REVIEW ARTICLE

Inhaled nitric oxide in preterm infants: An updated meta-analysis

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Background: In the past several years, randomized controlled trials (RCTs) have indicated that inhaled nitric oxide (iNO) can potentially lower for both the incidence of bronchopulmonary dysplasia (BPD) and mortality in affected infants. Other research has, however, disagreed with these findings. **Materials and Methods:** We performed an updated meta analysis of all relevant RCTs to assess the benefits of iNO in preterm infants by searching PubMed, EMBASE, Cochrane databases, Wanfang, VIP, and CNKI databases for English and Chinese references. **Results:** Ultimately, 22 RCTs were incorporated. (1) Risk of BPD was significantly lower in preterm infants supplemented with iNO (relative risk [RR] = 0.88; $P = 0.0007$). There are no differences concerning pulmonary hemorrhage (PH) (RR = 0.94; $P = 0.72$). (2) Incidences of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and severe intracranial hemorrhage (ICH) were compared. No significant difference was discovered concerning these risks (RR = 1.21, $P = 0.08$; RR = 1.01, $P = 0.89$; and RR = 0.99, $P = 0.86$). (3) In addition, no significant differences were found between experimental and control groups with respect to morality. (RR = 1.00, $P = 0.98$). **Conclusion:** Our meta analysis has shown a beneficial effect in BPD and morality. In addition, our meta analysis suggests that iNO therapy does not increase the risk of common complications, such as NEC and ROP, and that it may also have no adverse effect on bleeding tendency diseases (severe ICH and PH).

Key words: Meta-analysis, nitric oxide, preterm

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INTRODUCTION

Under physiological conditions, endogenous production of nitric oxide (NO) is by catalysis of l-arginine by NO synthase. Moreover, in normal infants, there is a surge of endogenous NO from exhaled gas of breath at 0.2–2 ppm, which is 10–100 times of the level in adult. By rebreathing, it infused into intrapulmonary tissue by diffusion, dilating smooth muscles of resistive pulmonary arteries and arterioles, augmenting pulmonary blood flow, orchestrating ventilation-perfusion with alveolar expansion, and lung fluid absorption in the postnatal adaptation.[1] After a long time of experimental and clinical studies, in term infants, both persistent pulmonary hypertension of the newborn (PPHN) and hypoxic respiratory failure (HRF) have been treated effectively with inhaled NO (iNO) therapy,[2,3] and this treatment has been applied routinely to term babies in clinical work. However, when it comes to preterm babies, different randomized controlled trials (RCTs) of iNO in premature newborns have yielded conflicting results to date. Some researches found improvements in pulmonary morbidity and mortality in preterm babies.[4,5] Theoretically, iNO does minimize oxidant stress by the downregulation of lung-derived cytokines, suggesting decreases in brain injury and mortality of infants. However, on the contrary, using the similar study design as before,

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the EUNO trial[6] involved 800 preterm infants with gestational age <29 weeks, and their work showed that early use of low-dose iNO did not improve survival rate in very premature babies without brain injury (such as intracranial hemorrhage [ICH]).

Considering the aforementioned uncertainties about efficacy and safety of iNO with severe respiratory distress syndrome (RDS) or respiratory failure, our updated meta-analysis was designed to focus on the uncertainties in three areas. First, are there significant differences between experimental and control groups concerning bronchopulmonary dysplasia (BPD) and pulmonary hemorrhage (PH)? Second, with respect to the possible side effects of extrapulmonary lesions, are the incidences of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and severe ICH higher in the experimental group? Third, based on potential influence on death, is there significant difference between experimental and control groups with respect to mortality?

METHODS

Study selection

Guidelines from the CONsolidated Standards of Reporting Trials (CONSORT) group and the CONSORT statement were followed for this systematic review and meta-analysis.[7,8] To screen eligible studies published since each database was established, a search was conducted by two investigators involved in this research in PubMed, EMBASE, and Cochrane databases for English studies and Wanfang, VIP, and CNKI databases for Chinese studies (databases were last launched on July 1, 2015). The following search terms were employed: "Nitric oxide," "preterm infants," "neonates," and "NO." The inclusion criteria of this meta-analysis were as follows: (1) RCT involving preterm infants (without consideration of birth weight) who were receiving respiratory support (either mechanical ventilation or continuous positive airway pressure); (2) administration of iNO within the newborn period. Hence, reviews, meta-analyses, animal experiments, non-iNO experiments, and studies without sufficient clinically relevant data were excluded from the study. Any discrepancy was independently resolved by a third investigator involved in this research.

