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Controversies in neonatology: The efficacy of inhaled nitric oxide in preterm infants with persistent pulmonary hypertension

Gonca Vardar, Meliha Aksoy Okan, Nilgun Karadağ, Sevilay Topçuoğlu, Elif Özalkaya, Hande Özgün Karatepe, Güner Karatekin

University of Health Sciences, Zeynep Kamil Maternity and Children's Disease Health Training and Research Center, İstanbul, Turkey

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ABSTRACT

Introduction: There is limited and conflicting information in literature regarding use of inhaled nitric oxide (iNO) in preterm infants. In this study we examined the characteristics of preterm infants with persistent pulmonary hypertension (PHT) who responded and did not respond to iNO therapy .

Material and Method: We retrospectively reviewed data of infants <34 weeks of gestational age with hypoxic respiratory failure that received iNO for PHT after being diagnosed with severe respiratory distress syndrome after birth. The data of responders and non-responders to iNO therapy were compared.

Results: Twenty-five infants were included in our study. Twelve (48%) had a positive response to iNO administration for PHT. As an antenatal characteristic, oligohydramnios was significantly higher in responders [5 (41.7%) vs 0%, p=0.015] and mortality rate was lower (66% vs. 100%, p=0.039). The SpO_2/FiO_2 ratio before iNO treatment predicted the response to iNO in preterm neonates with PHT. The ROC analysis yielded an area under curve AUC for SpO_2/FiO_2 ratio before iNO of AUCSpO_2/FiO_2before was 0.756; 95% CI, 0.554-0.959; P=0.03. A cut-off value of 79 point by the SpO_2/FiO_2 ratio before iNO treatment predicted the response to iNO treatment with 83% sensitivity and 70% specificity.

Conclusion: In infants born <34 weeks gestation, response to iNO in PHT has a significant effect on improving survival. The presence of oligohydramnios may be an important factor in prediction of positive response. SpO_2/FiO_2 ratio can be useful for estimating the effectiveness of iNO.

Keywords: Nitric oxide therapy, premature, pulmonary hypertension

INTRODUCTION

Nitric oxide (NO), a naturally produced lipophilic endogenous free radical, is synthesized by nitric oxide synthase from the amino acid L-arginine (1). Endogenous NO, which has a biological half-life of a matter of seconds, is produced by venous and arterial endothelial cells, inflammatory cells (macrophages, neutrophils), smooth muscle cells, epithelial cells, fibroblasts as well as non-cholinergic and non-adrenergic cells. Nitric oxide relaxes the smooth muscles of both the pulmonary vessels and bronchi and therefore has a role in the control of pulmonary artery pressure and bronchial tone (2).

In cases of unsuccessful intrauterine to extrauterine transition, persistent increased pulmonary vascular resistance leads to higher risk of mortality and morbidity and is clinically characterized by hypoxemic respiratory failure (HRF) due to persistent pulmonary hypertension of the newborn (PPHN) (3). Hyaline membrane disease, sepsis, and pulmonary hypoplasia may be the underlying etiopathogenetic factors. Inhaled nitric oxide (iNO) has been demonstrated to increase survival in hypoxemic term or near term infants by reducing the need for use of extracorporeal membrane oxygenation (ECMO) (4,5).

The incidence of PPHN per 1000 live births ranges 1.2–4.6 in Asian countries, compared to 1.8–1.9 in the USA. The higher incidence in Asian countries may be due to prematurity, neonatal infection, and low-middle income as well as lack of treatment options such as iNO and ECMO (6).

Corresponding Author: Gonca Vardar, gncvrd14@gmail.com
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Many studies have failed to demonstrate the benefit of iNO in preterm infants born before 34 weeks of gestation, possibly due to insufficient standardization of patients and lack of disease stratification (7). However, there are cohorts of preterm infants < 30 weeks gestation with PHT demonstrating that iNO decreases fraction of inspired oxygen (FiO_2) and oxygenation index (OI) leading to a rapid recovery of oxygen levels (8,9).

Herein, we evaluated the effectiveness of iNO with regards to acute oxygenation and clinical status in premature infants with confirmed acute PHT.

MATERIAL AND METHOD

Approval was granted by the Ethics Committee of University of Health Sciences Zeynep Kamil Maternity and Children's Research and Training Hospital (Date: 03.07.2018, Decision No: 30). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants were enrolled in this retrospective cohort study that was performed at a tertiary neonatal intensive-care unit (NICU) (65 incubators and over 1200 newborn admissions per year) between January 2013 and July 2018.

