

Title: Does prolonged on- and off-label use of inhaled nitric oxide in the Neonatal Intensive Care Unit improve outcomes? A single center experience.

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Background:

Inhaled Nitric Oxide (iNO) is a potent pulmonary vasodilator often used in the Neonatal Intensive Care Unit (NICU) for term or near-term infants with hypoxic respiratory failure (HRF) due to persistent pulmonary hypertension of the newborn (PPHN). Selective use in preterm infants with HRF is controversial. A recent multicenter observational study found comparable efficacy of iNO use for improving oxygenation in preterm neonates with HRF associated with pulmonary hypertension (PH) when compared to term and near term neonates.¹ While the use of iNO may provide temporary improvement in oxygenation in preterm infants, the effects of long-term use of iNO are unknown. Characterization of neonatal patients treated with iNO and their outcomes may provide valuable information for clinicians when delivering care at the bedside and counseling parents. We hypothesized that prolonged iNO therapy in neonatal patients with hypoxic respiratory failure and suspected pulmonary hypertension would not result in higher likelihood of survival.

Methods:

This study was approved by the Institutional Review Board at Hawai'i Pacific Health. Retrospective chart review was performed for all patients admitted to NICU at Kapiolani Medical Center who were treated with iNO for any duration at any time during their hospital stay, from 2010 – 2018. Initiation and discontinuation of iNO was at the discretion of the attending physician. The primary outcome of interest is survival in relation to duration of iNO therapy. Descriptive statistics were used for demographics and clinical measures. Non-parametric tests were used to compare the differences in numeric variables with non-normal distribution between study groups, and fisher's exact test was used for categorical variables. Cox Proportional Hazards Regression model was used to estimate the survival probability after adjustment for selected variables.

Results:

A total of 230 infants were treated with iNO during the NICU stay from 2010 to 2018. We found bimodal distribution of patients in two gestational age groups: Group A (<28 weeks, n=63) and Group B ($\geq$ 34 weeks, n=136). Group A infants were older when starting iNO (postnatal age: 6 d [1 – 47] vs 1 d [0 – 3], $p < 0.01$) and had higher oxygenation index (OI) prior to initiation of iNO therapy (36.5 [22.0 – 54.0] vs 27.7 [17.7 – 41.3], $p < 0.01$), but there was no difference in mean total iNO duration between the two groups (72 h [14 – 214] vs 76 h [32 – 142]). Both groups showed similar decrease in OI at 1, 2, 6, 12 and 24 hours after initiation of iNO. Group A had higher mortality (54.0% vs 22.1%, $p < 0.01$) and survivors had more need for home oxygen (27.6% vs 7.5%, $p < 0.01$). One-fifth of patients in Group B were eventually treated with extracorporeal membrane oxygenation. After adjustment, survival analysis demonstrated increased survival probability in Group A until one week treatment with iNO, after which, survival probability decreased. In contrast, survival probability in Group B increased with prolonged iNO treatment, even beyond one week (Figure 1A and 1B).

Conclusion:

