ISSN 0971-9032
Curr Pediatr Res 2025; 29 (02): 1-4 www.currentpediatrics.com

Prolonged Inhaled Nitric Oxide Treatment for 25 weeks Gestation Extreme Preterm with Persistent Pulmonary Hypertension

Salem Deraz, Somar Alhourany, Yasser El Gohary*, Reem Mahmoud Suliman, Olfat Alzaabi, Mohamed Ali Kasem Hussien Eleimy, Basel Aoun, Mahmoud Allam, Luay Abdalwahab, Ribal Kasem

Department of pediatrics and neonatology, Fujairah hospital, Emirates health services (EHS), United Arab of Emirates

Received: *04 February, 2024, Manuscript No. AAJCP-25-162091;* **Editor assigned:** *06 February, 2024, Pre QC No. AAJCP-25-162091 (PQ);* **Reviewed:** *20 February, 2025, QC No. AAJCP-25-162091;* **Revised:** *27 February, 2025, Manuscript No. AAJCP-25-162091 (R);* **Published:** *11 March, 2025, DOI:10.35841/0971-9032.29.02.2531-2533*

Abstract

Persistent Pulmonary Hypertension of the Newborn (PPHN) is characterized by high pulmonary vascular resistance, leading to right-to-left shunting of blood and resultant hypoxemia. Inhaled Nitric Oxide (iNO) has been widely used for managing PPHN in term and near-term neonates, but its role in extremely preterm infants remains less clear. While trials of iNO in Very Low Birth Weight (VLBW) infants suggest its safety, the efficacy, optimal duration of treatment and the possibility of using it with noninvasive ventilation in extremely preterm infants with PPHN are areas of ongoing research. This case study highlights the use of a prolonged course of inhaled nitric oxide (including both invasive and noninvasive ventilation) in an extremely preterm neonate with severe PPHN, as well as the challenges encountered during treatment.

Keywords: Extreme preterm neonate; Extreme low birth weight; Inhaled nitric oxide; Persistent pulmonary hypertension; Pulmonary vascular resistance; Sildenafil

Accepted on 10th March, 2025

Abbreviations

inhaled Nitric Oxide (iNO); Patent Foramen Ovale (PFO); Patent Ductus Arteriosis (PDA); Presisitent Pulmonary Hypertension in Newborn (PPHN); Systolic Pulmonary Arterial Pressure (SPAP); Extreme Low Birth Weight (ELBW); Very Low Birth Weight (VLBW); Non Invasive Ventilation (NIV); High Frequency Oscillation of Ventilation (HFOV); Fraction Inspired Oxygenation (FIO2); Respiraory Distress Syndrome (RDS); Parts Per Million (ppm); Beat Per Minute (bpm); Congenital Heart Disease (CHD); Hypoxic Respiratory Failure (HRF); Post Menstrual Age (PMA)

Case Presentation

A female neonate weighing 600 grams was delivered *via* emergency cesarean section at 25 weeks of gestation. The pregnancy was complicated by maternal chorioamnionitis and prolonged rupture of membranes, which occurred 5 weeks prior to delivery. At birth, the infant's condition was critical, exhibiting cyanosis, hypotonia, weak respiratory effort and a heart rate below 100 bpm. Immediate resuscitation was performed and surfactant was administered. Her APGAR scores were 3 at 1 minute, 6 at 5 minutes and 8 at 10 minutes. A chest X-ray revealed bilateral granular opacities suggestive of Respiratory Distress Syndrome (RDS) (Figure 1).

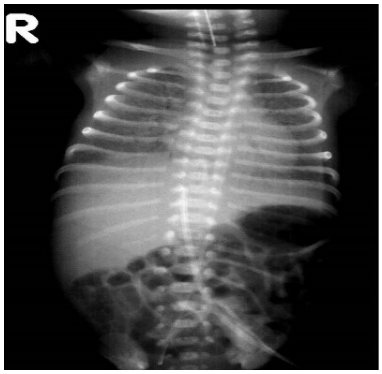

***Figure 1*:** Recommended nephrological follow-up in pediatric patients post HSCT.

Despite intensive supportive care, which included three doses of surfactant and mechanical ventilation with 100% oxygen, the infant continued to experience desaturation. An echocardiogram performed at 20 hours of life revealed Persistent Pulmonary Hypertension of the Newborn (PPHN), estimated Systolic Pulmonary Arterial Pressure (SPAPA): 30 mm Hg over systemic pressure 29 mm Hg at same time of study with right-to-left shunting across the Patent Ductus Arteriosus (PDA) and bidirectional shunting across the Patent Foramen Ovale (PFO) (Figure 2). Given the severity of Persistent Pulmonary Hypertension of the Newborn (PPHN), inhaled Nitric Oxide (iNO) was initiated at a dose of 20 ppm with inotropes.