Medical data of infants hospitalized in the NICU were evaluated and preterm infants born before 34 weeks of gestational age undergoing iNO therapy indicated for acute PHT were enrolled for evaluation. Exclusion criteria were: (1) iNO used for bronchopulmonary dysplasia (BPD), (2) Having congenital, genetic or cardiac anomalies (excluding patent ductus arteriosus), (3) transfer to or from NICU.

Patients' demographic characteristics (gestational age, birth weight, gender), perinatal (Preterm prolonged rupture of membranes [PPROM], oligohydramnios, antenatal steroids, delivery mode, Apgar scores), and neonatal characteristics (iNO initiation and duration time, echocardiography findings, ventilation strategy, number of surfactant doses, duration of invasive ventilation, concurrent use of inotropes, intraventricular hemorrhage [IVH], sepsis [confirmed by positive blood culture], necrotizing enterocolitis [NEC], development of BPD, and the overall survival) were recorded. Preterm prolonged rupture of membranes was defined as rupture of membranes >18h before 37 weeks of gestation and before the onset of labor (10). BPD was defined in accordance with criteria set by the National Institute for Child Health and Development (11). For IVH, the Papile cranial ultrasound classification was used (12). For the classification of rethinopathy of prematurity (ROP) and the definition of NEC, the standardized international criteria and the modified Bell criteria were used respectively (13,14).

Acute PHT diagnosis was either established by echocardiographic evaluation prior to or during the first 24 hours of iNO initiation or decision was made by clinical findings of hypoxemic failure, defined by need for FiO_2 >70% with pre/post-ductal saturation difference ≥10% (9). Echocardiographic evaluation was performed by a pediatric cardiologist and demonstration of PHT was made by measuring the peak velocity of tricuspid regurgitation (TR max). Modified Bernoulli equation was used to convert Doppler derivated velocity to pressure between the right ventricle and right atrium=4×TRmax2. By adding right atrial pressure (5 mmHg) to this pressure gradient systolic pulmonary arterial pressure was calculated. Hence, we diagnosed PHT when systolic pulmonary arterial pressure was >40 mmHg or it was ≥ systolic systemic arterial pressure. In the absence of a TR max measurement diagnosis of PHT was made according to right-to-left shunt via ductus arteriosus and/or foramen ovale, with or without flattening or bowing of the septum into the left ventricle at end-systole (8). Persistent pulmonary hypertension (PPHT) was defined with increased mean pulmonary pressure and right to left or bidirectional shunt at patent ductus arteriosus [PDA] and/or patent foramen ovale [PFO] level) as detected on echocardiography (6).

The standard approach to the infants with PHT in our hospital includes conventional or high- frequency oscillation ventilation, surfactant treatment, sedation plus use of inotropes as required (generally initially dopamine and dobutamine). iNO for acute PHT is administered as part of the standard care of infants > 34 weeks' gestation. Additionally, iNO was used in children <34 weeks of gestation that did not respond to treatment with surfactant and appropriate ventilation with conventional or high-frequency oscillation ventilation under consultant discretion. Lung expansion improvement is determined by the decrease in the fraction of inspired oxygen with the saturation target of 91-95% in the case of respiratory distress syndrome. Severe RDS was diagnosed when infants required FiO_2 >0.50 to maintain PaO_2 >50 mmHg after surfactant treatment and despite mechanical ventilation at mean airway pressure (MAP) >12 cmH_2O (8).

Blood oxygen saturation level (SpO_2) and fraction of inspired oxygen (FiO_2) was used for monitoring of neonates. The ratio of these two parameters SpO_2/FiO_2 ratio was used in the management of oxygenation status and defined as follows; SpO_2/FiO_2 ratio before iNO and SpO_2/FiO_2 ratio after iNO treatment. Pre-ductal SpO_2 calculations in all patients were recorded.