Disease definition

BPD is defined as oxygen use at 36 weeks' postmenstrual age or 28 days after birth; severe ICH is defined as Grade 3, blood acutely distending the lateral ventricles or Grade 4, blood within the ventricular system and parenchyma. NEC is diagnosed in the presence of abdominal distension, gastric residuals with or without bile-stained vomiting and bloody diarrhea or stools, hypotension, and suggestive abdominal radiogram. ROP is graded according to the International Classification. PH is diagnosed in the presence of pouring a lot of bloody discharge in endotracheal intubation.

Data abstraction

The CONSORT statement contains 22 items including participants, intervention, objectives, outcomes, randomization, blinding, statistical method, participant description, recruitment, baseline data, and others. The quality of all included RCTs was assessed by the CONSORT items and Jadad score. Finally, from the full text and corresponding supplement information, the following eligibility items were collected from each study: Author, year of publication, title and abstract, birth weight, gestation, participant description, baseline data, respiratory strategy, number of participants (experimental/control), exclusion criteria, start/max/weaning iNO, duration of iNO, outcomes, follow-up, randomization, blinding, Jadad score, and CONSORT items. Subsequently, the outcomes were divided into three parts. First of the questions was the effect of iNO on incidences of lung diseases (BPD and PH). Second, effect of iNO on incidences of possible extrapulmonary lesions including NEC, ROP, and severe ICH was compared between treatment and control groups. Third, mortality of preterm infants with iNO was further explored.

Statistical analysis

For each outcome (incidence of BPD, PH, NEC, ROP, severe ICH, and mortality), relative risk (RR) with the 95% confidence interval (95% CI) was calculated. Both fixed-effects and random-effects models were considered. For each meta-analysis, the Chi-square-based Q statistic test (Cochran Q statistic)[9] was applied to test for heterogeneity, and the I^2 statistic was also used to quantify the proportion of the total variation attributable to heterogeneity.[10] For $P < 0.10$ or $I^2 > 50$, the assumption of homogeneity was assumed to be invalid, and the random-effects model was used; for $P \geq 0.10$ and $I^2 \leq 50$, data were assessed using the fixed-effects model. Publication bias was investigated by funnel plot, and an asymmetric plot suggested possible publication bias. Statistical analyses were performed using Review Manager 4.2 (Cochrane Collaboration, Nordic Cochrane Centre). A two-tailed $P < 0.05$ was deemed statistically significant.

RESULTS

Demographic characteristics of the studies

After searching the above databases, 397 potentially relevant studies on NO for neonates were obtained. Details of the searching process are shown in Figure 1. After carefully reviewing and extracting data from the publications, three RCTs were further excluded from the study because of inconsistent research content pertaining to our topic or

an absence of relevant clinical data.[11-13] A search of other aforementioned databases did not identify any additional eligible study. Ultimately, we identified 22 original RCTs (18 in English, 4 in Chinese), including the experimental group (n = 2418) and the control group (n = 2483) [Table 1]. The quality of all RCTs included in this meta-analysis was assessed by Jadad score and CONSORT items [Table 2].

Effect of inhaled nitric oxide on bronchopulmonary dysplasia and pulmonary hemorrhage

With respect to BPD, data were reported by 20/22 trials (experimental group/control group = 1709/1756) [Figure 2]. There was no significant heterogeneity among these trials (χ^2 = 20.22, P = 0.38; I^2 = 6.0%). Meta-analysis of data using a fixed-effects model estimated a reduced risk of BPD in the treatment group. iNO was associated with a significantly decreased risk of BPD in preterm infants with an RR of 0.88 (95% CI, 0.82–0.95; P = 0.0007) compared with control group.

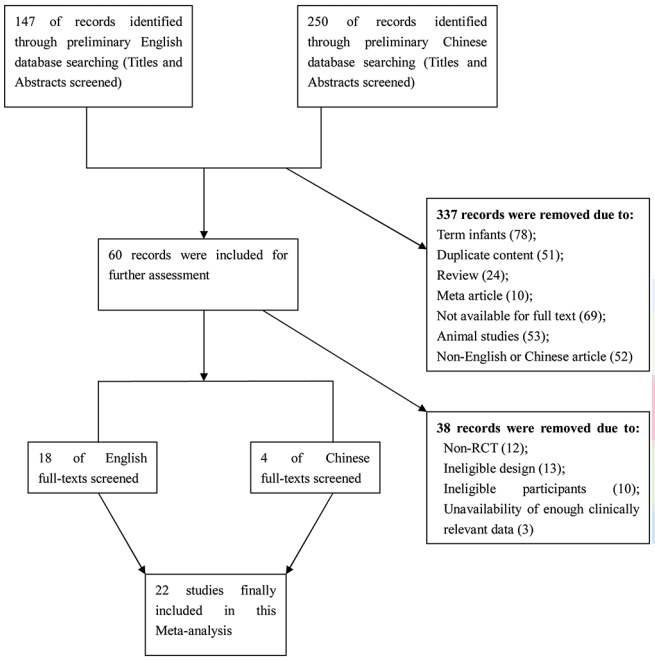

Figure 1: Flow diagram of selection of studies for inclusion in the meta-analysis

Regarding the effect of iNO on PH in preterm infants, there were 11 eligible studies included (experimental group/control group = 1105/1133), and no significant heterogeneity was detected among these trials (χ^2 = 3.38, P = 0.85; I^2 = 0%). There was not significantly difference between two groups (RR = 0.94; 95% CI, 0.66–1.33; P = 0.72) [Figure 3].

