

Guidelines for Rational and Cost-Effective Use of iNO Therapy in Term and Preterm Infants

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ABSTRACT

Inhaled nitric oxide (iNO) is an effective but costly therapy for infants with hypoxemic respiratory failure. The approved and solidly evidence-based indication is for treatment of late preterm and term infants with persistent pulmonary hypertension of the newborn (PPHN); however, off-label use of iNO has become widespread. Although iNO treatment of infants with congenital diaphragmatic hernia constitutes one of the approved indications, available evidence from randomized trials suggests marginal if any efficacy. Rescue therapy in preterm infants with severe respiratory failure has been studied extensively and is not supported by data from a number of controlled trials. Such use is widespread, but should be discouraged. There may be a subgroup of such infants with pulmonary hypoplasia and documented PPHN who may benefit from this treatment, but the data are limited. Several studies have examined the use of iNO for prevention of chronic lung disease with inconsistent results. This promising application requires more study before it can be recommended. There may be a role of iNO in treating infants with pulmonary hypertension complicating severe bronchopulmonary dysplasia, but there are limited data on long term outcomes. Alternate therapies such as sildenafil may be beneficial in this specific population as well as in other causes of pulmonary hypertension. Rational use of this expensive treatment will maximize cost:benefit and avoid potential exposure to unknown adverse effects not balanced by documentable benefits.

Key words:

Inhaled nitric oxide, off-label use, clinical guidelines

INTRODUCTION

Inhaled nitric oxide (iNO) is a specific pulmonary vasodilator that has been well studied and documented to be safe and effective in term and late preterm infants with hypoxemic respiratory failure. Although effective for the treatment of persistent pulmonary hypertension of the newborn (PPHN), the treatment is quite costly and its use needs to be guided by sound evidence in order to optimize benefit and manage cost. In recent years, the use of iNO for “off-label” indications, such as for rescue treatment of preterm infants with severe respiratory failure, babies with severe chronic lung disease complicated by pulmonary hypertension and for prevention of bronchopulmonary dysplasia (BPD) has increased greatly.^[1,2] Such off-label use is associated with potential exposure to unknown adverse effects not balanced by documentable benefit and incurs very high cost. The following guidelines summarize available evidence for the use of iNO in several distinct clinical conditions in which it has been used in recent years and formulates evidence-based recommendations for rational use of this therapy.

Term and late preterm infants with hypoxemic respiratory failure

Available evidence

There is Level I evidence in support of this indication from

two large randomized trials, and additional studies.^[3-5] This is the indication recognized by the United States Food and Drug Administration (FDA). Earlier initiation of iNO at oxygenation index (OI) between 15 and 25 resulted in shorter duration of iNO therapy, less likelihood of reaching OI of 25 and may lower the chance of reaching criteria for rescue treatment with extracorporeal membrane oxygenation (ECMO).^[6,7]

Recommendations

Treatment with iNO is indicated in infants who have clinical and/or echocardiographic evidence of pulmonary hypertension that is not relieved by optimization of respiratory support (including lung volume recruitment,

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Access this article online	
Quick Response Code:	Website: www.jcnonweb.com
	DOI: 10.4103/2249-4847.96739

when indicated), circulatory support and sedation. All aspects of care should be optimized prior to initiation of iNO, so that response to therapy can be judged accurately. The response to iNO is equally good or better at OI of 15-25 as it is at OI >25.^[8] Some infants have little or no lung disease and in that situation, increasing mean airway pressure to achieve a threshold OI may lead to more lung injury with no benefit in terms of oxygenation. Initiation of iNO at OI >15 is appropriate, provided that evidence of pulmonary hypertension persists despite optimal (not maximal) ventilatory support, hemodynamic support and appropriate sedation.

The starting and maximal dose is 20 PPM.^[9,10] Higher doses provide no added benefit and are associated with increased toxicity in the form of higher levels of nitrogen dioxide and methemoglobin. Weaning of the iNO dose should begin once FiO_2 has come down to <0.60-0.70. Increments of 5 PPM down to 5 PPM are usually well tolerated and can usually be achieved by 24 h of therapy.^[4]

