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Efficacy of inhaled nitric oxide in neonates with hypoxic respiratory failure and pulmonary hypertension: the Japanese experience

https://doi.org/10.1515/jpm-2017-0040
Received February 2, 2017. Accepted August 21, 2017.

Abstract

Objective: To analyze data from a registry of Japanese neonates with hypoxic respiratory failure associated with pulmonary hypertension (PH) to compare the effectiveness of inhaled nitric oxide (iNO) in neonates born <34 weeks vs. ≥34 weeks gestational age (GA).

Materials and methods: iNO was administered according to approved Japanese product labeling. Study data were collected before iNO administration and at predefined intervals until discontinuation.

Results: A total of 1,114 neonates were included (n = 431, <34 weeks GA; n = 675, ≥34 weeks GA; n = 8, missing age data). Mean decrease from baseline oxygenation index (OI) was similar in both age groups. OI reduction was more pronounced in the <34 weeks subgroups with baseline OI ≥25. Survival rates were similar in the <34 weeks GA and ≥34 weeks GA groups stratified by baseline OI (OI < 15, 89% vs. 93%; 15 ≤ OI < 25, 85% vs. 91%; 25 ≤ OI ≤ 40, 73% vs. 79%; OI > 40, 64% vs. 66%).

Conclusion: iNO improved oxygenation in preterm neonates as effectively as in late preterm and term neonates, without negative impact on survival. If clinically significant PH is present, as measured by pulse oximetry or echocardiography, a therapeutic trial of iNO might be indicated for preterm neonates.

Keywords: Hypoxic respiratory failure; inhaled nitric oxide; preterm neonate; pulmonary hypertension.

Introduction

Inhaled nitric oxide (iNO; INOmax®, INO Therapeutics, Hampton, NJ, USA) selectively dilates the pulmonary vasculature, rapidly diffuses across the alveolar-capillary membrane, and binds to hemoglobin with minimal systemic effects [1, 2]. In pivotal studies of late preterm and term neonates with hypoxic respiratory failure (HRF) and pulmonary hypertension (PH), iNO therapy has been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation [3–6]. In the United States, iNO is indicated for the treatment of late preterm and term (>34 weeks' gestation) neonates with HRF associated with clinical or echocardiographic evidence of PH [7].

Given the lack of definitive evidence from randomized clinical studies regarding the benefits associated with the use of iNO in preterm neonates with HRF and PH, and the variability across published consensus guidelines regarding the use of iNO in this setting [8–10], assessment of a large observational data set could provide support for the clinical community in their need to define whether iNO should be utilized in their preterm neonatal patients. The observational Japanese registry evaluated in this report represents the largest data set currently available regarding the use of iNO in premature neonates with HRF and PH. In Japan, use of iNO is indicated for improvement of HRF with concurrent PH; its approved use is not limited to neonates >34 weeks gestational age (GA) [11], as in the United States. We analyzed the registry data compiled to date to determine the relative effectiveness of iNO in neonates born at <34 weeks GA compared with those born at ≥34 weeks.

Materials and methods

Registry overview

The registry was designed to collect data on the safety and effectiveness of iNO in real-world clinical utilization for the treatment of HRF associated with PH in all neonates in Japan. As required under

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Japanese Health Ministry guidelines for newly approved products, only authorized neonatal intensive care units (NICUs) may administer iNO therapy; patient data from this registry must be periodically evaluated until 2018. Data included in this report were collected from February 26, 2010, to October 9, 2012. The clinicians who participated were instructed to use iNO according to the product label and to record the relevant data on a paper survey slip for each patient. Survey slips were faxed to the central registration center; all data collected were recorded according to the clinicians' clinical utilization. The program was conducted through Air Water, Inc. (Tokyo, Japan) in accordance with Ministerial Ordinance No. 171 of the Ministry of Health, Labor and Welfare and other related governmental regulations, and the registry protocol was approved by the institutional review board at each participating center.

