## Inhaled nitric oxide use in newborns

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Inhaled nitric oxide (iNO) is a pulmonary vasodilator that plays a major role in regulating vascular muscle tone. It has emerged as a treatment for hypoxemic respiratory failure in newly born infants that is associated with persistent high pulmonary vascular pressure and resultant right-to-left shunting of blood (persistent pulmonary hypertension of the newborn). Current evidence shows that iNO improves oxygenation and decreases the combined outcome of death or need for extracorporeal membrane oxygenation in infants ≥35 weeks' gestational age at birth. Its role in managing preterm infants <35 weeks' gestational age is not yet established. iNO is safe when administered in tertiary care settings using strict protocols and monitoring. The recommended starting dose is 20 ppm with gradual reduction of the dose following improvement in oxygenation.

Key Words: Newborn; Nitric oxide; Pulmonary hypertension; Respiratory failure

Nitric oxide (NO) plays a major role in regulating vascular muscle tone (1). The administration of inhaled NO (iNO) has emerged as a new form of treatment for newborn infants with hypoxemic respiratory failure associated with persistent high pulmonary vascular pressure and resultant right-to-left shunting of blood through the foramen ovale, ductus arteriosus and intrapulmonary channels, referred to as persistent pulmonary hypertension of the newborn (PPHN) (2-4). Recent studies have examined the role of iNO in preterm infants. It is important that health professionals who care for newborns understand the appropriate use of iNO. The purpose of the present practice point is to summarize the available evidence-based information on the use of iNO for managing severe newborn hypoxemia.

NO is generated in the lung endothelium from L-arginine by the enzymatic activity of NO synthases (5). NO diffuses into vascular muscle cells and activates the enzyme guanylate cyclase, leading to increased cyclic guanosine monophosphate production, pulmonary vasodilation and improved ventilation/perfusion matching (6). iNO, as a selective pulmonary vasodilator for term newborn infants with hypoxemic respiratory failure and PPHN, was introduced in 1992. Several research groups reported that iNO improved oxygenation without significant toxicity or effects on the systemic circulation. Subsequently, a large number of single and multicentre prospective clinical trials of late-preterm and term infants with severe hypoxemia reported that iNO improved oxygenation, reducing both the incidence of death and the need for extracorporeal membrane oxygenation (ECMO) (3,4).

The systematic review of iNO randomized trials published by the Cochrane Collaboration (7) provides evidence that iNO at

# L'utilisation d'oxyde nitrique inhalé chez les nouveau-nés

L'oxyde nitrique inhalé (iNO) est un vasodilatateur pulmonaire qui joue un rôle majeur dans la régulation du tonus musculaire vasculaire. Il a émergé comme traitement de l'insuffisance respiratoire hypoxémique chez les nouveau-nés ayant une pression vasculaire pulmonaire qui demeure élevée et entraîne une dérivation droitegauche du sang (hypertension pulmonaire persistante du nouveau-né). Les données probantes actuelles révèlent que l'iNO améliore l'oxygénation et réduit l'issue combinée de décès ou d'administration d'oxygénation extracorporelle chez les nourrissons d'au moins 35 semaines d'âge gestationnel. Son rôle dans la prise en charge des nourrissons prématurés de moins de 35 semaines d'âge gestationnel n'est pas encore établi. L'iNO est sécuritaire lorsqu'il est administré dans des établissements de soins tertiaires selon des protocoles et une surveillance stricts. La dose de départ recommandée, de 20 parties par million, est réduite graduellement lorsque l'oxygénation s'améliore.