Subsequent weaning should be in increments of 1 PPM. The FiO_2 usually needs to be increased by about 0.10 with final discontinuation of iNO to prevent rebound hypoxemia.^[11] Most infants can be weaned from iNO within 96 h.^[4] PaO_2 target range of 60-80 mmHg is appropriate and will facilitate weaning off high FiO_2 and iNO as well as minimizing pulmonary oxygen toxicity. There is no evidence that targeting hyperoxic PaO_2 is beneficial, and increasing evidence that hyperoxia increases pulmonary vasoreactivity.^[12] Hyperoxia should especially be avoided in infants with perinatal asphyxia where it may worsen brain injury mediated by reactive oxygen species. If there is no significant response (defined as PaO_2 improvement of ≥ 10 mmHg within 15-30 min of initiation of treatment), iNO should be stopped and re-evaluation of the underlying cause of hypoxemia considered. Continued use of iNO in infants who had no initial response has been associated with deterioration when iNO is later withdrawn.^[13]

Term and late preterm infants with congenital diaphragmatic hernia and hypoxemic respiratory failure

Available evidence

Congenital diaphragmatic hernia (CDH) is one of the on-label indications and supported by early anecdotal reports. However, the single randomized controlled trial (RCT) and subanalyses from two other large RCTs show no improvement in survival or reduction in the need for ECMO in this population.^[4,14,15] Modest and/or transient improvement in oxygenation is often seen and this may be important in stabilizing the infant for long enough to successfully implement ECMO, where available, or

transport to more advanced facilities. Occasional infants have a more dramatic and sustained response.^[16] Poor left ventricular function and/or left ventricular hypoplasia sometimes seen in infants with CDH may account for some of the poor response to iNO.

Recommendations

A trial of iNO is appropriate in infants with CDH, but expectations should be lowered and appropriate counseling of families considered. All other aspects of care as in previous paragraph, except for less aggressive lung volume recruitment and more gentle ventilation strategy. It is important to recognize that overexpansion of the hypoplastic lungs compresses intra-alveolar capillaries and aggravates pulmonary hypertension. As always, iNO should only be started after optimizing other aspects of care (hemodynamic support, gentle ventilation, etc.) so that response can be accurately judged.

Preterm infant with severe respiratory failure (early rescue use)

Available evidence

Several RCTs have examined this question and uniformly show no improvement in survival or any other important outcome.^[17-23] Oxygenation typically improves at least transiently, but this does not appear to translate into improved outcomes.^[24] The National Institutes of Child Health and Development (NICHD) Consensus Development conference concluded that “the available evidence does not support use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation.”^[25] Because iNO impairs platelet aggregation and may increase the risk of intraventricular hemorrhage (IVH), it should be used with great caution during the first week of life in very immature infants. The PiNO National Research Network randomized controlled trial (RCT) found significantly increased mortality and severe IVH in infants <1000g.^[23] Taken together, these studies constitute Level 1 evidence against the rescue use of iNO in preterm infants, especially when <1000g.^[23]

Several small cohort studies and case series suggest that infants with prolonged preterm rupture of the membranes (PPROM) and pulmonary hypoplasia who have relatively clear lungs and documented pulmonary hypertension may benefit from iNO therapy.^[26-29]

The NICHD Consensus Development conference concluded that “There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied, in which iNO may have benefit in infants <34 weeks gestation.”^[25] However, the level of evidence in support of such use is only Level 3-4.

Recommendations

Routine use of iNO in this population is not indicated and may be specifically contraindicated. Most infants with severe respiratory distress syndrome (RDS) have some degree of pulmonary hypertension by echocardiography. In infants with severe RDS, pulmonary hypertension is most effectively relieved when lung inflation is optimized. It is important to understand that iNO is not effective in a poorly aerated lung.

Specific patients may benefit from this off label use if there is documented PPHN despite well-aerated lungs and a reversible underlying pathophysiology. In particular, a subgroup of preterm infants with PPROM and pulmonary hypoplasia may uniquely benefit iNO therapy, but the risk/benefit ratio is unknown. iNO should only be started AFTER optimizing other aspects of care, so that response can be accurately judged. If there is no significant response (defined as PaO₂ improvement of ≥ 10 mmHg within 15-30 min of initiation of treatment), iNO should be stopped, to avoid complications.

Preterm infant with mild - moderate RDS and at risk for BPD (Prophylactic use / PBD prevention)

Available evidence

There are convincing animal data demonstrating multiple positive effects of iNO on the injured developing lung, including improved angiogenesis, improved alveolarization and reduced inflammatory response.^[30] Two RCTs have shown reduction in the rate of BPD^[31,32] and in neuroimaging abnormalities.^[31,33] One showed improved neurodevelopmental outcome in iNO treated infants at 2 years of age.^[34] Other large RCTs failed to confirm these findings.^[33,35,36] The benefit appeared to be confined to the larger, less sick infants.^[31,33] The NICHD Consensus Development conference concluded that “The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation” and did not advocate the use of iNO for prevention of BPD.^[25]

Recommendations

The conflicting trial data leave too much uncertainty to recommend routine prophylactic use of iNO in this population. Such use should be avoided until ongoing studies clarify the possible benefits.

