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ORIGINAL ARTICLE / RESEARCH

Inhaled Nitric Oxide in Hypoxic Respiratory Failure in Preterms: Audit of Ten Years of Practice

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ABSTRACT

Objective: We set out to ascertain the patient profile and practice pattern regarding use of inhaled Nitric Oxide (iNO) in preterm population with oxygenation failure in last ten years. Furthermore, we aim to identify characteristics of patients who respond to iNO.

Study Design and Setting: Retrospective chart review in a tertiary teaching referral hospital.

Subjects and Intervention: All preterm babies less than 34 weeks gestation with oxygenation failure who were treated with iNO were assessed for inclusion. Response to iNO therapy was defined as decline in oxygenation index by 50% 4 hours after start of iNO.

Results: iNO was administered to 26 preterm babies during the study period. Of these, 23 (88.5%) met the inclusion criteria. Total of 13 (56%) infants survived. The iNO responders had a higher gestation age (29 weeks Vs 26.5 weeks), birth weight (1279g Vs 999g), lower initial oxygenation index (38.7 Vs 58), earlier initiation of therapy (20 hours Vs 41.4 hours) and less mortality (25% Vs 86%) when compared to non-responders.

Conclusions: Although the infants were at a higher end of spectrum for severity of respiratory illness, nitric administration was successful in improving oxygenation. Characteristics of responders might help in better patient selection and optimize timing of intervention, in case use of Nitric Oxide therapy is being considered.

Key words: Nitric Oxide, oxygen index, preterm, respiratory failure

Introduction

Premature infants in hypoxic respiratory failure can have dramatic improvements after treatment with exogenous surfactant. However, a subset of premature infants has suboptimal responses to surfactant therapy and echocardiographic studies have shown that pulmonary hypertension

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frequently complicates the course of severe cases [1]. Physiologically, inhaled Nitric Oxide (iNO) may be of help in selectively dilating pulmonary vascular bed. Early introduction in the course of the disease is expected to reverse pulmonary vasoconstriction and improve ventilation-perfusion mismatch, thereby decreasing barotrauma and toxic effects of oxygen, especially on immature lungs [2]. While efficacious in term babies, iNO is a controversial treatment for premature babies and is considered a very contentious area in neonatal medicine. While it has been demonstrated to improve oxygenation in the short term, there is lack of consensus on its impact on decrease in mortality and/or chronic lung disease. The evidence from multicentric clinical trials published so far does not support the use of iNO to reduce mortality and risk of chronic lung disease in preterm infants [3],[4].

This study describes the practice pattern of use of iNO in last ten years in the preterm population with severe oxygenation failure. Secondly, it also highlights important characteristics of babies who responded to therapy which might give future guidance towards selection of population and optimal timing of intervention, leading to potential refinement of approach. We hypothesized that inhaled nitric oxide for oxygenation failure in preterm babies would be more effective in improving oxygenation if initiated early. Furthermore, we hypothesized that maximum response is seen in relatively mature infants. Audits of practice also serve as excellent learning tools with a potential to optimize protocols and guidelines.

Methodology

The study was designed as a retrospective chart review of practice at the Department of Newborn Care, Liverpool Hospital, Sydney, NSW, Australia, a tertiary level teaching hospital. About 3000 deliveries take place annually and the unit also serves as the referral center for high risk deliveries in South Western Sydney. Nitric Oxide has been in use in the unit for past ten years (since 1996). Neonatal audit database and medical records were reviewed for all preterm babies who received iNO therapy. For this review, preterm infants were defined as those born at less than 34 weeks gestation. Babies with congenital heart disease other than Patent Ductus Arteriosus (PDA) and those greater than two weeks at intervention were excluded. Demographic and clinical information like gestation, birth weight, mode of delivery, Apgar score, gender and underlying diagnosis was collected and details of concurrent modalities of treatment, arterial blood gas values, baseline ventilator & iNO parameters and response to therapy were recorded. The oxygenation index (OI) was calculated as 100 × the Fraction of Inspired Oxygen (FiO2) × the Mean Airway Pressure (MAP) (in cm of water) ÷ the Partial Pressure of Arterial Oxygen (post ductal PaO2) (in mm of Hg). In terms of improvement in oxygenation, responders were defined as decline in OI by 50% when assessed after 4 hours of iNO therapy. Safety profile in terms of biochemical and cranial ultrasound (US) findings was also recorded. Data is presented as median and interquartile with p value < 0.05 taken as significant. Fisher Exact tests were used for testing significance of comparative data.