doses of 10 ppm to 80 ppm significantly improves oxygenation, as assessed by the oxygenation index (OI =  $FiO_2$  x mean airway pressure x 100/PaO<sub>2</sub>), when compared with placebo or standard care (mean OI difference 45.49 [95% CI 34.66 to 56.3]) and also decreases the incidence of death or need for ECMO in infants with PPHN (RR 0.68 [95% CI 0.59 to 0.79]) (7). This difference was due mainly to a reduction in the need for ECMO (RR 0.63 [95% CI 0.54 to 0.75]) without an effect on death (RR 0.91 [95% CI 0.60 to 1.37]) (7). iNO therapy did not reduce the incidence of death in infants with congenital diaphragmatic hernia (RR 1.09 [95% CI 0.95 to 1.26]). Early initiation of iNO at a lower OI, of 15 to 25, improved oxygenation without decreasing the incidence of death or need for ECMO, when compared with initiation at OI >25 (8). iNO has no impact on adverse neurodevelopmental outcomes (RR 0.97 [95% CI 0.66 to 1.44]); however, long-term outcomes have not been studied (7,9-11).

#### Who should be treated with iNO?

Current evidence supports the use of iNO for infants ≥35 weeks' gestational age at birth with hypoxemic respiratory failure who fail to respond to appropriate respiratory management. For infants with pulmonary disease, treatment may include optimizing tidal volume/pressure and the use of manoeuvers to recruit lung units such as surfactant, high-frequency oscillatory ventilation and/or jet ventilation. Ideally, all newborn candidates for iNO therapy should undergo echocardiographic evaluation to rule out cyanotic congenital heart disease, and to assess for pulmonary hypertension and cardiac function. iNO is usually started in infants with an OI >20 to 25, or when the PaO<sub>2</sub> remains less than 100 mmHg, despite optimal ventilation with 100% oxygen (3,4,7,8).

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#### Use of iNO in premature infants

The use of iNO in very sick premature infants <35 weeks' gestational age with PPHN was first described in case reports (12), was continued in unblinded trials and then followed by large multicentre trials (13,14). Fourteen randomized trials were analyzed in the Cochrane Collaboration review (15). The trials of early rescue treatment, within the first one to two postnatal days for very sick infants (based on need for high inhaled oxygen and high mean airway pressure), showed no effect on reducing mortality or bronchopulmonary dysplasia (BPD) (RR 0.94 [95% CI 0.87 to 1.01]) (15). Routine use of iNO in intubated infants weighing ≥1000 g, who were less sick, showed a minor reduction in the combined outcome of death or BPD in two studies (RR 0.91 [95% CI 0.84 to 0.99]) (15). There was a trend toward an increased risk of severe intraventricular hemorrhage or periventricular leukomalacia in sick iNO-treated premature infants (RR 1.16 [95% CI 0.93 to 1.44]), but not when iNO was used as routine treatment for intubated infants weighing >1000 g (RR 0.70 [95% CI 0.53 to 0.91]) (15).

Due to conflicting evidence, there is some uncertainty about the impact of iNO on long-term outcomes for premature infants. Routine use of iNO in moderately ill infants weighing >1000 g decreased the risk of cerebral palsy (16). One additional report, not included in the Cochrane review, found significant improvement in neurodevelopmental outcomes at two years of age for moderately ill infants (RR 0.53 [95% CI 0.33 to 0.87]) (17). In a small study, premature newborns with a history of oligohydramnios secondary to prolonged rupture of the membranes and treated with iNO, had lower rates of death and BPD (18).

Overall, iNO does not appear to be effective as a rescue treatment or as a routine treatment for preterm infants who require assisted ventilation. It may be beneficial for a small number of critically ill infants in defined clinical situations, such as respiratory failure associated with oligohydramnios.

#### Administration of iNO

iNO therapy should be initiated and supervised by experienced physicians at tertiary neonatal intensive care units (NICUs) with advanced modes of ventilatory and multispecialist support, including ECMO. Continuous iNO therapy can be provided during transport to level 3 NICU centres. Approved delivery systems provide a constant source of iNO gas and can be used with conventional, high-frequency oscillatory or high-frequency jet ventilation.

iNO is very expensive and should only be used when other forms of therapy have failed.