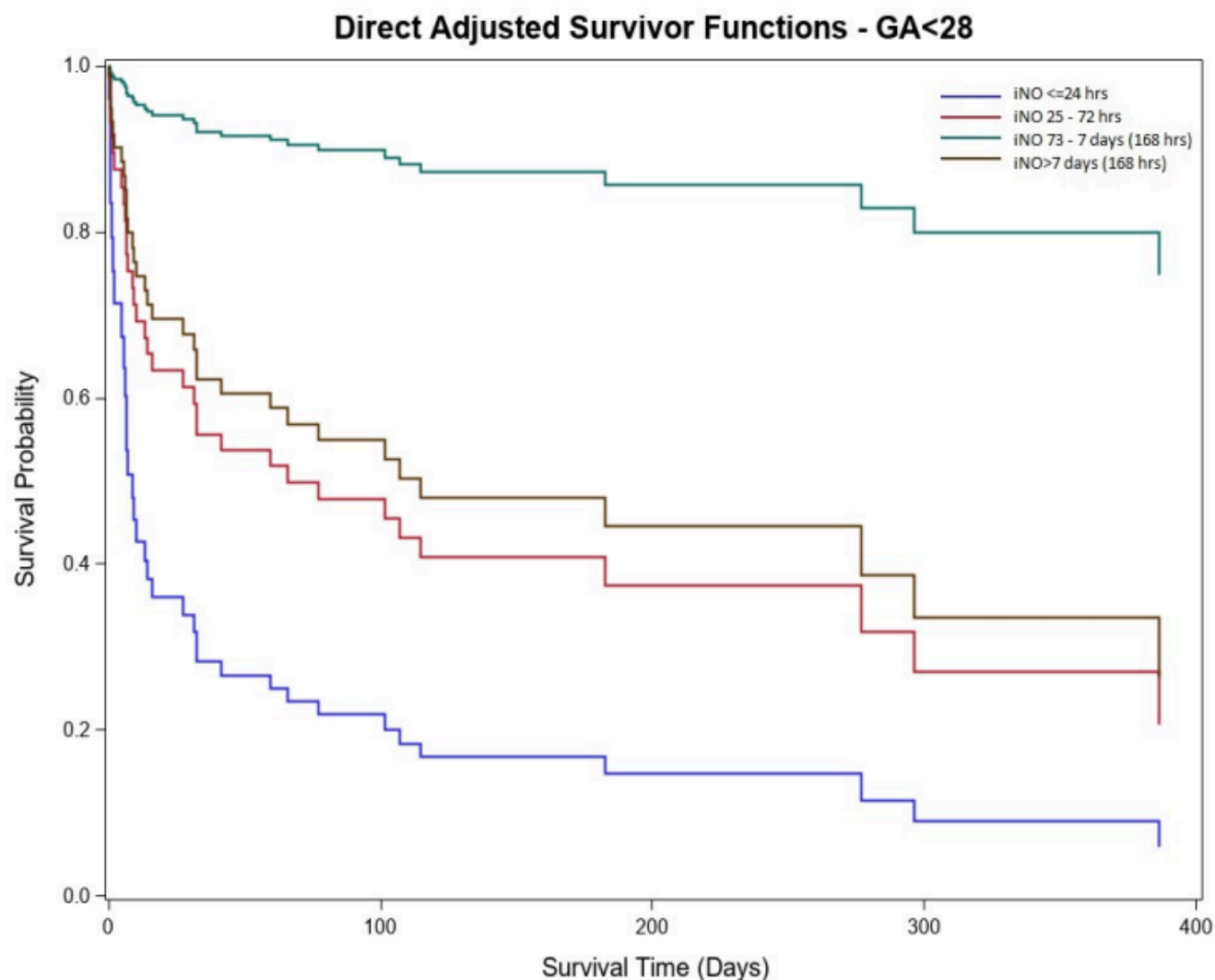
Administration of iNO for HRF with suspected or documented PH resulted in similar improvement in OI in both extremely preterm and term or near-term infants. However, prolonged treatment beyond 1 week was not associated with improved survival probability in extremely preterm infants. Better understanding of outcomes following prolonged treatment with iNO may help clinicians prescribe care at the bedside, counsel families and manage resources.

References:

1. Nelin L, et al. Use of inhaled nitric oxide in preterm vs term/near-term neonates with pulmonary hypertension: results of the PaTTERN registry study. J Perinatol. 2022;42:14-18; <https://doi.org/10.1038/s41372-021-01252-x>