Inhaled nitric oxide was commenced using a dose of 20 parts per million (ppm). For this study, patients with a

reduction in the FiO_2 by 20% within 3h of commencing iNO therapy were defined as "positive responders" and those in which FiO_2 increased, remained unchanged or reduced by <20% were defined as "negative responders". If clinical response was not observed to hypoxemia, the dose of iNO was increased to 40 ppm, since NO improvement to oxygenation is largely dose dependent and higher doses of iNO (20-80ppm) may cause progressive pulmonary vasodilatation (15-17). Blood gases and levels of methemoglobin were analyzed prior to initiation of iNO therapy and every 4h thereafter. Complete blood count was also performed within 48 h of starting iNO. Acute PHT was defined as "early" if it developed within the first 72 h of life, or "late" if it developed thereafter. For the weaning process in positive responders, iNO was lowered initially to 5 ppm by decreasing 2 ppm every 4h, then slowly to 1 ppm. In negative responders, weaning was achieved by decreasing to 5 ppm by lowering 5 ppm every 15 minutes, and then by 1 ppm every 15 minutes thereafter. Echocardiographic controls of the infants who respond to iNO and survived has been done during iNO and inotrope therapies.

Study Outcomes

To evaluate the treatment effect of iNO therapy, the primary outcome was established as the difference in FiO_2 requirements caused by iNO therapy (≥20% in infants < 34 weeks, as based on the current definitions). Additionally, neonatal characteristics, IVH, BPD, ROP, and NEC were compared according to positive and negative response.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics for Windows (IBM Corp. Released 2017, Version 25.0. Armonk, NY, USA). Patient characteristics were reported using descriptives. Continuous variables were expressed as mean±standard deviation (SD) or median [Interquartile range (IQR)]. Normality of data for continuous variables was tested with the Shapiro-Wilks test and compared with either the unpaired Student's t-test or Mann-Whitney U test. Categorical data were expressed as n (%) and compared using Fisher's exact test. Subgroups of preterm infants that received iNO were compared using the paired Student's t-test or Mann-Whitney test. Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the SpO_2/FiO_2 ratio in predicting responding to iNO treatment. Area under the curve (AUC) and reliability data were reported with 95% confidence interval (CI). Cut-off values showed the highest sensitivity. P<0.05 were considered to be statistically significant.

RESULTS

The records of 61 infants born < 34 weeks of gestation who were diagnosed with PHT were reviewed for eligibility. Of these, 30 infants were found to receive iNO during the study period. Those excluded from the study were: iNO administered for chronic PHT (n=2), transferred while receiving iNO (n=1), congenital heart disease (n=1) and congenital anomalies (n=1). Following the exclusion of these patients, twenty-five infants with an average gestational age of 28.3±3.2 weeks and birth weight of 1147±635 gr were included in the study. **Figure 1** shows the CONSORT diagram for the study.

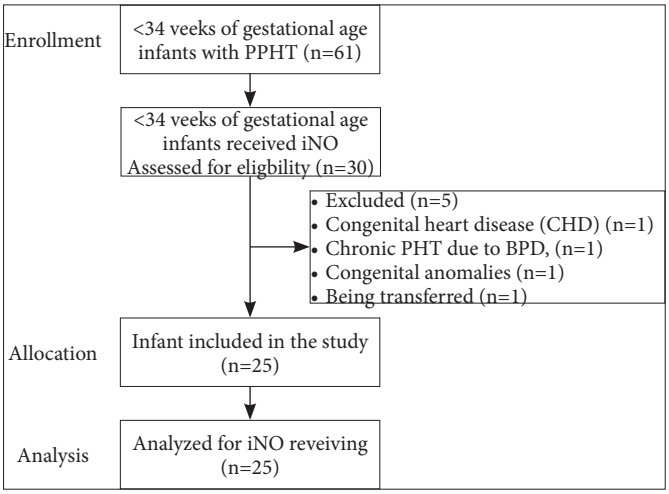

Figure 1. CONSORT chart for selection of eligible infants in the study

Echocardiographically proven acute PHT existed in 23 (92%) infants, while the remaining 2 infants' (8%) diagnosis was clinically based on the presence of ≥10% difference between pre-ductal and post-ductal saturation. However, PHT has been echocardiographically proven to exist in both of these patients after iNO initiation. Moderate-to-large PDA existed in 9 (36%) infants, while 8 (72.7%) of them were <28weeks of gestation. Infants responded to iNO with moderate-to-large PDA (16.7% vs 53.8%, p=0.053) were not significantly different from non-responders.