The older preterm infant with severe BPD and pulmonary hypertension

Available evidence

Infants with severe BPD typically have varying degrees of pulmonary hypertension (PH). Those who eventually die of the disease do so with progressive PH and biventricular

hypertrophy and eventual right ventricular (RV) failure, i.e., cor pulmonale.^[36]

There is limited (level 3-4) evidence of potential benefit, primarily as measured by short-term improvement in oxygenation,^[37] but no data regarding long-term outcome. A single study examined the response to iNO with each patient as his/her own control and demonstrated improvement in oxygenation, allowing substantial lowering of FiO₂. However, about half the infants eventually died. The long-term benefits are unknown.^[38]

Anecdotal experience suggests that some infants do have a sustained response, but they are often unable to wean off iNO for extended periods. Limited published evidence suggests that phosphodiesterase inhibitors, such as sildenafil may offer similar benefits.^[39-41] Sildenafil is being widely used in centers that have a large experience with PH (personal communication) and are easier to administer and not as prohibitively expensive as iNO. It should be recognized that while iNO improves V/Q matching, systemic sildenafil may worsen V/Q matching, even as it lowers pulmonary artery pressure (PAP) and improves hemodynamic status.

Recommendations

Evidence for the use of iNO and/or sildenafil in this population is only level 3-4 with insufficient studies to formulate a clear recommendation. If iNO is used in such patients, every effort should be made to determine whether there is a clear response and to discontinue the drug if there is no or minimal response. In responders, it may be reasonable to continue iNO for several days to a couple of weeks and attempt periodic weaning. In all cases, an effort should be made to find the lowest effective dose. Available data suggest that the improvement in V/Q matching is more effective at lower doses of iNO that result in less distant diffusion of the gas. The dose and duration of exposure should be limited, because we lack data on the long-term safety of very prolonged exposure to moderately high doses of iNO.

While early use of iNO may be effective in preventing BPD in some infants, there is no evidence that established BPD can be reversed by prolonged iNO therapy. In infants, who appear to be iNO dependent, it may be appropriate to transition to sildenafil therapy. The best way to accomplish this is unknown. Anecdotally and based on very limited published data, a starting dose of 0.5 mg/kg/dose every 8 hours is suggested.^[41]

This dose should be increased as necessary to achieve the desired clinical effect (improved echocardiogram findings, improved clinical status, or both) to a maximum dose

of 2 mg/kg/dose every 6-8 hours. iNO should then be gradually reduced and discontinued, if the improvement can be sustained. Wherever iNO is unavailable, initiating treatment with sildenafil is warranted.

SUMMARY

Treatment with iNO is safe and effective in the treatment of PPHN in the late preterm and term population. Other indications are not currently supported, with certain exceptions. Treatment with oral or intravenous sildenafil may be effective alone or in combination with iNO, but more data are needed before definitive recommendations can be made. Wherever indicated, iNO therapy should only be started AFTER optimizing other aspects of care, so that response can be accurately judged. The starting and maximal dose of iNO is 20 PPM. Weaning of the dose should begin once FiO_2 has come down to <0.60 - 0.70 . Increments of 5 PPM down to 5 PPM are usually well tolerated. If there is no significant response (defined as PaO_2 improvement of ≥ 10 mmHg within 15-30 min of initiation of treatment), iNO should be stopped. This can be done abruptly after short exposure. Weaning to a minimum effective dose and discontinuing the drug as soon as weaning is tolerated should be the goal of therapy for all medications, including iNO. iNO is very short acting with a rapid onset of action. If weaning to a lower dose of iNO is not tolerated, this will be manifest within 10-15 min. Transient deterioration in oxygenation beyond that period are common and may have a variety of causes. Reflexively increasing the dose of iNO instead of seeking and addressing other potential causes (agitation, secretions, hemodynamics) may result in missed opportunities to improve care.

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How to cite this article: Keszler M. Guidelines for Rational and Cost-Effective Use of iNO Therapy in Term and Preterm Infants. *J Clin Neonatol* 2012;1:59-63.

Source of Support: Nil, **Conflict of Interest:** None declared.

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