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Review

Nitric Oxide for preterm infants

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Abstract

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that has demonstrated its efficacy when used to treat severe hypoxemic respiratory failure associated to pulmonary hypertension in term or near term newborns since 1992.

Premature newborn infants are not included in the approved indication of iNO use, but in some circumstances, when pulmonary hypertension is associated to severe respiratory failure iNO has been demonstrated as an effective therapy to improve respiratory failure. Also iNO demonstrated in animal studies its potential use to treat or prevent BPD, but clinical trials have failed to demonstrate any beneficial effect of this drug when used as routine or rescue therapy, and probably only in a selected group of preterm infants, used soon after delivery and not severely ill it could have a role if any.

The neuro-protective effect found in some experimental studies and clinical reports gives a new attractive potential indication of iNO use in this population, but current data of follow-up multicenter randomized controlled trials do not support this effect.

Keywords

Inhaled nitric oxide, prematurity, bronchopulmonary dysplasia, pulmonary hypertension, neuro-protection.

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Introduction

Nitric oxide (NO) is a free radical gas molecule generated in the vascular endothelium and derived from L-arginine by the enzymatic activity of NO synthases. NO diffuses into the vascular muscle cells and activates the enzyme guanylate cyclase leading to increased cyclic guanosine monophosphate (cGMP) production resulting in relaxation of the smooth muscle. It was recognized as the endothelial-derived vasodilator molecule in 1987, and although it is a signaling molecule throughout the body, its vasodilator activity remains as the main therapeutic function in neonatology.

Because of its gas characteristic, it can be given inhaled (iNO), and due to its short half live (< 5 sec), it can reach the open alveoli, dilate the constricted vessel beneath to it and metabolized to nitric derived substances in blood by reducing hemoglobin, so its action is mostly limited to the pulmonary vascular bed. This selective effect on pre-constricted vessels of the ventilated airspaces improve the V/Q mismatching of the damaged lung [1, 2] and decrease the pulmonary vascular resistance (PVR) and right ventricle afterload without a fall in the systemic vascular resistance (SVR), a tipical side-effect of systemic vasodilators.

Recently, it has been proposed that a low dose of iNO can also improve oxygenation by redirecting blood from poorly ventilated to better aerated distal air spaces, known as a "microselective" effect [3]. Other effects of NO are antioxidant and anti-inflammatory effects in animal models, although a possible toxic lung injury due to promotion of oxidative stress, inactivation of surfactant and stimulation of inflammation has been described [4, 5], but also a protective effect on surfactant function by molecular interactions between nitric oxide and lung surfactant has been proposed [6, 7].

A new systemic effect of iNO in which there is a remote delivery of NO has been described. Probably red blood cells and specific plasma proteins play a major role in the transport and delivery of NO from the lung to peripheral tissues [8, 9]. This effect of improvement of the systemic microcirculation by iNO has been described in children with hypoxemic respiratory failure, where iNO improves the functional capillary density in a distal microvascular bed in hypoxemic respiratory failure with no effect on global hemodynamic parameters [10], also, in a neonatal model of stroke in rats, 20 ppm iNO can be transported into the rat brain and mediate blood flow redistribution during ischemia leading to reduced infarct volume and cell injury [11] as a possible neuro-protector effect of iNO.

Use of iNO in newborn infants

Regulatory approval for iNO use in newborn infants > 34 weeks gestation in the US in 1999 and in Europe in 2001 was granted after it was demonstrated, mostly from two large randomized clinical trials, that the use of iNO, to term and near term newborns with severe hypoxemic respiratory failure and pulmonary hypertension can improve oxygenation and reduce by 40% the risk of needing ECMO. The improvement is mainly due to a reduction in the need for ECMO, since mortality was not reduced [12, 13].

For the approval indication in term and near term newborn infants, iNO has demonstrated to be a safe therapy, 12 to 24 months follow-up studies indicate that there is no negative effect of iNO in the incidence of chronic lung disease nor neurodevelopmental impairment [14, 15].

iNO in premature infants.

Premature infants, are not included in the approved indication of iNO, as they were not included in the large randomized controlled trials for iNO approval and because their lower risk of developing persistent pulmonary hypertension of the newborn (PPHN) and higher risk of intracranial hemorrhage. Because of its potential side effect due to the inhibition of platelet aggregation [16, 17] and its toxicity when forming NO_2 and other Nitric derived substances [18], iNO if given, must be administrated with caution in the premature infants, a population at risk of developing hemorrhagic complications, mostly in the sicker infants.

Several potential indicatios for iNO in preterm infants have been porposed, but can be summarized into three:

- treatment of pulmonary hypertension associated to severe respiratory failure;
- improvement of the lung growth;
- neuro-protection.

Treatment of pulmonary hypertension associated to severe respiratory failure

In some circumstances, when pulmonary hypertension is associated to severe respiratory failure and there is no response to other therapy,

iNO has been used in preterm infants with positive results [19] and its use is of clinical relevance [20].

Although iNO has not demonstrate a proven effect in randomised controlled trials in premature infants with severe hypoxemia and pulmonary hypertension, there is some evidence for its potential beneficial effect for a small number of critically ill preterm infants with failure associated with oligohydramnios and PPHN.