Twelve infants (48%) were found to be positive responders. Oligohydramnios [5 (41.7%) vs 0%, p=0.015] and mortality [8 (66%) vs 13 (100%), p=0.039] were significantly different between positive versus negative responders.

iNO was administered for a median of 2.5 days in positive and 1 day in negative responders (p=0.016) with maximum median iNO dose of 20 and 40 (p=0.001) for positive and negative responders, respectively. pH in blood gas analysis 4h after commencement of iNO was determined to be significantly increased in

positive responders (7.29±0.14 vs 7.13±0.21, p=0.044). SpO_2 before iNO and 1h after iNO was found to be significantly higher in the positive versus negative responders [80 (78-83) vs 70 (70-80), p=0.025] and [(90 (88-94) vs 72 (70-80), p<0.001)]. SpO_2/FiO_2 ratio was significantly increased in positive versus negative responders [115 (110-126) vs.77 (71-86), p<0.001)] 1 h after iNO commencement. There was a lower mortality rate in the positive versus negative responders [8 (66%) vs 13 (100%), p=0.039]. Patients' characteristics such as gestational age, gender, antenatal steroids, PPROM, early PHT, number of surfactant doses, Apgar values, HFOV application, SpO_2, pH value before iNO were found to be not statistically significantly related with respect to positive response to iNO. Factors found to have a statistically significant difference between positive and negative responders are shown in **Table 1**.

Fifteen infants (60%) were diagnosed with early and 10 (40%) with late acute PHT. Preterm infants having early-onset acute PHT were initiated on iNO at a median of 2 (2-2) days compared to 6 (4-12.5) days (p<0.001) in the late group. Patients with late acute PHT had higher pH in blood gasses analyses before iNO administration compared with the early acute PHT group (7.11±0.17 vs 7.27±0.19, p=0.044). No difference was detected in any other parameter between the groups with regards to survival. There was no significant difference between SpO_2/FiO_2 ratios in early and late PHT after iNO [110 (74-120) vs. 97 (83.5-107.5), p=0.739) (**Table 2**).

Patients with early acute PHT were analysed and their data is shown in **Table 3**. Eight (53%) of these infants had a positive response. Antenatal characteristics and the neonatal morbidities were similar between positive and negative responders except for a significantly higher rate of SpO_2 before and 1h after iNO in the positive responders when compared to the negative responders ([80 (80-85) vs 70 (65-70), p=0.003] and [90 (90-97) vs 70 (65-72), p=0.001]) respectively. In blood gas analysis, positive responders with early acute PHT had a significantly higher pH compared to non-responders (7.30±0.16 vs 7.02±0.17, p= 0.007) 4 h after iNO. Preterm infants with early-onset PHT had higher SpO_2/FiO_2 ratio before and 1h after iNO in the positive responders when compared to the negative responders which was significantly higher [80 (80-85) vs 70 (65-70) p=0.003] and [119 (112-137), vs 74 (68-77), p=0.001] respectively.

Table 1. Antenatal and neonatal characteristics of preterm neonates with acute pulmonary hypertension (aPHT) treated with inhaled nitric oxide (iNO); comparisons between positive and negative responders

