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Treatment of respiratory failure in preterms

Is nitric oxide effective in preterm infants?

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There is insufficient evidence to support the routine use of inhaled nitric oxide in preterms with respiratory failure

Inhaled nitric oxide is a selective pulmonary vasodilator used to treat neonates with respiratory failure. The first reports of its use were published in 1991 and the Food and Drug Administration (FDA) approved its use in the USA in 1999. However, it has only relatively recently received regulatory approval in Europe for use in hypoxaemic respiratory failure associated with pulmonary hypertension in neonates ⩾34 weeks' gestation. Inhaled nitric oxide is often used outside the licensed indication (off-label) in preterm neonates.

Three randomised controlled trials investigating the efficacy of inhaled nitric oxide in preterm infants have been published recently.[1–3] This article reviews the evidence base for the use of inhaled nitric oxide in the preterm population in the light of these new studies.

RATIONALE FOR THE USE OF INHALED NITRIC OXIDE IN PRETERM INFANTS

Inhaled nitric oxide is potentially beneficial in preterm infants for two main reasons. First, it may improve gas exchange in infants with established respiratory failure through enhanced ventilation–perfusion matching and/or a reversal of extrapulmonary shunting resulting in a lowering of respiratory support requirements and hence reduced ventilator and oxygen-induced lung injury.[4] Second, inhaled nitric oxide has been shown to reduce lung inflammation and oxidant stress, preserve surfactant function, and promote lung growth and pulmonary vascular development in various laboratory studies and experimental models of bronchopulmonary dysplasia (BPD).[5–10] These effects of inhaled nitric oxide may potentially attenuate preterm lung injury and therefore reduce the risk or severity of BPD if it is used at an early stage in the disease process.

RECENTLY PUBLISHED RANDOMISED CONTROLLED TRIALS

Kinsella and colleagues randomised 793 preterm infants ⩽34 weeks' gestation to receive 5 ppm inhaled nitric oxide or nitrogen placebo gas.[1] Infants were eligible for inclusion into the study if they were <48 h of age and receiving mechanical ventilation, irrespective of the severity of respiratory disease. The median age at trial entry was approximately 30 h, the mean oxygenation index at trial entry of the babies treated with inhaled nitric oxide and controls was 5.4 and 5.8, respectively, and the median duration of gas treatment was 14 days, indicating this was a study investigating the efficacy of early, low-dose, prolonged ''prophylactic'' inhaled nitric oxide in ventilated preterm infants with mild respiratory disease. Although the overall results showed no evidence of a benefit in the combined primary outcome of death and/or BPD (relative risk (RR) 0.95, 95% CI 0.87 to 1.03), prespecified subgroup analyses showed that inhaled nitric oxide reduced BPD/death in larger preterm infants with a birth weight of between 1000 g and 1250 g (RR 0.60, 95% CI 0.42 to 0.86). Interestingly, and in line with another study of early prophylactic treatment,[11] inhaled nitric oxide reduced the risk of cerebral injury on cranial ultrasound, defined as severe intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL) or ventriculomegaly (RR 0.73, 95% CI 0.55 to 0.98, number needed to treat (NNT) 16); subgroup analysis suggested that this protective effect of inhaled nitric oxide on brain injury was confined to babies with a birth weight of 750–999 g.

In another large, multicentre placebo-controlled randomised controlled trial conducted in the USA, Ballard and colleagues enrolled 582 preterm infants ⩽32 weeks' gestation receiving nasal continuous positive airway pressure or mechanical ventilation and aged between 7 days and 21 days.[2] Infants initially received 20 ppm of inhaled nitric oxide for 48–96 h with the dose being weaned thereafter to 10 ppm, 5 ppm and 2 ppm at weekly intervals; gas treatment was continued for a minimum of 24 days (median 25 days). Most of the babies were ventilated but had relatively mild respiratory support requirements and their median age at trial entry was 16 days, indicating this was a study designed to test the efficacy of late inhaled nitric oxide treatment in improving survival without chronic lung disease (CLD) (ie, preventing death/CLD) in preterm babies requiring ongoing respiratory support. Survival without CLD at 36 weeks postmenstrual age was improved in infants treated with inhaled nitric oxide (RR 1.23, 95% CI 1.01 to 1.51; NNT 14). Post hoc analyses indicated that this benefit was evident only in infants aged 7–14 days at randomisation and there was no evidence of an effect on outcome of birth weight or the severity of underlying respiratory disease. Infants treated with inhaled nitric oxide were discharged earlier and received mechanical respiratory support and supplemental oxygen