Analysis population

Neonates with HRF associated with PH who were receiving iNO were eligible for inclusion. Diagnosis was based on either echocardiography or the neonatologist's clinical judgment; neonates who had echocardiography performed after treatment with iNO was initiated to confirm normal cardiac anatomy were not included in the registry. Per the prescribing information for iNO in Japan, neonates with cardiac disorders dependent on right-left shunts were excluded from the analysis as use of iNO may decrease right-to-left blood flow and be a threat to life in these neonates [12].

Treatment

Clinicians participating in the registry were expected to administer iNO according to the approved prescribing information in Japan [11]. Healthcare reimbursement policies in Japan require that iNO be started within 7 days of birth in order for healthcare institutions to receive reimbursement for its use; neonates who started iNO treatment after 7 days were not included in the registry. Neonates received iNO according to these criteria, and treatment was allowed to continue until oxygen saturation improved or there was a failure of treatment. Per labeling recommendations, treatment was initiated at a concentration of 20 ppm NO, continued for 4 h, then reduced to 5 ppm, when the partial pressure of arterial oxygen (PaO_2) was >60 mm Hg or the pulse oximetry arterial oxygen saturation (SpO_2) was >92%. With the dose maintained at 5 ppm, the fraction of inspired oxygen (FiO_2) was reduced from an initial concentration of 1.0 until the PaO_2 was >70 mm Hg at an FiO_2 of 0.4–0.6. iNO was discontinued by gradual reduction to a concentration of 1 ppm, then stopped after increasing the FiO_2 by 0.1. If the oxygenation worsened, iNO was resumed at 5 ppm and discontinuation of therapy was reconsidered after 12 to 24 h. Assessments of arterial blood gases were conducted as per the standard of care in Japan.

Data collection

All neonates in the analysis population received iNO. Data were collected before drug initiation; at 1, 4, 12, and 24 h after drug initiation; and at 48, 72, and 96 h, and at 24-h intervals afterward, if necessary. Data were also collected just before discontinuation of iNO. Clinicians were asked to provide information on the following parameters: patient background information/history, prior drugs/therapies, systemic blood pressure, echocardiography, chest X-ray, PaO_2, SpO_2, blood methemoglobin, inspired NO concentration, inspired nitrogen dioxide concentration, mechanical ventilation information, oxygenation index (OI), laboratory tests, concomitant drugs/therapy and secondary outcomes. OI was calculated using the following formula:

$$OI = \text{mean airway pressure} * FiO_2 * 100/PaO_2.$$

Study hypothesis and data analysis

Data were compiled and analyzed to test the hypothesis that there would not be a variable effect of iNO in the subpopulation of neonates who were <34 weeks GA compared with the subpopulation who were ≥34 weeks.

Data reported by study respondents on effectiveness (measured as change in OI) and safety were summarized using descriptive statistics and stratified according to GAs of <34 and ≥34 weeks. The analyses of individual parameters were based on the number of evaluable neonates for each parameter (not every neonate had evaluable data for every parameter). Patient data for differences in the frequency of complications and survival rates were compared using Fisher's exact test. Between-group differences for mean percentage change in OI from baseline were compared using an analysis of variance model.

Results

Baseline demographics

A total of 1114 neonates were included in the current analysis; 431 were <34 weeks GA, and 675 were ≥34 weeks. GA data were missing for eight neonates. Baseline demographic and clinical characteristics are summarized in Table 1. Overall, the mean [standard deviation (SD)] duration of treatment with iNO was 5.0 (10.3) days (median, 2.8 days; range, 0–250.5 days); mean (SD) duration in the <34 weeks GA group was 3.5 (5.5) days compared with 6.0 (12.3) days in the ≥34 weeks GA group.

Effectiveness of iNO

Effectiveness was evaluated by OI and comparative OI between preterm neonates versus late preterm/term neonates. The mean last OI value obtained for neonates who had evaluable data in the study stratified by mean baseline OI (<15, 15 to <25, 25 to ≤40 and >40) and GA subgroup are summarized in Table 2. Overall, the mean of the last OI value was similar in the two age groups at

Table 1: Baseline demographics and clinical characteristics.