Patient Characteristic	Positive responders	Negative responders	p
Gestational age, weeks, mean±SD	28.75±3.5	27.85±3.1	0.504
Birth weight, g, median (IQR)	1012 (715-1995)	911 (582-1240)	0.479
Gender, male, n (%)	8 (66)	6 (46)	0.428
Mode of delivery, CS, n(%)	10 (83)	10 (76)	1.000
PPROM, n (%)	3 (25)	5 (13)	0.387
Oligohydamnios, n (%)	5 (41)	0	0.015*
Antenatal steroids n(%)	4 (33)	5 (38)	1.000
Apgar 1st minute, median (IQR)	4 (3-5)	4 (3-4)	0.321
Apgar 5th minute, median (IQR)	6 (6-8)	6 (6-6)	0.081**
Surfactant doses, median (IQR)	2 (1-2.75)	2 (1-2.5)	0.863
HFOV application prior to iNO, n(%)	6 (50)	7 (53)	1.000
Invaziv ventilation duration, days, median (IQR)	7 (3-26.5)	9.54 (3-12)	0.460
iNO max dose, ppm, median (IQR)	20 (20-35)	40 (40-40)	<0.001*
Erarly iNO, n (%)	8 (66)	7 (53)	0.688
iNO initiation, days, median (IQR)	2 (2-4)	3 (2-10)	<0.001*
iNO duration, days, median (IQR)	2.5 (2-4.75)	1 (1-2)	0.016*
Methemoglobinemia >1.8%, n(%)	3 (25)	2 (15)	0.645
Sepsis, n(%)	1 (8)	3 (23)	0.593
Thrombocytopenia <150000/mm, n (%)3	4 (33)	1 (7)	0.160
IVH III-IV, n (%)	4 (33)	2 (15)	0.378
ROP, n (%)	2 (50)	0	
BPD, n (%)	4 (66)	1 (100)	1.00
NEC, n (%)	2 (16)	4 (30)	0.645
Inotropes (Dopamine, dobutamine, adrenaline), n (%)	12 (12)	13 (13)	0.483
pH prior to iNO, mean±SD	7.16±0.20	7.18±0.19	0.763
pH 4 h after iNO, mean±SD	7.29±0.14	7.13±0.21	0.044*
SpO_2 prior to iNO, median (IQR)	80 (78-83)	70 (70-80)	0.025*
SpO_2 1 h after iNO, median (IQR)	90 (88-94)	72 (70-80)	<0.001*
SpO_2/FiO_2 prior to iNO, median (IQR)	80 (69-85)	70 (65-77)	0.0025*
SpO_2/FiO_2 1h after iNO, median (IQR)	115 (110-126)	77 (71-86)	<0.001*
Mortality, n (%)	8 (66)	13 (100)	0.039*

SD: Standart deviation; IQR: Interquartile range; PPROM: Premature prolonged rupture of membranes; CS: Caesarean section; iNO: Inhaled nitric oxide; HFOV: High frequency oscillatory ventilation; IVH: Intraventricular haemorrhage; BPD: Bronchopulmonary dysplasia; SpO_2: Blood oxygen saturation level; *p<0.05: Statistically significant results are shown in bold and italic font type.

Table 2. Comparison of baseline characteristics in patients with early or late acute PHT

Patient Characteristics	Early PHT (n=15)	Late PHT (n=10)	p
Gestational age, weeks, mean±SD	28.87±3.4	27.40±2.9	0.283
Birth weight, g, median (IQR)	1160 (730-1820)	702 (605-1192)	0.090
Gender, male, n (%)	9 (60)	5 (50)	0.697
Mode of delivery, CS, n (%)	13 (65)	7 (35)	0.358
PPROM, n(%)	3 (20)	5 (50)	0.194
Oligohydamnios, n (%)	4 (26)	1 (10)	0.615
Antenatal steroids, n (%)	4 (26)	5 (50)	0.397
Apgar 1st minute, median (IQR)	4 (3-5)	4 (3-4)	0.858**
Apgar 5th minute, median (IQR)	6 (6-7)	6 (5-6)	0.187
Surfactant doses, n (%)	2 (1-2)	2 (1.75-3)	0.266
HFOV application prior to iNO, n (%)	9 (60)	4 (40)	0.428
Duration of invasive ventilation, days, median (IQR)	3 (2-8)	9 (5.5-17)	0.026*
iNO initiation, days, median (IQR)	2 (2-2)	6 (4-12.5)	<0.001*
iNO duration, days, median (IQR)	2 (1-2)	2 (1-5)	0.64
Methemoglobinemia >1.8, n (%)	2 (13)	3 (30)	0.358
Sepsis, n (%)	2 (13)	2 (20)	1.000
Thrombocytopenia<150000/mm, n (%)3	4 (26)	1 (10)	0.615
IVH III-IV, n (%)	4 (26)	2 (20)	1.000
ROP, n (%)	1 (33)	1 (100)	1.00
BPD, n (%)	4 (80)	1 (50)	1.000
NEC, n (%)	0	6 (60)	0.001
Inotropes, n (%)	12 (80)	9 (90)	0.626
pH prior to iNO, mean±SD	7.11±0.17	7.27±0.19	0.044*
pH 4 h after iNO, mean±SD	7.17±0.21	7.26±0.16	0.284
SpO_2 prior to iNO, median (IQR)	80 (70-80)	77 (73-80)	0.909
SpO_2 1 h after iNO, median (IQR)	88 (70-90)	84 (79-90)	1.00
SpO_2/FiO_2 prior to iNO, median (IQR)	80(70-80)	77(73.75-80)	0.909
SpO_2/FiO_2 1h after iNO, median (IQR)	110 (74-120)	97 (83.5-107.5)	0.739
Mortality, n (%)	12 (80)	9 (90)	0.626

