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Practice Point

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Inhaled nitric oxide use in newborns

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ABSTRACT

Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, is used as a therapeutic modality in infants with hypoxemic respiratory failure (HRF) associated with persistent pulmonary hypertension of the newborn (PPHN). iNO should ideally be initiated following echocardiographic confirmation of PPHN. Use of iNO is recommended in late preterm and term infants who develop HRF despite optimal oxygenation and ventilation strategies. However, routine iNO use in preterm infants on respiratory support is not recommended. iNO may be considered as a rescue modality in preterm infants with early-onset HRF when associated with prolonged rupture of membranes or oligohydramnios, or late-onset HRF in the context of bronchopulmonary dysplasia-associated pulmonary hypertension (PH) with severe right ventricular failure. A trial of iNO may also be considered for infants with congenital diaphragmatic hernia with persistent HRF despite optimal lung recruitment, and with echocardiographic evidence of supra-systemic PH and adequate left ventricular function.

Keywords: Hypoxemic respiratory failure; Inhaled nitric oxide; Newborn; Persistent pulmonary hypertension of the newborn.

Inhaled nitric oxide (iNO) is used as a therapeutic modality in infants with hypoxemic respiratory failure (HRF) associated with persistent high pulmonary vascular resistance and resultant right-to-left shunting of blood through the foramen ovale, ductus arteriosus, and/or intrapulmonary channels, referred to as persistent pulmonary hypertension of the newborn (PPHN) (1–3). This practice point updates a previous CPS document published in 2012 (4).

MECHANISM OF ACTION

Nitric oxide (NO) is produced endogenously from L-arginine by NO synthase. NO diffuses into vascular smooth muscle cells leading to vasodilation and improved ventilation/perfusion (V/Q) matching (5,6). When administered, iNO is a selective pulmonary vasodilator in infants with HRF associated with pulmonary arterial hypertension.

ADMINISTRATION

iNO therapy using approved delivery systems should be initiated and supervised by experienced clinicians at tertiary neonatal intensive care units (NICUs) as well as other units providing critical care to newborns. Continuous iNO therapy can be initiated during neonatal transport by trained neonatal retrieval personnel.

INITIATION AND DOSING

Recommendation: The diagnosis of PPHN should be established with echocardiography before initiating iNO if possible, or if not possible, echocardiography should certainly be obtained after iNO is initiated.

Initiation of iNO may be guided by oxygenation index (OI) (see discussion in 'Indications for use' section). However, OI requires a value of partial pressure of oxygen (PaO_2) by arterial sampling, which may not always be feasible. Recently, the oxygen saturation index (OSI), using oxygen saturation (SpO_2) by pulse oximetry, has been described as well correlated with OI in neonates with HRF, allowing for continuous monitoring without arterial sampling. Studies are needed to further outline the role of OSI in the initiation and titration of iNO (7), but this marker may be useful in resource-limited settings, such as during neonatal transport (8).

iNO should be initiated at 20 ppm in near-term and term infants (2,9). The expected clinical response (improved oxygenation, cardio-respiratory stability), is rapid, occurring in <30

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minutes (2,9). If there is no clinical response, the iNO dose may be increased up to 40 ppm (2). If after 30 minutes there is no clinical response, iNO should be discontinued.

In very or extreme preterm infants, iNO may be initiated at 5 to 10 ppm and increased up to 20 ppm (10,11). The concentration of NO_2 (nitrogen dioxide) in the inspired mixture should be maintained below 0.5 ppm.

WEANING

Weaning protocols should be implemented as part of care bundles to reduce practice variation, costs, and unnecessary exposure (12,13). After clinical response, iNO may be weaned by 50%, provided the OI remains at ≤10, pre-ductal SpO_2 does not decrease by ≥5%, and/or FiO_2 does not increase by ≥10% (4,14). When a dose of 5 ppm has been reached, iNO may be decreased by steps of 1 ppm (every 30 minutes to 2 hours) until discontinuation, provided the infant remains well oxygenated at <60% FiO_2 (2,15). Abrupt cessation of iNO should be avoided because it may be followed by rebound severe hypoxemia (16). If deterioration occurs during weaning or after treatment discontinuation, the dose should be increased to the prior level or iNO therapy should be re-started. When the infant has improved, weaning should be re-attempted based on clinical or echocardiographic evaluations (or both) (4).

