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

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**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 ($5.2 \pm 1.5$ vs $7.8 \pm 2.8$ [$\sum FiO_2 \times$ 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 |

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Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development/National Institutes of Health 1K23HD083511-01A1 (to V.K.). The authors declare no conflicts of interest.



https://doi.org10.1016/j.jpeds.2017.08.074

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

hearing loss that does not permit the child to understand directions from the examiner and communicate with or without amplification. Because a Bayley III motor composite score of <85 may overestimate NDI, a modified moderate-to-severe NDI also was calculated, where the only difference was a Bayley III motor composite score of <73 instead of <85.[37] Severe NDI was defined as any of the following: severe cerebral palsy with GMFCS score ≥4, Bayley III cognitive and motor score <70, bilateral blindness, or no functional hearing with amplification.[36]

The composite of death and/or moderate-to-severe NDI was the primary outcome of the study. Prespecified secondary outcomes included death, severe IVH, PVL, BPD, severe ROP, NEC, moderate-to-severe NDI, severe NDI, and individual components of the neurodevelopmental assessment. These outcomes were chosen because oxidative stress has been implicated in the pathogenesis of these clinical morbidities in neonates born preterm.[3]

### Statistical Analyses

SAS, version 9.2 (SAS Institute Inc, Cary, North Carolina) was used to perform statistical analyses. Descriptive statistics were calculated to compare LOX and HOX neonates. Categorical variables were analyzed by the Pearson $\chi^2$ or Fisher exact test as applicable. Continuous variables were analyzed by the Student *t* test or Wilcoxon rank sum test. A 2-sided .05 level of significance was used for all analyses. For the outcomes of BPD and NDI, stepwise forward multiple logistic regression was performed to account for confounders. In addition to those prespecified variables known to be associated with the outcomes of interest, all variables with *P* values <.1 were included in the logistic regression. For neurodevelopmental outcomes, GA, antenatal corticosteroids, and antenatal magnesium administration were included in the logistic regression. Confounding variables included for BPD as an outcome were GA, chorioamnionitis, pre-eclampsia, antenatal corticosteroids, sex, intubation in the delivery room, surfactant use, symptomatic PDA, and intrauterine growth restriction.

## Results

During the study period, 255 neonates were born at 23-28 weeks' GA (**Figure**). After we excluded neonates who received only comfort care at the request of their family and those who were enrolled in a delivery room randomized control trial of different oxygen strategies,[8] 199 neonates were included in the study. Of these, 89 were resuscitated with LOX and 110 were resuscitated with HOX. After we accounted for mortality before neurodevelopmental assessment and loss to follow-up, 87% of the study cohort completed the primary outcome assessment.

There were no differences in baseline maternal characteristics between the 2 groups, including maternal age, receipt of antenatal corticosteroids, maternal diabetes, pre-eclampsia, prolonged rupture of membranes, chorioamnionitis, abruption, placenta previa, and cesarean delivery. However, antenatal magnesium was given more often in the LOX group (**Table I**).

There were no differences in sex distribution, obstetric GA, birth weight, intrauterine growth restriction, multiple gestations, arterial cord pH, or base deficit. By definition, infants in the LOX and HOS groups had different initial concentrations of $FiO_2$ during resuscitation (**Table I**). Although neonates in the HOX and LOX groups had a similar $FiO_2$ on admission to NICU, neonates in the HOX group were exposed to greater oxygen load in the delivery room (**Table I**). The number of neonates requiring positive pressure ventilation for >1 minute, intubation, chest compressions, and epinephrine were similar between groups. There were no differences in Apgar scores.

