Heart & Lung xxx (2014) 1–4

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

Use of inhaled nitric oxide in preterm infants: A regional survey of practices

Arun Sasi, MD, DM [a], Arvind Sehgal, MD, MRCPCH, FRACP [a,b,*]

[a] Monash Newborn, Monash Children's Hospital, Melbourne, Australia
[b] Department of Pediatrics, Monash University, Melbourne, Australia

ARTICLE INFO

Article history:
Received 3 March 2014
Received in revised form
16 April 2014
Accepted 17 April 2014
Available online xxx

Keywords:
Inhaled nitric oxide
Preterm
Survey
Practice
Echocardiography

ABSTRACT

Objectives: To conduct a regional survey of neonatal intensive care unit (NICU) Directors in Australia and New Zealand (ANZ) to ascertain current practice.
Background: Use of inhaled nitric oxide (iNO) therapy in infants < 34 weeks gestational age is not supported by current evidence.
Methods: A cross-sectional electronic survey based on structured questionnaire was conducted amongst the Directors of all the tertiary neonatal intensive care units in Australia and New Zealand Neonatal Network (ANZNN). Information was collected on indications, dosage, monitoring response and weaning for iNO therapy.
Results: The survey was sent to 28 units, of which 2 were quaternary units' not routinely admitting preterm infants, hence were excluded from analysis. The response rate was 77% (20/26). Majority of units (16; 80%) did not have preterm specific protocol. In almost all units nitric was used as early rescue for hypoxemic respiratory failure (95%; 19/20). Neonatologist performed functional echocardiography (fECHO) was frequently used for prior assessment (90%) and monitoring (65%). Variations were noted regarding initiating criteria, dosage and weaning strategies.
Conclusions: Wide variation in practice was noted highlighting the need for the formulation of consensus guidelines.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is an acute condition characterized by hypoxemic respiratory failure (HRF). It reflects failure of extra-uterine adaptation and continued elevation of pulmonary pressures and carries with it high risk of mortality and morbidity. The underlying etiopathogenesis could include severe hyaline membrane disease, sepsis or pulmonary hypoplasia. Inhaled nitric oxide (iNO) is efficacious in improving oxygenation in PPHN in term infants' ≥ 34 weeks gestation at birth. It has also been shown to reduce the combined outcome of death or use of extracorporeal membranous oxygenation.[1] However, unlike its well-established role in late preterm and term infants, its use is highly contentious in infants born at <34 weeks gestational age in terms of indications, dosage and timing of initiation. In one of the earliest trials Kinsella et al investigated use of low dose iNO (5 ppm) in improving survival without increasing bleeding complications in preterm infants.[2] Survival, chronic lung disease (CLD) and discharge on oxygen and rates of severe intracranial hemorrhage (ICH) were comparable to controls. Schreiber and colleagues randomized 207 preterm infants to iNO (10 ppm on day 1 followed by 5 ppm for 6 days) or oxygen in a double blind, placebo-controlled study.[3] The combined incidence of death or CLD was less in the iNO group (48.6% vs 63.7%, relative risk, 0.76; 95% CI: 0.60–0.97; $P = 0.03$). A recent Cochrane analysis of randomised and quasi-randomised controlled trials (RCTs) of 'early rescue therapy' noted no significant effects on mortality or BPD.[4]

Despite lack of firm evidence from RCTs, its off label use in preterm infants is increasing with a wide variation in practice across different treating units. A retrospective study from the United States reported a 6-fold increase (0.3–1.8%) in its usage in

Abbreviations: (PPHN), Persistent pulmonary hypertension of the newborn; (HRF), Hypoxemic respiratory failure; (iNO), Inhaled nitric oxide; (CLD), Chronic lung disease; (ICH), Intracranial hemorrhage; (RCTs), Randomised controlled trials; (NICU), Neonatal intensive care unit; (ANZ), Australia and New Zealand; (fECHO), Functional Echocardiography; (OI), Oxygenation index; (BPD), Bronchopulmonary dysplasia; (PPROM), Preterm premature rupture of membrane; (ANZNN), Australia and New Zealand Neonatal Network.

Declaration of interest or financial disclosures: none.

* Corresponding author. Monash University, 246, Clayton Road, Clayton, Melbourne, VIC 3168, Australia. Tel.: +61 3 95945197.
E-mail address: Arvind.Sehgal@monash.edu (A. Sehgal).

0147-9563/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.hrtlng.2014.04.014

preterm infants from the year 2000–2008, with the largest increase (0.8–6.6%; ~8 fold) in extremely preterm infants (23–26 weeks gestation).[5] The 2010 National Institute of Health consensus statement concluded that the available evidence does not support its use in preterm infants.[6] The use of iNO in preterm infants increased in the United States from 1.8% to 5.7% after the consensus statement.[7] However, preliminary evidence of its usefulness in subgroups like pulmonary hypertension, oligohydramnios and pulmonary hypoplasia is emerging.[8] Lack of agreed guidelines in the region for initiating and weaning therapy, and escalating costs have contributed to equipoise on the issue. We therefore conducted a regional survey of neonatal intensive care unit (NICU) Directors in Australia and New Zealand (ANZ) to ascertain current practice, with the aim to provide information that could rationalize usage.