Table 1 Categories of randomised controlled trials of inhaled nitric oxide in preterm infants

Category	Description	RCTs	References
Early prophylactic treatment	Treatment of babies requiring mechanical ventilation or nasal CPAP, <72 h of age and at risk of death/BPD, irrespective of the severity of respiratory disease	2	1,11
Early rescue treatment	Treatment of babies with established respiratory failure in the first week of life, based on severity of respiratory disease	5	3, 12–15
Late treatment	Treatment of babies requiring ventilation or nasal CPAP ≥72 h and at risk of death/BPD, irrespective of the severity of respiratory disease	2	2, 16

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure, RCT, randomised controlled trial.

treatment for a shorter period, suggesting less severe CLD.

Dani and colleagues recently published a small open-label randomised controlled trial of inhaled nitric oxide in preterm infants with severe respiratory distress syndrome.[3] Forty infants <30 weeks' gestation and <7 days of age were randomised to receive inhaled nitric oxide (at a starting dose of 10 ppm) or continued conventional treatment. The mean age at trial entry was 44 h, the mean oxygenation index was 16.4 for babies treated with inhaled nitric oxide and 15.1 for controls, and the median duration of gas treatment was 99 h; this was therefore a study of relatively early, brief ''rescue'' inhaled nitric oxide treatment in preterm infants with established respiratory failure. Inhaled nitric oxide was effective in reducing death/BPD (RR 0.56, 95% CI 0.35 to 0.88, NNT 3) but a birth weight <750 g was significantly and independently predictive of the failure to respond acutely to inhaled nitric oxide (adjusted odds ratio 12.0, 95% CI 1.3 to 13.3).

OVERVIEW OF AVAILABLE EVIDENCE

Eleven randomised controlled trials have now been published investigating the use of inhaled nitric oxide in 2536 preterm infants.[1–3 11–18] This review only includes trials investigating the medium-term to long-term efficacy of inhaled nitric oxide in preterm babies. Two studies allowed ''back up'' inhaled nitric oxide treatment, which would have permitted ''contamination'' of the control group (where control infants receive the intervention to be studied) and so may have potentially diluted the observed effect of inhaled nitric oxide treatment, and were therefore excluded.[17 18] Individual trials vary in terms of timing, dose and duration of inhaled nitric oxide treatment as well as degree of exposure to antenatal steroids and concomitant respiratory treatments. Clearly all these variables have the potential to influence important clinical outcomes, and one should be wary of important differences between trials when interpreting pooled estimates of effects derived from a systematic review and meta-analysis. Tables 1 and 2 summarise the key characteristics of the trials included in this review.

Table 3 and supplemental figures 1A–D (see http://adc.bmj.com/supplemental) provide an overview of the efficacy of inhaled nitric oxide treatment with respect to important clinical outcomes in preterm infants categorised by study type. Many studies have shown convincing evidence of a short-term response in oxygenation with inhaled nitric oxide treatment, but the outcomes of greatest importance in preterm infants are, arguably, mortality, brain injury and lung injury. Any assessment of the efficacy of an intervention should ideally include long-term outcomes. However, often the only available evidence relates to short-term to medium-term mortality or surrogate markers of long-term morbidity such as CLD (usually defined as oxygen dependency at 36 weeks postmenstrual age) and cerebral injury on cranial ultrasonography (severe IVH and/or PVL). Unfortunately, short-term markers may not accurately reflect long-term outcomes. For example, although cranial ultrasonography may be useful in identifying a preterm baby with severe IVH/PVL, an infant with a normal cranial ultrasound scan may still have considerable neurodisability, underscoring the importance of long-term follow-up in any assessment of brain injury.

Early ''prophylactic'' treatment

Early prophylactic inhaled nitric oxide treatment is associated with a reduction in mortality and death/BPD. The magnitude of effect is such that treating 17 babies with inhaled nitric oxide will prevent 1 baby dying and/or developing BPD. Subgroup analyses in these trials indicate that inhaled nitric oxide may be more effective in larger preterm infants (≥1000 g) and those with milder respiratory disease (oxygenation index <7). In this setting, inhaled nitric oxide treatment also reduces the risk of severe IVH/PVL; treating 14 babies with inhaled nitric oxide will prevent 1 baby developing severe IVH/PVL.

