Inhaled Nitric Oxide Therapy (iNO)

THE ROYAL HOSPITAL FOR WOMEN - PROCEDURE GUIDELINE

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<td>Dr J. Smyth</td>
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DATE REVISED: REVISED BY

APPLICABLE TO: Newborn Care Centre Staff – Nursing & Medical

IMPLICATIONS: To be included in induction training of all nursing /medical staff. 15 staff to be randomly audited on the procedure for evidence of knowledge of the procedure.

DATE POSTED ON NCC WEBSITE: 31/10/14

APPROVED BY: NCC Quality Committee on 13/10/2014

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ABBREVIATIONS & DEFINITIONS OF TERMS

<table>
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<th>CXR – Chest X-Ray</th>
<th>ECMO – Extracorporeal Membrane Oxygenation</th>
<th>iNO – Inhaled Nitric Oxide</th>
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<td>PPHN-Persistent Pulmonary Hypertension</td>
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INTRODUCTION

The use of iNO as a pulmonary vasodilator is well established in term infants with Pulmonary Hypertension be it primary or secondary. In 2 large randomised trials in near term and term infants, iNO reduced the need for ECMO by ≈ 40%. It did not reduce mortality, length of hospitalisation or risk of neurodevelopmental impairment. Echocardiography can assist in directing appropriate use of iNO. The best response is often seen in infants with a relatively normal CXR but ECHO evidence of marked PPHN suggesting primary PPHN. The benefits of iNO use in Preterm infants, particularly extremely preterm infants is not proven and data is limited. No RCT’s or meta-analyses have shown that rescue or routine use of iNO improves survival in preterm infants with respiratory failure. The preponderance of evidence also does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe IVH or other neonatal morbidities. It is however generally regarded as a safe treatment in these infants. Early use of iNO with CPAP/non-invasive IMV/IMV may be of some benefit to reduce lung injury in preterm infants.

AIM:

To appropriately determine, implement and wean iNO therapy in neonates (Rationale 1-3).

EQUIPMENT

INOMax DS IR

PROCEDURE

General Indications in Term infants & Preterm infants > 32 weeks gestation:

- any infant with severe hypoxic respiratory failure: ie: PaO₂ cannot be maintained > 50mmHg or O₂ saturation > 90% despite optimal ventilation with FiO₂ > 80%
- any ventilated infant with > 60% FiO₂ requirement and Echocardiographic evidence of PPHN (pulmonary artery pressures close to or above systemic pressures) and/or evidence of poor cardiac output (RVO <150ml/kg/min) or low mean left pulmonary artery blood flow velocity (< 0.2 m/sec)
- Early use of iNO can be considered in infants with suspected pulmonary hypoplasia (e.g. after prolonged oligohydramnios or prolonged preterm rupture of membranes), congenital diaphragmatic hernia (CDH) or congenital pulmonary adenomatoid malformation (CPAM) as these infants may benefit from gentle
ventilation to avoid barotrauma and airleaks. Infants with a history of oligohydramnios frequently have a good response to iNO\textsuperscript{7,8}.

**General Indications in Preterm infants ≤ 32 weeks gestation:**
- any ventilated preterm infant with severe hypoxic respiratory failure unable to maintain PaO\textsubscript{2} > 50mmHg or O\textsubscript{2} sats > 90% despite moderate ventilatory requirements (Moderate ventilator requirements can be defined as Mean Airway Pressure 12-14 cmH\textsubscript{2}O, with FiO\textsubscript{2} 60% to maintain PaO\textsubscript{2} > 40 mmHg (equates to Oxygenation Index ≤ 20)) and/or ECHO evidence of high pulmonary artery pressure, low cardiac output or low lung perfusion (as defined above).
- Early use of iNO can be considered in infants with suspected pulmonary hypoplasia (e.g. after prolonged oligohydramnios or prolonged preterm rupture of membranes), congenital diaphragmatic hernia (CDH) or congenital pulmonary adenomatoid malformation (CPAM) as these infants may benefit from gentle ventilation to avoid barotrauma and airleaks. Infants with a history of oligohydramnios frequently have a good response to iNO\textsuperscript{7,8}

**Contraindications** (these are relative contraindications)\textsuperscript{2}:
- caution with iNO in babies < 26 wks gestation
- infants < 30 weeks should have a head ultrasound to check for an IVH, though this is a relative contraindication
- any evidence of a coagulopathy (particularly in preterm infants < 32 wks)