Effect of inhaled nitric oxide on necrotizing enterocolitis, retinopathy of prematurity, and severe intracranial hemorrhage

In assessing the major risks of extrapulmonary lesions, NEC, ROP, and severe ICH were compared between experimental and control groups in this meta-analysis.

- Data for NEC between experimental and control groups were reported by 12 trials (experimental/control group = 1659/1709). There was no significant heterogeneity among these trials (χ^2 = 15.52, P = 0.16; I^2 = 29.1%). Therefore, a fixed-effects model was applied. The result showed no significant difference in the experimental versus the control group (RR = 1.21; 95% CI, 0.98–1.49; P = 0.08) [Figure 4]
- Data for ROP in infants with iNO were reported in 11 trials (experimental group/control group = 1204/1245). There was no significant heterogeneity among the trials (χ^2 = 6.32, P = 0.79; I^2 = 0%). Therefore, a fixed-effects model was applied. No significant difference in the risk for ROP was found between the two groups (RR = 1.01; 95% CI, 0.92–1.10; P = 0.89) [Figure 5]
- Data for severe ICH in infants with INO were reported in 17 trials (experimental/control group = 1311/1355).

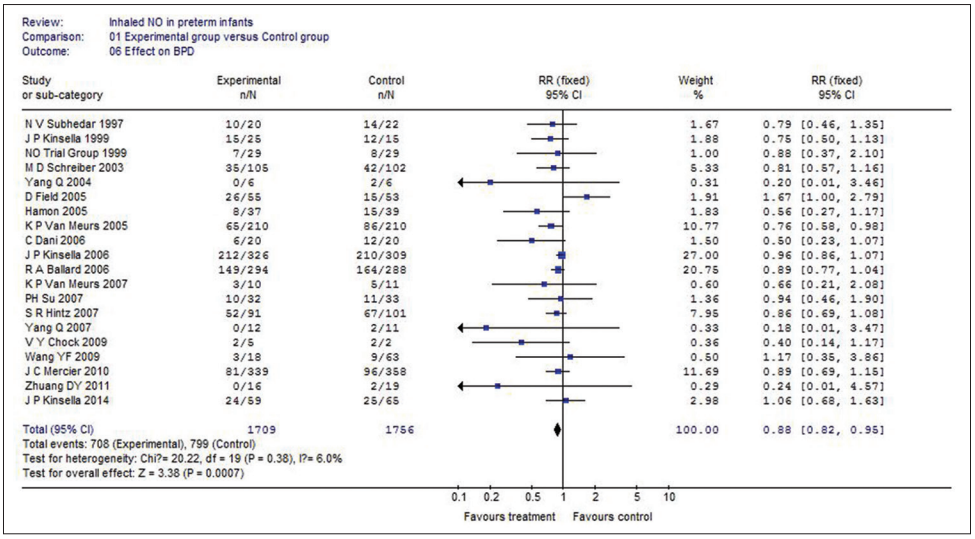

Figure 2: Effect of inhaled nitric oxide on bronchopulmonary dysplasia

Table 1: Demographic characteristics of trials included in the meta-analysis

Study	Birthweight (g)	Gestation (weeks)	Respiratory strategy	Treatment ages; experiment/control	Exclusion criteria	Start/max/ weaning iNO, (ppm)	Duration of iNO, (days)	Primary outcomes
Subhedar *et al.* 1997[14]	882 (416-1354)/750 (520-1400)	27 (24-30)/27 (22-31)	MV (surfactant; CLD score)	>96 h; 20/22	Hemorrhage; cardiac defect	20/20/75	3-4	CLD; death
Kinsella *et al.* 1999[15]	1040 (461)/988 (387)	27.1 (2.5)/26.8 (2.5)	MV (surfactant; a/AO_2<0.1)	30 h (mean); 48/32	Fatal anomalies	5/5/0	7-14	CLD; death; ventilator days; ICH
Franco-Belgium Collaborative NO 1999[16]	1200 (570)/1150 (520)	29.6 (2.6)/29.0 (3.1)	MV (surfactant; OI=12.5-30)	<7 days; 40/45	OI >30; severe asphyxia; septic	10/20/0	NM	CLD; death; ICH
Srisuparp *et al.* 2002[17]	874 (70)/901 (73)	26.8 (0.5)/27.2 (0.5)	MV (surfactant; OI □4-12)	8.3 h (mean); 16/18	Fatal anomalies	20/20/5	<7	Methemoglobin death; ICH