A single study on long-term outcome has shown that early inhaled nitric oxide treatment is associated with improved neurodevelopmental status at 2 years of age, corrected for prematurity.[19] Abnormal developmental outcome (defined as cerebral palsy, severe visual or hearing impairment or severe developmental delay) was observed less commonly in infants treated with inhaled nitric oxide compared with controls (RR 0.53, 95% CI 0.33 to 0.87, NNT 5). Specifically, fewer babies treated with inhaled nitric oxide had a Bayley Mental Developmental Index score <70 (RR 0.53, 95% CI 0.29 to 0.94, NNT 6).

Early ''rescue'' treatment

Interpretation of the results of early rescue treatment is hampered by the heterogeneity among studies with regard to the blinding of the intervention, timing of treatment and severity of respiratory disease at trial entry. When used as early rescue treatment inhaled nitric oxide may have a beneficial effect. The pooled estimate indicates a modest reduction in death/BPD, which is of borderline clinical and statistical significance (see table 3). However, post hoc analysis in the largest study again suggested that treatment with inhaled nitric oxide is more effective in larger preterm babies.[15] Van Meurs and colleagues found inhaled nitric oxide was associated with a decrease in death/BPD in the subgroup of infants with a birth weight >1000 g (RR 0.72, 95% CI 0.54 to 0.96). Conversely, there was higher mortality among babies ≤1000 g treated with inhaled nitric oxide compared with controls (RR 1.28, 95% CI 1.03 to 1.88) and a higher rate of severe IVH (RR 1.40, 95% CI 1.03 to 1.88). The baseline severity of respiratory disease did not have an appreciable impact on outcome.

There is currently little information regarding long-term outcomes in babies receiving early rescue treatment with inhaled nitric oxide. The single trial that has reported neurodevelopmental outcome showed no evidence of an effect of inhaled nitric oxide on neurological impairment, neurodisability or developmental delay at 12 months of age, corrected for prematurity.[14]

Late treatment

Late treatment with inhaled nitric oxide in babies requiring ongoing respiratory support may be effective in reducing death/BPD (and the duration of respiratory support and hospitalisation) but this effect is of borderline clinical and

Table 2 Details of randomised controlled trials of inhaled nitric oxide (iNO) in preterm babies*

Study	Study type	N	Population studied	Age at trial entry	Respiratory disease severity at trial entry	Dose/duration of iNO used	Comments
Schreiber *et al* (2003)[11]	Early prophylactic treatment	207	Infants <34 weeks' gestational age and birth weight <2000 g	<72 h	Ventilated, median OI: babies treated with iNO 7.3; controls 6.8	5–10 ppm for maximum duration of 7 days	Blinded intervention. Low antenatal steroid exposure; factorial design with infants also randomised to receive high-frequency oscillatory ventilation
Kinsella *et al* (2006)[1]	Early prophylactic treatment	793	Infants ⩽34 weeks' gestational age	<48 h	''Respiratory failure requiring ventilation'' mean OI: babies treated with iNO 5.4; controls 5.8	5 ppm for a median duration of 14 (range 0–24) days	Blinded intervention
Kinsella *et al* (1999)[12]	Early rescue treatment	80	Infants <34 weeks' gestational age	<7 days of age, mean age 27–30 h	Ventilated with a/A <0.10, mean Pa_{O_2}/Fi_{O_2} 5.6	5 ppm for a maximum of 11 days	Blinded intervention
Srisuparp *et al* (2002)[13]	Early rescue treatment	34	Infants <2000 g	<72 h	Ventilated with OI >4–12 depending on birth weight, mean OI: babies treated with iNO 10.8; controls 11.9	1–20 ppm, maximum duration of 7 days	Non-blinded intervention. Low antenatal steroid exposure
INNOVO (2005)[14]	Early rescue treatment	108	Infants <34 weeks' gestational age	<48 h	''Severe respiratory failure'' requiring ventilation, median OI 32	5–40 ppm, duration <48 h in 45% of babies	Non-blinded intervention. Frequent use of other vasodilators
Van Meurs *et al* (2005)[15]	Early rescue treatment	420	Infants <34 weeks' gestational age	<5 days, mean age 26–28 h	Ventilated with OI >7.5–10, mean OI: babies treated with iNO 23; controls 22	5–10 ppm, maximum duration of 14 days	Blinded intervention
Dani *et al* (2006)[3]	Early rescue treatment	40	Infants <30 weeks' gestational age	<7 days, mean age 43.7 h	Ventilated with Fi_{O_2} >0.50 and a/A <0.15, mean OI: babies treated with iNO 16.4; controls 15.1	2–10 ppm, median duration 98.5 h	Non-blinded intervention. Low antenatal steroid exposure
Subhedar *et al* (1997)[16]	Late treatment	42	Infants <32 weeks' gestational age	>96 h	''High risk'' of developing BPD using a risk score, median OI: babies treated with iNO 7.9; controls 3.9	5–20 ppm for maximum duration of 72 h	Non-blinded intervention. Factorial design with infants also randomised to receive dexamethasone
Ballard *et al* (2006)[2]	Late treatment	582	Infants <1250 g and ⩽32 weeks' gestational age	7–21 days	Mechanical ventilation or nasal CPAP, median FiO2 × MAP 3.5 (ie, mild lung disease at trial entry)	2–20 ppm for a minimum duration of 24 days	Blinded intervention