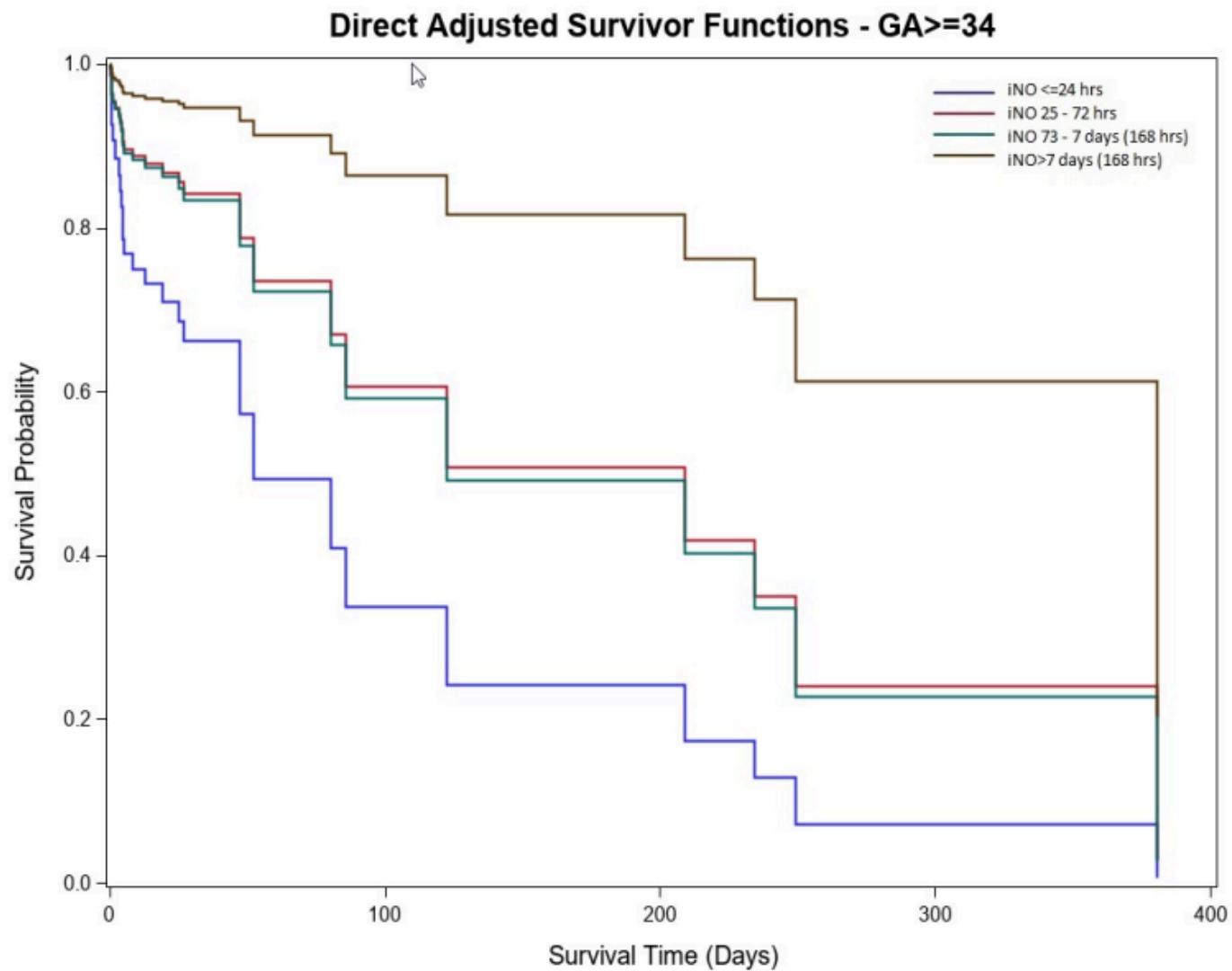
Figure 1A & 1B: Survival analysis by duration of iNO (< 24 hours, 25 – 72 hours, 72 hours – 7 days and > 7 days) in extremely preterm (Group A) and term or near-term infants (Group B).

Figure 1A



Adjusted with Sex, BW 10%ile, Genetic Condition, PDA, Pneumo, Pulm Hypo, HIE, Severe IVH, Sepsis, NEC and Trach status.

Figure 1B



Adjusted with Sex, BW 10%ile, Genetic Condition, PDA, PHTN PFC, Meconium Aspiration Syndrome, RDS, Pneumo, Pulm Hypo, CDH, HIE, Severe IVH, Sepsis, Trach and ECMO status.