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Inhaled Nitric Oxide in Preterm Infants: A Systematic Review

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Inhaled Nitric Oxide in Preterm Infants: A Systematic Review

abstract

CONTEXT: Studies of the efficacy of inhaled nitric oxide (iNO) to prevent or treat respiratory failure in preterm infants have had variable and contradictory findings.

OBJECTIVES: To systematically review the evidence on the use of iNO in infants born at ≤34 weeks' gestation who receive respiratory support.

METHODS: Medline, Embase, the Cochrane Central Register of Controlled Studies, PsycInfo, ClinicalTrials.gov, and proceedings of the 2009 and 2010 Pediatric Academic Societies meetings were searched in June 2010. Additional studies from reference lists of eligible articles, relevant reviews, and technical experts were considered. Two investigators independently screened search results and abstracted data from eligible articles. We focus here on mortality, bronchopulmonary dysplasia (BPD), the composite outcome of death or BPD, and neurodevelopmental impairment.

RESULTS: Fourteen randomized controlled trials, 7 follow-up studies, and 1 observational study were eligible for inclusion. Mortality rates in the NICU did not differ for infants treated with iNO compared with controls (risk ratio [RR]: 0.97 [95% confidence interval (CI): 0.82–1.15]). BPD at 36 weeks for iNO and control groups also did not differ for survivors (RR: 0.93 [95% CI: 0.86–1.003]). A small difference was found in favor of iNO in the composite outcome of death or BPD (RR: 0.93 [95% CI: 0.87–0.99]). There was no evidence to suggest a difference in the incidence of cerebral palsy (RR: 1.36 [95% CI: 0.88–2.10]), neurodevelopmental impairment (RR: 0.91 [95% CI: 0.77–1.12]), or cognitive impairment (RR: 0.72 [95% CI: 0.35–1.45]).

CONCLUSIONS: There was a 7% reduction in the risk of the composite outcome of death or BPD at 36 weeks for infants treated with iNO compared with controls but no reduction in death alone or BPD. There is currently no evidence to support the use of iNO in preterm infants with respiratory failure outside the context of rigorously conducted randomized clinical trials. *Pediatrics* 2011;127:e414–e422

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KEY WORDS

nitric oxide, premature infant, systematic reviews

ABBREVIATIONS

iNO—inhaled nitric oxide
BPD—bronchopulmonary dysplasia
NDI—neurodevelopmental impairment
RCT—randomized controlled trial
PMA—postmenstrual age
RR—risk ratio
CI—confidence interval
CP—cerebral palsy
MDI—Mental Developmental Index

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Disorders related to prematurity and respiratory distress are among the leading causes of infant mortality in the United States.[1] Preterm infants suffer from both acute and chronic respiratory failure because of anatomic and biochemical disruption of lung function, lung inflammation and oxidative stress, nutritional deficiencies, and arrest of tracheobronchial and pulmonary vascular growth. Multiple etiologies make finding an effective treatment for respiratory failure in preterm infants challenging. Inhaled nitric oxide (iNO), a selective pulmonary vasodilator that decreases pulmonary vascular resistance without affecting systemic vascular tone,[2] has demonstrated efficacy in improving oxygenation and reducing the need for extracorporeal membrane oxygenation in late-preterm infants born after 34 weeks' gestation and term infants with respiratory failure; there is no evidence of long-term benefits or harm.[3] As use in this population increased, attention refocused to iNO use in more immature preterm infants with hypoxic respiratory failure, despite differences in disease pathophysiology.

Studies of the efficacy of iNO in preterm infants born at ≤34 weeks' gestation have been conducted in clinically diverse populations with varying birth weights and severity of illness and with significant variability in their clinical indications. iNO has been given as prophylaxis to prevent bronchopulmonary dysplasia (BPD), as rescue therapy for severe acute respiratory failure, and as treatment for severe BPD. Variable and contradictory findings regarding effects on the developing lung and on the developing brain have been reported. Reports of neurodevelopmental outcomes into early childhood are just emerging.

The Johns Hopkins University Evidence-Based Practice Center was commissioned to complete a systematic review of the evidence addressing both short-term and long-term outcomes in infants born at ≤34 weeks' gestation in preparation for a National Institutes of Health consensus-development conference. Specifically, we were asked to synthesize the evidence about the effect of iNO on survival and BPD and to assess short-term risks, rates of complications of prematurity, and long-term neurodevelopmental outcomes. Other interests included identifying the effects of iNO on subgroups of preterm infants and whether characteristics of iNO delivery influence outcome. The full evidence report provides a synthesis of the evidence for all outcomes we were asked to assess.[4] We focus here on the primary short-term outcomes of mortality and BPD and the composite outcome of death or BPD, as well as the longer-term outcomes of neurodevelopmental impairment (NDI) and death after NICU discharge.

METHODS

Details about our methods are available from the full evidence report.[4] We searched Medline (using PubMed), Embase, the Cochrane Central Register of Controlled Studies, and PsycInfo databases. The most recent search was completed in July 2010. We also searched the proceedings of the Pediatric Academic Societies meetings for 2009 and 2010 and scanned the reference lists of all eligible articles.