Schreiber *et al.* 2003[18]	1017 (369)/949 (387)	27.4 (2.5)/27.0 (2.8)	MV (surfactant)	<72 h; 105/102	Fatal anomalies	10/10/5	7	CLD; death; NEC; Sepsis; ROP; ICH
Yang 2004[19]	1722 (397)/1278 (517)	31.9 (1.8)/29.7 (3.4)	MV (surfactant)	25.5 h (mean); 6/6	Fatal anomalies; hemorrhage; severe anemia; shock	10/10/0	33.8 h (mean)	PH; ICH; CLD; death; aerothorax
Hascoet *et al.* 2005[20]	NM	<32	MV (surfactant; FiO_2>0.4; a/AO_2 <0.22)	□48 h; 61/84	Fatal anomalies; platelet <50; refractory	5/10/2	NM	CLD; death; ICH
Hamon *et al.* 2005[21]	1083 (58)/1102 (54)	27.3 (0.4)/27.9 (0.4)	MV (surfactant; FiO_2 >0.4; a/AO_2 <0.22)	<48 h; 37/39	Fatal anomalies; platelet <50; refractory	5/10/2	NM	CLD; death; NEC; ICH
Field *et al.* 2005[22]	1066 (395)/890 (343)	27.4 (2.6)/26.3 (2.4)	MV (surfactant)	<28 days; 55/53	Fatal anomalies; platelet <50; intraperitoneal	5/40/5	2-3	CLD; death; disability
Van Meurs *et al.* 2005[23]	840 (264)/837 (260)	26 (2)/26 (2)	MV (surfactant; OI >7.5)	26 h (mean); 210/210	Congenital lung anomaly; platelet <50	5/10/0	<14	CLD; death; ICH; ROP
Dani *et al.* 2006[24]	937 (298.0)/825 (299.3)	26.3 (2.6)/26.7 (1.9)	MV (surfactant; OI □7.5)	43.7 h (mean); 20/20	Fatal anomalies; platelet <50	10/10/6	98.5 h (mean)	BPD; death; ICH; ROP; NEC
Kinsella *et al.* 2006[5]	796 (190)/788 (185)	25.6 (1.7)/25.6 (1.8)	MV (surfactant)	30.5 h (mean); 398/395	Fatal anomalies; air leak	5/5/NM	<21 or until extubation	CLD; death; ICH; ROP; NEC; sepsis; PH
Ballard *et al.* 2006[4]	766 (161)/759 (155)	26 (1.5)/26 (1.5)	MV (surfactant)	7-21 days; 294/288	Fatal anomalies; Grade 4 ICH	20/20/2	>24	CLD; death; sepsis; NEC; ROP
Su and Chen 2008[25]	1020 (230)/1050 (210)	27.4 (2.3)/27.9 (1.8)	MV (surfactant; OI >25)	2.45 days (mean); 32/33	Fatal anomalies; hemorrhage; severe ICH	5/20/1	4.9 days (mean)	CLD; death; ICH; ROP; PH; NEC; sepsis
Van Meurs *et al.* 2007[26]	1790 (391)/2168 (441)	31.1 (1.2)/31.4 (1.1)	MV (surfactant; OI >15)	25.1 h (mean); 14/15	Platelet <50	5/10/0	<14	BPD; death; ICH; ROP; disability
Yang *et al.* 2007[27]	1722 (333)/1457 (380)	32.0 (2.3)/30.4 (2.3)	MV (surfactant)	18.1 h (mean); 12/11	Fatal anomalies; severe anemia; hemorrhage; aerothorax	5-10/5-10/0	>72 h	PH; ICH; CLD; death; aerothorax

Contd...

Table 1: Contd...