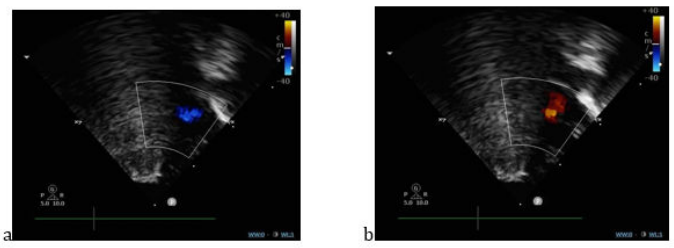

***Figure 2*:** Recommended nephrological follow-up in pediatric patients post HSCT.

Initially, the neonate responded well, showing a gradual improvement in oxygen saturation. However, on day 6 estimated systolic pulmonary arterial pressure (SPAP) by Echo was 30 mmHg under systemic pressure 57 mmHg at same time of study, inhaled nitric oxide (iNO) was weaned and subsequently stopped. Two hours later, the baby experienced significant desaturation, which improved only after restarting iNO. A repeat echocardiogram on day 8 revealed closure of the Ductus Arteriosus (PDA), a reversal of the Patent Foramen Ovale (PFO) shunt to left-to-right and pulmonary pressure below systemic pressure (Figure 3). At that time, another attempt to stop iNO was made, but it failed due to desaturation that improved only with the resumption of iNO. A subsequent echocardiogram showed reopening of the PDA with right-to-left shunting (SPAP was 60 mmHg which was supra systemic pressure 48 mmHg). The infant's clinical course became increasingly complicated by persistent pulmonary hypertension, necessitating high levels of oxygen support.

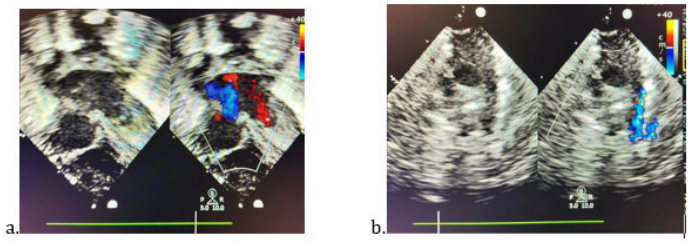

***Figure 3*:** Recommended nephrological follow-up in pediatric patients post HSCT.

The infant continued inhaled Nitric Oxide (iNO) at a dose of 20 ppm, along with supportive care that included milrinone (to improve the RV function and decrease the pulmonary vascular resistance) and noradrenaline (optimize blood pressure) as well as mechanical ventilation, including High-Frequency Oscillatory Ventilation (HFOV). Sildenafil was introduced on day 21 of life to enhance pulmonary vasodilation, as it had not been started earlier due to oral intake intolerance.

Later, the baby was extubated at the age of 31 days to noninvasive ventilation while continuing to use iNO in conjunction with this mode of ventilation.

The baby underwent three trials of discontinuing (iNO), but failed as followed by desaturation and required resuming iNO. The remarkable point that resuming iNO only with lower dose (2 ppm) was enough to keep the baby stable and maintaining saturation. In Last Trial Inhaled Nitric Oxide was resumed with dose 2 ppm lasted for 2 days then decreased to 1 ppm lasted for 6 days. The successful discontinuation occurred at 39 days of life, following three failed trials of stopping iNO. That thing raises questions about exact or suitable protocol (period and dose) of iNO in extreme preterms.

Sildenafil therapy was continued, with the dose increased to the maximum allowed (1 mg/kg every 6 hours), Sildenafil was stopped on day 41.

Throughout the treatment period, the infant was monitored for potential adverse effects, including methemoglobin levels (which remained below 2%), platelet count (which was within the normal range) and brain scans (which showed no evidence of intraventricular hemorrhage).

