Non-invasive inhaled nitric oxide in term and preterm newborns: A therapeutic option in selected patients☆

Óxido nítrico y ventilación no invasiva en neonatos. Posibilidad terapéutica en pacientes seleccionados

Dear Editor:

The administration of inhaled nitric oxide (iNO) has proven effective for treatment of persistent pulmonary hypertension of the newborn (PPHN) in neonates born to term of after 34 weeks of gestation.[1–3] In preterm neonates born before 34 weeks of gestation, the use of iNO is controversial, although its off-label use as rescue therapy has been increasing in clinical practice.[2] Until a few years ago, iNO was administered exclusively through invasive mechanical ventilation, with the risks that this approach involves, especially in preterm infants. Therefore, given the current preference for minimally invasive respiratory support, it may be worth considering the option of administering iNO through non-invasive ventilation devices (iNO-NIV).[3,4]

In a period of 4 years, 8 patients with gestational ages ranging from 25 to 41 weeks and birth weights from 900 to 3700 g received iNO-NIV in our unit. Table 1 summarises the clinical characteristics and outcomes of the patients. The inclusion criteria were: need of a fraction of inspired oxygen (FiO_2) greater than 60%; normocapnia in NIV (capillary partial pressure of carbon dioxide [pCO_2] < 55 mmHg); haemodynamically stable (normal heart rate, blood pressure and serum lactate for gestational age and weight); suspected PPHN with a difference between preductal and postductal saturations greater than 10% and/or compatible findings of echocardiography at admission (estimated pulmonary pressure in relation to the patent ductus arteriosus or tricuspid regurgitation pressure gradient and/or deviation of the interventricular septum). The exclusion criteria were: air leak, severe apnoea of prematurity, pH < 7.25 or any other absolute indication for mechanical ventilation.

The source of iNO was the INOvent® delivery system (INO Therapeutics, Datex-Ohmeda Inc, Madison, WI, USA) with INOmax® 800 ppm cylinders. Non-invasive ventilation was delivered with the Infant Flow SiPAP® system (Vyasis™ Healthcare, Bird Products, Palm Springs. CA, USA). Previous studies have found the use of these devices for administration of iNO-NIV safe.[4]

Our patients with PPHN responded quickly and optimally to iNO-NIV, with a quick descent in oxygen requirements, and none required mechanical ventilation during the stay. Our results were similar to those reported by Sahni et al.[3] in patients of comparable characteristics (haemodynamically stable PPHN with normal pH). It seems reasonable to hypothesise that early administration of iNO-NIV could prevent clinical worsening in these cases, in addition to the use of a high FiO_2 for prolonged periods.[1,5] However, in the 2 patients with pulmonary hypertension secondary to meconium aspiration syndrome the response was less favourable and mechanical ventilation could not be avoided. Less favourable outcomes have also been observed in patients with meconium aspiration syndrome in other case series,[3] probably due to the high prevalence of pulmonary disease intrinsic to this condition. Therefore, the correct identification of patients that may benefit from iNO-NIV is key, and ultrasound may be very helpful for this purpose.[6] Seven of our patients had indirect signs of pulmonary hypertension at treatment initiation.

Doses of 5–20 ppm proved sufficient in our patients, without an associated increase in nitrogen dioxide or methaemoglobin.[4,5] In theory, iNO acts as an antiplatelet agent, but we found no evidence of an association with an increased incidence of interventricular haemorrhage or necrotising enterocolitis in the reviewed literature.[2,5] No direct adverse effects were observed during treatment. There was only 1 case of patent ductus arteriosus that required surgical correction, but it occurred in an extremely preterm infant and in association with clinically significant sepsis in the second week of life. Previous studies have not found an increase in the incidence of persistent patent ductus arteriosus or pulmonary haemorrhage with the use of iNO, although its effects on the pulmonary circulatory system of preterm infants should be evaluated in future studies on this treatment.

In conclusion, early use of iNO-NIV could be an adequate alternative in selected cases of PPHN with hypoxaemia, without hypercapnia and in haemodynamically stable patients. These patients could benefit from the avoidance of sedation, intubation, mechanical ventilation and delivery of high oxygen concentrations and their potential complications, something that can be even more important in preterm infants. Randomised trials in larger samples are needed to obtain rigorous conclusions.

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Table 1 Clinical characteristics and outcomes of patients treated with inhaled nitric oxide through non-invasive ventilation.