Category	GA < 34 weeks	GA ≥ 34 weeks
GA (weeks)	n = 431[a]	n = 675[a]
Mean (SD)	27.1 (3.5)	38.6 (1.9)
Median (range)	26.3 (20.3, 33.9)	38.6 (34.0, 42.3)
Weight at birth (kg)	n = 431	n = 673
Mean (SD)	1.043 (0.593)	2.832 (0.520)
Median (range)	0.823 (0.301–3.629)	2.853 (1.164–4.318)
Weight at birth (kg), n (%)		
<1.5	342 (79)	8 (1)
1.5–2.9	84 (20)	400 (59)
≥3.0	5 (1)	265 (39)
Age at treatment start (h)	n = 422	n = 649
Mean (SD)	9.6 (16.8)	16.8 (24.0)
Median (range)	4.8 (0.0–112.8)	7.2 (0.0–163.2)
Gender, n (%)		
Male	220 (51)	382 (57)
Female	211 (49)	293 (43)
Methemoglobin (%)	n = 246	n = 364
Mean (SD)	1.07 (0.81)	0.96 (0.59)
Median (range)	1.00 (0, 6.4)	0.9 (0, 6.4)
Underlying disease, n (%)		
Idiopathic	26 (6)	58 (9)
Meconium aspiration syndrome	2 (0.5)	142 (21)
Respiratory distress syndrome	229 (53)	30 (4)
Pneumonia/sepsis	40 (9)	30 (4)
Congenital diaphragmatic hernia	6 (1)	110 (16)
Other	125 (29)	298 (44)
Missing	3 (0.7)	7 (1)
Reason for administration of iNO, n (%)		
Improve HRF associated with PH	429 (99)	667 (99)
Complications/conditions, n (%)[b]		
None	195 (45)	244 (36)
Lung hypoplasia	79 (18)	184 (27)
Congenital heart disease	22 (5)	97 (14)
Multiple abnormalities	16 (4)	39 (6)
Other	180 (42)	217 (32)

GA = Gestational age, HRF = hypoxic respiratory failure, iNO = inhaled nitric oxide, PH = pulmonary hypertension.
[a]Gestational age data were missing for eight patients.
[b]A patient may have more than one condition.

Table 2: Mean last OI value stratified by baseline OI and GA.

Baseline OI	Last OI value, Mean (SD)	
	GA < 34 weeks	GA ≥ 34 weeks
OI <15	n = 70	n = 150
	6.2 (7.9)	6.5 (11.0)
15≤ OI <25	n = 58	n = 78
	10.3 (18.2)	8.9 (13.8)
25≤ OI <40	n = 51	n = 69
	13.4 (19.3)	17.5 (23.7)
OI ≥40	n = 42	n = 57
	20.7 (25.6)	25.1 (27.5)

GA = Gestational age; OI = oxygenation index, measured as cm H_2O/mm Hg; SD = standard deviation.

the lowest mean baseline OI category (OI <15). The mean percent change in OI from baseline at 1 h, 24 h and last value stratified by baseline OI is shown for the <34 weeks and ≥34 weeks GA subgroups in Figure 1. Greater mean reductions in OI were observed in subgroups of the <34 weeks GA group who had high baseline OI values. The <34 weeks GA group had a greater mean decrease at most timed assessments across the baseline OI categories; between-group differences reached statistical significance ($P < 0.05$) in the younger group versus the older group in the baseline OI < 15 category. Treatment with iNO resulted in a rapid and sustained decrease in OI in both GA groups. The reduction of OI was more pronounced in neonates with a higher OI at baseline.