Study	Birthweight (g)	Gestation (weeks)	Respiratory strategy	Treatment ages; experiment/control	Exclusion criteria	Start/max/ weaning iNO, (ppm)	Duration of iNO, (days)	Primary outcomes
Hintz *et al.* 2007[28]	835 (265)/830 (261)	25.9 (2.3)/25.9 (2.2)	MV (surfactant; OI >10)	>4 h; 198/200	Congenital lung anomaly; platelet <50	5/10/0	<14	Sepsis; NEC; BPD; ICH; ROP; death; disability
Chock *et al.* 2009[29]	1039 (355)/1179 (369)	27 (2)/29 (3)	MV (surfactant)	12 h (mean); 6/6	NM	5/10/0	<14	CLD; death; ICH
Wang *et al.* 2009[30]	1809 (416)/1715 (314)	31.5 (1.8)/31.5 (1.6)	MV (surfactant; OI >10)	11 h (mean); 18/63	Fatal anomalies; hemorrhage; platelet <l 00; shock	5/5/0	74.1 h (mean)	CLD; death; PH; ICH; NEC; ROP
Mercier *et al.* 2010[6]	851 (207)/864 (192)	26.4 (1.3)/26.6 (1.3)	MV (surfactant; FiO_2>0.3)	<72 h; 399/401	Fatal anomalies; FiO2 >0.5; lung hypoplasia	5/5/NM	7-21	BPD; brain damage; NEC; sepsis; PH
Zhuang *et al.* 2011[31]	1622 (330)/1457 (380)	32.1 (2.1)/31.4 (2.6)	MV (surfactant)	14.1 h (mean); 16/19	Fatal anomalies; severe anemia; hemorrhage	5/20/5	>72 h	PH; ICH; CLD; death
Kinsella *et al.* 2014[32]	961 (186)/968 (159)	27.5 (1.6)/27.3 (1.8)	CPAP	44.1 h (mean); 59/65	Fatal anomalies	10/10/5	>14 days and <30 weeks PMA	CLD; deaths; NEC; sepsis; ROP

CLD = Chronic lung disease; ICH = Intracranial hemorrhage; ROP = Retinopathy of prematurity; PH = Pulmonary hemorrhage; NEC = Necrotizing enterocolitis; PMA = Postmenstrual age; NM = Not mentioned; MV = Mechanical ventilation; OI = Oxygenation index; iNO = Inhaled nitric oxide; BPD=Bronchopulmonary dysplasia

There was no significant heterogeneity among the trials (χ^2 = 15.61, P = 0.41; I^2 = 3.9%). Therefore, a fixed-effects model was applied. No significant difference in the risk for severe ICH was found between the two groups (RR = 0.99; 95% CI, 0.83–1.16; P = 0.86) [Figure 6].

Effect of inhaled nitric oxide on mortality

Regarding the potential effect of iNO on mortality, data were reported in all 22 trials (experimental/control group = 2418/2483). There was no heterogeneity among these two trials (χ^2 = 18.36, P = 0.63; I^2 = 0%). Therefore, a fixed-effects model was applied. The result showed that there was no difference for mortality between the experimental and the control groups (RR = 1.00; 95% CI, 0.92–1.09; P = 0.98) [Figure 7].

Publication bias

All trials included in the meta-analysis had Jadad quality scores ≥4. A funnel plot was performed to assess the potential publication bias in this meta-analysis. In analyzing the effect of iNO on death, we visually evaluated the symmetry of funnel plot shape and did not find obvious evidence of asymmetry [Figure 8].

DISCUSSION

RDS and PPHN are common and serious diseases, and they are difficult to treat in clinical work. According to incomplete statistics, the mortality of RDS in Shenzhen area is 1.95% per year.[33] Previous treatments are mainly limited in mechanical ventilation and pulmonary surfactant. However, for critically ill infants, the success rate is not high. Since 1992, several randomized trials have shown that iNO significantly improved oxygenation in term or near-term infants, with a significant reduction in the use of extracorporeal membrane oxygenation. Therefore, this treatment has been widely applied in clinical work to term infants at home and abroad. Nevertheless, the role of iNO in preterm infants with HRF or PPHN remains controversies. For example, the National Institute of Child Health and Human Development Neonatal Network Trial showed iNO given to critically ill premature infants weighing <1500 g did not decrease the mortality or the incidence of BPD.[23] Beside the effectiveness, concerns have been also raised about specific side effects of this new molecule. Based on the above points, we performed this updated meta-analysis. To the best of our knowledge, this is the first meta-report that includes the latest literature not only in English but also in Chinese.

The first issue is the effectiveness of iNO. On one hand, our results showed that there was no significant difference between experimental and control groups for mortality (RR = 1.00; 95% CI, 0.92–1.09; P = 0.98). This