Aikio et al. [21] recently demonstrate a transient deficiency in the inflammatory response, including a defect in nitric oxide generation in airspaces in preterm infants (< 32 weeks gestation) with prolonged preterm rupture of membranes who developed hypoxic respiratory failure with pulmonary hypertension and acutely respond to iNO. This positive effect of iNO in this group of patients was related by the authors as a result of pulmonary smooth muscle relaxation improving alveolar perfusion, gas exchange and ventilation.

Improvement of the lung growth

Other potential indication of iNO in premature infants is to prevent or treat bronchopulmonay dysplasia (BPD). There is enough experimental evidence for a potential role of iNO in preventing and treating BPD, based on its potential stimuli in lung growth, angiogenesis and airway growth [22-28]. Moreover, iNO improves oxygenation by optimizing the ventilation-to-perfusion mismatching and decreases pulmonary vascular resistance, reducing lung trauma related to mechanical ventilation, and decreases FiO_2, factors related to the risk of developing BPD [29].

Also, there are other mechanisms of improving lung function, such as its anti-inflammatory effect by inhibiting neutrophils accumulation in the lung and protection of pulmonary surfactant [6, 7].

Although experimental data support the potential role of iNO in preventing BPD, randomized clinical trials did not demonstrate a significant benefit in preterm infant at risk of BPD development. Even more, results for inhaled nitric oxide use in randomized controlled trials with the primary end point of decreasing BPD or death are confusing, because of differing study designs, population treated with different severity of diseases, different dose and length of therapy.

In a recent Cochrane review [30], fourteen randomized controlled trials were analyzed, including the European trial reported by Jean-Christophe Mercier and colleagues [31]. Due to the wide variations of the patients studied in these trials, dosing, duration of treatment and respiratory failure severity, Barrington and Finer grouped the trials into three categories depending on entry criteria [30]:

1. preterm infants enrolled in the study in the first 3 days of life based on oxygenation criteria, defined as early-rescue treatment (9 trials);
2. early routine use in preterm babies with pulmonary disease (3 trials);
3. later enrollment (> 3 days of life) of infants based on an increased risk of BPD (2 trials).

Although small and marginal effects were observed in reducing death or BPD in studies of iNO in routine use before the EUNO trial was added to the meta-analysis, after the EUNO trial, this effect disappeared. In each of the three subgroups, no relevant clinical effect of iNO was demonstrated.

Recently, Askie et al. [32] published an individual-patient data meta-analysis of randomized controlled trials of preterm infants, where data from 3,298 infants in 12 trials (96%) were analyzed. There was no significant effect of iNO on death or chronic lung disease (CLD), or severe neurologic events on imaging. Overall, death or CLD occurred in 59% of iNO-treated infants versus 61% of control infants (RR: 0.96 [95% CI: 0.92-1.01]; p = .11). Also severe neurologic events occurred in 25% of infants in the iNO group compared with 23% of infants in the control group (RR: 1.12 [95% CI: 0.98-1.28]; p = .09). So the authors concluded that routine use of iNO for treatment of respiratory failure in preterm infants cannot be recommended.

Probably the lack of effect of iNO in premature infants to prevent BPD is due to its multifactorial etiology. Inflammation, before and after delivery, respiratory support, nutrition, ethnic and genetic factors are some of the most important, but immaturity of the preterm infant constitutes the most important one in the genesis of BPD, so a single therapy should be improbable to decrease this chronic lung condition.

Neuro-protection of iNO

It has been proposed that iNO can produce some neuro-protective effect.

In a single-center study of iNO [33] where a beneficial effect in decreasing the risk of severe intraventricular hemorrhage or periventricular

leukomalacia was demonstrated, the two years follow up of 138 preterm children [34] showed an improvement in neurodevelopmental outcomes of the iNO treated group compared with patients receiving placebo (RR: 0.53 [95% CI: 0.33-0.87]; p = .01). Investigators speculated that this beneficial effect was mediated by enhancement of somatic growth or by direct effect in the brain through mechanisms involving the cerebral vasculature [35] or neuronal maturation [36, 37].

Also in a historical cohort study [38] in preterm singleton infants (< 34 gestational weeks) with hypoxemic respiratory failure caused by persistent pulmonary hypertension of the newborn who received inhaled nitric oxide (16 patients) or 100% oxygen (15 patients) therapy, a statistically significant decrease in the incidence of cerebral palsy was found in those who received iNO.

But the follow-up of the EUNO trial at 1 and 2 years [39] found no significant difference in neurological development and respiratory outcome function between the iNO and the placebo groups (including the incidence of cerebral palsy).

Conclusions

In summary, routine or rescue use of iNO cannot be recommended in preterm infants with respiratory failure, certain selected groups of preterm infants, mostly those with prolonged preterm rupture of membranes who developed hypoxic respiratory failure with pulmonary hypertension can benefit by the use of iNO. Long term follow up studies demonstrated that iNO given at 5 ppm early to preterm infants with respiratory failure is a safe and well tolerated therapy, but no beneficial effect on neurological development or respiratory function is found at one and two years follow up.

Declaration of interest

Manuel Sánchez Luna has received advisory board consulting fees and travel support from INO Therapeutics. All authors declare that they have no other conflicts of interest.

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