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Comparative efficacy of low-dose versus high-dose inhaled nitric oxide in extreme preterm infants with hypoxic respiratory failure: A retrospective cohort study

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To the Editor,

Inhaled nitric oxide (iNO) has shown efficacy in term infants with persistent pulmonary hypertension of the newborn (PPHN) and in preterm infants with pulmonary hypertension secondary to bronchopulmonary dysplasia (BPD). However, because there is little information on the best dosage and possible hazards, its use in extremely preterm neonates is still debatable (1). Controversy exists regarding the use of different iNO dosages in preterm infants, with studies producing conflicting results on its efficacy and safety. Some researchers argue that low-dose iNO (5–10 ppm) improves oxygenation with fewer side effects, while others suggest that higher doses (15–20 ppm) may be necessary to achieve optimal pulmonary vasodilation in severe cases of respiratory failure (2). Nonetheless, it has been noted that elevating the dosage beyond 20 ppm does not improve outcomes and may heighten the risk of complications, including methemoglobinemia and compromised platelet function. Despite these concerns, higher doses continue to be used in some clinical settings, particularly in infants who fail to respond to lower doses. Moreover, the timing of iNO administration is another point of debate. Some studies suggest that initiating iNO therapy early may prevent the development of BPD, while others contend that the benefits are limited to infants with established pulmonary hypertension (3). We conducted a retrospective cohort study at the Women's Wellness and Research Center NICU, which included 150 extreme preterm infants (<28 weeks gestation) with hypoxic respiratory failure, admitted between January 1, 2015, and April 30, 2021. Infants with major congenital anomalies, cardiovascular compromise, or bilateral grade IV intraventricular hemorrhage (IVH) were excluded. Our patients were divided into two groups: high-dose (20 ppm) and low-dose (10 ppm) iNO. The aim of our study was to evaluate the dose-response relationship of iNO in extreme preterm infants with hypoxic respiratory failure by comparing the effects of two iNO dosages (10 ppm and 20 ppm) on oxygenation parameters, including arterial PaO2, oxygen saturation, and oxygen index (OI). Additionally, the study aims to assess the impact of these dosages on key clinical outcomes, such as mortality, BPD, retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), and IVH, to help identify the optimal dosing strategy for this vulnerable population (Table 1).

Our study didn't find a marked difference between the two groups in the demographic characteristics, including gestational age, birth weight, sex, or Apgar score. Infants in the 10 ppm group showed a significantly greater increase in arterial PaO_2 (mean increase of 18.2 mmHg) compared to those in the 20 ppm group (mean increase of 12.5 mmHg, $p<0.01$). Additionally, the 10 ppm group had a higher average increase in O_2 saturation (15% vs. 10%, $p<0.05$) and a more substantial reduction in oxygen index (OI) (6.8 vs. 4.2, $p<0.05$). These results indicate that a lower dose of iNO is more effective in enhancing oxygenation in extreme preterm infants. A more optimal balance between vasodilation and ventilation-perfusion matching in the lungs may explain the improved

Table 1. Clinical Outcomes Comparison Between 10 and 20 ppm iNO Groups

Outcome	10 ppm iNO Group (n=75)	20 ppm iNO Group (n=75)	p-value
PaO2 Improvement (mmHg)	18.2 ± 6.5	12.5 ± 5.4	<0.01
O2 Saturation Increase (%)	15% ± 5	10% ± 4	<0.05
Oxygen Index Reduction	6.8 ± 3.2	4.2 ± 2.8	<0.05
BPD Incidence (%)	28%	38%	<0.05
Mortality (%)	15%	22%	0.15
ROP Incidence (%)	18%	25%	0.12
PVL Incidence (%)	6%	8%	0.45
IVH Incidence (%)	10%	14%	0.32

oxygenation with 10 ppm iNO. Higher doses of iNO may lead to excessive vasodilation, potentially causing ventilation-perfusion mismatch and less efficient oxygenation. This is consistent with previous findings suggesting that increasing iNO doses beyond 20 ppm does not confer additional benefits and may even be detrimental. Our study also found that the 10 ppm iNO group showed a lower incidence of BPD at 36 weeks gestational age (28% vs. 38%, p<0.05), suggesting that a lower dose of iNO may reduce the risk of developing chronic lung disease. BPD is significant morbidity in preterm infants, often resulting from prolonged mechanical ventilation and oxygen therapy. The reduction in BPD incidence with 10 ppm iNO may be due to its more effective improvement in oxygenation, allowing for reduced ventilator settings and oxygen exposure. The mortality rate was lower in the 10 ppm group compared to the 20 ppm group (15% vs. 22%), although this difference was not statistically significant (p=0.15). Similarly, the incidences of ROP, PVL, and IVH grade III were lower in the 10 ppm group, but these differences were not statistically significant. These findings suggest that there is a trend toward better overall outcomes with the lower iNO dose, although larger studies are necessary to confirm these observations. The comparison of studies over the past 20 years on the use of inhaled nitric oxide (iNO) in preterm infants reveals almost consistent findings regarding the optimal dosing and effectiveness of iNO therapy. Many studies indicate that lower doses of iNO (typically 10 ppm) are more effective in improving oxygenation and reducing the risk of bronchopulmonary dysplasia (BPD) without adding significant risks (3). Meta-analyses suggest that increasing the dose beyond 20 ppm does not confer additional benefits and may even introduce adverse effects such as methemoglobinemia and impaired platelet function (4) (5). Additionally, randomized trials found no significant reduction in mortality or BPD with higher doses of iNO, supporting the preference for lower doses. Overall, the evidence indicates that while iNO can be beneficial in improving clinical outcomes, especially oxygenation, in preterm infants with respiratory failure, lower doses (e.g., 10 ppm) are generally more effective and safer, with higher doses offering no additional benefit and posing greater risks.

Ethic Approval: This study was approved by Hamad Medical Corporation ABHATH Committee under number MRC-01-22-538, approved on 1/10/2022.

Conflict of Interest: Each author declares that he has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

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