Search results were independently screened by 2 reviewers at the abstract and full-text-article level for eligibility. We excluded an article if it did not report any original data, include human infants born at ≤34 weeks' gestation receiving respiratory support, or address any of the research questions. Only randomized controlled trials (RCTs) were considered for NICU mortality, BPD, and short-term risks. We considered other study designs for the other research questions. Disagreements about eligibility were resolved by discussion.

Two reviewers independently completed all relevant data abstraction and risk-of-bias assessment. The risk of bias in RCTs was assessed by using the Cochrane Collaboration tool for assessing risk of bias from the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] The Newcastle-Ottawa Scale was adapted to determine the risk of bias of the reported data in cohort studies.[6] The body of evidence for each outcome was graded by using the methods outlined in the Evidence-based Practice Center draft methods guide.[7,8]

We conducted meta-analyses, using random-effects models, if an outcome was reported in multiple articles and was measured in a similar manner across studies. Analyses were run by using MetaAnalyst.[9]

RESULTS

We identified 3104 unique citations. Abstract and full-article screening resulted in 31 articles that were eligible for inclusion in the systematic review; these articles reported 14 RCTs with 7 follow-up studies and 1 observational study. Table 1 provides a summary of the study and patient characteristics. The 14 RCTs included samples ranging from 29 to 800 (median: 96.5) infants of varying gestational age, birth weight, and clinical conditions. The observational study was small and included a sample of 31 infants with documented pulmonary hypertension. Data from 3461 infants were available for the review. Infants were enrolled in studies from birth to 27 days. The dose of iNO varied among studies from a maximum dose of 5 ppm to a range from 5 to 40 ppm, depending on the response.

Figure 1 provides a summary of the risk of bias for the RCTs. Six of the 14 RCTs (along with their 5 follow-up stud-

TABLE 1 Study Design of RCTs and Observational Studies of iNO in Preterm Infants

Author (Year)	Sample Size, *n*	Age at Enrollment	GA, wk	BW, g	Start/Max iNO, ppm	Duration of iNO, d	Sites, *n*	Follow-up Study (Year)
RCTs								
Mercier et al[23] (2010)	800	<24 h	24–28.9	>500	5/5	7–21	36	—
Su and Chen[26] (2008)	65	Mean: 2.4–2.5 d	<32	≤1500	5/20	Mean: 4.9	1	—
Van Meurs et al[14] (2007)	29	24–25 h	<34	>1500	5/10	Maximum: 14	16	—
Ballard et al[11] (2006)	582	7–21 d	≤32	500–1250	20/20	Minimum: 24	21	Hibbs et al[16] (2007); Walsh et al[18] (2010)
Kinsella et al[13] (2006)	793	<48 h	≤34	500–1250	5/5	Maximum: 21	16	Watson et al[12] (2009)
Dani et al[28] (2006)	40	<7 d	<30	—	10/10	Mean: 4.1	1	—
Hascoet et al[22] (2005)[a]	145	6–48 h	<32	—	5/10	—	10	Hamon et al[35] (2005)
Field et al[24] (2005)	108	<28 d, median: 1 d	<34	—	5/40	Mean: 3.5	15	Huddy et al[30] (2008)
Van Meurs et al[15] (2005)	420	Mean 26–28 h	<34	401–1500	5/10	Maximum: 14	16	Hintz et al[10] (2007)
Schreiber et al[19] (2003)	207	<72 h	<34	<2000	10/10	7	1	Mestan et al[17] (2005)
Srisuparp et al[27] (2002)[a]	34	<72 h		<2000	20/20	Maximum: 7	1	—
Kinsella et al[20] (1999)	80	≤7 d	≤34	—	5/5	7–14	12	—
Franco-Belgian Collaborative NO Trial Group[21] (1999)	85	<7 d	<33	—	10/20	—	33	—
Subhedar et al[25] (1997)	42	4 d	<32	—	20/20	3–4	1	Bennett et al (2001) (31)
Cohort trial								
Tanaka et al[29]	31	—	<34	Median: 818–838	5-30	Median: 19.8 h	1	—
Total (15 trials)	3461	Birth to 27 d	≤34	401–2000	5–20/5–40	<1 to 24	1–36	—

All included infants were intubated on mechanical ventilation or continuous positive airway pressure. GA indicates gestational age; BW, birth weight; Max iNO, maximum dose of iNO.
[a] Studies reported only physiologic response to iNO and outcome to 28 days and, thus, were excluded from analyses.

