data for cost-benefit analysis were only provided by one trial (385 participants) [31]. The authors described similar hospital costs in the inhaled nitric oxide group (48,500 USD) and in the control group (47,800 USD), p = 0.8; quality of evidence: high.

Sensitivity analysis excluding data from articles published as abstracts did not change the overall results regarding significance.

For overall mortality, three paediatric trials, with a total of 185 participants, showed no statistically significant beneficial effect of inhaled nitric oxide (RR (95% CI) 0.78 (0.51–1.18; I^2 = 22%)), nor did the adult population subgroup (RR (95% CI) 1.08 (0.93–1.25); I^2 = 0%; quality of evidence: moderate; Fig. 6] [30, 32, 37].

Twelve trials with a total of 1190 participants had a median duration of intervention longer than 1 week [17, 30, 31, 34–42]. The current evidence does not support a longer duration of intervention (RR (95% CI) 1.07 (0.89–1.29); I^2 = 0%) nor a shorter duration of intervention (RR (95% CI) 1.04 (0.84–1.29); I^2 = 0%).

Comparing estimates of the pooled intervention effect based on the random sequence generation, allocation concealment, blinding, follow up, sample size calculation, early stopping and the overall risk of bias, did not result in any statistically significant finding in any of the subgroups examined. We identified four low risk of bias trials, which showed no statistical significance for our primary endpoint (see Table S1 in File S1) [17, 31, 35, 37].

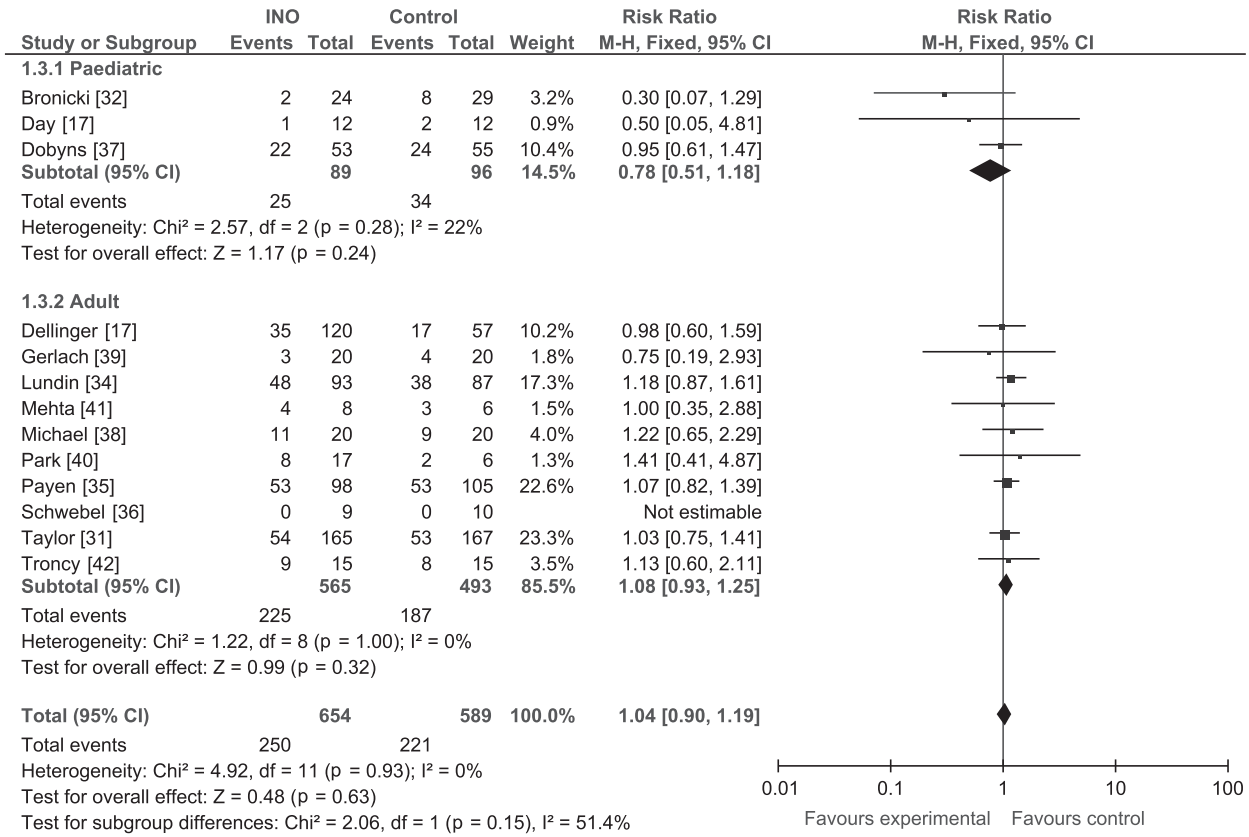

Figure 6 Forest plot for paediatric trials. INO, inhaled nitric oxide; M–H, Mantel–Haentzel.

Discussion

In this systematic review of 14 trials with 1275 participants with acute hypoxaemic respiratory failure, we found no evidence of benefit of inhaled nitric oxide on survival. The analysis of mortality showed no heterogeneity and was robust when subjected to different subgroup and sensitivity analyses. Conversely, inhaled nitric oxide increased the risk of renal failure in adults. It transiently improved oxygenation, but only for the first 24 h. The sparse data on mortality are not promising, but are not evidence of the absence of a beneficial effect; the data suggest that a potentially beneficial effect of inhaled nitric oxide must be modest at best, and the point estimate actually suggests it may be harmful. In addition, our mortality analysis on the longest follow-up may be influenced by the fact that only one trial provided long-term follow up of more than 6 months [43].

