

Subject: Inhaled Nitric Oxide (iNO) in the Preterm Newborn

Date Reviewed: 06/2007

This is a guideline and may not apply to the individual circumstances of each infant. This guideline is intended to assist individualized decision making, not replace it.

Background

iNO was approved by the US Food and Drug Administration on December 23, 1999 for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. The limited data to date on hypoxic preterm neonates suggest that low-dose iNO improves oxygenation but does not improve survival. Additional large randomized trials of iNO in premature neonates are required because they may experience more toxic effects than term and near-term infants.

See:

Cochrane database review 2001 (Inhaled nitric oxide for respiratory failure in preterm infants, Barrington KJ, Finer NN,
<http://www.nichd.nih.gov/COCHRANE/Barrington/BARRINGTON.HTM#Finer%202001>).

Implications for practice

There is currently no clear evidence to support the use of inhaled nitric oxide in preterm infants. Rescue therapy of very sick preterm infants who meet criteria for poor oxygenation does not improve their survival, survival without BPD, or brain injury. Oxygenation may be improved in the short term.

In view of these findings inhaled nitric oxide should not be routinely used for preterm infants as a rescue therapy in cases of hypoxic respiratory failure. Other potential uses of nitric oxide should be subjected to rigorous evaluation prior to being instituted.

The protocol outlined is not intended to encourage iNO therapy in preterm infants with severe hypoxic respiratory failure. This intent of this protocol is to outline guidelines for the provider that will determine whether iNO therapy is effective or ineffective and shorten its' unnecessary use.

Parental Consent

iNO therapy has been approved by the FDA for use in infants with GA \geq 34 weeks only. The benefits and risks of iNO in preterm infants (GA < 34 weeks) should be discussed and documented with the parents or guardian prior to treatment.

Inhaled Nitric Oxide For Treatment Of Hypoxic Respiratory Failure In The Preterm Infant

* Eligibility Criteria

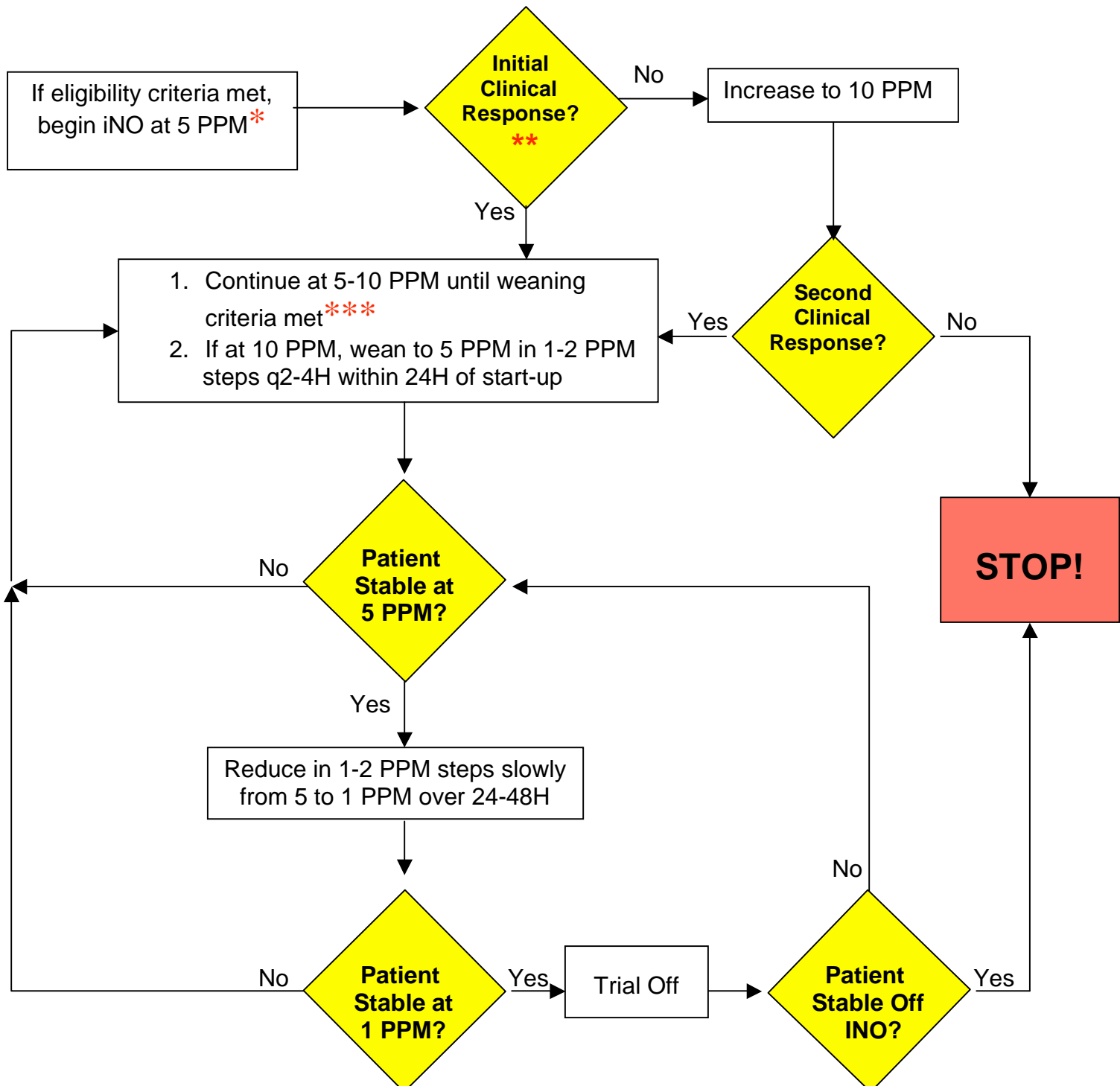
1. GA < 34 weeks
2. Diagnosis of HRF/PPHN
3. Need for assisted ventilation
 - BW < 1.5kg: O.I. > 10x2 > 30min.
 - BW ≥ 1.5kg: O.I. > 15x2 > 30min.
4. ECHO to R/O CHD

