Impact of the Neonatal Resuscitation Program–Recommended Low Oxygen Strategy on Outcomes of Infants Born Preterm

Vishal S. Kapadia, MD[1], Charitharth V. Lal, MD[2], Venkat Kakkilaya, MD[1], Roy Heyne, MD[1], Rashmin C. Savani, MBChB[1], and Myra H. Wyckoff, MD[1]

Objective To evaluate the impact of the Neonatal Resuscitation Program (NRP)-recommended low oxygen strategy (LOX) on neonatal morbidities, mortality, and neurodevelopmental outcomes in neonates born preterm.

Study design In March 2011, Parkland Hospital changed from a high oxygen strategy (HOX) of resuscitation with initial 100% oxygen and targeting 85%-94% oxygen saturation for delivery room resuscitation to a LOX with initial 21% oxygen and titrating oxygen to meet NRP-recommended transitional target saturations. Neonates ≤28 weeks' gestational age born between August 2009 and April 2012 were identified. In this retrospective, observational study, neonates exposed to LOX vs HOX were compared for short-term morbidity, mortality, and long-term neurodevelopmental outcomes. Regression analysis was performed to control for confounding variables.

Results Of 199 neonates, 110 were resuscitated with HOX and 89 with LOX. Compared with HOX, neonates exposed to LOX had lower oxygen exposure in the delivery room (5.2 ± 1.5 vs 7.8 ± 2.8 [$\sum FiO_2 \times$ time $_{min}$], $P < .01$), spent fewer days on oxygen (30 [5, 54] vs 46 [11, 82], $P = .01$), and had lower odds of developing bronchopulmonary dysplasia (aOR 0.4 [0.2, 0.9]). There was no difference in mortality (17 [20%] vs 20 [18%]), but neonates exposed to LOX had greater motor composite scores on Bayley Scales of Infant and Toddler Development–Third edition assessment (91 [85, 97] vs 88 [76, 94], $P < .01$).

Conclusion The NRP-recommended LOX strategy was associated with improved respiratory morbidities and neurodevelopmental outcomes with no increase in mortality. Prospective trials to confirm the optimal oxygen strategy for the resuscitation of neonates born preterm are needed. *(J Pediatr 2017;191:35-41).*

Oxygen is an essential fuel source and plays a major role in numerous oxidative metabolic reactions and physiologic processes.[1] However, excess oxygen exposure can result in the production of oxygen free radicals. Unchecked, such reactive oxygen species can damage lipids, proteins, and DNA, resulting in tissue injury and cell death.[2-4] Birth is an oxidative challenge to the newborn as it adapts from a low oxygen intrauterine environment to the greater oxygen extrauterine environment.[1] Neonates born preterm especially are vulnerable to oxidative stress due to decreased enzymatic and nonenzymatic oxygen defenses and the frequent need for resuscitation with oxygen exposure at birth.[3,5,6] Although multiple, small, randomized controlled trials have examined various initial oxygen concentrations for preterm resuscitation at birth, the optimal oxygen strategy for preterm neonatal resuscitation remains unknown.[7-13] An optimal oxygen strategy would avoid both hypoxia and hyperoxia. Hyperoxemia during resuscitation results in oxidative stress and is associated with various neonatal morbidities such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP).[4,8,12-19] Although newborns with high fetal hemoglobin and high cardiac output physiologically should be able to tolerate lower oxygen saturation (SpO_2) during transition,[1] exposure to prolonged hypoxia also results in increased neonatal morbidities such as intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) and increased mortality.[13,20,21]

Before 2011, the American Heart Association/American Academy of Pediatrics Neonatal Resuscitation Program (NRP) recommended that neonates born preterm receive 100% oxygen as the preferred gas during delivery room resuscitation/stabilization.[22] Based on the 2010 International Liaison Committee on Resuscitation Consensus on Science and Treatment recommendations,[23] the 2011 NRP recommended starting with lower oxygen concentrations (21%-30%) for preterm delivery room resuscitation.

Bayley III	Bayley Scales of Infant and Toddler Development – Third edition
BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GMFCS	Gross Motor Function Classification System
HOX	High oxygen strategy
IVH	Intraventricular hemorrhage
LOX	Low oxygen strategy
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NRP	Neonatal Resuscitation Program
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SpO_2	Oxygen saturation

From the [1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; and [2]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

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The oxygen concentration was titrated with an oxygen blender to achieve goal SpO_2 based on the approximated median transitional saturations observed in healthy neonates born at term. The most recent International Liaison Committee on Resuscitation[24] scientific review and NRP[25] guidelines continue these recommendations that emphasize the need to provide sufficient oxygen to correct any hypoxic state while trying to avoid excess oxygen exposure.