Table 2: Report quality of trials included in the meta-analysis

Study	Title and abstract	Participant description	Baseline data	Multicenter	Randomization	Blinding	Follow-up	CONSORT items (22)	Jadad score (5)
Subhedar *et al*. 1997[14]	Yes	Yes	Yes	No	Yes (with description of allocation concealment)	No	Yes	19	4
Kinsella *et al*. 1999[15]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	21	5
Franco-Belgium Collaborative NO 1999[16]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	22	5
Srisuparp *et al*. 2002[17]	Yes	Yes	Yes	No	Yes (without description of allocation concealment)	No	No	18	4
Schreiber *et al*. 2003[18]	Yes	Yes	Yes	No	Yes (with description of allocation	Yes	Yes	22	5
Yang 2004[19]	Yes	Yes	Yes	Yes	No	No	No	17	4
Hascoet *et al*. 2005[20]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	No	19	4
Hamon *et al*. 2005[21]	Yes	Yes	Yes	No	Yes (with description of allocation concealment)	Yes	Yes	22	5
Field *et al*. 2005[22]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	21	5
Van Meurs *et al*. 2005[23]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	22	5
Dani *et al*. 2006[24]	Yes	Yes	Yes	No	Yes (with description of allocation concealment)	No	Yes	20	4
Kinsella *et al*. 2006[5]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	21	5
Ballard *et al*. 2006[4]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	21	5
Su and Chen 2008[25]	Yes	Yes	Yes	No	Yes (with description of allocation concealment)	No	Yes	21	5
Van Meurs *et al*. 2007[26]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	22	5
Yang *et al*. 2007[27]	Yes	Yes	Yes	Yes	No	No	No	17	4
Hintz *et al*. 2007[28]	Yes	Yes	Yes	Yes	Yes (without description of allocation concealment)	Yes	Yes	21	5
Chock *et al*. 2009[29]	Yes	Yes	Yes	Yes	Yes (without description of allocation concealment)	No	Yes	19	4
Wang 2009[30]	Yes	Yes	Yes	Yes	Yes (without description of allocation concealment)	No	Yes	19	4
Mercier *et al*. 2010[6]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	Yes	Yes	22	5
Zhuang *et al*. 2011[31]	Yes	Yes	Yes	No	Yes (without description of allocation concealment)		No	18	4
Kinsella *et al*. 2014[32]	Yes	Yes	Yes	Yes	Yes (with description of allocation concealment)	No	No	20	5

