Early Cumulative Supplemental Oxygen Predicts Bronchopulmonary Dysplasia in High Risk Extremely Low Gestational Age Newborns

Katherine C. Wai, BS[1], Michael A. Kohn, MD, MPP[2], Roberta A. Ballard, MD[3], William E. Truog, MD[4], Dennis M. Black, PhD[2], Jeanette M. Asselin, MS, RTT-NPS[5], Philip L. Ballard, MD, PhD[3], Elizabeth E. Rogers, MD[3], Roberta L. Keller, MD[3], on behalf of the Trial of Late Surfactant (TOLSURF) Study Group*

Objective To assess the prognostic accuracy of early cumulative supplemental oxygen (CSO) exposure for prediction of bronchopulmonary dysplasia (BPD) or death, and to evaluate the independent association of CSO with BPD or death.

Study design We performed a secondary analysis of the Trial of Late Surfactant, which enrolled 511 infants born at ≤28 weeks gestational age who were mechanically ventilated at 7-14 days of life. Our primary outcome was BPD or death at 36 weeks postmenstrual age, as determined by a physiological oxygen/flow challenge. Average daily supplemental oxygen (fraction of inspired oxygen - 0.21) was calculated. CSO was calculated as the sum of the average daily supplemental oxygen over time periods of interest up to 28 days of age. Area under the receiver operating curve (AUROC) values were generated to evaluate the accuracy of CSO for prediction of BPD or death. The independent relationship between CSO and BPD or death was assessed in multivariate modeling, while adjusting for mean airway pressure.

Results In the study infants, mean gestational age at birth was 25.2 ± 1.2 weeks and mean birth weight was 700 ± 165 g. The AUROC value for CSO at 14 days was significantly better than that at earlier time points for outcome prediction (OR, 0.70; 95% CI, 0.65-0.74); it did not increase with the addition of later data. In multivariate modeling, a CSO increase of 1 at 14 days increased the odds of BPD or death (OR, 1.7; 95% CI, 1.3-2.2; $P < .0001$), which corresponds to a 7% higher daily supplemental oxygen value.

Conclusion In high-risk extremely low gestational age newborns, the predictive accuracy of CSO plateaus at 14 days. CSO is independently associated with BPD or death. This index may identify infants who could benefit from early intervention to prevent BPD. *(J Pediatr 2016;177:97-102).*

Preterm infants are at high risk for bronchopulmonary dysplasia (BPD). There are up to 15 000 new cases of BPD annually nationwide, and more than 70% of extremely low gestational age newborns (ELGANs) who require ventilatory support after 7 days of age are affected.[1] BPD is associated with long-term pulmonary disability, neurodevelopmental abnormalities, and death.[2-5]

The etiology of abnormal pulmonary development is complex and involves inflammation and volutrauma, as well as derangements in lung function, repair of injury, and ongoing growth and development.[6] Oxygen exposure contributes to injury; fetuses develop in a low-oxygen environment, and premature infants have immature antioxidant systems, making them more susceptible to oxidant stress.[7] In addition, biochemical markers of oxidative stress and clinical markers of oxygen exposure correlate with development of lung disease.[7-10]

The risk for respiratory disease often has been quantified by the duration of supplemental oxygen use[11]; however, it is likely that both the duration and concentration of supplemental oxygen contribute to oxygen toxicity and serve as markers for disease severity. To date, only Stevens et al have attempted to quantify total oxygen exposure, including the duration and concentration of supplemental oxygen use.[12] They found that among very low birth weight infants without BPD,

AUROC	Area under the receiver operating curve
BPD	Bronchopulmonary dysplasia
CSO	Cumulative supplemental oxygen
ELGAN	Extremely low gestational age newborn
FiO$_2$	Fraction of inspired oxygen
GA	Gestational age
iNO	Inhaled nitric oxide
MAP	Mean airway pressure
PMA	Postmenstrual age
TOLSURF	Trial of Late Surfactant

cumulative oxygen exposure at 72 hours of life independently predicted symptomatic airway disease at 1 year. These data suggest that differences in oxygen exposure can discriminate among infants early in their neonatal course, which may be beneficial as new therapies emerge.

The aim of the present study was to determine the earliest time point at which cumulative supplemental oxygen (CSO) exposure, which accounts for both the duration and concentration of oxygen exposure, best predicts BPD or death before 36 weeks postmenstrual age (PMA) among high-risk infants. In addition, we evaluated the independent effect of this identified index of early CSO exposure on BPD or death.

