AMERICAN ACADEMY OF PEDIATRICS

Committee on Fetus and Newborn

Use of Inhaled Nitric Oxide

ABSTRACT. Approval of inhaled nitric oxide by the US Food and Drug Administration for hypoxic respiratory failure of the term and near-term newborn provides an important new therapy for this serious condition. This statement addresses the conditions under which inhaled nitric oxide should be administered to the neonate with hypoxic respiratory failure.

ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; FDA, US Food and Drug Administration.

Hypoxic respiratory failure in neonates born at or near term may be caused by such conditions as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, pneumonia or sepsis, and congenital diaphragmatic hernia. Conventional therapies, which have not been validated by randomized controlled trials, include administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation.[1] Despite aggressive conventional therapy, neonatal respiratory failure was associated with a high rate of mortality before the development of extracorporeal membrane oxygenation (ECMO).[2,3] Survival and short-term morbidity rates have been superior in term and near-term infants (≥34 weeks' gestation) treated with ECMO compared with conventional therapy[4]; however, questions remain about the long-term safety of ECMO.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator for which the mechanism of action involves guanylyl cyclase activation leading to production of cyclic guanosine monophosphate and subsequent smooth muscle relaxation.[5–7] Although several studies have suggested that iNO improves oxygenation,[8–14] the US Food and Drug Administration (FDA) evaluated 2 large randomized multicenter controlled trials of term and near-term neonates with hypoxic respiratory failure that demonstrated improved outcome with iNO therapy. The Neonatal Inhaled Nitric Oxide Study Group trial documented that iNO reduced the need for ECMO[15] without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age.[16] These results were strengthened by the Clinical Inhaled Nitric Oxide Research Group trial, in which iNO reduced the need for ECMO and the incidence of chronic lung disease.[17] iNO was not effective for infants with congenital diaphragmatic hernia.[18]

The limited data to date on hypoxic preterm neonates suggest that low-dose iNO improves oxygenation but does not improve survival.[14,19] Additional large randomized trials of iNO in premature neonates are required because they may experience more toxic effects than term and near-term infants.[14,19,20]

It is critical that infants with hypoxic respiratory failure in whom conventional ventilator therapy fails or is predicted to fail be cared for in institutions that have **immediate availability** of personnel, including physicians, nurses, and respiratory therapists, who are qualified to use multiple modes of ventilation and rescue therapies. Radiologic and laboratory support required to manage the broad range of needs of these infants is also essential.

iNO should be administered using FDA-approved devices that are capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle. Infants who receive iNO therapy should be monitored according to institutionally derived protocols designed to avoid the potential toxic effects associated with iNO administration. These effects include methemoglobinemia (secondary to excess nitric oxide concentrations), direct pulmonary injury (attributable to excess levels of nitrogen dioxide), and ambient air contamination.

In the trials of iNO therapy reported to date, the indication for use has been failure of ventilatory therapy. ECMO, a therapy of proven efficacy, usually is initiated if iNO therapy fails. Therefore, institutions that offer iNO therapy generally should have ECMO capability; if a center lacks ECMO capability, it should work in collaboration with an ECMO center to prospectively establish appropriate iNO failure criteria and mechanisms for the timely transfer of infants to the collaborating ECMO center. The diversity of geography, climate, and transport capabilities necessitates that the "timely transfer" be dictated by the location-specific transport limitations as well as the severity of the infant's illness. Because hypoxic respiratory failure is often rapidly progressive and abrupt discontinuation of iNO may lead to worsening oxygenation,[21] the risk of delayed provision of ECMO must be considered carefully when determining the appropriate time of transfer.

Plans for the care and referral of these infants should incorporate the following recommendations.

RECOMMENDATIONS

1. Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
2. iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label (http://www.fda.gov). An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
3. iNO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
4. Generally, iNO should be initiated in centers with ECMO capability. If iNO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of iNO therapy.
5. Centers that provide iNO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
6. Centers that provide iNO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, use of alternative therapies, and outcomes.
7. Administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

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