Patient	1	2	3	4	5	6	7	8
Gestational age (weeks + days)	33^{+1}	36^{+2}	38^{+0}	31^{+5}	25^{+2}	41^{+1}	40^{+2}	37^{+0}
Weight (grams)	1415 g	2795 g	2415 g	1490 g	900 g	3575 g	3680 g	2680 g
Gestational and perinatal history	- Oligoamnios - Urgent caesarean due to abnormal CTG and reversed end-diastolic flow -No antenatal steroids -Apgar 6/8. Resuscitation with PPV and FiO_2 of up to 100%. - Immediate increased work of breathing	- Preeclampsia and gestational diabetes -Urgent caesarean due to placental abruption -Apgar 4/6. Resuscitation with PPV and FiO_2 of up to 100%. - Immediate increased work of breathing	- Normal vaginal delivery. Light meconium-stained fluid - Apgar 9/9 - Admitted to neonatal unit with cyanosis ($SatO_2$: 80—85%). Normal hyperoxia test	-Premature rupture of membranes and preterm labour - Antenatal steroids - Apgar 7/8. Resuscitation with PPV and FiO_2 of up to 60% - Immediate increased work of breathing	- Premature rupture of membranes. Cervical incompetence - Caesarean section - Antenatal steroids - Apgar 4/7. Resuscitation with PPV and FiO_2 of up to 100%.	- Urgent caesarean due to abnormal CTG. - Meconium-stained fluid - Resuscitation with PPV and FiO_2 of up to 100%. - Immediate increased work of breathing	- Urgent caesarean due to abnormal CTG - Meconium-stained fluid - Apgar 3/8/8 - Resuscitation with PPV and FiO_2 of up to 100%. Cardiac massage for 30 s - Immediate increased work of breathing	- Premature rupture of membranes - Caesarean due to breech presentation - Apgar 9/10 - Progressive increase in work of breathing and hypoxaemia
Diagnostic tests at admission	- RX: HMD - Echo: dilated right heart chambers and paradoxical septal motion (right-left). TI. PDA. PP not estimated	- RX: cardiomegaly. Normal lung parenchyma -Echo: thickened septum. TI. PDA with estimated PP of 45—50 mmHg	- RX: normal - Echo: 2 mm VSD with left-right shunt and estimated PP of 35—40 mmHg. PDA	- RX: HMD - No echo	- RX: HMD - Echo: PDA. TI with an estimated PP of 40—50 mmHg	- RX: Meconium aspiration - Echo: TI a d PDA with estimated PP of 55—65 mmHg	- RX: meconium aspiration - Echo: dilated right heart chambers and paradoxical septal motion (right-left). PDA. TI with estimated PP of 55—65 mmHg	- RX: HMD - Echo: dilated right heart chambers and paradoxical septal motion (right-left). TI. PDA. PP not estimated

Table 1 (*Continued*)

Patient	1	2	3	4	5	6	7	8
Initial respiratory support	- BiPAP (MAP: 6 cmH_2O) - Surfactant (LISA)	- CPAP (5 cmH_2O)	- CPAP (5 cmH_2O)	- BiPAP (MAP: 6 cmH_2O) - Surfactant (LISA), no improvement	- BiPAP. (MAP: 6−7 cmH_2O) - Surfactant (LISA)	- BiPAP (MAP: 6−7 cmH_2O)	- CPAP (MAP: 6 cmH_2O)	-CPAP (MAP 6 cmH_2O) - Surfactant (LISA)
MAP (mmHg)	33	37	40	35	32	60	65	55
Pre- to post-ductal difference (%)	10	15	10	10	10	7	10−12	10−12
FiO_2 pre-iNO	60−70%	100%	90%	60%	70%	80%	80	60%
Dose of iNO-NIV and outcome	- 10 ppm - Reduction to FiO_2 25% in 1 h - Gradual removal of iNO in 24 h	- 20 ppm Reduction to FiO_2 21% in 2 h - Gradual removal over 24 h	- 20 ppm Reduction to FiO_2 21% in 2 h - Gradual removal over 24 h	- 10 ppm Reduction to FiO_2 21% in 2 h - Gradual removal over 24 h	- 5 ppm, no response −10 ppm: Reduction to FiO_2 21% in 2 h - Gradual removal over 36 h	- 20 ppm - Transient reduction to FiO_2 of 60% - Mechanical ventilation due to hypoxaemia at 6 h post birth. - HFOV and inotropic agents -No difference in pre-postductal saturations after 15 h. Gradual removal of iNO over 72 h	- 20 ppm - Transient reduction to FiO_2 50% - Mechanical ventilation due to hypoxaemia and hypercapnia at 48 h post birth - HFOV and inotropic agents - No difference in pre-postductal saturations after 24 h. Gradual removal of iNO over 72 h	- 20 ppm - Reduction to FiO_2 30% in 6 h - Gradual removal over 30 h

BiPAP, bi-level positive airway pressure system; CPAP, continuous positive airway pressure; CTG, cardiotocography; Echo, echocardiogram; HMD, hyaline membrane disease; FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation iNO, inhaled nitric oxide; LISA, less-invasive surfactant administration; MAP, medium airway pressure; PDA, patent ductus arteriosus; PP, pulmonary pressure; PPV, positive-pressure ventilation; RX, X-ray; $SatO_2$, oxygen saturation; TI, tricuspid insufficiency.

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