Methods

This study was a secondary analysis of infants enrolled in the randomized controlled Trial of Late Surfactant (TOLSURF), conducted under the original Institutional Review Board approval. The study protocol and initial outcomes have been described in detail previously.[13] In brief, 511 infants at ≤28 0/7 weeks gestational age who required endotracheal intubation any time between 7 and 14 days of life, putting them at high risk for BPD or death, were randomized to late surfactant and inhaled nitric oxide (iNO) versus iNO alone.[1,14] The primary outcome for the trial was survival without BPD at 36 weeks PMA, as determined by physiological oxygen/flow reduction challenge. No difference was seen between the treatment and control groups for the primary outcome, so the infants were treated as a single cohort for these analyses.

Neonatal clinical data were collected prospectively into the study database. Birth weight percentile was generated according to the Fenton 2013 growth curves.[15] Respiratory support measurements were recorded 3 times per day at approximately 8:00 a.m., 4:00 p.m., and 12:00 a.m. in accordance with protocol. A daily average of supplemental oxygen (recorded fraction of inspired oxygen (FiO_2) − 0.21) was calculated for each 24-hour time period; this daily average was chosen to generate a overall estimate of an infant's supplemental oxygen exposure on a given day, because more frequent recordings were not collected. The recorded FiO_2 was converted to effective FiO_2 when the infant had a nasal cannula, under the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity trial assumptions.[16] CSO was defined as the sum of the daily average over the time period of interest up to 28 days of age (ie, CSO at 14 days = average supplemental oxygen day 1 + average supplemental oxygen day 2 + . . . + average supplemental oxygen day 14). For example, if the average FiO_2 value was 0.3 on day 1, 0.5 on day 2, and 0.4 on day 3, then CSO at 3 days = (0.3 − 0.21) + (0.5 − 0.21) + (0.4 − 0.21) = 0.57. Cumulative mean airway pressure (MAP) was calculated similarly to CSO, with a daily average for MAP summed over various time periods, using data from both invasive and noninvasive ventilation. For the present study, infants missing a complete day of oxygenation data were excluded (n = 16).

Although the TOLSURF trial was largely conducted following dissemination of the results for oxygen saturation targets from the Surfactant, Positive Pressure, and Oxygenation Ran-

domized Trial,[17] we compared oxygen exposure and ventilation management for infants born before and after December 1, 2010, to evaluate consistency in the relationship of oxygen exposure to respiratory support needs. This date was chosen based on the timing of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial publication and a pause in TOLSURF enrollment for an interim safety analysis.[13]

Primary Outcome and Statistical Analyses

The primary outcome for the current study was BPD or death before 36 weeks PMA. Data were analyzed using the 2 test or t test as appropriate, with Stata 14.0 (StataCorp, College Station, Texas). The area under the receiver operating characteristic curve (AUROC) was used to assess the predictive value of CSO at days of life 1, 3, 7, 10, 14, 21, and 28. These days were chosen because previously published models have identified important predictors for BPD or death in extremely premature infants at these time points.[18,19] Published risk factors for BPD were considered a priori for inclusion into the multivariate model. Those variables selected for potential inclusion had a significant relationship ($P < .05$) with BPD or death on univariate analyses. Using backward selection, covariates were removed at a significance of $P > .10$; gestational age was forced to stay in the model. Generalized estimating equations were used to account for nonindependence between siblings. Predictive performance of unadjusted and adjusted models was assessed using the C-statistic, which corresponds to the AUROC. In unadjusted analyses, the covariate with the largest C-statistic was considered to make the greatest contribution to the predictive accuracy of the model.

Results

Of the 511 infants enrolled in TOLSURF, 16 (3%) were excluded for missing ≥1 days of oxygenation data. Among those 495 infants included, 283 (57%) had BPD and 53 (11%) died. The infants were predominantly male, with a mean gestational age and birth weight similar to the infants enrolled in the trial (25.2 ± 1.2 weeks and 700 ± 165 g, respectively) (Table I).[13] Although 143 infants were products of multiple gestation, only 105 (21%) had a sibling enrolled in TOLSURF.

To evaluate the value of CSO in prediction of BPD or death, we assessed the AUROC value at various time points up to 28 days of life. The AUROC increased from day of life 1 to day 14, and then plateaued at ~0.70 through 28 days (Table II). We compared the AUROC value for CSO at each individual time point to the CSO at 14 days, and found that the CSO at 14 days was significantly better than that at earlier time points and did not improve with additional days of data (Table II).

After identifying CSO at 14 days as the earliest and most accurate predictor for oxygen exposure in the first 28 days, we evaluated other respiratory support measurements at 14 days for their association with the outcome of BPD or death. The average CSO at 14 days was higher in the BPD or death group compared with the survivors without BPD (2.4 ± 1.4 vs 1.5 ± 0.98; $P < .0001$), which corresponded to a daily average of 17% supplemental oxygen over 14 days in the BPD or death