a/A, arterial–alveolar ratio; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; iNO, inhaled nitric oxide; MAP, mean airway pressure; OI, oxygenation index.
*Excluding two trials in which back-up treatment with iNO was permitted.

Table 3 Meta-analyses of randomised controlled trials of inhaled nitric oxide in preterm babies: overview of outcomes

Outcome	Relative risk (95% CI)	Absolute risk reduction (95% CI)	Number needed to treat
Early prophylactic treatment			
Severe IVH/PVL	0.70 (0.53 to 0.91)	−0.07 (−0.12 to −0.02)	14
BPD at 36 weeks	0.92 (0.83 to 1.02)		
Death	0.77 (0.61 to 0.98)	−0.06 (−0.11 to −0.01)	17
Death or BPD	0.92 (0.85 to 0.99)	−0.06 (−0.12 to 0)	17
Early rescue treatment			
Severe IVH/PVL	1.02 (0.80 to 1.31)		
BPD at 36 weeks	0.93 (0.78 to 1.09)		
Death	1.05 (0.89 to 1.22)		
Death or BPD	0.93 (0.87 to 1.00)		
Late treatment			
Severe IVH/PVL	No data available		
BPD at 36 weeks	0.90 (0.78 to 1.04)		
Death	1.06 (0.64 to 1.74)		
Death or BPD	0.90 (0.80 to 1.02)		

BPD, bronchopulmonary dysplasia; IVH/PVL, intraventricular haemorrhage/periventricular leucomalacia.

statistical significance (see table 3). There is some evidence that late treatment may be more effective when started at 7–14 days than at 15–21 days.[2] The only study to report long-term outcomes in this setting did not show any long-term benefit or harm with inhaled nitric oxide treatment.[20]

Toxicity

Potential complications of treatment include toxicity related to inhaled nitric oxide or its metabolites.[21] Nitric oxide is oxidised in the presence of oxygen to form nitrogen dioxide which may lead to airway inflammation and lung injury. Nitric oxide also combines with the superoxide radical to form peroxynitrite (a highly reactive oxidant molecule) which may induce lipid peroxidation and protein oxidation and lead to surfactant dysfunction.[22] Other theoretical complications of inhaled nitric oxide treatment include methaemoglobinaemia and a prolongation of bleeding time as a result of abnormal platelet adhesion and aggregation.

Despite this array of potential side effects, none of the randomised controlled trials in preterm infants has shown an excess of clinically important adverse effects with inhaled nitric oxide treatment. Although earlier, uncontrolled, clinical studies had raised concerns about a link between inhaled nitric oxide and IVH,[23] data from randomised trials do not support such an association.

IMPLICATIONS FOR CLINICAL PRACTICE

Inhaled nitric oxide is already widely used to treat term and near-term infants with hypoxaemic respiratory failure (with or without persistent pulmonary hypertension of the newborn (PPHN)). Anecdotally, many units are also using pulmonary vasodilators, and specifically inhaled nitric oxide, to treat hypoxaemic preterm infants in the acute or chronic phase of their respiratory illness. Is this use of inhaled nitric oxide in preterm infants with respiratory failure supported by the available evidence? The data presented above suggest that there is currently insufficient evidence to recommend the *routine* use of inhaled nitric oxide for early ''prophylactic'' treatment, early ''rescue'' treatment or as late treatment in preterm infants.