We did not find any statistically significant difference when examining the effects in subgroups according to duration of intervention, intervention among different populations (paediatrics, adults) and sensitivity analysis, excluding trials only published as abstracts. The three paediatric trials [30, 32, 37] that provided information on mortality had a total of 185 participants combined, which is insufficient to demonstrate any benefits or harms of inhaled nitric oxide therapy in paediatric ALI and ARDS. Subgroup and sensitivity analyses assessing the impact of varied primary aetiologies, reversal of ALI, resolution of multi-organ failure, quality of life assessment and bias assessment did not result in statistically significant findings. Additional analyses, such as adverse events, indicated an increased risk of renal failure among adults, while there were no signs of increased risk of bleeding, methaemoglobinaemia or increased nitrogen dioxide concentration except possibly among participants receiving inhaled nitric oxide doses above 80 ppm. Outcomes such as duration of stay in both the ICU and hospital, and other clinically relevant outcomes, were inconsistently reported. The subgroup analysis of reversal of ARDS was not performed as insufficient data were provided.

There are several possible explanations for why inhaled nitric oxide may not be beneficial. By reducing the ventilation-perfusion mismatch that exists in patients with ARDS, inhaled nitric oxide appears to initially improve oxygenation. However, inhaled nitric oxide could theoretically worsen the clinical condition by reversing hypoxic pulmonary vasoconstriction, thereby causing vasodilation in poorly ventilated areas, increasing the ventilation–perfusion mismatch and resulting in worsening oxygenation [44]. However, there appears to be little evidence to support the latter based on both the published data and our analyses [26]. Additonally, prolonged exposure to inhaled nitric oxide and its toxic metabolites could cause sensitisation and outweigh its possible benefits [39]. Improved oxygenation is not associated with increased survival since improved oxygenation does not necessarily indicate improved lung function, reduction of lung injury or resolution of the underlying cause of ARDS and the often co-existing multi-organ failure [45]. Nitric oxide is an important regulator of renal vascular tone and a modulator of glomerular function. At the same time, there are suggestions that changes in nitric oxide production could cause acute renal failure by altering the function of mitochondria, various enzymes, deoxyribonucleic acid and membranes [26]. The latter is in accordance with our finding of a possible harmful effect of inhaled nitric oxide on renal function.

Our systematic review has several potential limitations, that is, our findings and interpretations are limited by the quality and quantity of available evidence. The risk of bias of the included trials was mainly assessed by using the published data, which ultimately may not reflect the truth. All authors were contacted, but only a few responded and provided further information. We were unable to retrieve protocols of the published trials, and thus were unable to compare the published outcomes with the proposed outcomes in the protocols. Furthermore, the fact that only a small number of trials contributed to our subgroup and sensitivity analyses does limit the value of these analyses. In addition, there was variation: in the patient populations; the type, dose and duration of inhaled nitric oxide treatment; and length of follow up. We observed a consistent lack of improved survival across trials; the most beneficial effect was among the subgroup of trials with high risk of bias,

although this did not reach statistical significance. This minimises the possibility that some subgroups of patients may benefit from inhaled nitric oxide. No trial has used short-term inhaled nitric oxide among the subgroup of patients with critically low oxygenation in order to 'buy time' to instigate other treatments to improve lung function, and this issue remains controversial.

Although there was minimal heterogeneity among trial results on mortality, we are aware that we pooled heterogeneous trials in terms of age, patients, settings and treatment regimens. Thus, the validity of our meta-analysis may be criticised. However, all trials included patients with acute respiratory failure with similar inflammatory pathways. Therefore, we think that there is a strong biological rationale for performing a broad meta-analysis; this also considerably increases the generalisability and usefulness of the review. Furthermore, a broad meta-analysis increases power, reduces the risk of erroneous conclusions and facilitates exploratory analyses which can generate hypotheses for future research [46].

In general, our review, which is the update of a Cochrane review [28], reaches the same conclusions as Adhikari et al. [26]. However, we included more trials and thus have more precise estimates on mortality. Furthermore, we applied several sensitivity and subgroup analyses, trial sequential analysis and GRADE, which supported the overall results.

In conclusion, there is a need for large randomised trials with low risk of bias with a sample size of up to several thousand participants to evaluate inhaled nitric oxide for adults and children before this intervention can be definitely rejected or accepted for critically ill patients with ALI and ARDS. However, the current results are not promising and any potential benefit would seem modest; in addition, the actual point estimate of the intervention effect on mortality suggests that it may be harmful. Despite the heterogeneity that might exist in the patient populations in the included trials, and the high mortality rate among patients with ARDS and ALI, we believe that inhaled nitric oxide should only be used in the setting of a randomised clinical trial.

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Competing interests

No external funding or competing interests declared, apart for JW who is a member of the Copenhagen Trial Unit (CTU) task force. The CTU develops the theory and software for Trial Sequential Analysis (TSA) which is available free of charge at: www.ctu.dk/tsa.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plot of comparison of longest follow-up mortality.

Figure S2. Funnel plot of comparison of 28–30 day mortality.

File S1. Trial sequential analysis.