[Table/Fig 1] Demographic characteristics and underlying diagnosis

Gestational age (weeks) (mean +/- S.D., median)	28.4 +/- 0.65, 28
Birth weight (g) (mean +/- S.D., median)	1247 +/- 96, 1170
Male gender	12/23 (52%)
Mode of delivery	
Vaginal	12/23 (52%)
Caesarian section	11/23 (48%)
Inborn babies	20/23 (87%)
Apgar scores	
5 minute (median, interquartile range)	7 (4-8)
Underlying diagnosis*	
Respiratory distress syndrome	17/23 (74%)
Sepsis	7/23 (30%)
Pulmonary haemorrhage	4/23 (17%)
Pulmonary hypoplasia	3/23 (13%)
Chylothorax	1/23 (4%)

*Multiple causes in some.

Results

A total of 26 preterm babies less than 34 weeks gestation were administered iNO during the study period. Two neonates with Total Anomalous Pulmonary Venous Connection and one greater than two weeks at intervention were excluded from analysis. Data from remaining 23 babies was analyzed. The mean gestation age

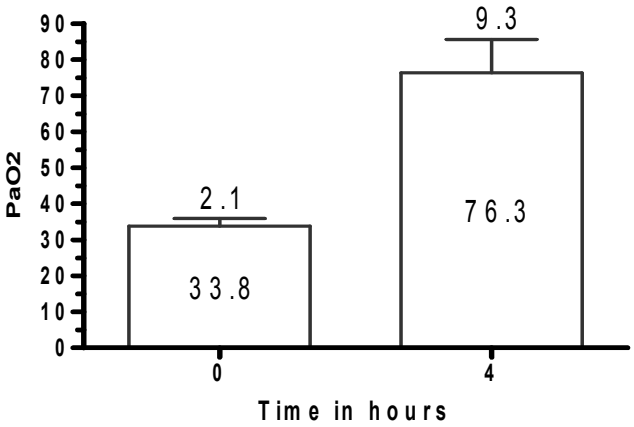
was 28.4 weeks (range 23 to 33.6 weeks) and mean birth weight was 1247g (range 630g to 2000g). [Table/Fig 1] describes the demographic characteristics and underlying diagnosis in the study population. Survival in the study population was 56% (13/23). Concurrent modalities of treatment like surfactant, muscle relaxation, sedation, volume expansion, inotropic support, and sodium bicarbonate were used prior to administration of iNO. Relevant findings on echocardiographic analysis were tricuspid regurgitation and bidirectional PDA. Seven out of 23 babies had blood culture proven sepsis, while risk factors for sepsis like maternal fever and prolong rupture of membranes were present in two others.

[Table/Fig 2] Overall baseline ventilator and iNO parameters of study population

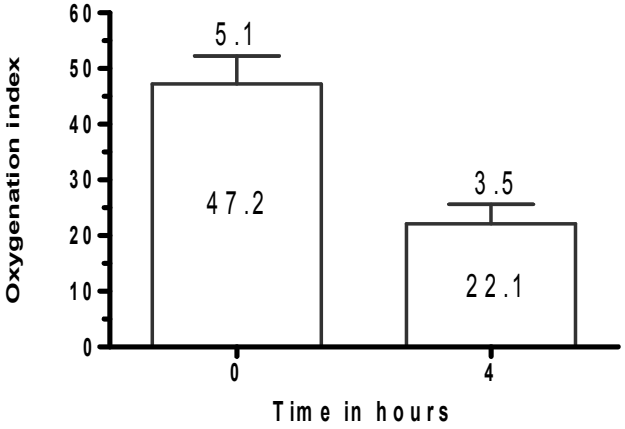
Variable	Median	Interquartile
Mean Airway Pressure (cm H2O)	18.5	18.1-19.6
FiO2 (%)	90.1	86.3-91.7
PaO2 (mm Hg)	34.1	32.3-35
Oxygenation index	48.3	43.6-50.9
Age at start of iNO (hours)	47.6	29.2-61.7
Concentration of iNO at start (ppm)	20.	19.1-21.2
Maximum concentration of iNO (ppm)	21.8	20.7-22.1
Total duration of iNO therapy (hours)	37.4	32.1-41.8
NO2 levels (ppm)	0.7	0.55-0.81
Methaemoglobin levels*	0.5	0.47-0.56

*Values available for 13/23 patients.