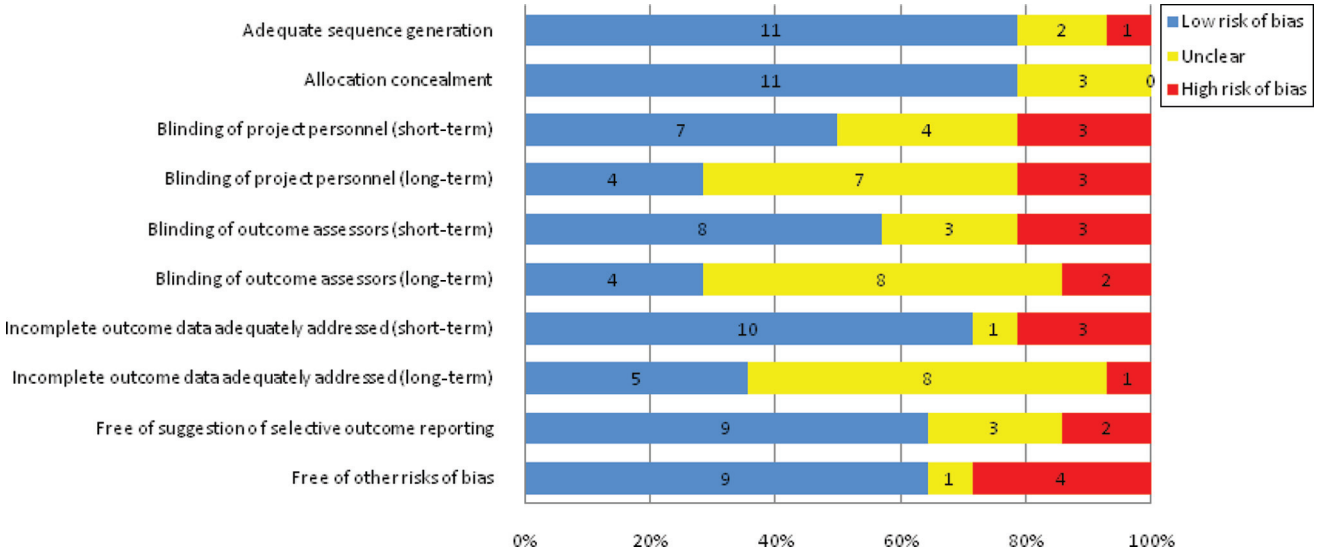

FIGURE 1
Summary of risk of bias for 14 RCTs.

ies) were assessed as having low risk of bias.[10–20] Three of the RCTs were determined to have an unclear risk of bias,[21–23] and the remaining 5 RCTs were at high risk of bias.[24–28] The observational study had a low risk of bias[29] (see the full evidence report[4] for details).

The grade of a body of evidence addressing an outcome is based on the risk of bias of the individual studies, as well as on other aspects such as the magnitude and consistency of the effect. The grade of the evidence for each short-term and long-term outcome was low to moderate (Table 2).

Mortality

Mortality data were reported for each of the 14 RCTs, but there was variation in the measurement of the time of death or survival (eg, death by 7 days, 28 days, 36 weeks' postmenstrual age [PMA], while in the NICU, or to 1 year of age, corrected for degree of prematurity). No matter how the trials defined or reported death or survival, no statistically significant difference between iNO and control groups was reported for any of the 14 RCTs.

TABLE 2 Summary of Meta-analyses for Short-term and Long-term Outcomes and the Grade of the Body of Evidence for Each Outcome

Outcome	Studies Included in the Meta-analysis, *n*	Participants Included in Meta-analysis, *n*	Grade	RR (95% CI)
Short-term outcomes				
Survival/death in the NICU	11	3136	Moderate	0.97 (0.82–1.15)
BPD at 36 wk PMA	8	1880	Moderate	0.930 (0.860–1.003)
Death or BPD at 36 wk PMA	11	3129	Low	0.93 (0.87–0.99)
Brain injury	5	1862	Low	0.86 (0.56–1.29)
Patent ductus arteriosus	9	2663	Moderate	1.01 (0.86–1.19)
Sepsis	8	2578	Low	1.05 (0.95–1.18)
Necrotizing enterocolitis	7	2476	Moderate	1.23 (0.94–1.26)
Retinopathy of prematurity, treated	8	1983	Moderate	1.01 (0.82–1.24)
Pulmonary hemorrhage	4	1758	Moderate	0.89 (0.60–1.33)
Air leak	7	2041	Moderate	0.96 (0.71–1.28)
Long-term outcomes				
Survival/death after NICU discharge	7	2157	Moderate	1.02 (0.86–1.20)
CP	7	914	Low	1.07 (0.67–1.71)
MDI < 70	3	339	Low	0.78 (0.39–1.60)
NDI	6	1299	Low	0.91 (0.74–1.12)

In a meta-analysis of 11 RCTs that reported death by 36 weeks' PMA or in the NICU, the pooled risk ratio (RR) was 0.97 (95% confidence interval [CI]: 0.82–1.15) (Fig 2).

Nine studies reported mortality or survival beyond the NICU from 1 to 4 to 5 years of age; none reported a difference between iNO and control groups.[10,12,14,16–18,24,30,31] A meta-analysis performed with 7 trials[10,12,14,17,18,24,31] that reported mortality from 12 to 30 months of age (median: 18–22 months) revealed no difference with iNO therapy compared with controls (RR: 1.02 [95% CI: 0.86– 1.20]).