Early ''prophylactic'' treatment

Although early treatment of all preterm infants requiring respiratory support appears to be a promising strategy, there is currently little information about the long-term safety or toxicity of inhaled nitric oxide in this population; follow-up data from the recently published trial by Kinsella and colleagues may provide this important information. Additional data about short-term and long-term outcomes will also be available in the next few years once the ongoing EUNO INOT-27 European trial of inhaled nitric oxide is complete.

Even if it were to be shown that inhaled nitric oxide was clinically effective (and safe) in this setting, inhaled nitric oxide is one of the most expensive treatments used in neonatal medicine, and this will raise questions about its cost effectiveness. Economic arguments are especially pertinent because large numbers of preterm infants will be potentially suitable for early treatment and because this strategy will require prolonged treatment for up to three weeks.

Early ''rescue'' treatment

Recommendations regarding early ''rescue'' treatment with inhaled nitric oxide will perhaps be the most problematic and controversial. It has been argued that there is no convincing evidence that inhaled nitric oxide is beneficial in ventilated preterm infants with established respiratory failure and, therefore, that treatment should be limited to babies treated within the context of a clinical trial.[24] However, this recommendation does not recognise an important dilemma facing clinicians: what therapeutic options are available for treating a preterm baby with severe hypoxaemic respiratory failure? In the absence of any alternative interventions with robust evidence of short-term or long-term efficacy (such as ''extra'' doses of surfactant, high-frequency ventilation and alkalosis) many clinicians are prepared to use a vasodilator in an attempt to improve oxygenation. If one accepts this ''real-life'' scenario, arguably inhaled nitric oxide should be the vasodilator of choice because it offers the theoretical advantage of pulmonary selectivity combined with clinical evidence of short-term efficacy and safety.

It is recognised that the oxygenation response to inhaled nitric oxide is related to the underlying diagnosis, radiographic severity of lung disease and the presence of an extrapulmonary shunt. Babies with the best response to inhaled nitric oxide are those with relatively clear lung fields on chest *x* ray and/or documented extrapulmonary shunt on echocardiography.[25–27] However, none of the trials of inhaled nitric oxide to date has been designed or specifically powered to be able to detect a beneficial effect in these babies, who form the subgroup that may have the greatest potential benefit from a pulmonary vasodilator such as inhaled nitric oxide. A planned further analysis of the data from Van Meurs and colleagues' study may help to define more clearly the clinical characteristics that are predictive of a beneficial response to inhaled nitric oxide. On the basis of the available evidence, our own practice is to use inhaled nitric oxide selectively, solely in preterm babies with severe hypoxaemic respiratory failure (oxygenation index >15) complicated by echocardiographic evidence of extrapulmonary shunting (ie, PPHN). Perhaps an even more cautious approach is warranted in extremely low birthweight babies given the data indicating increased mortality and brain injury—this is probably the group in which early rescue treatment with inhaled nitric oxide should be confined to those enrolled into a clinical trial.

Late treatment

There is currently little evidence to support the strategy of using inhaled nitric oxide routinely as late treatment in preterm babies requiring ongoing respiratory support. Any clinical benefit such as that observed in the trial conducted by Ballard and colleagues will probably be modest and confined to improved respiratory

outcomes. As discussed above, the safety and long-term clinical and cost effectiveness of inhaled nitric oxide treatment in this setting will need to be shown before it can be recommended as part of routine clinical management.

SUMMARY

- Recently published data investigating the efficacy of inhaled nitric oxide in the preterm infant have added considerably to the body of information available.
- The present overview of randomised controlled trials suggests there is currently insufficient evidence about long-term safety and efficacy to recommend the routine use of inhaled nitric oxide. There is also a paucity of data regarding the optimal timing, dose and duration of treatment.
- The most promising indication for inhaled nitric oxide in preterm infants is early ''prophylactic'' treatment to prevent death/BPD.
- A large ongoing European randomised controlled trial of early inhaled nitric oxide treatment may provide further useful information about the safety and efficacy of inhaled nitric oxide in this setting.

Arch Dis Child Fetal Neonatal Ed 2007;**92**:337–341.
doi: 10.1136/adc.2006.107490

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Accepted 14 March 2007

Competing interests: NS is a member of the Steering Committee of the European iNOCare Nitric Oxide Registry, which receives an unrestricted educational grant from INOTherapeutics.

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