**NB:** It is important to optimise Respiratory, Circulatory & Haematological/Biochemical management prior to initiation of iNO therapy (see below points 1-3):

1. **Optimise Ventilation as per lung disease**
2. **Circulatory:** assess cardiac dysfunction, ensure adequate circulating blood volume & correct poor contractility with inotropes
   - **INOTROPES\textsuperscript{2}**:
     1. **1st line:** Dobutamine: Dobutamine ↓ both pulmonary and systemic vascular resistance and is likely to ↑ cardiac output
     2. **2nd line:** Adrenaline: Adrenaline ↑ systemic more than pulmonary vascular resistance & ↑ cardiac output at doses of 0.05µg/kg/min up 0.37µg/kg/min.
   - **Target mean arterial BP ≥ 40 mmHg in Term infants**
     - **Caution:** Dopamine ↑ pulmonary and systemic vascular resistance to a similar degree, especially at doses > 10 µg/kg/min\textsuperscript{1}. Consider use of PG to maintain ductal patency in patients with moderate-severe PPHN
3. **Haematological/Biochemical abnormalities:** keep Hb >100 -120g/L, normalise glucose & Ca

**Starting Dosage:**

1. **Term infants & infants > 32 weeks gestation:** start at 10ppm ↑ to 20ppm depending on response (higher doses are unlikely to be of benefit & doses > 40ppm are associated with methaemoglobinaemia)
2. **Preterm infants ≤ 32 weeks gestation:** start at 5ppm increasing to a max of 10-20ppm depending on response

**Prescribing iNO:**
iNO is now a registered drug with the Australian Therapeutic Goods Administration (TGA). As a fully registered drug, starting dose of iNO must be prescribed on the medication chart in PRN section. Start and stop time and dose changes must be charted accurately.

**Response to iNO therapy is evidenced by:**
- expected response within 30 min with a paO\textsubscript{2} increase by ≥20 mmHg
- FiO\textsubscript{2} should ↓ by 10% or more while maintaining the desired pre-ductal saturation range with or without changes to ventilation strategy
- also get normalisation of pre/post-ductal SaO\textsubscript{2} difference

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Inhaled Nitric Oxide(iNO) Therapy
iNO Lack of dose response:
- There is no consistent evidence of a dose-response effect with iNO:
  Attempts should be made to ↓ iNO dose to the minimal effective dose. If a trial of ↑ nitric dose fails to improve oxygenation or haemodynamics then ↓ dose back to original dose.

Weaning iNO:
- Weaning from iNO should be considered when an infant shows clinical improvement and is stable for a 4-6hr period with FiO2 < 60%
- ↓ iNO in increments of 1-2 ppm every 1-4 hrs until ceased

Aim is to deliver the minimum dose compatible with normal oxygenation and haemodynamics.

In Term babies there may be an advantage in maintaining a low dose of iNO (2-5 ppm) while O₂ and ventilator pressures are weaned, particularly if is echocardiographic evidence of persistently ↑ pulmonary artery pressures

In Preterm babies, aim should be to wean off iNO as soon as possible and not to continue beyond what is required!

Failure or difficulties with iNO weaning:
- While there is no clear definition for failure, one can define failure as increasing FiO₂ by ≥ 20% &/or persistent requirements of FiO₂ > 60%
- If weaning or discontinuation of iNO results in a clinically evident return of PPHN and hypoxaemia (as per criteria above) iNO therapy should be returned to the last effective dose (usually 5 ppm) Once the infant has improved, weaning should be slower, taking place over a 24-48 hr period.
- Consider starting treatment with Sildenafil & grade up dose as per drug protocol

Methaemoglobin monitoring:
NO can theoretically cause methaemoglobinaemia although none of the RCTs using doses of 20 ppm or less have reported any increase in the incidence of methaemoglobinemia. Preterm infants are more susceptible because of relatively low levels of the enzyme methaemoglobin reductase. Methaemoglobin levels should be checked regularly and they are displayed on our blood gases. If levels rise above 5% iNO should be reduced or stopped.

RATIONALES
Rationale 1 | Appropriate patient selection and use of iNO
Rationale 2 | Safe and considered use of iNO in Preterm infants
Rationale 3 | Cost effective use of iNO

References
1. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database of Systematic Reviews 2006, DOI: 10.1002/14651858.CD000399.pub2.