SAFETY CONSIDERATIONS

iNO has a short half-life of 2 to 6 seconds. No severe side effects have been reported at the starting dose of 20 ppm and up to 40 ppm. Potential toxicities include: NO_2 (causing pulmonary cytotoxicity) and methemoglobin production (levels >2.5% may contribute to toxicity), decreased platelet aggregation, increased risk of bleeding, and surfactant dysfunction (2,17).

One Australian cohort study demonstrated that iNO was associated with a significantly higher risk of childhood cancer (aOR 4.3: 2.3 to 8.2) (18). However, confounding by indication cannot be ruled out, because infants receiving iNO were also sicker and substantially exposed to other potential carcinogenic agents, such as imaging radiation and prolonged oxygen therapy (18,19).

INDICATIONS FOR USE

Use in late-preterm and term infants

Evidence from randomized controlled trials (RCTs) suggests that iNO use in near-term and term infants with HRF reduces the combined outcome of need for extracorporeal membrane oxygenation (ECMO) or death, but may not impact the rates of neurodevelopmental impairment (NDI) (15) (Table 1). Controversy exists regarding the degree of HRF severity at which to initiate iNO therapy. The incidence of death or ECMO appears to be strongly correlated with the OI at trial enrolment. Infants in the early RCTs, where iNO was initiated at a mean OI of >40, had a mortality or ECMO rate of >40%, while infants who received iNO at an OI of 15 to 20 had a mortality or ECMO rate of 10.2% (20).

Recommendation: Use of iNO is recommended in late preterm or term infants with HRF (OI >15 to 20 or PaO_2 <100 mmHg in 100% oxygen) despite implementation of management strategies to optimize oxygenation and ventilation. Echocardiographic confirmation of normal left ventricular function and absence of congenital heart disease characterized by ductal-dependent systemic blood flow before initiating iNO are recommended.

Use in preterm infants born <35 weeks gestational age (GA)

Substantial practice variation has been documented with iNO use in preterm infants in Canada. A retrospective analysis of

Table 1. Effect of iNO on clinical outcomes: evidence from RCTs

Near-term or term infants with HRF		
Outcomes	**Number of participants (studies)**	**Relative risk (95% CI) [and GRADE certainty of evidence]**
Death or use of ECMO	859 (8 RCTs)	RR 0.66 (0.57–0.77)[High]
ECMO before discharge	815 (7 RCTs)	RR 0.60 (0.50–0.71)[High]
NDI at 18–24 months among survivors	301 (2 RCTs)	RR 0.97 (0.66–1.44)[Low]
Near-term or term infants with congenital diaphragmatic hernia and HRF		
Death or use of ECMO	84 (2 RCTs)	RR 1.09 (0.95–1.26)[Moderate]
ECMO before discharge	84 (2 RCTs)	RR 1.27 (1.00–1.62)[Moderate]
Preterm infants with early-onset acute HRF (<3 days)		
Death before discharge	1066 (10 RCTs)	RR 1.02 (0.89–1.18)[High]
Death or BPD	958 (8 RCTs)	RR 0.94 (0.87–1.01)[High]
Severe IVH (grade 3 or 4)	773 (6 RCTs)	RR 1.20 (0.98–1.47)[High]
Preterm infants >3 days of age at risk for BPD		
Death before discharge	1,075 (3 RCTs)	RR 1.18 (0.81–1.71)[High]
Death or BPD		RR 0.92 (0.85–1.01)[High]
NDI	498 (2 RCTs)	RR 0.90 (0.74–1.09)[Moderate]

BPD Bronchopulmonary dysplasia; CI Confidence interval; ECMO Extracorporeal membrane oxygenation; GRADE Grading of Recommendation, Assessment, Development, and Evaluation; HRF Hypoxemic respiratory failure; iNO Inhaled nitric oxide; IVH Intraventricular hemorrhage; NDI Neurodevelopmental impairment; RCT Randomized controlled trial; RR Relative risk.

newborns <34 weeks admitted to NICUs participating in the Canadian Neonatal Network showed that 4% received iNO (831/19,525), with a variation in iNO use by centre ranging from 0% to 15.5% (21). iNO has been considered in the following scenarios:

Early-onset acute HRF

RCT evidence suggests that iNO does not reduce death or bronchopulmonary dysplasia (BPD) when initiated as a therapeutic modality for early-onset (≤3 days of age) HRF, and may result in a small increase in severe intraventricular hemorrhage (IVH) (9) (Table 1). Routine iNO use in preterm infants does not reduce death or BPD, and has no impact on severe IVH or neurodevelopment (9). A cohort study (n = 7,639) demonstrated that iNO in early HRF (maximal FiO_2 >60% on day 1 or 3) in infants born <26 weeks GA or in extremely low birth weight (<1,000 g) infants did not reduce death or NDI (22). Recent observational studies described an association between iNO use and improved survival without brain injury or NDI in extremely preterm infants who developed refractory HRF following exposure to prolonged rupture of membranes (PROM) (23,24). A recent cohort study showed that early iNO treatment may slightly improve survival among extremely preterm neonates with pulmonary hypoplasia and PPHN (hazard ratio 0.67; 95% CI, 0.45 to 1.01) (25).

Recommendation: Routine iNO use in preterm infants on respiratory support is not recommended. iNO may be considered as a rescue modality in preterm infants with early-onset refractory HRF when associated with PROM or oligohydramnios.

Rescue iNO therapy for acute-onset HRF in infants with BPD

A small observational study (n = 10) using cardiac catheterization showed that infants with BPD demonstrated reduction in pulmonary artery pressures and pulmonary-to-systemic vascular resistance ratio (PVR/SVR) when exposed to iNO (26). Another small observational study (n = 10) showed that exposure to iNO for 15 minutes improved echocardiographic markers of right ventricular (RV) function and PVR in extremely preterm infants with BPD-PH (27). No RCTs have been conducted on iNO use in this specific population. During an acute PH crisis with RV failure, expert consensus from the American Heart Association and American Thoracic Society suggests use of iNO as a part of a multi-modal management strategy (28).

Recommendation: In preterm infants with HRF or severe RV failure in the context of BPD-PH, rescue therapy with iNO may be considered if other respiratory management strategies, such as optimized ventilator support or postnatal corticosteroids (or both), have failed to resolve the hypoxemic crisis or RV failure. When there is no clinical response following initiation of iNO, therapy should be promptly discontinued.

Use in congenital diaphragmatic hernia (CDH)

Despite lack of RCT evidence, infants with CDH are still exposed to iNO, with one study (n = 3,367) reporting an average of 62% iNO use per centre (range, 0% to 100%) (29). In this study, 36% of infants without PH were treated with iNO and, adjusting for other clinically relevant variables, iNO use was associated with increased mortality (29). A cohort of 131 infants with CDH (95 received iNO) demonstrated that iNO improved oxygenation and reduced ECMO need in the subpopulation with PH and normal left ventricular (LV) function (30).

Recommendation: In infants with CDH and HRF despite optimal lung recruitment and with echocardiographic evidence of supra-systemic PH and adequate LV function, a trial of iNO may be considered. In the absence of appreciable echocardiographic or clinical improvement, iNO therapy should be promptly discontinued.

FUTURE RESEARCH

Benefits and harms of iNO in extremely preterm infants with early acute and severe BPD-associated HRF need to be accurately quantified to develop strong recommendations for or against the increasing use of iNO for such conditions.

SUMMARY OF KEY RECOMMENDATIONS

1. The diagnosis of persistent pulmonary hypertension of the newborn should be established with echocardiography before initiating iNO if possible, or if not possible, echocardiography should certainly be obtained after iNO is initiated.
2. Use of iNO is recommended in late preterm or term infants with HRF despite implementation of management strategies to optimize oxygenation and ventilation.
3. Routine iNO use in preterm infants on respiratory support is not recommended. iNO may be considered as a rescue modality in preterm infants with early-onset refractory HRF when associated with prolonged rupture of membranes or oligohydramnios.
4. In preterm infants with HRF or severe RV failure in the context of BPD-PH, rescue therapy with iNO may be considered if other respiratory management strategies have failed to resolve the hypoxemic crisis or RV failure.
5. In infants with CDH and HRF despite optimal lung recruitment and with echocardiographic evidence of supra-systemic PH and adequate LV function, a trial of iNO may be considered.

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POTENTIAL CONFLICTS OF INTEREST

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