CONSORT = CONsolidated Standards Of Reporting Trials

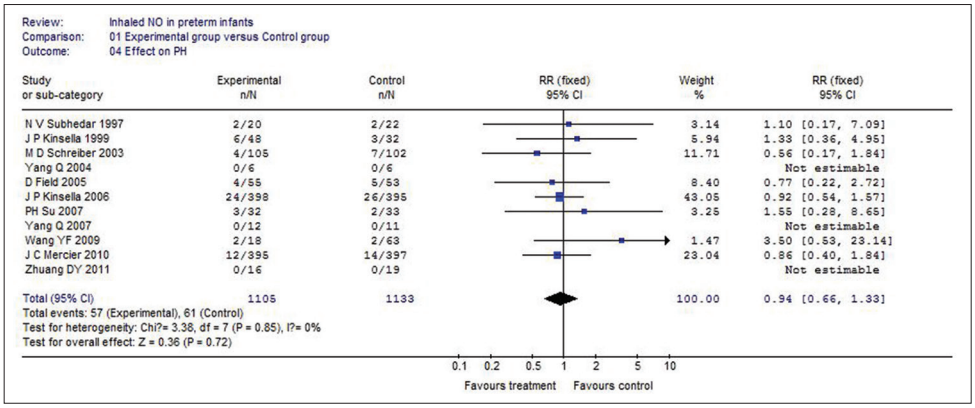

Figure 3: Effect of inhaled nitric oxide on pulmonary hemorrhage

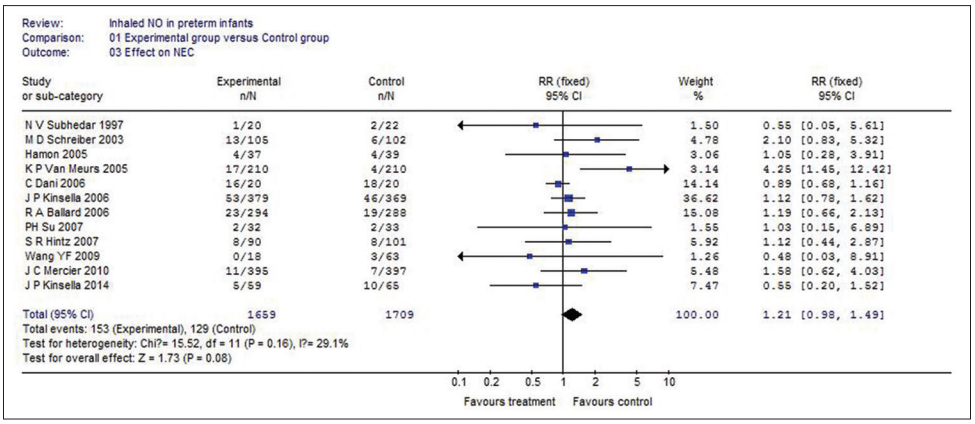

Figure 4: Effect of inhaled nitric oxide on necrotizing enterocolitis

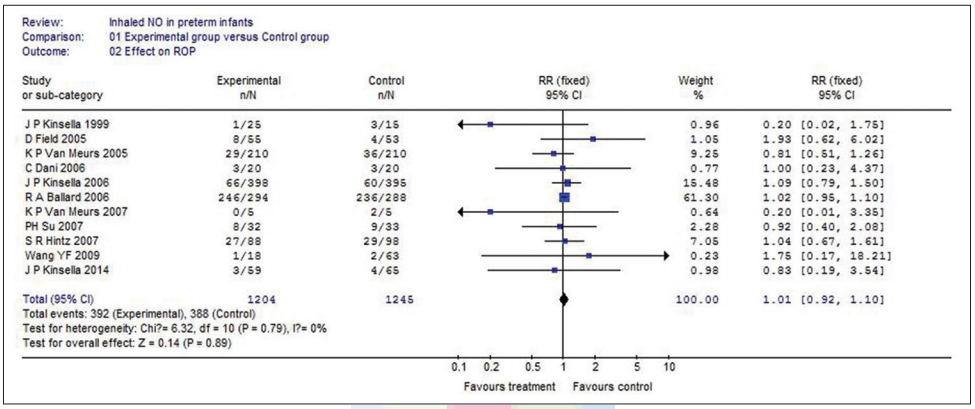

Figure 5: Effect of inhaled nitric oxide on retinopathy of prematurity

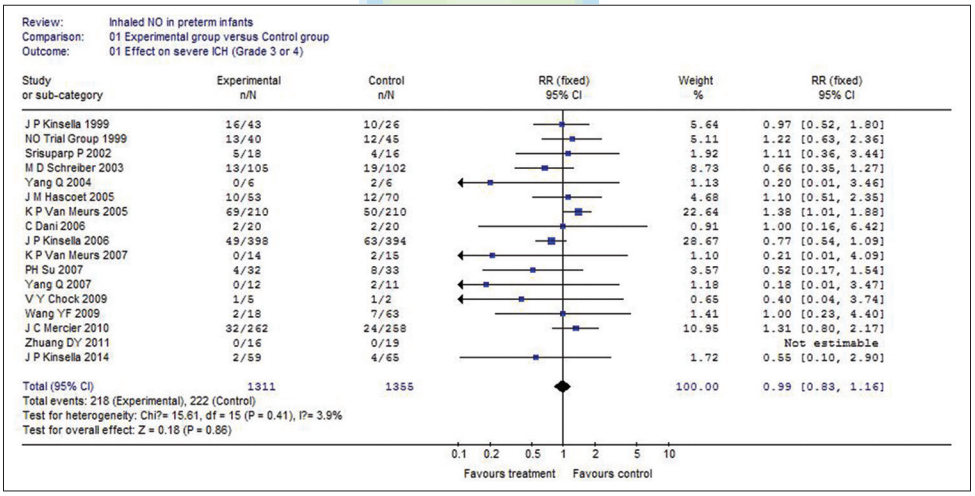

Figure 6: Effect of inhaled nitric oxide on severe intracranial hemorrhage

suggested that iNO therapy does not increase or decrease the risk of mortality. On the other hand, this analysis showed a significant protective effect in the prevention of BPD (RR = 0.88; 95% CI, 0.82–0.95; *P* = 0.0007). With respect to BPD, there are different opinions among neonatologists. Some meta-analyses found that the overall effect of iNO on BPD is not significant,[34] which is contradictory to our results. It can be explained that our study first added all involved Chinese research articles (Yang *et al*. 2004; 2007, etc.,) into meta-analysis, which may be contributed to this different result. After the CONSORT and Jadad check, we evaluate outcomes of these references with high quality and believable. In fact, Kinsella *et al*. and Love and Bradshaw[5,35] once showed that when comparing treatment and placebo in infants weighing between 1000 and 1250 g at birth, iNO therapy did show a reduction