SD: Standart deviation; IQR: Interquartile range; PPROM: Prolonged rupture of membranes; CS,caesarean section; iNO: Inhaled nitric oxide; HFOV: High frequency oscillatory ventilation; IVH: Intraventricular haemorrhage; BPD: Bronchopulmonary dysplasia; SpO_2: Blood oxygen saturation level. *p<0.05: Statistically significant results are shown in bold and italic font type.

Table 3. Comparison between positive and negative responders in patients with early acute PHT

Patient Characteristics	Positive responders (n=8)	Negative responders (n=7)	p
Gestational age, weeks, mean±SD	29±3.2	28±3.8	0.662
Birth weight, g, median (IQR)	1012 (760-2093)	1200 (700-1820)	0.908
Gender, male, n (%)	6 (75)	3 (57)	0.315
Mode of delivery, CS, n (%)	7 (87)	6 (85)	1.000
PPROM, n (%)	1 (12)	2 (28)	0.569
Oligohydamnios, n (%)	4 (50)	0	0.077
Antenatal steroids, n (%)	2 (25)	2 (28)	1.000
Apgar 1st minute, median (IQR)	4 (3-6)	4 (3-4)	0.352
Apgar 5th minute median (IQR)	7 (6-8)	6(6-6)	0.062
Surfactant doses, mean±SD	2±1	1.43±1	0.334*
HFOV application prior to iNO, n (%)	3 (37)	3 (42)	1.00
Invaziv ventilation duration, days, median (IQR)	5.5 (2.25-37.25)	3 (2-5)	0.287
iNO initiation, days, median (IQR)	2 (1.25-2)	2 (2-2)	0.370**
iNO duration, days, median (IQR)	2 (1.25-3.5)	1 (1-2)	0.216
iNO max dose, ppm, median (IQR)	20 (20-40)	40 (40-40)	0.066
Methemoglobinemia >1.8, n (%)	1 (12)	1 (14)	1.000
IVH III-IV, n(%)	3 (37)	1 (14)	0.569
pH prior to iNO, mean±SD	7.13±0.21	7.09±0.12	0.641*
pH 4 h after iNO, mean±SD	7.30±0.16	7.02±0.17	0.007*
SpO_2 prior to iNO, median (IQR)	80 (80-85)	70 (65-70)	0.003*
SpO_2 1 h after iNO, median (IQR)	90 (90-97)	70 (65-72)	0.001*
SpO_2/FiO_2, median (IQR)	80(80-85)	70(65-70)	0.003*
SpO_2/FiO_2, median (IQR)	119 (112-137)	74 (68-77)	0.001*
Mortality, n (%)	5 (62)	7 (100)	0.2

SD: Standart deviation; IQR: Interquartile range; PPROM: Prolonged rupture of membranes; CS,caesarean section; iNO: Inhaled nitric oxide; HFOV: High frequency oscillatory ventilation; IVH: Intraventricular haemorrhage; BPD: Bronchopulmonary dysplasia; SpO_2: Blood oxygen saturation level. *p<0.05: Statistically significant results are shown in bold and italic font type.

The SpO_2/FiO_2 ratio before iNO treatment predicted the response to iNO in preterm neonates with PHT. The ROC analysis yielded an area under curve AUC for SpO_2/FiO_2 ratio before iNO treatment of AUCSpO_2/FiO_2 before as 0.756; 95% CI, 0.554-0.959; P=0.03 (**Figure 2**). A cut-off value of 79 point by the SpO_2/FiO_2 ratio before iNO treatment predicted the response to iNO treatment with 83% sensitivity and 70% specificity. The predictive value of SpO_2/FiO_2 ratio before iNO treatment for responding to iNO treatment was higher than the value of blood gas pH. The ROC analysis yielded an AUC for SpO_2/FiO_2 ratios and pH values before iNO treatment as AUCSpO_2/FiO_2 ratio before= 0.756; 95% CI, 0.554-0.959, P=0.03; AUCpH before=0.497; 95% CI, 0.257-0.737, P=0.978, respectively (**Figure 3**).