Infants were on a high MAP and FiO2 at the time of initiation of iNO, still resulting in poor oxygenation as reflected by low PaO2 and high mean OI of 47.2. The mean age at which iNO was started was 45.6 hours. Details of baseline ventilator and iNO parameters are mentioned in [Table/Fig 2]. When assessed 4 hours after start of intervention, significant improvement in oxygenation in terms of increase of PaO2 and a decline in OI ([Table/Fig 3] & [Table/Fig 4]) was observed. Eight babies had documented intracranial hemorrhages on cranial US after therapy, mainly grade I-II, while two infants had severe hemorrhages (grade III-IV) with no periventricular leucomalacias. iNO was well tolerated in terms of NO2 and methaemoglobin levels and dose reduction was not required in any case. [Table/Fig 5] shows the characteristics of responders (16/23) and non- responders (7/23). Responders had a higher gestational age & birth weight, much lower OI, were started on iNO relatively early in disease process and had lower mortality. The incidence of culture proven sepsis was higher in the responders group, while the dose and duration of iNO in both groups were comparable.



[Table/Fig 3] Increase in PaO2 after 4 hours of iNO. Baseline Mean PaO2 +/- standard error = 33.8 +/- 2.1. After 4 hours Mean PaO2 +/- standard error = 76.3 +/- 9.3.



[Table/Fig 4] Decline in oxygenation index after 4 hours of iNO. Baseline Mean OI +/- standard error = 47.2 +/- 5.1. After 4 hours Mean OI +/- standard error = 22.1 +/- 3.5.

[Table/Fig 5] Characteristics of iNO responders and non-responders

Variable	Non responders (n=7)	Responders (n=16)	P-value
Gestation age, weeks	26.9 (26, 28.1)	29 (27,30.5)	0.65
Birth weight, g	999 (963, 1101)	1279 (1219, 1391)	0.59
Female gender	5 (71)	6 (37)	0.72
Surfactant	7 (100)	16 (100)	1
Air leaks	3 (43)	2 (12)	0.69
Sepsis	1 (14)	6 (37)	0. 55
Antenatal steroids	7 (100)	13 (81)	0.78
Use of dopamine	6 (86)	5 (31)	0.02
Baseline MAP, cm of water	18.7 (18.1, 21)	16 (15.4, 17)	0.67
Baseline FiO2, %	91 (89, 94)	80 (76, 89.2)	0.72
Baseline OI	58 (50, 74)	38.7 (36.1, 42)	0.02
Age at start of iNO, hrs	41.1 (64, 100.1)	20 (18.6, 25.1)	0.02
Dose of iNO at start, ppm	21 (19.7, 23.7)	18.1 (18, 20.4)	0.68
Duration of iNO, hrs	32 (24, 51)	36 (33, 41.7)	0.65
Underlying diagnosis			
Pulmonary hypoplasia	3 (43)	0 (0)	N/A
RDS	3 (43)	16 (100)	0. 02
Chylothorax	1 (14)	0 (0)	N/A
Mortality	6 (86)	4 (25)	0.02

Data are presented as median (interquartile range) or number (%). iNO denotes inhaled Nitric Oxide; FiO2, Fraction of Inspired Oxygen; MAP, Mean Airway Pressure; OI, Oxygenation Index RDS, Respiratory Distress Syndrome.

Discussion

The use of inhaled Nitric Oxide in management of oxygenation failure in preterm infants is a contentious issue. Although considered controversial, it is still used in many centers after concurrent modalities of treatment fail to improve oxygenation. Many of these infants may have underlying persistent pulmonary hypertension. With increasing use of antenatal steroids and surfactant, the pattern of preterm lung disease has undergone a transformation, with a small minority of them developing severe acute respiratory failure. Nitric Oxide may benefit such infants by selectively dilating pulmonary vasculature, improving ventilation-perfusion matching, and decreasing the pulmonary inflammatory response [5–7]. Trials of iNO were previously focused on those preterm infants who continued to have major respiratory problems despite antenatal steroids and surfactant, i.e. the sickest and smallest infants. These individual trials [3],[8],[9] each reported that iNO produced statistically significant short-term improvements in oxygenation, but none showed a statistically significant impact on any medium- or longer-term outcome measure. A recent retrospective audit [10] showed an 83% response to iNO in preterm babies ranging from 29 to 34 weeks.