There is ample evidence that resuscitation of neonates born preterm with a low oxygen strategy (LOX) starting with 21% oxygen is feasible.[8,9] However, several studies, systematic reviews, and meta-analyses have given conflicting results about the impact of a low vs high initial oxygen strategy on short-term clinical outcomes and mortality in neonates born preterm.[7-13,19,21,26-28] Little evidence is available regarding the effect of delivery room oxygen strategies on long-term neurodevelopmental outcomes.[28] The primary objective of this study was to evaluate the impact of the change from the long-standing initial 100% oxygen strategy to the initial 21% oxygen strategy on morbidity, mortality, and long-term neurodevelopmental outcomes in neonates born preterm.

Methods

A retrospective cohort study was conducted to examine neonates born preterm at ≤28 weeks' gestational age (GA) between August 2009 and April 2012 at Parkland Hospital, Dallas, Texas. The study was approved by University of Texas Southwestern Medical Center institutional review board.

At Parkland Hospital before March 2011, in compliance with the 2006 NRP guidelines,[22] neonates born preterm were resuscitated in the delivery room with a high oxygen strategy (HOX) where stabilization was initiated with 100% oxygen and the oxygen concentration was adjusted to achieve preductal goal saturations of 85%-94%. In March 2011, the new 2011 NRP recommendations of using an initial LOX for resuscitation of neonates born preterm was adopted.[25] With LOX, resuscitation was initiated with 21% oxygen, and oxygen was titrated to achieve the transitional preductal NRP-recommended goal saturations. These goal saturations are approximated median preductal saturations observed in healthy neonates born at term.[29,30]

This primary objective of the study was to compare short- and long-term outcomes of neonates resuscitated with the HOX vs LOX strategy. All neonates born preterm at 23-28 weeks' GA during the study period were identified from the Parkland Neonatal Resuscitation Registry. Neonates enrolled in a competing randomized control trial,[8] with prenatally diagnosed cyanotic congenital heart disease, and those with planned comfort care only were excluded. The cohort was divided into those resuscitated with the HOX vs LOX strategy based on their date of birth and verified by chart review.

Baseline maternal and infant characteristics, resuscitation details, morbidities, and mortality were collected for comparison. Data were obtained from the electronic medical record, the Parkland Neonatal Resuscitation Registry, and the Parkland neonatal intensive care unit (NICU) Database, which prospectively collects data on all neonates admitted to the Parkland NICU. Prolonged rupture of membrane was defined as rupture of membranes ≥18 hours before birth. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development expert panel definition for chorioamnionitis was used.[31] In April 2010, Parkland Hospital adopted a policy of giving antenatal magnesium for neuroprotection to all neonates born preterm at <28 weeks' GA. For the current study, antenatal magnesium given either for neuroprotection or for maternal pre-eclampsia was recorded. Intrauterine growth restriction was defined by Ponderal Index <10th percentile for GA.

All deliveries of infants ≤28 weeks' GA at Parkland hospital are attended by the neonatal resuscitation team. An obstetric circulating nurse joins the team to record details of the resuscitation, including the infant's vital signs, SpO_2, and interventions such as changes in fraction of inspired oxygen (FiO_2) on a resuscitation record every 30 seconds during the stabilization. This delivery room resuscitation record becomes part of the patient's medical record. Resuscitation data such as heart rate, FiO_2, SpO_2 during first 10 minutes after birth, prolonged positive pressure ventilation >1 minute, need for continuous positive airway pressure, intubation, chest compressions, and epinephrine administration in the delivery room were abstracted from these records. Oxygen load (inspired oxygen) for first 10 minutes after birth was calculated with the equation: $\sum FiO_2 \times time_{min}$ as previously described.[8]

Morbidities such as respiratory distress syndrome (RDS), pneumothorax, pulmonary arterial hypertension (PAH), BPD, sepsis, severe IVH, necrotizing enterocolitis (NEC), clinically significant patent ductus arteriosus (PDA), severe ROP, length of hospitalization, and death during NICU stay were recorded from the NICU database. RDS, PAH, and clinically significant PDA were recorded if the clinician documented these morbidities as present in the patient's electronic chart. BPD was defined as the need for supplemental oxygen at 36 weeks' postmenstrual age. Bacteremia/sepsis were recorded only if the blood culture was positive for a pathogenic organism. Severe IVH was defined as grade III or greater on any ultrasound scans of the head unilaterally or bilaterally as per Papile criteria.[32] NEC was defined stage 2 or greater based on the modified Bell criteria.[33] Severe ROP was defined as stage 3 or greater based on the international classification of ROP.[34]

Neonates ≤28 weeks' GA who are born at Parkland Hospital undergo systematic standardized neurologic assessment, including the Bayley Scales of Infant and Toddler Development–Third edition (Bayley III)[35,36] at the Children's Medical Center Dallas Thrive Program at 22-26 months' corrected age. The providers at the follow-up clinic were not aware of the initial oxygen concentration used during resuscitation at birth. The Gross Motor Function Classification System (GMFCS) score was used to classify functional impairment in children with cerebral palsy. Hearing and visual impairment also were assessed. Moderate-to-severe neurodevelopmental impairment (NDI) was defined as the presence of any one of the following: cerebral palsy with a GMFCS score ≥2, Bayley III cognitive or motor score <85, or visual impairment or permanent