LOX and HOX neonates had similar rates of RDS, surfactant use, pneumothorax, PAH, days on the ventilator, and days on continuous positive airway pressure (**Table II**). However, neonates in the LOX group had lower rates of BPD and fewer days spent on oxygen during their NICU stay. There was no difference in sepsis, severe IVH, NEC, symptomatic PDA, severe ROP, length of hospitalization, or death before discharge. Respiratory failure followed by late-onset sepsis and that was

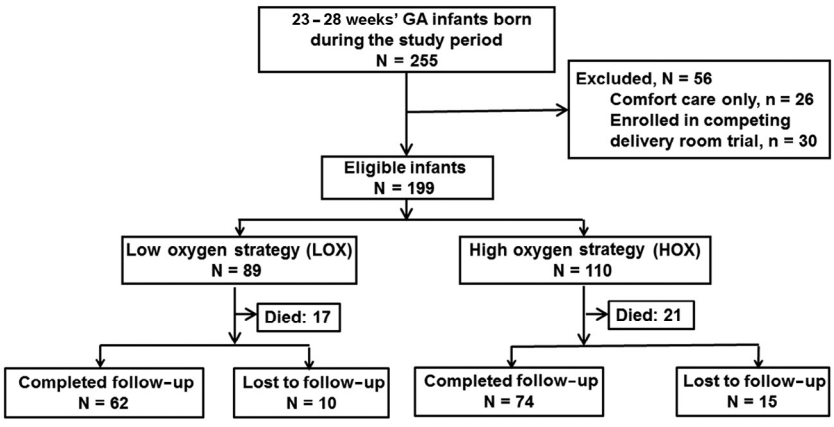


**Figure.** Flow diagram of study population.

**Table I. Maternal/infant characteristics and delivery room interventions**

| Characteristics | HOX n = 110 | LOX n = 89 | *P* value |
|---|---|---|---|
| Maternal | | | |
| Age, y, mean ± SD | 27 ± 6 | 26 ± 5 | NS |
| Antenatal steroids, n (%) | 60 (54) | 45 (51) | NS |
| Maternal diabetes, n (%) | 15 (14) | 14 (16) | NS |
| Pre-eclampsia, n (%) | 28 (25) | 26 (29) | NS |
| Antenatal magnesium, n (%) | 39 (35) | 50 (56) | .04 |
| Prolonged rupture of membranes, n (%) | 22 (20) | 18 (20) | NS |
| Chorioamnionitis, n (%) | 9 (8) | 7 (8) | NS |
| Abruption, n (%) | 5 (4) | 4 (4) | NS |
| Placenta previa, n (%) | 4 (3) | 3 (3) | NS |
| Cesarean delivery, n (%) | 74 (67) | 59 (66) | NS |
| Infant | | | |
| Male sex, n (%) | 58 (53) | 43 (48) | NS |
| Obstetric gestation age, wk, mean ± SD | 26 ± 1 | 26 ± 1 | NS |
| Birth weight, g, mean ± SD | 939 ± 255 | 983 ± 224 | NS |
| Intrauterine growth restriction, n (%) | 4 (4) | 4 (4) | NS |
| Multiple gestations, n (%) | 23 (21) | 22 (25) | NS |
| Arterial cord pH, mean ± SD | 7.23 ± 0.1 | 7.25 ± 0.1 | NS |
| Arterial cord base deficit, mEq/L, mean ± SD | 7 ± 5 | 6 ± 3 | NS |
| Delivery room interventions and Apgar scores | | | |
| Initial $FiO_2$ | 0.21 | 1.0 | |
| Final $FiO_2$, median (IQR) | 0.40 (0.30, 0.50) | 0.40 (0.30, 0.70) | NS |
| Oxygen load ($\sum FiO_2 \times time_{min}$), mean ± SD | 7.8 ± 2.8 | 5.2 ± 1.5 | <.01 |
| Positive pressure ventilation >1 min, n (%) | 85 (77) | 79 (89) | NS |
| Intubation in the delivery room, n (%) | 64 (58) | 62 (70) | NS |
| Chest compressions, n (%) | 1 (1) | 2 (2) | NS |
| Epinephrine, n (%) | 1 (1) | 2 (2) | NS |
| Apgar scores | | | |
| 1 min, median (IQR) | 5 (3, 7) | 5 (2, 6) | NS |
| 5 min, median (IQR) | 7 (6, 8) | 7 (6, 8) | NS |

*NS*, not significant.

followed by NEC and IVH were the major causes of mortality in both groups. There was no statistical difference in cause of death between both groups. Using multiple logistic regression, compared with neonates in the HOX group, we found that neonates in the LOX group had a lower incidence of BPD even after we controlled for GA, chorioamnionitis, pre-eclampsia, antenatal corticosteroids, sex, intubation in delivery room, surfactant administration, rates of symptomatic PDA, and rates of intrauterine growth retardation (aOR 0.4, 95% CI 0.2-0.9, $P = .03$).