In the current review, the predominant underlying clinical diagnosis was Respiratory Distress Syndrome (RDS) associated with preterm lung disease. A high incidence (30%) of culture proven sepsis was also noted. Multiple factors can contribute to high pulmonary vascular resistance (PVR) which includes hypoxia, acidosis, low lung volumes or sepsis and iNO may have additional benefits in reducing pulmonary edema and lung neutrophil accumulation in severe experimental hyaline membrane disease [11]. Subsequent work in animals found that inhaled Nitric Oxide reduces lung inflammation [12], improves surfactant function [13], attenuates hyperoxic lung injury [14] and promotes lung growth. Another recent study has shown that sepsis, preterm prolonged rupture of membranes, chorioamnionitis and pulmonary hypoplasia significantly predisposed to pulmonary hypertension [10]. The survival in preterm infants receiving iNO was significantly less as compared to near term & term babies which suggests that the underlying pathophysiology as well as potential risks differ

substantially in the two groups and response to therapy may depend on the etiopathogenesis. It is plausible that anatomic differences in vascular smooth muscle as well as molecular level differences in preterm babies as compared to term babies play a part in reduced responsiveness to iNO in the former [10]. Data from animal studies has shown that the pulmonary vasodilator response to oxygen (mediated by iNO) improves with advancing age [15]. It is important to appreciate that babies in this review were towards the more severe spectrum of oxygenation failure, as manifest by poor oxygenation in presence of optimal ventilation and use of concurrent modalities of treatment. OI is a sensitive indicator of hypoxia and if greater than 25, correlates with 50% risk (80% if greater than 40) of mortality and need for ECMO [16], an option which is not feasible for small preterm babies. In many cases iNO was started after disease process had been quite progressed. Within limitations of this being a retrospective audit, a possible explanation could be individual staff preference to not to initiate iNO in view of earlier reports of lack of impact on survival and concerns regarding its safety profile in preterm infants. The unit has no protocol for initiation of iNO in preterm babies and decisions are taken by the medical team on individual basis. The Franco-Belgian randomized trial of inhaled Nitric Oxide had shown no significant decrease in bronchopulmonary dysplasia or death in a cohort of premature infants with a median oxygenation index of approximately 20 [8]. Although the Food and Drug Administration (FDA) approved inhaled Nitric Oxide for use in term newborns, the safety and efficacy of such therapy in premature newborns with respiratory failure remain unproven.

Another objective of this review was to identify characteristics of the population that is more likely to respond with the aim to refine approach. Keeping this in mind the population was divided into responders and non-responders, the former defined here as showing a decline in oxygenation index by 50% when assessed after 4 hours of initiation of iNO. As mentioned, responders had a higher gestation and birth weight. In a recent study on babies with severe oxygenation failure, post hoc analyses showed that infants with a birth weight above 1000 g seemed to benefit from iNO therapy, with a decrease in the incidence of death or bronchopulmonary dysplasia without any increase in the rate of intraventricular hemorrhage [4]. In contrast, infants with a birth weight of 1000 g or less who were treated with iNO had an apparent increase in mortality and a higher rate of intraventricular hemorrhage. A recently published audit showed similar findings in which responders (defined as increase in PaO2 by 20 mm Hg by 30 minutes) had significantly higher gestation age and birth weight and lower mortality [10]. The beneficial effects to babies > 1000g were also seen by Kinsella and colleagues [17], although in a moderately sick population.

An interesting observation was the higher incidence of culture proven sepsis in the responders group. The effects of iNO on early neutrophil accumulation may have important clinical implications because neutrophils play an important part in the inflammatory cascade that contributes to lung injury and the evolution of the most important sequel of respiratory distress syndrome, chronic lung disease. [18–21]. It is plausible that along with its vasodilatory effects, iNO was exerting its anti-inflammatory effect as well. Clearly, both groups had babies who had severe oxygenation failure, though OI was lower in responders group. Our understanding is that this group faired better due to multiple factors that included earlier initiation of iNO therapy in the course of the disease. Limitations of this study include a small sample size, retrospective study design and limited statistical analysis due to small size. It does give us useful information which could guide towards optimization of therapy in preterm oxygenation failure. At present, it is tempting to speculate that early initiation of iNO in refractory oxygenation failure with proven underlying PPHN could show a significant improvement in its efficacy in reducing mortality and long term morbidity. Benefits to survivors could come in terms of reduced time spent on ventilators and less barotrauma. In a trial of 80 premature infants with severe hypoxemic respiratory failure, Kinsella et al reported a decrease in the number of days spent on a ventilator and a trend towards decreased incidence of bronchopulmonary dysplasia [7]. On the other hand, a Cochrane review concluded that currently published evidence from randomized controlled trials does not support the use of iNO in preterm infants with respiratory failure [22].

To conclude, this study addresses a very controversial and contentious aspect of neonatal practice. While consensus eludes, we know from practice and experience, that there exists a subset of neonates, who have refractory hypoxemia and underlying PPHN, which responds to iNO therapy. Although the infants were at a higher end of spectrum for severity of respiratory illness, nitric administration was successful in improving oxygenation. The real challenge is to sub-select a population, in which an impact on mortality and long term neurological & pulmonary morbidity could be demonstrated.

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