To investigate the effect of iNO dose on mortality and other outcomes, the RCTs were grouped as follows: dose restricted to 5 ppm; dose restricted to a maximum of 10 ppm; and dose given as 20 ppm or titrated to response with a maximum of 20 to 40 ppm. Meta-analyses were conducted with trials from which death in the NICU at ≥36 weeks' PMA was reported. There was no statistically significant difference between the iNO-treated infants and controls when iNO was given at 5 ppm (RR: 0.97 [95% CI: 0.70–1.35]),[13,20,23] 10 ppm (RR: 1.00 [95% CI: 0.73–1.38]),[14,15,19,28] or 20 ppm or titrated to response (RR: 0.91 [95% CI: 0.63–1.30]).[11,21,25,26]

Four RCTs investigated whether iNO therapy had a differential effect according to birth weight.[11,13,15,19] Birth-weight subgroup analyses were planned a priori in 2 trials[11,13] and were performed post hoc for the other 2 trials.[15,19] There was no statistically significant difference in the rate of death between iNO and control infants in the birth-weight subgroups (<750, 750–999, 1000–1250, and ≤1000 g and others [see the full report[4] for a complete discussion]). For infants with a birth weight of >1000 g, it was reported from 1 study that the iNO-treated infants had a higher mortality rate than those in the control group (62% vs 48%) (RR: 1.28 [95% CI: 1.06–1.54]).[15] Meta-analyses of trials from which outcomes according to birth-weight subgroups were reported were not performed because of the differences in definitions of birth-weight categories and differences in outcomes reported from these few trials.

Bronchopulmonary Dysplasia

Twelve RCTs provided data on BPD at 36 weeks' PMA, but there was variability in how BPD was defined. Six RCTs defined BPD as simply receiving supplemental oxygen at 36 weeks' PMA.[14,15,20,21,24,28] The others added radiologic evidence of BPD[13,19,25,26] or an oxygen-challenge test.[11,23] The denominator used to calculate the rate of BPD also varied: 5 used the total number of infants enrolled in each group,[11,24–26,28] and 8 RCTs used the number of survivors in each group.[13,14,15,19–21,22]

Despite variations in how BPD was defined and calculated, there were no statistically significant differences in rates of BPD at 36 weeks' PMA between the iNO group and controls in any of the RCTs. A meta-analysis with the 8 studies that reported BPD at 36 weeks' PMA among survivors revealed no statistically significant difference between infants treated with iNO and controls (RR: 0.93 [95% CI: 0.86–1.003]) (Fig 2).

BPD developed as frequently in those treated with 5-ppm iNO in 3 studies as controls when measured at 36 weeks' PMA (RR: 0.94 [95% CI: 0.87–1.02]).[13,20,23] The risk of BPD was mixed when iNO was given at a maximum dose of 10 ppm in 4 trials.[14,15,19,28] Our meta-analysis with these 4 RCTs revealed a 25% reduction in the risk of BPD at 36 weeks for infants treated with iNO compared with controls (RR: 0.75 [95% CI: 0.61–0.91]). The rate of BPD at 36 weeks' PMA was not different when we compared infants treated with 20 ppm or iNO titrated to response to those who received standard care in the 4 RCTs that used this dosing strategy (RR: 1.00 [95% CI: 0.74–1.34]).[11,21,25,26]

Only 1 trial of 2 from which the incidence of BPD at 36 weeks' PMA was reported revealed a difference be-