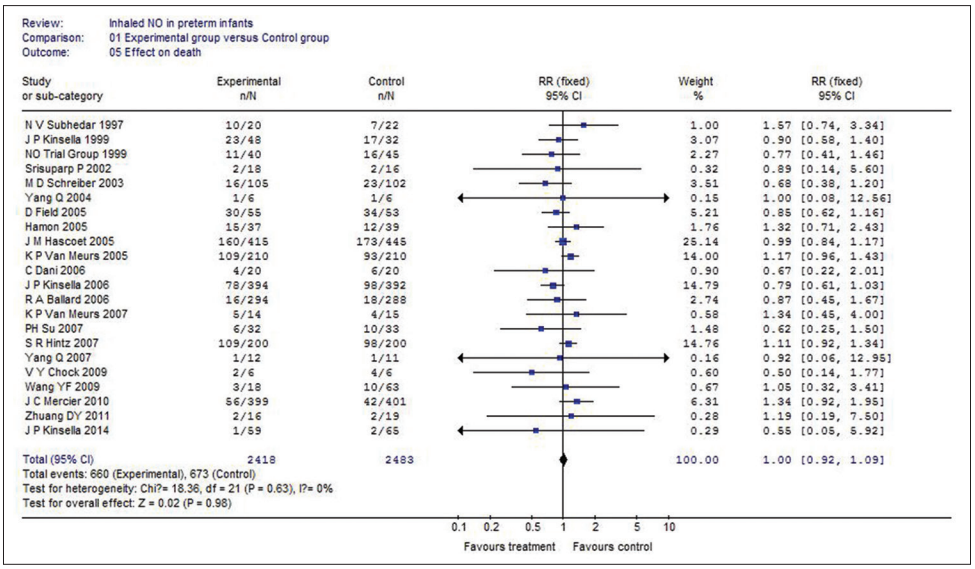

Figure 7: Effect of inhaled nitric oxide on mortality

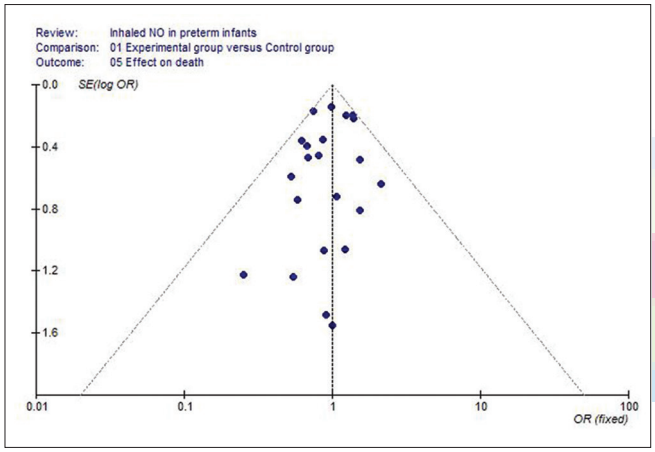

Figure 8: Funnel plot to assess publication bias

in the incidence of BPD. Hence, it appears that iNO has potential as an effective way to prevent BPD in preterm infants to some extent.

In addition, there remain some concerns which limited the clinical use, such as the safety problem. First, NO could inhibit platelet aggregation and is related to the cascade leading to cerebral lesions in perinatal experimental models of hypoxic-ischemic injuries.[36] Hence, neonatologists remain cautious in the risk for increased brain damage including severe ICH and periventricular leukomalacia.[37] Our meta-analysis, 17/22 RCTs (experimental group/control group = 1311/1355), showed no significant difference in the risk for severe ICH with an RR = 0.99 (95% CI, 0.83–1.16; *P* = 0.86) compared with the control group. Furthermore, iNO may interact with oxygen to form nitrogen dioxide and peroxynitrites which would enhance pulmonary toxicity. In our analysis, we found 11/22 studies (experimental group/control group = 1105/1133) that reported no significant difference in the risk for PH between the two groups (RR = 0.94; 95% CI, 0.66–1.33; *P* = 0.72).

ROP and NEC are common complications of prematurity. We subsequently explored the incidences of these two diseases for the 1st time. It showed no differences between the two groups (RR = 1.01; 95% CI, 0.92–1.10; *P* = 0.89 and RR = 1.21; 95% CI, 0.98–1.49; *P* = 0.08). This may give us confidence that iNO does not increase the risk of common complications in preterm infants.

Besides the aforementioned concerns, we must note additional limitations to some recent researches. For example, starting and maximum dose of iNO might be associated with different outcomes, but because there were differences in the designs of the trials included in the analyses, it requires further examination. In addition, methods of specific randomization and weaning iNO are generally not included in some published reports. Some studies include the declaration that the research to date is not adequate to draw precise conclusions. Given these limitations, perhaps, the focus of future studies should not be directed simply at questioning the benefits of iNO but should rather explore in more depth, optimal dosing, and duration of therapy for specific birth weight and gestational age groups.

CONCLUSION

The available data for the use of iNO in the management of preterm neonates suggest that a beneficial effect depends on preterm infants. In addition, our meta-analysis suggests that iNO therapy does not increase the risk of common complications, such as NEC and ROP, and that it may also have no adverse effect on bleeding tendency diseases (severe ICH and PH).

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Conflicts of interest
The authors have no conflicts of interest.

AUTHORS' CONTRIBUTION

- XYZ contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- YF and YY contributed in the conception of the work, conducting the study, writing and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- JJP contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- XGZ contributed in the design of the work, approval of the final version of the manuscript, and agreed for all aspects of the work.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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