Oxygen-Saturation Targets in Preterm Infants

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In the 1940s, Wilson et al. observed that periodic breathing in premature infants was nearly eliminated with the use of 70% oxygen.[1] Although Wilson cautioned against unrestricted use of oxygen, other investigators and the American Academy of Pediatrics advocated its liberal use, which led to an epidemic of retinopathy of prematurity. Subsequently, in a randomized clinical trial, investigators found that high oxygen concentrations were associated with an increased risk of severe retinopathy of prematurity.[2] However, it soon was evident that restricted use of oxygen (60 to 70% saturation vs. oxygen as clinically required) was associated with an increased risk of cerebral palsy and early neonatal death (16 deaths for each case of blindness prevented).

In the ensuing decades, observational studies showed that the incidence of both retinopathy of prematurity and bronchopulmonary dysplasia could be reduced by restricting oxygen exposure in premature infants. On the basis of such studies, a target saturation range of 85 to 95% was postulated as desirable, but supporting data were lacking.[3]

In four recently completed randomized clinical trials, investigators used similar protocols to compare the outcomes of infants receiving supplemental oxygen delivered at target oxygen saturations of 85 to 89% (lower-target group) versus 91 to 95% (higher-target group). The results of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)[4] were published in 2010, whereas the findings of the Benefits of Oxygen Saturation Targeting (BOOST) II trials in the United Kingdom, Australia, and New Zealand[5] appear now in the *Journal*.

In these studies, in order to hide the intervention, pulse oximeters were programmed to read either 3% higher or 3% lower than their actual values, and caretakers were instructed to maintain oxygen saturations in the displayed range of 88 to 92%. Both studies showed that a lower target for oxygen saturation was associated with a decreased incidence of severe retinopathy of prematurity but a higher risk of death.

Both the SUPPORT and BOOST II trials were designed to clarify persistent uncertainty about the risks of retinopathy of prematurity within the low and high portions of the accepted saturation range. In all the studies, given the high expected rate of death among premature infants, death was included as an outcome because it competed with retinopathy of prematurity as a risk, not because a difference in mortality was expected as a result of differences in oxygenation. The Office for Human Research Protections of the Department of Health and Human Services recently criticized the wording in the consent form for the SUPPORT trial. However, at the time these studies were initiated, there was no evidence of excess mortality or foreseeable additional risk related to caring for infants at the lower-target range.

In the BOOST II trial, more than 2400 infants were enrolled at 54 hospitals in three countries. During the course of this trial, the calibration algorithm for the pulse oximeters was changed at sites in the United Kingdom and Australia, and the corrected calibration algorithm provided clearer separation in oxygen-saturation distributions between the two randomization groups. The mortality difference that was detected in the lower-target group, as compared with the higher-target group, was 7.2 percentage points in the BOOST II trials and 3.7 percentage points in SUPPORT. However, in the BOOST II trials, a significant between-group difference was found only among infants for whom the intended target saturation ranges were attained after revision of the oximeter algorithm. The increased mortality in the lower-target group was sufficiently large that the data and safety monitoring committee halted enrollment in the United Kingdom and Australian trials. (At that point, the New Zealand trial had finished recruiting.)

How should clinicians respond to these results? Although pulse oximetry has become the standard for assessing oxygenation in critically ill infants, technical limitations can produce low readings falsely indicative of hypoxemia. Pulse oximetry is less reliable than measurement of arterial blood gases for detecting hyperoxemia. Furthermore, at any given oxygen-saturation value, there is a range of potential values for the

partial pressure of oxygen, depending on the amount of fetal versus adult hemoglobin that is present, along with other physiological variables. Understanding the saturation ranges that are associated with morbidity or mortality is not synonymous with pinpointing safe and unsafe saturation levels, because the ideal saturation range may differ among infants at various gestational ages.[6] Finally, it is difficult to maintain an infant requiring oxygen within a given saturation range. In a study of whether the oxygen-saturation level had an effect on intermittent hypoxemia in premature infants, Di Fiore et al.[7] found that the mean number of intermittent hypoxemic events could exceed 100 per day, and the frequency of such events was more common among infants who were randomly assigned to a lower oxygen-saturation range. Frequent manual adjustments in the amount of inspired oxygen have had limited success and may induce oxidative stress if the hypoxemic event is followed by hyperoxia.

Although the results of the BOOST II trials are concordant with the main findings in SUPPORT, long-term outcomes for the three BOOST II trials and a Canadian trial are still awaited. There was no significant difference in the composite outcome of death or neurodevelopmental impairment at 18 to 22 months of age for infants enrolled in SUPPORT.[8] Since all five trials used a similar study design, a prospective meta-analysis is planned when follow-up of study infants has occurred in the last trial, the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration.[9] Given the increased mortality observed at lower oxygen-saturation ranges in BOOST II and similar trials, it now appears prudent to aim to maintain an oxygen-saturation level in the 90 to 95% range. Yet, such an approach may result in an increased incidence of retinopathy of prematurity. Furthermore, maintaining an infant in a given saturation range can be difficult and does not guarantee an optimal outcome.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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