Study objective

The objective was to gather information on the current clinical practice of use of iNO in premature infants especially regarding the indications, dosage, monitoring and weaning strategies.

Methods

A cross-sectional survey was designed and piloted amongst the NICU consultants of the parent institution; questions were modified as appropriate. The survey was sent as an electronic linked questionnaire through the website (www.surveymonkey.com) to the Directors of all 28 tertiary NICUs during the period from December 2012 to February 2013. Non-responders were contacted by posting a paper copy of the questionnaire. Some questions had multiple choices and respondents were allowed to select one or more answers as necessary. The identities of respondents were kept anonymous and no personal identifiers were used. Consent was implied by voluntary participation and no financial incentive or reward was given for completing the survey. The survey was approved by the institution's research ethics committee.

Statistical analysis

Descriptive statistics were performed on respondent demographics, indications for iNO use, dosage and weaning strategies, adjuvant therapies and estimated increase in cost of therapy. The data is expressed as numbers or as percentage of respondents unless specified otherwise.

Results

Twenty of the 28 NICU Directors completed the survey. Of the non-responders, 2 were quaternary units, not admitting preterm infants, and were excluded from the final analysis, resulting in a response rate of 20/26 (77%). More than half the respondents (12; 60%) had greater than 20 years of NICU experience. Half the units admitted 500–1000 preterm infants ≤34 weeks annually over the last 5 years while 2 units (10%) admitted greater than 1000 infants. Two units treated more than 30 such infants annually while most (12; 60%) treated <10 infants ≤34 weeks per year with iNO over last 5 years. Most of the units (16; 80%) did not have a written protocol specifically for the use of iNO in this gestational age group. The most common indication to use iNO was PPHN confirmed by neonatologist performed functional echocardiography (fECHO) (14; 70%). Others included rescue therapy in all infants with HRF (11; 55% respondents), clinical setting for pulmonary hypoplasia (antenatal history of oligohydramnios, 11; 55% respondents). 19 (95%) of the responders used iNO as early rescue therapy (<72 h of age for oxygenation failure). Early routine therapy strategy based on the potential risk of development of CLD was not noted in our study; one unit used it as late rescue (>72 h of age) for *prevention* of CLD. Majority of units used high frequency oscillation to optimize ventilation prior to initiating iNO (17; 85%).

Table 1
Parameters used to define the need for nitric oxide therapy.

Parameter	*N* (%)
Fractional inspired oxygen	13 (65)
Pre-post ductal gradient	12 (60)
Oxygenation index	11 (55)
Partial pressure of oxygen (PaO_2)	11 (55)
Alveolar-arterial oxygen gradient	3 (15)
Alveolar/arterial PaO_2	1 (5)

Table 1 depicts various parameters used to define the need for iNO. Eleven (55%) units used oxygenation index (OI) as criteria to start iNO (7 used OI > 20 and 4 used OI of 11–20; none started at OI < 10). Neonatologist performed fECHO was performed commonly prior to starting iNO [always 6; 30% & mostly 12; 60%] for documentation of pulmonary hypertension and the assessment of cardiac function. Eleven units (55%) used it for monitoring response to therapy as well. The commonest starting dose of iNO was reported as 10 ppm (10; 50%) while 20 ppm was the commonest maximum dose (18; 90%). An increase in partial pressure of oxygen by 10–20 mm Hg was the most common indicator of 'response' to therapy (17; 85%). Close to half the respondents used fECHO derived information to facilitate weaning from iNO. Others used fractional inspired oxygen (20, 100%), OI (8, 40%) and increase in partial pressure of oxygen in blood gas (6, 30%). For infants deemed non-responders to iNO, it was tapered and stopped within 24 h by 15; 75% units (5; 25% within 6 h). Others ceased therapy by 48 h (3; 15%) while in one unit lack of response did not influence the decision. Of the other adjuvant therapies the most favored were sildenafil (11; 55%) (Table 2). Dopamine was the preferred drug for hypotension (9; 45%) compared to dobutamine (6; 30%). Milrinone or vasopressin was not used for inotropic support; though some used it as an adjuvant pulmonary vasodilator.

A pre-treatment cranial ultrasound was done always or mostly in 11; 55% responses. However, a severe ICH (grade III or IV) was not considered a contraindication for starting iNO in 15; 75% responses. Introduction of pay per hour system significantly increased annual budgetary allocations [<100,000 AUD (9; 45%) and 100,000–200,000 (3; 15%)]. For other units the cost estimation was not available.

Discussion

This regional survey is the first appraisal of the use of iNO in preterm infants in ANZ. Only a minority of the units had

Table 2
Adjuvant pulmonary vasodilators used for treatment of hypoxemic respiratory failure.[a]

Drug used	*N* (%)
Sildenafil	11 (55)
Milrinone	8 (40)
Alprostodil	4 (20)
Bosentan	3 (15)
Magnesium sulfate	3 (15)
Vasopressin	1 (5)
Sodium nitroprusside	1 (5)
Tolazoline	1 (5)
Adenosine	1 (5)
Levosimendan	0 (0)
None	6 (30)

[a] Multiple responses were allowed.