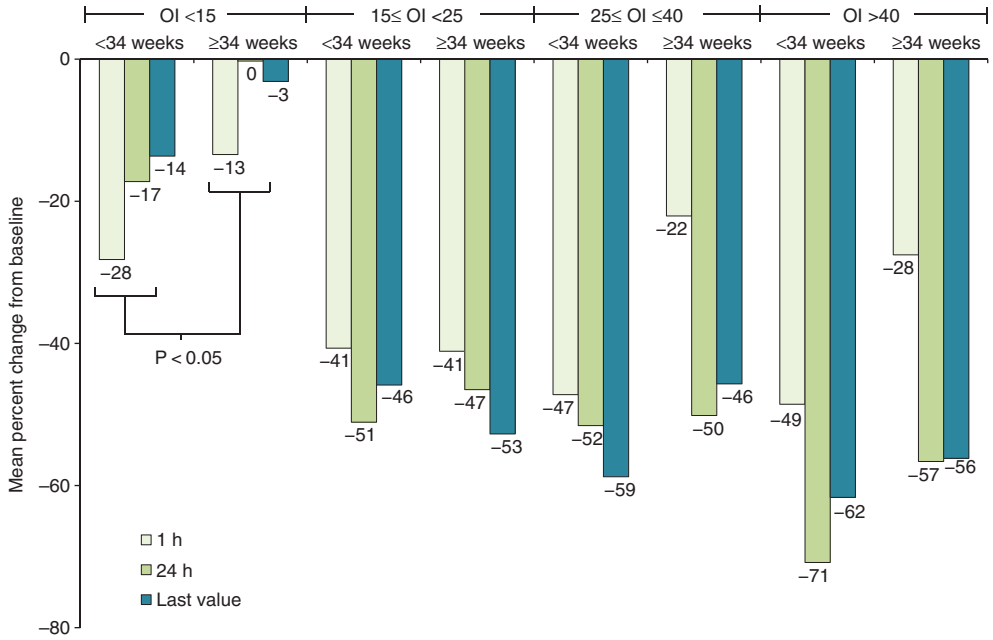

Figure 1: Mean percent change in oxygenation index (OI) over time stratified by baseline OI.
GA = Gestational age.

Safety

The incidence of severe intraventricular hemorrhage was significantly higher in the <34 weeks GA group (4%) compared with the ≥34 weeks GA group (0.3%; P < 0.0001). There were no incidences of neonatal necrotizing enterocolitis in either age group; three subjects (0.7%) in the <34 weeks GA group experienced late-onset sepsis compared with none in the ≥34 weeks GA group. The highest observed mean (SD) methemoglobin level in the <34 weeks GA group was 1.5% (1.2%) vs. 1.4% (1.3%) in the ≥34 weeks GA group. Survival rates were significantly higher (P = 0.001) among neonates who had an OI <15 at baseline compared with those who had an OI >40 at baseline (Figure 2).

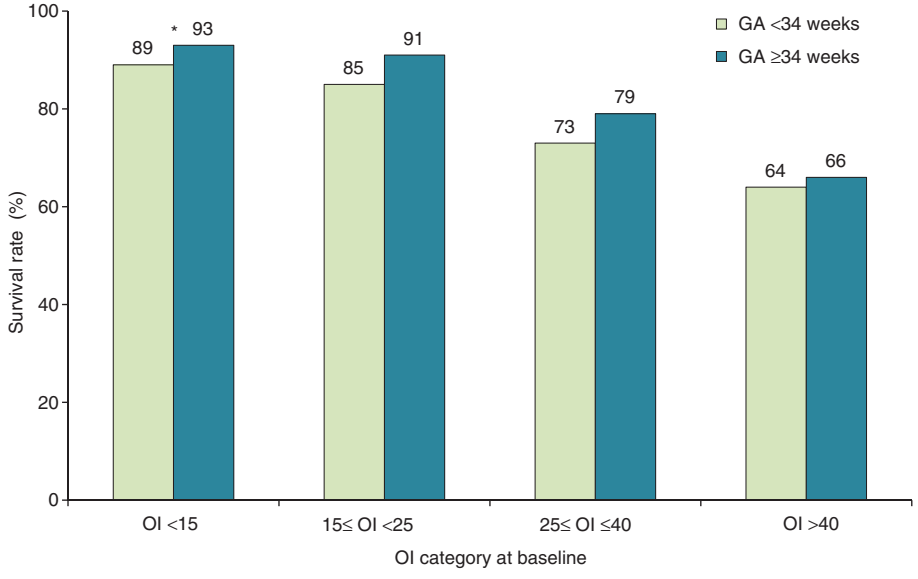

Figure 2: Survival rates stratified by baseline oxygenation index (OI).
*P = 0.001 for comparison of subjects in the OI <15 category vs. subjects in the OI >40 category. GA = Gestational age.