Neurodevelopmental assessment was available in 85% of neonates alive at 22-26 months' corrected age (**Table III**). Neonates who were lost to follow-up (n = 25) were more mature than those who had their follow-up assessment done (GA 27 ± 0.5 weeks vs 26 ± 1.5 weeks, $P < .01$). In the neonates who had their follow-up assessment done, there were no differences in rates of cerebral palsy, GMFCS scores ≥2, vision impairment, permanent deafness, or need for hearing aids between neonates in the HOX and LOX groups. In addition, there

**Table II. Neonatal short- and long-term clinical outcomes (unadjusted)**

| Outcomes | HOX n = 110 | LOX n = 89 | *P* value |
|---|---|---|---|
| RDS, n (%) | 98 (89) | 79 (89) | NS |
| Surfactant use, n (%) | 80 (73) | 64 (72) | NS |
| Pneumothorax, n (%) | 13 (12) | 8 (9) | NS |
| PAH, n (%) | 9 (8) | 5 (6) | NS |
| BPD, n (%) | 36 (33) | 14 (16) | .01 |
| Days on ventilator, median (IQR) | 6 (1, 26) | 4 (1, 14) | NS |
| Days on continuous positive airway pressure, mean ± SD | 22 (6, 36) | 24 (12, 33) | NS |
| Days on oxygen, mean ± SD | 46 (11, 82) | 30 (5, 54) | .01 |
| Sepsis, n (%) | 35 (32) | 27 (30) | NS |
| Severe IVH, n (%) | 21 (19) | 10 (11) | NS |
| Necrotizing enterocolitis, n (%) | 7 (6) | 7 (8) | NS |
| Symptomatic PDA, n (%) | 46 (42) | 27 (30) | NS |
| Severe ROP, n (%) | 14 (13) | 4 (4) | NS |
| Length of hospitalization, median (IQR) | 94 (65, 120) | 87 (71, 107) | NS |
| Death before discharge, n (%) | 20 (18) | 17 (20) | NS |
| Death or BPD, n (%) | 50 (45) | 29 (33) | .02 |

were no differences in moderate-to-severe NDI or death. Although the Bayley III composite cognitive and language scores were similar between the LOX and HOX groups, motor composite scores were greater in neonates in the LOX group (**Table III**). This difference persisted even after we controlled for GA, antenatal corticosteroids, and antenatal magnesium

**Table III. Neurodevelopmental outcomes at 22-26 months' corrected age follow-up**

| Outcomes | HOX n = 74 | LOX n = 62 | *P* value |
|---|---|---|---|
| Age at follow-up assessment, mo, median (IQR) | 23 (22, 24) | 24 (22, 25) | NS |
| Cerebral palsy, n (%) | 8 (11) | 5 (8) | NS |
| GMFCS score ≥2, n (%) | 6 (8) | 1 (2) | NS |
| Vision impairment, n (%) | 4 (5) | 0 | NS |
| Permanent deafness, n (%) | 2 (3) | 2 (3) | NS |
| Needs hearing aid, n (%) | 4 (5%) | 0 | NS |
| Bayley III cognitive composite score, median (IQR) | 85 (75, 90) | 85 (80, 95) | NS |
| Bayley III motor composite score, median (IQR) | 88 (76, 94) | 91 (85, 97) | .01 |
| Bayley III language composite score, median (IQR) | 79 (71, 86) | 83 (74, 90) | NS |
| Moderate to severe NDI, n (%) | 41 (55) | 25 (40) | NS |
| Modified NDI,* n (%) | 32 (43) | 21 (34) | NS |
| Severe NDI, n (%) | 13 (18) | 3 (5) | .04 |
| | **HOX n = 110†** | **LOX n = 89†** | |
| Death before follow-up assessment,‡ n (%) | 21 (19) | 17 (19) | NS |
| NDI or death,† n (%) | 62 (54) | 42 (47) | NS |
| Severe NDI or death,† n (%) | 34 (31) | 20 (22) | NS |

*Modified moderate to severe NDI was calculated with Bayley III motor composite score cut off <73 instead of <85 as used in NDI definition.
†For primary outcome, denominator changed to total study population.
‡One infant died in HOX group after discharge from NICU. No death in LOX group after discharge from NICU.