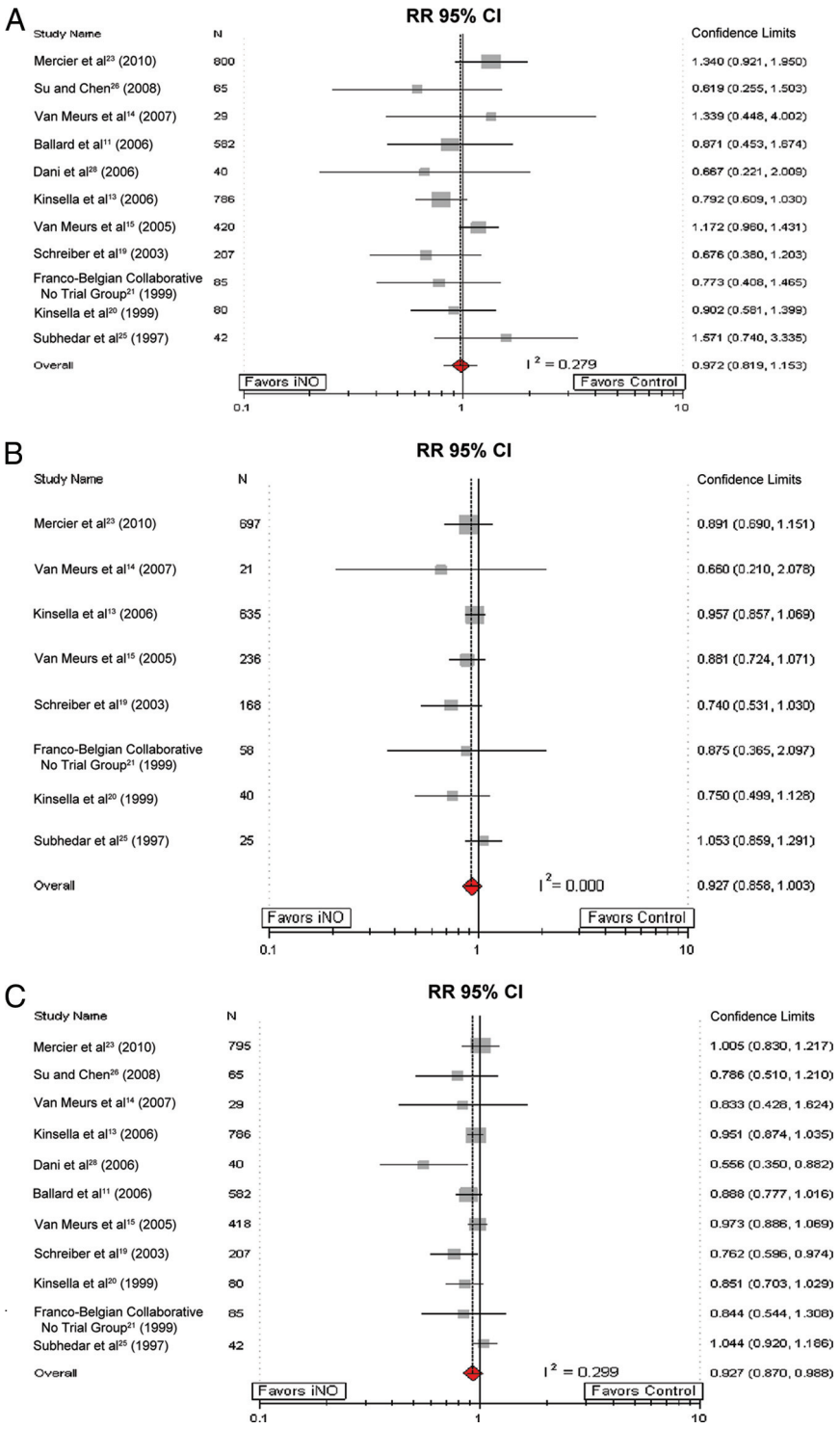

FIGURE 2
Meta-analyses of RCTs that described death (A), BPD (B), and the composite variable death or BPD (C) at 36 weeks' PMA

tween infants treated with iNO and controls for any birth-weight subgroup.[13,15] Among the 1000- to 1250-g birth-weight stratum, Kinsella et al[13] reported a lower rate of BPD for infants treated with iNO compared with controls (29.8% vs 59.6%) (RR: 0.50 [95% CI: 0.32–0.79]).

Death or BPD

The composite outcome of death or BPD at 36 weeks' PMA was reported from 11 RCTs.* Eight RCTs reported no statistically significant difference between iNO-treated infants and controls, and 3 RCTs reported statistically significant differences between the groups.[11,19,28]

Ballard et al[11] found a statistically significant benefit in survival without BPD at 36 weeks' PMA for the iNO group ($n = 294$) compared with placebo controls ($n = 288$) (44% vs 37%) (RR: 1.23 [95% CI: 1.01–1.51]). For comparison with the other RCTs, we calculated the complement composite variable, death or BPD at 36 weeks' PMA (56% of the iNO group vs 63% of the control group), to include in the meta-analysis (Fig 2).

Schreiber et al[19] reported the rate of death or BPD as 49% in the iNO group ($n = 105$) compared with 64% in the placebo control group ($n = 102$) (RR: 0.76 [95% CI: 0.60–0.97]). This RCT enrolled larger infants than the other RCTs (those with a birth weight of <2000 g).

The small RCT ($n = 40$) reported by Dani et al[28] was stopped early because an unplanned interim analysis revealed a statistically significant difference ($P = .02$) in death or BPD: 50% of infants in the iNO group compared with 90% of infants in the control group (RR: 0.11 [95% CI: 0.02–0.61]).

A meta-analysis with all 11 RCTs from which death or BPD at 36 weeks' PMA was reported revealed a small but statistically significant difference favoring iNO (RR: 0.93 [95% CI: 0.87–0.99]) (Fig 2).

The study by Ballard et al[11] was different in design than the other RCTs in that it enrolled infants from 7 to 21 days of age with evolving BPD and treated them for a minimum of 24

*Refs 11, 13–15, 19–21, 23, 25, 26, and 28.

days.[11] Because of this difference, a sensitivity analysis was performed by removing it from the meta-analysis. The result did not change the effect estimate for death or BPD at 36 weeks' PMA (RR: 0.93 [95% CI: 0.87–1.000]) but did influence the CIs.