Discussion

The benefits of iNO have been previously demonstrated in neonates >34 weeks GA with HRF associated with PH [3–6], but its effectiveness in preterm neonates with HRF and PH has not been adequately studied [13], and published consensus statements regarding the benefits of iNO in preterm neonates vary. The National Institutes of Health (NIH) consensus panel (2011) and the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (2014) reported that the available evidence was insufficient to recommend the routine use of iNO in premature neonates of <34 weeks' gestation who need respiratory support to prevent or ameliorate bronchopulmonary dysplasia (BPD) [8, 9]. However, the NIH statement did suggest that some neonates of <34 weeks' gestation, such as those with PH, may benefit from iNO. In November 2015, joint guidelines for the management of pediatric PH were published by the American Heart Association and the American Thoracic Society, and concluded that available evidence is sufficient to recommend that iNO use be considered for preterm as well as late preterm and term neonates with HRF associated with PH [10]. Thus, controversy remains regarding the question of whether iNO use is beneficial in the preterm setting, particularly for clinicians faced with inadequate treatment alternatives for these neonates.

Despite the fact that iNO has not been extensively studied in premature neonates with PH, there is no evidence to indicate that it would act differently in premature neonates than in late preterm or term neonates [14]. In a published response to the AAP committee recommendations, Schreiber [14] noted evidence from several retrospective studies demonstrating the efficacy of iNO in preterm neonates with PH [15–17] and recommended that clinicians be allowed to use clinical judgment regarding the best use of iNO in this patient population pending further study. As clinicians, we recognize that iNO is, in fact, already being used off label in this preterm population. Ironically, while expert committees such as the NIH and AAP are unable to make a definitive recommendation on this issue because of lack of evidence from randomized, controlled trials, conducting such definitive trials in preterm neonates with HRF and PH appears improbable due to ethical and funding considerations [14].

We evaluated data from this observational registry to assess the treatment effects of iNO therapy initiated within the first week of life in preterm as well as late preterm and term neonates with HRF and PH in NICUs in Japan. This registry represents the largest data set compiled to date on the use of iNO in a preterm neonatal population with HRF and PH. It should be noted that this analysis did not include assessments related to the prevention or amelioration of BPD. By definition, registry data are observational and are therefore limited by potentially confounding factors, such as missing data and/or variations in practice patterns. For the purposes of the registry, diagnosis of PH could be based on the neonatologist's clinical judgment, which could also be considered a limitation of the analysis, but is reflective of real-world clinical practice where the diagnosis of PH in neonates is frequently made based on the clinical evidence available for an individual patient and the judgment of the attending neonatologist.

We are aware of no published, large, randomized clinical trials that have compared preterm versus late preterm/term neonates treated with iNO. One study comparing iNO and control ventilation without iNO in term and preterm neonates failed to demonstrate a statistically significant benefit of iNO for improving oxygenation in the preterm neonate group [18]. One potential explanation for this result is that because this study did not pre-specify a diagnosis of PH (only respiratory distress), treatment with iNO would be of limited benefit in a population without PH. More likely, the 39% decrease from baseline in OI in the preterm iNO group (n = 40) was not statistically different from the 16% decrease in the preterm control group (n = 45), reflecting the relatively small sample size of the study population.

In a post hoc analysis of two studies conducted by Chock et al. [17], iNO was evaluated in preterm neonates (<34 weeks GA) with a diagnosis of preterm premature rupture of membranes, oligohydramnios, and suspected pulmonary hypoplasia, which are conditions that place these neonates at high risk for PH. In this analysis, iNO was associated with lower mortality and lower BPD compared with placebo controls. The data also suggest that iNO produced an acute improvement in oxygenation as well as a shorter duration of oxygen use and mechanical ventilation.