Discussion

It was previously believed that persistent Pulmonary Hypertension of the Newborn (PPHN) primarily occurs in term or late-preterm infants, with incidence rates varying from 0.12% to 0.46% across different regions [1-2]. However, a retrospective multicenter cohort study has reported that the prevalence of PPHN among extremely preterm infants can be as high as 8.1% [3]. Additionally, a population-based cohort study of very preterm infants in France found a prevalence of pulmonary hypertension (PH) of 6% [4].

There are many causes of Hypoxemic Respiratory Failure (HRF) in premature infants, including parenchymal lung diseases, disorders with increased airway resistance, Congenital Heart Disease (CHD) and Persistent Pulmonary Hypertension of the Newborn (PPHN). PPHN results from the failure of pulmonary circulatory adaptation at birth. In extremely preterm infants, who are born during the canalicular stage of lung development, the reduced cross-sectional area of the pulmonary circulation contributes to the development of PPHN. Additionally, PPHN is associated with pulmonary hypoplasia secondary to preterm premature rupture of membranes in this population [5].

Regarding the reasons behind the prolonged period of Persistent Pulmonary Hypertension of the Newborn (PPHN) and inhaled Nitric Oxide (iNO) treatment in our presented case, we suggest that the infant initially exhibited pulmonary hypoplasia due to the mother's oligohydramnios. This was followed by the development of chronic lung disease characterized by interstitial emphysema. Both factors contribute to the persistence of primary pulmonary hypertension.

As is well known, Persistent Pulmonary Hypertension of the Newborn (PPHN) in extremely premature infants is a risk factor for worse outcomes, including Bronchopulmonary Dysplasia (BPD) and visual impairment. Earlier studies on the use of inhaled Nitric Oxide (iNO) for premature infants born at less than 34 weeks of gestation who require respiratory support did not provide conclusive evidence of benefit [6](14). However, recent studies support the trial of iNO in premature infants with persistent hypoxia despite optimal respiratory support. Questions remain regarding the optimal dose of iNO and the duration of the initial iNO trial in these patients [5].

Additionally, more cases are demonstrating that treatment with inhaled Nitric Oxide (iNO) should be considered as a rescue therapy for preterm newborns experiencing acute hypoxic respiratory failure due to severe pulmonary hypertension [7]. Recommendations include the selective use of iNO in infants born preterm who have documented evidence of severe PPHN contributing to hypoxemia [8], particularly when associated with prolonged rupture of membranes or oligohydramnios [9].

Some studies have suggested that initiating inhaled Nitric Oxide (iNO) at 20 ppm for high-risk preterm infants on postnatal days 5 to 14 and continuing for 24 days appears to be safe. However, this approach did not improve survival without Bronchopulmonary Dysplasia (BPD) at 36 weeks of Postmenstrual Age (PMA) or respiratory and neurodevelopmental outcomes at 18 to 24 months' PMA [10]. Other strategies have also been prescribed [9].

Inhaled Nitric Oxide (iNO) is effective when used in conjunction with tracheal intubation and mechanical ventilation for treating arterial pulmonary hypertension and Hypoxemic Respiratory Failure (HRF) in near-term and term newborns. It can also be administered *via* noninvasive modes; however, the effectiveness of iNO delivery through noninvasive ventilation remains unknown [11].

Sildenafil has facilitated the weaning off iNO in most evaluated preterm neonates without adverse side effects [12]. Inhaled nitric oxide has been shown to reduce the incidence of Bronchopulmonary Dysplasia (BPD) in neonates at 36 weeks of gestation, with the treatment's effectiveness depending on factors such as neonatal age, birth weight, duration and dose of iNO. Therefore, iNO can be considered a promising treatment for the potential prevention of BPD in premature infants [13].

This case underscores the complexities involved in managing Persistent Pulmonary Hypertension of the Newborn (PPHN) in extremely preterm neonates. The prolonged use of iNO, extending to 39 days in this case, highlights the severity of PPHN and its potential resistance to conventional therapies. The intermittent failure to wean off iNO and the necessity for additional medications, such as sildenafil and inotropes, emphasize the challenges in managing this condition in neonates who are both underdeveloped and at high risk for other complications.