($P < .01$). There was no difference in modified moderate-to-severe NDI where the Bayley III motor composite score cutoff was changed from <85 to <73.[37] Although there was a lower rate of severe NDI in neonates who received LOX with unadjusted analysis, this difference was no longer statistically significant when adjusted for GA.

## Discussion

This study demonstrates that neonates born preterm resuscitated with the NRP-recommended LOX strategy were exposed to lower oxygen load in the delivery room, had fewer days on oxygen in the NICU, and had a lower incidence of BPD, even after we adjusted for confounding variables. Infants resuscitated with LOX also had no increase in mortality and had greater Bayley III motor composite scores at 2-year follow-up.

It is possible that the reduced oxygen load in the delivery room resulted in a lower content of oxygen free radicals as a potential mechanism for the improved neonatal outcomes observed with the LOX strategy.[38,39] In animal models, even a brief exposure to 100% oxygen results in very high partial pressure of oxygen in the brain and other tissues.[40,41] Furthermore, multiple studies in animals and humans have found adverse effects of hyperoxemia during resuscitation resulting in tissue injury and worse outcomes.[2,3,9,12,16,17,19,40-47] In contrast, several studies comparing initial oxygen concentrations and outcomes in neonates born preterm have reported conflicting findings.[7-10,12,13,21,25,26,28,48]

Our current finding of reduced respiratory morbidities in the LOX group is similar to a small, randomized controlled trial conducted at this institution,[8] as well as a trial of low vs high initial oxygen strategy conducted by Vento et al.[12] A recent meta-analysis of the available trials showed no differences in rates of BPD between low and high initial oxygen strategies.[9] However, the meta-analysis compared multiple randomized control trials with varying oxygen titration strategies, and thus with varying exposure to oxygen loads in the delivery room. Given that our study's HOX group started with 100% oxygen and targeted 85%-94% saturation from the first minute of life, it is possible that this group of infants had greater oxygen exposure compared with some of the randomized control trials included in the meta-analysis, resulting in bigger differences between groups. It also is possible that the observed reduction in the incidence of BPD might be due to type I error or a result of unrecognized change in NICU practice during the course of the study. To the best of our knowledge, no major practice change or quality improvement initiative occurred at Parkland NICU during the study period to account for the difference in respiratory morbidity seen between LOX and HOX neonates.

The current study found no change in mortality with adoption of the LOX strategy, similar to the previous trial from this institution.[8] In contrast, in the recent To2rpido trial, neonates born preterm at <29 weeks who were resuscitated with an initial oxygen concentration of 21% had a greater mortality compared with those initially resuscitated with 100% oxygen.[13]

The differences in outcomes between the current study and To2rpido also may be due to differences in the oxygen-titration strategies. In the To2rpido trial, oxygen was adjusted by increasing $FiO_2$ by ≤10% every minute for $SpO_2$ <65% for the first 5 minutes of life and $SpO_2$ <80% after 5 minutes, as well as decreasing $FiO_2$ by 10% for $SpO_2$ ≥95% at any time. In the current study, oxygen for the LOX group was titrated by 10%-20% every 30 seconds to reach the NRP-recommended goal saturations, which were greater than the targets used in the To2rpido trial. In the To2rpido trial, the observation of increased mortality in infants born preterm at <29 weeks was a post-hoc analysis on significantly underpowered subgroups (21% oxygen group n = 46, 100% oxygen group n = 54).