** Clinical Response

1. Occur ≤ 120 min.
2. Response includes at least one of below:
 - ↑ PaO₂ > 20mm Hg
 - 20% ↓ O.I.
 - 20% ↑ PaO₂/FiO₂

*** Weaning Criteria

1. FiO₂ < 0.6
2. PaO₂ > 60mmHg



Discussion

In the Cochrane database review eight published randomized controlled trials in preterm infants were reviewed: (Skimming 1997; Subhedar 1997; Kinsella 1999; Mercier 1999; INNOVO 2005; Schreiber 2003; Van Meurs 2005; Hascoet 2005). The Skimming study randomly compared the effects of two different concentrations of iNO for 15 minutes, and there was no untreated control group. Those data were excluded from this review.

The effect of iNO on the following parameters were assessed:

1. Death prior to hospital discharge
 - None of the trials showed a significant effect.
2. Death prior to 36 weeks postmenstrual age
 - There was no significant effect of inhaled nitric oxide on this outcome.
3. Bronchopulmonary dysplasia (oxygen dependence among survivors at 36 weeks corrected age)
 - None of the individual trials found a significant effect.
4. Combination of death or bronchopulmonary dysplasia
 - None of the individual trials found a significant effect, except the study by Schreiber showed a significant reduction in this combined outcome, (RR 0.76, 95% CI 0.60. 0.97
5. Intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL)
 - Overall, grade 3 or 4 IVH or PVL was not affected by the intervention. Schreiber 2003 showed a significant reduction in the risk of grade 3 or 4 IVH or PVL (RR 0.51, 95% 0.27, 0.97).
6. Neurodevelopmental outcome
 - The only studies to report on neurodevelopmental outcome are Schreiber and INNOVO. Schreiber's study was the only study to show a reduction in serious ultrasound diagnosed brain injury. This study showed a significant reduction at 2 years of age corrected in the frequency of a composite outcome of neurodevelopmental disability, (cerebral palsy, bilateral blindness, bilateral hearing loss, or a score on the Bayley scales of infant development >2 SD below the mean). This improvement was largely the result of a decrease in the incidence of a Bayley score more than two SD below the mean. Cerebral palsy was no different between the groups.
7. Oxygenation within two hours of therapy
 - Overall it appeared that improvements in oxygenation are probably more frequent when infants receive iNO compared to no therapy. Improvements were generally short-lived lasting not much greater than 120 minutes.
8. Pulmonary artery pressure.
 - Subhedar reported a reduction in pulmonary artery pressure as assessed by echocardiography within 30 minutes of treatment compared to no change in the controls.
9. Duration of assisted ventilation. Kinsella found a significant reduction in ventilator days among iNO survivors (median 26, range 3 to 69 days with iNO, median 37, range eight to 395 days in controls).

The Cochrane review did not find any advantages of iNO compared to control treatment in preterm infants for any of the following clinically relevant outcomes: death prior to hospital discharge, bronchopulmonary dysplasia (oxygen dependence at 36 weeks postmenstrual

age), death or bronchopulmonary dysplasia. However, the study by Schreiber et al introduces heterogeneity into the analysis and did demonstrate a reduction in the combined outcome of death or BPD.

Oxygenation within two hours of therapy with iNO appears to have been increased although the magnitude of the effect could not be calculated. This improvement in oxygenation did not lead to significantly improved survival or reduced lung injury.

Only the study of Schreiber et al showed a reduction in serious ultrasound diagnosed brain injury, the overall analysis does not show an improvement in brain injury

Cochrane database review 2001 (Inhaled nitric oxide for respiratory failure in preterm infants, Barrington KJ, Finer NN,
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