**Dose:** iNO has a short half-life (2 s to 6 s) and has been used in newborns at doses of 1 ppm to 80 ppm, which is then titrated to achieve the desired effect. Doses greater than 40 ppm have the potential to increase toxicity without additional benefits. The recommended starting dose for term infants is 20 ppm (3,7,8). The expected response is rapid, occurring in less than 30 min with a  $PaO_2$  increase  $\geq$ 20 mmHg (3,7,8). If there is no response, the iNO dose may be increased up to 40 ppm (3). The dose used in studies involving premature infants was 10 ppm and was increased up to 20 ppm in nonresponders (14,15). The concentration of  $NO_2$  in the inspired mixture should be maintained as low as possible – below 0.5 ppm.

Weaning: Following improvement in oxygenation and after a 4 h to 6 h period of stability, during which the inspired oxygen concentration is decreased to 60% to 80%, or the OI falls to  $\leq$ 10, the dose of iNO should be weaned. An accepted method of weaning is to decrease the dose by 50% at 4 h to 6 h intervals as long as the OI remains at  $\leq$ 10. Once a dose of 5 ppm has been attained, the dose should be decreased more gradually, by 1 ppm every 4 h and discontinued at 1 ppm if the infant remains well oxygenated in

<60% oxygen with PaO<sub>2</sub> consistently >50 mmHg (3,7). Abrupt cessation of iNO therapy may be followed by severe hypoxemia secondary to the downregulation of endogenous NO production and should be avoided (19). If deterioration occurs during weaning or after treatment has been discontinued, the dose should be increased to the previous level or iNO therapy should be restarted. Once the infant has improved, weaning should be slower, taking place over a 24 h to 48 h period.

**Duration of use:** The safe duration of iNO therapy is unknown. The mean duration of therapy in trials was 48 h to 96 h, and most randomized trials demonstrated that 90% of treated infants were off iNO therapy within one week of its initiation (3,4,7). Infants who cannot be weaned from iNO after seven days should be carefully evaluated for other forms of lung pathology and cardiac disease.

#### Is iNO toxic?

The potential toxicity of iNO is important to consider when initiating therapy. The main concerns involved with iNO toxicity include production of  $\rm NO_2$  and methemoglobin, decreased platelet aggregation, increased risk of bleeding and surfactant dysfunction. No severe side effects of iNO have been reported, and at the starting dose of 20 ppm, and up to 40 ppm, there is minimal toxicity (2-4,7-11).

 $NO_2$  production: One of the concerns with the use of iNO is the chemical reaction that converts NO to  $NO_2$  in high oxygen concentrations in the ventilator circuit and airways.  $NO_2$  is cytotoxic and can cause pulmonary injury at concentrations >5 ppm. In the iNO clinical trials, the peak level of  $NO_2$  was  $0.8\pm1.2$  ppm; no gas was discontinued due to toxicity (3). iNO at doses <80 ppm is not associated with significant  $NO_2$  levels.

Methemoglobin: NO is absorbed into the blood where its binds to the ion of the heme protein, subsequently producing nitrosylhemoglobin, which is oxidized to methemoglobin with the release of nitrates (20). Methemoglobin levels should be measured frequently and kept <2.5%. With standard iNO doses, methemoglobinemia is unusual. In the Neonatal Inhaled Nitric Oxide Study Group (NiNOS) trial, the peak level of methemoglobin was 2.4%±1.85% (3). Premature infants are at a higher risk of methemoglobin toxicity due to reduced levels of methemoglobin reductase, but at iNO doses of <20 ppm, methemoglobin levels were not elevated (13,14).

#### **SUMMARY**

iNO use in the term infant with severe hypoxic respiratory failure improves oxygenation and decreases the combined outcome of death or need for ECMO, mainly by decreasing the use of ECMO. iNO use is not effective for most infants with congenital diaphragmatic hernia. Its role in the management of the preterm infant has yet to be established. iNO use is safe when administered in tertiary care NICUs under strict protocols and monitoring. The starting dose in term infants is 20 ppm, with gradual reduction of the dose following improvement of oxygenation. At the recommended doses, iNO is associated with minimal toxicity.

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