The dose of iNO had no differential effect on the composite outcome of death or BPD, and there was a similar risk for infants treated with 5-ppm iNO compared with controls (RR: 0.94 [95% CI: 0.88–1.01]),[13,20,23] a maximum dose of 10-ppm iNO compared with controls (RR: 0.81 [95% CI: 0.64–1.03]),[14,15,19,28] or with 20-ppm iNO or titrated to response compared with controls (RR: 0.94 [95% CI: 0.84–1.06]).[11,21,25,26]

No study reported a statistically significant difference between iNO-treated and control infants for the <1000-g birth-weight groups (<750, 750–999, and <1000 g). For the 1000- to 1250-g birth-weight stratum, Kinsella et al[13] reported a significant reduction in the combined outcome of death or BPD for the iNO-treated infants compared with controls (38.5% vs 64.1%) (RR: 0.60 [95% CI: 0.42–0.86]). In posthoc analyses for the subgroup of infants with a birth weight of >1000 g, Van Meurs et al[15] also found a lower rate of the composite outcome of death or BPD for the iNO-treated group compared with the control group (50% vs 69%; $P = .03$) (RR: 0.72 [95% CI: 0.54–0.96]) but no difference in death alone or the rate of BPD.

Short-term Risks of iNO

There was no evidence in the RCTs or from our meta-analyses that treatment of preterm infants with iNO influences the rates of other complications of prematurity, including patent ductus arteriosus, sepsis, necrotizing enterocolitis, severe retinopathy of prematurity, pulmonary hemorrhage, or air leaks (Table 2). From no study was accumulation of toxic levels of methemoglobin reported. A complete discussion of the short-term risks of iNO is provided in the full evidence report.[4]

Neurodevelopmental Impairment

Any discussion of NDI in preterm infants must be in the context of brain injury, which is common in preterm infants on mechanical ventilation. Studies that compared head ultrasound results before and after treatment can best determine if exposure to iNO has a toxic or neuroprotective effect on the brain. Only 4 RCTs obtained head ultrasounds at or before enrollment and compared them to subsequent serial ultrasounds.[11,13,20,25] Kinsella et al[13] reported no worsening intraventricular hemorrhage or intraparenchymal hemorrhage during or after treatment between iNO and placebo control groups (12.3% vs 16.0%, respectively) (RR: 0.77 [95% CI: 0.54–1.09]). However, a statistically significant reduction in the incidence of periventricular leukomalacia was seen in infants in the iNO group (5.2%) compared with controls (9.0%) (RR: 0.58 [95% CI: 0.33–1.00]; $P = .048$). There were no differences between the iNO and control groups in the evolution of neurologic findings in the other 3 studies that obtained head ultrasounds before and after iNO treatment.[11,20,25]

Five RCTs compared the rate of a composite outcome of brain injury, defined as intraventricular hemorrhage with ventriculomegaly, intraparenchymal hemorrhage, or periventricular leukomalacia between infants treated with iNO and controls.[11,13–15,19] In a meta-analysis of these studies, there was no statistically significant difference between the groups (RR: 0.86 [95% CI: 0.58–1.29]). It is not surprising that the 2 RCTs with the lowest RR of brain injury differed from the other studies by including larger preterm infants (those with a birth weight of >1500 g).[14,19] Similarly, a meta-analysis of the 5 RCTs from which the incidence of periventricular leukomalacia was reported revealed no difference between the iNO and control groups (RR: 0.78 [95% CI: 0.37–1.62]).[14,20,23,26,28]

Cerebral palsy (CP) cannot be diagnosed in the neonate; it requires a neurologic examination and assessment of motor function ≥1 years after birth. Authors of most studies of iNO have reported moderate-to-severe CP assessed at 18 months to 4 to 5 years. A pooled estimate of the risk for CP calculated from the 7 studies[10,14,17,18,29,30,31] from which this outcome was reported revealed no difference between iNO-treated infants and controls (RR: 1.07 [95% CI: 0.67–1.71]) (Fig 3).

Cognitive outcomes were reported from 6 RCTs. Three studies defined cognitive impairment as a Mental Developmental Index (MDI) of <70 (2 SDs below the mean) on the Bayley Scales of Infant Development II.[10,14,17] Our meta-analysis with these 3 studies revealed no statistically significantly difference between those treated with iNO and controls (RR: 0.78 [95% CI: 0.39–1.60]) (Fig 3). No difference was reported between iNO-treated infants and controls for studies that defined cognitive delay as an MDI of <85 (1 SD below the mean),[31] cognitive impairment as 2 SDs below the mean on the General Conceptual Ability Score of the British Ability Scales,[30] or normal cognition as an MDI of >85.[18]

Seven studies reported the proportion of children with NDI, a combined variable that included cognitive, neuromotor, and sensory impairments.[10,12,14,17,18,30,31] Six trials from which comparable neurodevelopmental outcomes were reported (MDI < 70, moderate-to-severe CP, blindness, hearing impairment) at 12 to 30 months of age were included in a meta-analysis, which revealed no statistically significant difference in the