Furthermore, this case demonstrates the importance of ongoing monitoring and individualized care in managing preterm infants with PPHN. Although iNO is generally considered safe for use in preterm infants, the duration of therapy and optimal weaning protocols remain uncertain and require careful clinical judgment. The use of sildenafil, a phosphodiesterase inhibitor, has shown promise in some studies for supporting iNO therapy and improving pulmonary outcomes, as evidenced by its application in this case.

The formulas recommended for calculating eGFR according to KDIGO and our own opinion for children up to 12 years of age are: The one-marker Schwartz formula from 2009, the three-marker Schwartz formula from 2009 and the U25 formula from 2021. For children older than 12 years, adult formulas may be used [59]. In cases of growth deficiencies, the appropriate age for height, rather than the patient's chronological age, should be used. Any abnormalities found in the mentioned tests should prompt a quick referral for a nephrology consultation.

Conclusion

This case highlights the potential for the prolonged use of inhaled Nitric Oxide (iNO), even in conjunction with Noninvasive Ventilation (NIV), for managing Persistent Pulmonary Hypertension of the Newborn (PPHN) in extremely preterm neonates. Despite the associated risks and challenges, iNO remains a critical therapeutic option. Its effectiveness may be enhanced when combined with other agents, such as sildenafil, to optimize outcomes in extremely preterm and Extremely Low Birth Weight (ELBW) neonates. Further studies are needed to establish the most effective treatment protocols and to assess long-term outcomes for these vulnerable infants.

References

1. Nakwan N, Jain S, Kumar K, et al. An Asian multicenter retrospective study on persistent pulmonary hypertension of the newborn: Incidence, etiology, diagnosis, treatment and outcome. J Matern Fetal Neonatal Med 2020; 33(12): 2032-2037.
2. Steurer MA, Jelliffe PLL, Baer RJ, et al. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics 2017;139(1).
3. Nakanishi H, Suenaga H, Uchiyama A, et al. Persistent pulmonary hypertension of the newborn in extremely preterm infants: A Japanese cohort study. ADC Fetal and Neonatal 2018; 103(6):F554-F561.
4. Breinig S, Ehlinger V, Roze JC, et al. Pulmonary hypertension among preterm infants born at 22 through 32 weeks gestation in France: Prevalence, survival, morbidity and management in the EPIPAGE-2 cohort study. Early Hum Dev 2023; 184:105837.
5. Osman A. The early use of inhaled nitric oxide in premature infants requiring respiratory support. Ann Med 2023; 55(2):2266633.
6. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev 2017(1).
7. Buse M, Graziano F, Lunetta F, et al. Inhaled nitric oxide as a rescue therapy in a preterm neonate with severe pulmonary hypertension: A case report. Ital J Pediatr 2018; 44:1-4.
8. Lakshminrusimha S, Kinsella JP, Krishnan US, et al. Just say no to iNO in preterms-really?. J Pediatrics 2020; 218:243-252.
9. Mitra S, Altit G. Inhaled nitric oxide use in newborns. Paediatrics Child Health 2023; 28(2):119-122.
10. Hasan SU, Potenziano J, Konduri GG, et al. Effect of inhaled nitric oxide on survival without bronchopulmonary dysplasia in preterm infants: A randomized clinical trial. JAMA Pediatrics 2017; 171(11):1081-1089.

11. Sahni R, Ameer X, Ohira KK, et al. Non-invasive inhaled nitric oxide in the treatment of hypoxemic respiratory failure in term and preterm infants. J Perinatology 2017;37(1):54-60.
12. Khawaja H, Sanders TA, Schreiber M, et al. Sildenafil as bridge therapy for inhaled nitric oxide in preterm neonates. J Pediatr Pharmacol Therap 2024;29(5):525-529.
13. Feng Z, Wu X, Xu X, et al. Efficacy of inhaled nitric oxide in preterm infants 34 weeks: A systematic review and meta-Analysis of randomized controlled trials. Front Pharmacol 2024;14:1268795.
14. Ellsworth KR, Ellsworth MA, Weaver AL, et al. Association of early inhaled nitric oxide with the survival of preterm neonates with pulmonary hypoplasia. JAMA pediatrics. 2018;172(7):e180761.

Corresponding Authors:

Yasser Mohamed El Gohary

Department of Pediatric and Neonatology,

Fujairah hospital, Emirates health services (EHS), United Arab of Emirates

Email: yasser.elgohary@ehs.gove.ae