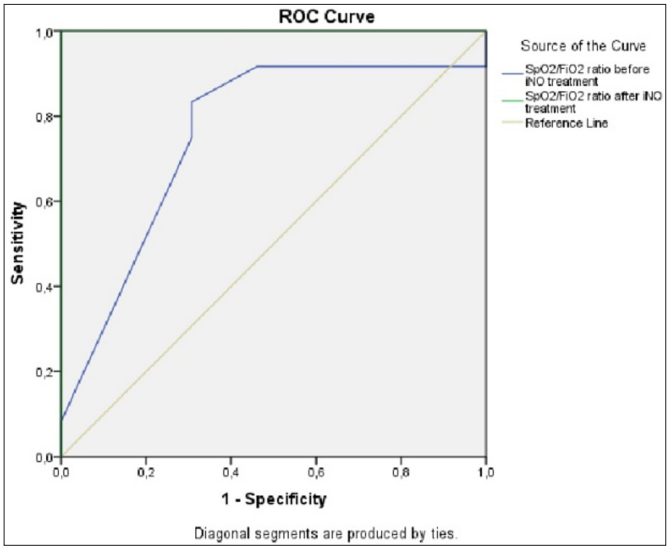

Figure 2. The ROC analysis of SpO_2/FiO_2 ratios before iNO treatment for predicting of Positive Responders in Neonates with PHT. The blue line indicates the SpO_2/FiO_2 ratios before iNO treatnemt. The ROC analysis yielded an AUC for SpO_2/FiO_2 ratios before iNO treatment $AUC_{SpO2/FiO2ratios\ before}$=0.756; 95% Cl, 0.554-0.959, P=0.03.

CL: Confidence interval, iNO: Inhaled nitric oxide, ROC: Receiver operating characteristic curve, SpO_2/FiO_2 ratio PHT: Pulmonary hypertaension

DISCUSSION

Although the indications for iNO treatment in preterm children are vague, our study suggests that it is useful in leading to improvement of HRF in preterm infants with acute PHT.

The rate of mortality in premature infants is severely affected by the presence of respiratory distress syndrome (RDS). Mortality related to RDS in preterm infants changes according to gestational age and ranges from 50-100% (8). Surfactant therapy, advanced ventilation techniques and continuous positive airway pressure have significantly reduced pulmonary morbidity in extremely preterm infants (18). When not treated, RDS may lead to right-to-left extrapulmonary shunting and/or intrapulmonary shunting due to pulmonary hypertension and poor ventilation-perfusion matching respectively (19-21). Preterm infants<28 weeks of gestation have 50-70% moderate- to- large ductal shunt that can increase pulmonary blood pressure and flow and decrease lung compliance stated as 72.7% in our study. On the other hand the presence of an open ductus can regulate extreme elevations in pulmonary arterial pressure as a pop-off valve (22,23).

On the other hand, transition to postnatal circulation may be averted by impaired pulmonary vascular development leading to PHT and HRF (9). This could be the explanation for positive responders to iNO in our study. PPHN is a clinical syndrome that occurs when there is a failure to initiate or sustain the transition to extrauterine life. Affected infants have elevated pulmonary vascular resistance, pulmonary arterial pressure, and right-to-left shunts at atrial and ductal levels at varying degrees (24,25).

In 1999, the FDA approved iNO for use in term and near term infants with PPHN. iNO, a potent, selective pulmonary vasodilator, combines with hemoglobin to form methemoglobin in the intravascular space, preventing systemic vasodilation (selective effect). Additionally it reduces ventilation perfusion mismatch by diverting pulmonary blood to adjacent dilated pulmonary arterioles to only ventilated alveoli (26). Furthermore, iNO can provide a decrease in pulmonary vascular remodeling and lung inflammation by improving airway structure (27,28).

Recent data on the incidence for PHT in term and late preterm infants is reported to be 1-2 per 1000 live births. The exact incidence and clinical features of PHT in extremely premature infants is not known although it is proposed that iNO may be useful in hypoxic respiratory failure secondary to a vascular etiology. Previous cohorts have reported that oligohydramnios and PPROM were more common among infants with early-onset pulmonary hypertension (EOPAH). Infants with EOPAH presenting with HRF have been shown to respond well to iNO treatment (29). As literature on PHT primarily centres on preterm infants with moderate or severe BPD, data on EOPAH and HRF is scarce. Despite significant evidence demonstrating that iNO has no effect on reducing the morbidity or mortality of extremely premature neonates, the off-label prescription of iNO is increasing (30,31). On the other hand, evidence suggests that iNO can be beneficial for a selected subpopulation of extremely premature neonates (32,33). A recent cohort stated that preterm neonates with acute PHT who had positively responded to iNO were associated with a survival benefit (34).