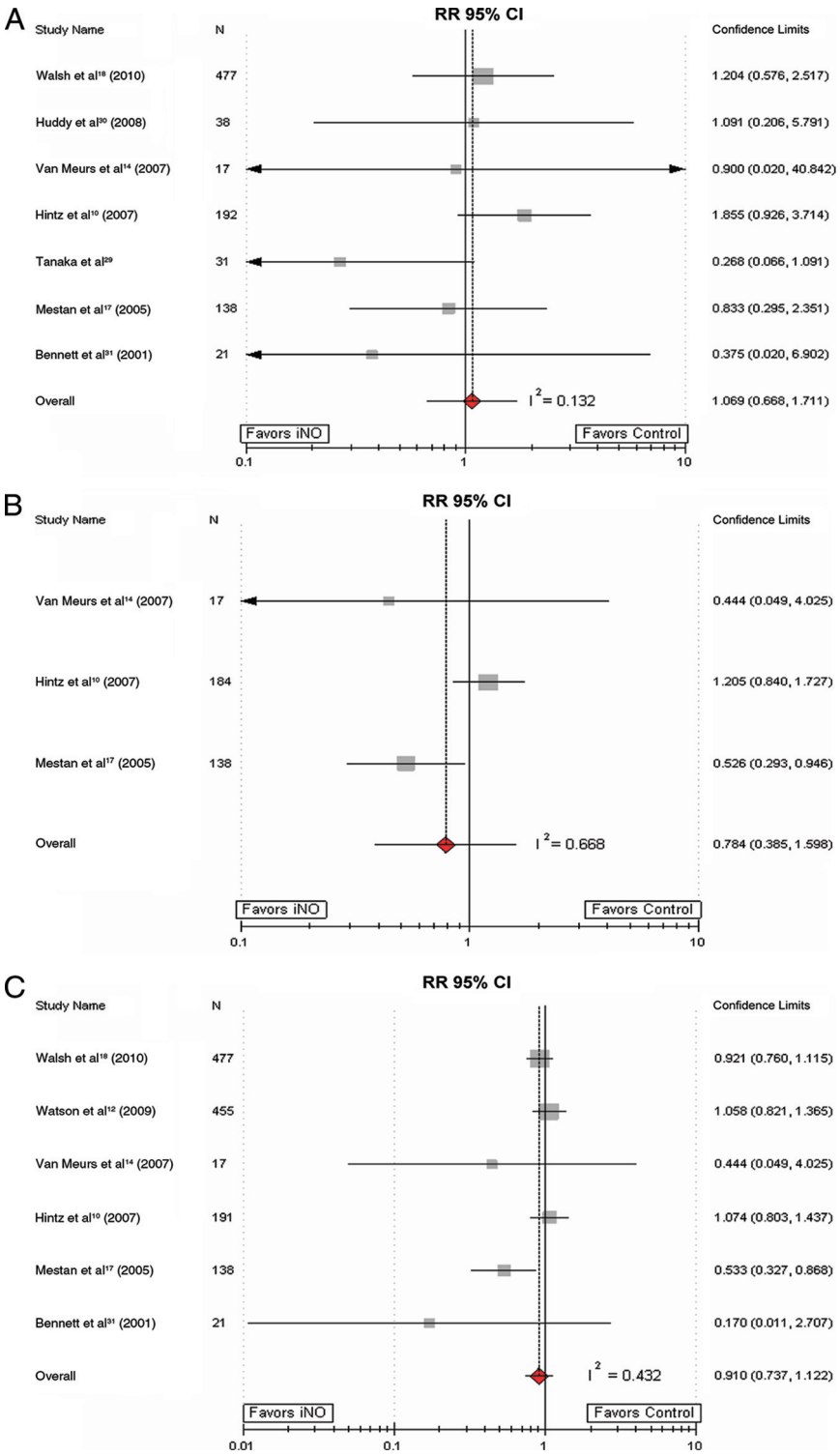

FIGURE 3
Meta-analyses of CP (A), cognitive impairment (B), and NDI (C).

proportion of infants with NDI between those who received iNO when compared with the control group (RR: 0.91 [95% CI: 0.77–1.12]) (Fig 3).

No meta-analyses were conducted for dose of iNO and NDI, because the definition of impairment varied widely between studies that used similar dosing strategies. There was no statistically significant difference in NDI between iNO and control groups at doses of 5 ppm,[12] or 20 ppm or titrating the dose to response[10,17,18,24,25,30,31]; however, at 10 ppm, results were inconsistent. Hintz et al[10] found that moderate-to-severe CP was increased in the iNO group (20% vs 11%), a difference that was not significant in univariate analysis but reached significance in multivariable models after adjustment for infant characteristics at study entry in 1 model (RR: 2.01 [95% CI: 1.01–3.98]) and infant characteristics and NICU morbidities in another model (RR: 2.41 [95% CI: 1.01–5.75]). Mestan et al,[17] who reported on the outcome of survivors at 2 years of age, described a 47% decrease in the risk of cognitive impairment, defined as an MDI of <70 (RR: 0.53 [95% CI: 0.29–0.94]) but no effect on motor impairment. Fewer infants treated with iNO had NDI than infants treated with placebo (24% vs 46%, respectively; $P = .01$). This difference in the composite outcome was the result of fewer infants with cognitive impairment in the iNO group, because there was no difference between the groups in the rate of CP or vision or hearing loss.