Furthermore, when all enrolled infants were included in the analyses, the 21% oxygen group needed fewer days of respiratory support and did not have a greater mortality than the 100% oxygen group. Although To2rpido is the largest randomized controlled trial to compare 21% vs 100% oxygen as the initial oxygen concentration for resuscitation, the study was limited by early termination (stopped after reaching only 15% of target enrollment) because of inadequate enrollment. This was due to a prevailing bias in medical providers' preference for the low oxygen strategy, resulting in a large number of eligible infants not being enrolled.

A retrospective cohort study from 2004 to 2009 from the Canadian Neonatal Network by Rabi et al demonstrated an increased incidence of death and/or severe IVH/PVL following a change in Canadian policy to titrate oxygen from an initial 21% oxygen compared with the previous initial 100% oxygen used for infants born preterm at <28 weeks' GA.[21] In contrast, our study found no increases in IVH/PVL or mortality following the change to LOX. The difference between these studies could be due to differences in the oxygen titration strategies and their implementation. In addition, a recent meta-analysis of all randomized controlled trials showed no difference in mortality between an initial low oxygen concentration vs an initial high oxygen concentration during resuscitation.[9] It also demonstrated that studies conducted with low initial oxygen concentrations (21%-30%) after publication of NRP guidelines had lower risk of mortality compared with earlier studies. This observation may reflect a learning curve for titration of oxygen. There also was greater mortality in masked studies compared with unmasked studies.

There are limited data on the impact of the delivery room oxygen strategies on neurodevelopmental outcomes. A meta-analysis of 3 available studies found no differences in neurodevelopmental outcomes in infants born late preterm and infants born at term resuscitated with an initial low oxygen strategy.[49] In a randomized trial, Boronat et al compared 30%-60% initial oxygen and found no difference in neurodevelopmental outcomes in neonates born preterm.[28] This study used target $SpO_2$ values that were different from those currently recommended by NRP.[25] Our findings of improved neurodevelopmental outcomes could be due to differences in oxygen load between HOX and LOX groups compared with those achieved by Boronat et al. It is also possible that our findings may reflect a type 1 error.

The strengths of the current study are that we studied a large cohort of neonates born preterm at <29 weeks' GA, used prespecified and uniform definitions of outcomes, and long-term neurodevelopmental outcomes were available with standardized assessments and sufficient rates of follow-up. To our knowledge, this is the first study to report neurodevelopmental outcomes for infants resuscitated with the current NRP-recommended low oxygen strategy. Although this is a single-center, retrospective cohort study, the resuscitation details were collected prospectively for the Parkland Neonatal Resuscitation Registry. Importantly, the study included all neonates born preterm at <29 weeks' GA who are vulnerable to the effects of early hypoxia and hyperoxia, and the sample size of 199 infants allowed examination of the impact of the initial oxygen strategy on neonatal morbidity and mortality.

This study has several limitations. Obstetric circulating nurses manually recorded changes in $SpO_2$ and oxygen concentration during delivery room resuscitation in neonates in the LOX and HOX groups. Because direct download of pulse oximetry data was not available, total time spent outside goal saturations in the delivery room, compliance with the LOX strategy, and its effect on neonatal outcomes were not evaluated. Although regression analysis was conducted to account for all known confounding variables, oxygen strategy–associated improvements in BPD and neurodevelopmental outcomes could have been affected by unknown confounders. Because of the retrospective nature of the study, changes in NICU practice during the course of the study could have influenced neonatal outcomes. However, to the best of our knowledge, no major changes in practice occurred in the Parkland NICU during the study period. Furthermore, as retrospective studies cannot establish causality, caution must be taken when interpreting the results of this study.

In conclusion, the currently recommended NRP LOX strategy was feasible and was associated with improvement in BPD and neurodevelopmental outcomes without increased mortality in neonates born preterm at <29 weeks' GA. Larger, adequately powered randomized control trials focused not only on different initial oxygen concentrations but also on different target saturations and titration strategies, are needed to establish definitively the impact of the initial delivery room oxygen strategies on neonatal outcomes. ■

*We acknowledge Gaston Ofman, MD, Maricel Maxey, NNP, and Vaishali Mashruwala, MD, for assistance in collecting data for the study.*

Submitted for publication Apr 21, 2017; last revision received Jul 28, 2017; accepted Aug 28, 2017

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