Neonates, whether born preterm or early term, are at increased risk for respiratory morbidity, which can include HRF associated with PH [19]. Preterm birth may disrupt normal lung development, resulting in a deficit in pulmonary circulation, decreased surface area for gas exchange, increased vasoreactivity and hypoxic vasoconstriction, which lead to increased pulmonary vascular resistance [20, 21]. Persistent PH of the newborn (PPHN) can be associated with a number of neonatal cardiopulmonary diseases, including perinatal asphyxia, sepsis, or meconium aspiration syndrome, or it can be idiopathic. It also may be associated with respiratory distress syndrome, a disease most typically seen in the preterm

neonate [21]. Although the etiology of PPHN is multifactorial and its pathogenesis is unclear [22], it is believed that disruptions to the NO-cyclic guanosine monophosphate and endothelial NO synthase signaling pathways play an important role in the vascular abnormalities associated with PH [23]. Regardless of GA, the primary goal of therapy for PPHN is to achieve selective pulmonary vasodilation, which makes iNO well suited for treatment of this condition [23].

Throughout gestation, the fetal circulation is characterized by an elevated pulmonary resistance. This state is required in order to preferentially shunt blood away from the non-gas exchanging fetal lung. Adaptation to extrauterine life, at any gestation, requires a decrease in pulmonary vascular resistance. This decrease is mediated, in large part, through NO. The higher incidence of severe intraventricular hemorrhage observed in the <34 weeks GA compared with the ≥34 weeks GA group was also an expected observation, given that babies born at an earlier GA are known to be at increased risk for severe intraventricular hemorrhage [24, 25]. This finding was also consistent with findings from a larger Japanese observational study conducted by Kusuda and colleagues [26], which showed that in the 2145 very low birthweight infants studied (mean [SD] birthweight, 1024 [302] g; mean [SD] GA, 28.9 [3.4] weeks), the observed incidence of grade 3 or 4 intraventricular hemorrhage was 7%. In prospective, controlled studies of iNO conducted in premature neonatal populations with respiratory failure in the United States, the overall safety profile observed (including reported incidences of intraventricular hemorrhage) has been similar in the iNO treatment arms compared with patient groups who received placebo or no iNO [27–32].

The results of this analysis suggest that treatment with iNO improves oxygenation in preterm neonates with HRF and PH as effectively as it does in late preterm and term neonates, without a negative impact on other comorbidities or survival. While clinical use in preterm babies with HRF and PH in Japan does not greatly vary from the US, the single-payer system provided an opportunity to evaluate these populations. Given the fact that use of extracorporeal membrane oxygenation is not a viable option for low-birth-weight babies, conducting an adequately powered, prospective, randomized, controlled trial in this setting is likely not feasible. Despite the acknowledged limitations, the data collected from the registry are an important addition to the limited clinical study data available in preterm neonates with HRF and PH, and provide valuable insight into the real-world use of iNO. These data may help to address some of the ethical challenges NICU clinicians must face when considering use of iNO in their preterm neonates with HRF and PH. Because the observed response in the preterm neonates in this analysis was similar to the response observed in the near- and full-term neonates, a therapeutic trial of iNO might be indicated for preterm neonates with clinically significant PH.

Acknowledgments: This study was sponsored by Mallinckrodt Pharmaceuticals. Editorial and writing assistance was provided by Michael Morren, RPh, MBA, of Peloton Advantage, LLC, Parsippany, NJ, USA, funded by Mallinckrodt Pharmaceuticals.

Author's statement

Conflict of interest: Dr. Suzuki and Dr. Togari are members of the advisory board for the INOflo Post Market Surveillance Study in Japan for Mallinckrodt Pharmaceuticals, and have received honoraria and travel expense reimbursement from Mallinckrodt Pharmaceuticals as speakers. Dr. Potenziano is an employee of and stockholder in Mallinckrodt Pharmaceuticals. Dr. Schreiber has received honoraria as a consultant and is a scientific advisor to Mallinckrodt Pharmaceuticals, and has received funding for research from Mallinckrodt Pharmaceuticals.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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Supplemental Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2017-0040).