Although the number of preterm infants with positive or negative responses to iNO were approximately equal to each other, iNO response was associated with survival benefit. The inconsistency of response to iNO we observed may be due to several factors. Although the number of neonatal and perinatal characteristics such as birth weight, antenatal corticosteroids Apgar values and use of inotropes were found to be statistically insignificant, this may be due to the small sample size of our study and differences in severity of illness between the positive and negative responders.

Tworetzky et al. (35) reported that an initial dose of 20 ppm for iNO led to oxygen improvement with maximum pulmonary vasodilation with no serious side effects. In our study, the median maximum dose for iNO was observed to be 20 (20-35) among positive responders, compared to 40 (40-40) in negative responders. Inhaled nitric oxide has a good safety profile used at 20ppm, while lower doses may be equally as effective as higher doses. Moreover, higher doses do not provide any additional advantages. The absolute contra-indication of iNO is methemoglobinemia (36,37).

Due to proinflammatory cytokines and endogenous iNO attenuation, infants born with PROM tended to have pulmonary developmental disruptions (38). Pulmonary hypoplasia due to oligohydramnios led to pulmonary hypertension related to pulmonary vascular remodelling in the majority of infants (39). We found olygohydramnios as a significant factor related with a positive response to iNO in our study. In pregnancies complicated by PPROM and olygohydramnios, very low nitrite and nitrate levels were associated with HRF. During iNO initiation nitrite and nitrate concentrations increased (32). Also this finding is consistent with the literature that olygohydramnios and early acute PHT development were the most significant factors related to a positive response (9,40).

iNO therapy leads to an acute decrease in FiO_2 requirement and although the response in pulmonary hypoplasia is similar to that seen in other pulmonary disorders, the mortality rate remains very high in this group. On the other hand, although the mechanism of late-onset PHT is ambiguous, several mechanisms including hypoxia and inflammation have been suggested (41).

Our study aimed to present clinicians with possible indicative factors such as oligohydramnios that have been found to be linked to a positive response to iNO and its continued treatment. Also, it is important to note that our study sheds light on the association of lower mortality rate and positive response to iNO among preterm infants.

Oxygenation index (OI) is an essential indicator in managing neonates with hypoxic respiratory failure (HRF) and pulmonary hypertension (PH). However, the use of the OI is limited by the need for an arterial catheter in each patient. Different studies reported use of oxygen saturation index (OSI) and SpO_2/FiO_2 as non-invasive markers in the management of patients with respiratory failure. In comparison to OI is SpO_2/FiO_2 ratio is a practical non-invasive indicator obtained from mechanical ventilation settings and pulse oxymetry. This indicator does not require repeated samples from the arterial catheter while allowing continuous monitoring of oxygenation status (42). We would especially like to emphasize that SpO_2/FiO_2 ratio can be useful for estimating the effectiveness of iNO despite other invasive oxygenation indices. The SpO_2/FiO_2 ratio has advantages such as being an easy and non-invasive index that can be used at bed-side.

There are some limitations to our study. Firstly, the study was a retrospective analysis and includes a small sample size. Secondly, changes in OI and arterial-alveolar oxygen ratio were not reported as this data was not available for all patients.

CONCLUSION

Overall, our results indicate that infants < 34 weeks gestational age with PHT responded well to iNO with a significant proportion of survival. The use of iNO in the presence of PHT due to oligohydramnios can be a rescue therapy in preterm infants. SpO_2/FiO_2 ratio may be useful for estimating the effectiveness of iNO despite other invasive oxygenation indices. Controversies and confusion remain regarding the care of preterm infants with PHT. There is a need for clarity on the natural history of this diverse disease for early detection of at-risk patients for developing new approaches for diagnosis and treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was granted by the Ethics Committee of University of Health Sciences Zeynep Kamil Maternity and Children's Research and Training Hospital (Date: 03.07.2018, Decision No: 30).
Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The author has no conflicts of interest to declare.
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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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