No differences were reported in NDI between iNO and control infants in the 2 trials that assessed this outcome according to birth-weight subgroup.[10,12]

DISCUSSION

The impetus for the study of iNO in preterm infants who receive respiratory support is the search for an effective treatment that improves the survival rate and pulmonary health without increasing the risk of adverse short-term and long-term outcomes. Our systematic review of the published evidence revealed no benefit or increased risk to preterm infants born at ≤34 weeks' gestational age treated with iNO compared with control in-

fants for mortality, BPD at 36 weeks' PMA, short-term risks (patent ductus arteriosus, sepsis, necrotizing enterocolitis, treated retinopathy of prematurity, pulmonary hemorrhage, air leak, brain injury), or NDI. A small (7%) but statistically significant reduction in the risk of the composite outcome of death or BPD at 36 weeks' PMA was found to favor iNO therapy.

Our results are similar to those found by Barrington and Finer,[32] who divided 11 RCTs into categories on the basis of inclusion criteria: (1) the early routine use of iNO (treatment in the first 3 days after birth); (2) early rescue treatment based on oxygenation inclusion; and (3) enrollment based on increased risk of BPD ≥4 days after birth. A statistically significant reduction in the incidence of death or BPD (RR: 0.91 [95% CI: 0.84–0.99]) and in severe intraventricular hemorrhage, intraparenchymal hemorrhage, or periventricular leukomalacia (RR: 0.70 [95% CI: 0.53–0.91]) was seen only with early treatment. At the time of the Barrington and Finer publication, neurodevelopmental outcome was available for only 2 RCTs.[17,31] With the inclusion of 3 more RCTs,[14,23,26] including 1 with 800 infants,[23] and neurodevelopmental follow-up results from 8 RCTs,[10,12,14,16–18,30,31] we found no increase in the risk of brain injury and no differential effect of iNO therapy on neurodevelopmental outcomes into early childhood.

Whether the small, statistically significant reduction in the incidence of death or BPD is clinically meaningful depends on one's point of view. Many parents would grasp at even that small of a difference in their sick preterm infant's chances in surviving without BPD. Barrington and Finer[32] and Askie et al[33] in a preliminary report of an individual-patient-data meta-analysis contend that current evidence does not support the routine use of iNO to treat preterm infants, and we agree. We do not conclude, however, that we should abandon the possibility that iNO may someday become a component of a treatment strategy for some preterm infants who receive respiratory support. Several factors contribute to our recommendation to continue the study of iNO: (1) our finding a small but statistically significant difference in death or BPD at 36 weeks' PMA, the common primary outcome variable of 73% of RCTs conducted to date; (2) a lack of studies powered to detect meaningful differences in subgroups of preterm infants or in the longer-term functional outcome or quality of life of infants treated with iNO compared with routine therapy; and (3) advances in our understanding of the biological mechanisms of action of iNO in preterm infants, which suggest different study questions and designs than many of those previously reported.

As RCTs and cohort studies of iNO in preterm infants were being conducted, off-label use of iNO in this population dramatically increased. One publication reported a sixfold increase in its use between 2000 and 2008 in a large multisite pediatric group.[34] The lack of standardized definitions, measurements, and reporting of outcomes in studies of preterm infants make direct comparisons between trials and synthesis of data from multiple trials difficult and likely contributed to the off-label use of iNO. Future research should address gaps in knowledge concerning iNO therapy for preterm infants by using standardized measurements and outcomes, which is particularly true for neurodevelopmental outcomes. Our review also revealed no evidence for an optimal dose of iNO or an optimal duration of therapy.

CONCLUSIONS

Future studies on the efficacy of iNO therapy for preterm infants who receive respiratory support should have strong conceptual frameworks that test hypotheses on the mechanism by which iNO improves pulmonary or neurodevelopmental outcomes. Those who develop strategies for treatment need to consider how different preterm infants are from term infants. Their immature organ systems are not prepared to support extrauterine life, and they lack important natural defenses (eg, surfactant, cortisol, immune responses). The degree of lung and brain maturation is an important variable, and treatment should be viewed in terms of PMA, a construct that better reflects organ maturation than gestational age at birth or chronological age. iNO may also be viewed as a potential growth promoter of the lung and its underlying vascular bed, requiring a longer duration of treatment than has been previously studied and bears investigation. Future research should also measure biomarkers. Evaluating the effect of iNO on brain injury requires neuroimaging before treatment, as well as serial imaging during studies. BPD at 36 weeks' PMA and evidence of brain injury on ultrasound are intermediate variables and should be thought of in that context. Prolonged hospitalizations, use of supplemental oxygen and pulmonary medications after NICU discharge, prevalence of reactive airway disease, and recurrent hospitalizations are more important indicators of pulmonary function and health.[16] Neurodevelopmental outcomes and functional abilities in childhood are far more important outcomes than evidence of brain injury on neuroimaging studies. Ongoing basic science and clinical research on the developing lung and brain, and their response to and recovery from injury, can provide insights that lead to testable hypotheses for future RCTs.

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