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Oxygen Targeting in Infants Born Extremely Preterm Who Are Small for Gestational Age: A Need for Heightened Vigilance

Administration of supplemental oxygen is one of the most common therapies in neonatal medicine because many infants who are sick and infants who are born preterm have impaired lung function. To avoid both hypoxemia and hyperoxemia, pulse oximeters have been used for many years to monitor infants born extremely preterm during their stay in the neonatal intensive care unit; however, the optimal oxygen saturation target range remains uncertain. The late William A. Silverman referred to supplemental oxygen as the "albatross of neonatal medicine" and lamented the fact that neonatal clinicians remained ignorant for far too long about how to use oxygen effectively and safely.[1] At the time of this commentary, 5 randomized clinical trials of oxygen saturation targeting among infants born extremely preterm were in the planning stage and have since been completed.[2]

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Collectively, these 5 trials randomly assigned almost 5000 infants born extremely preterm to higher or lower saturation target ranges. Despite this large sample size, no statistically significant difference was found in pooled analyses for the primary outcome of death or disability at 18-24 months.[3] Among the secondary outcomes, targeting the higher range of 91%-95% reduced the risks of death and severe necrotizing enterocolitis but increased the risk of treated retinopathy of prematurity (ROP).[3] Many clinicians remain uncertain how to translate this evidence into practice. A recent report from Europe showed that 40 different oxygen saturation ranges were targeted in 193 neonatal intensive care units that were surveyed at the beginning of 2016.[4] What may explain this astonishing variability of practice?

One answer may be that the intervention in the 5 trials was a "black box" because the process of saturation targeting in the individually managed trials was not described in sufficient detail to enable clinicians to replicate the intervention with precision. Although all trials compared the same 2 target ranges on identically masked study oximeters, insufficiently answered questions include the following: (1) What were the alarm settings and what was the compliance with those settings? (2) How did the caregivers respond to alarms? and (3) What was the actual duration of study oximetry?

In this volume of *The Journal*, investigators from 1 of the 5 trials, the Surfactant, Positive Pressure and Oxygen Trial (SUPPORT),[5] report associations between achieved saturations during the first 3 days of life and 90-day survival for infants born small for gestational age (SGA) and appropriate for gestational age (AGA).[6] This group previously had published another post hoc analysis of the SUPPORT trial data suggesting that infants born SGA randomized to the lower oxygen target had significantly poorer survival than those randomized to the higher oxygen target whereas infants born AGA had similar mortality rates in the 2 target groups.[7] In the present study, the authors observed that infants born SGA in the lower target group achieved significantly lower median saturations than lower target infants born AGA. Moreover, lower target infants born SGA experienced significantly more frequent episodes of intermittent hypoxemia (defined as saturations <80%) lasting between 1 and 5 minutes than lower target infants born AGA.

The authors present this important observation simply as a prelude to their analysis of the relationship between achieved saturations, intermittent hypoxemia, and the risk of mortality. We suggest, however, that this observation is remarkable in its own right because it demonstrates that the trial intervention, namely tight control of displayed saturations, was not administered equally successfully to all study participants. Whether some of the intermittent hypoxemia in lower target infants born SGA could have been avoided with greater attention to oxygen management at the bedside remains an unanswered question. The important observation by Di Fiore et al[6] illustrates the difficulties we all face when we are trying to implement an intervention that depends heavily on poorly defined interactions between the display on the study oximeters and the bedside staff who were caring for the study participants.

AGA	Appropriate for gestational age
ROP	Retinopathy of prematurity
SGA	Small for gestational age
SUPPORT	Surfactant, Positive Pressure and Oxygen Trial

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Di Fiore et al[6] report that lower achieved oxygen saturations in the first 3 days of life were associated with lower survival at 90 days. This conclusion is likely a correct one, although the evidence provided is relatively weak and limited to infants born SGA with frequent short episodes of intermittent hypoxemia. The other 3 subgroup comparisons in Table 3 of their article do not have significant interaction *P* values and thus do not provide valid evidence of differences in the strength of the associations between patterns of oxygenation and mortality. In addition, it would have been interesting to know whether the prognostic effect of intermittent hypoxemia differed by random treatment assignment to higher vs lower target ranges as it did in the analysis of saturation data recorded in the Canadian Oxygen Trial.[8] In the Canadian Oxygen Trial, exposure to intermittent hypoxemia in infants who had been assigned randomly to a saturation target range of 91%-95% was associated with greater rates of adverse outcomes at 18 months than comparable exposure to intermittent hypoxemia in infants who had been assigned to a target range of 85%-89%.[8]

What are the implications of these ancillary SUPPORT analyses for our clinical practice? The authors ponder the question whether infants born SGA should be targeted >92% during the first few days of life, while acknowledging that "the potential benefit of a higher median oxygen saturation on survival must be balanced with the increased risk of morbidities associated with hyperoxia exposure such as ROP."[6] Add to this the caveat that infants born SGA are known to be at greater risk of severe ROP than infants born AGA,[9,10] and further, that severe ROP is a risk factor for visual as well as nonvisual childhood disabilities.[11]

Therefore, unless the pending subgroup analyses of the individual participant data meta-analysis confirm that infants born SGA who were assigned to the lower oxygen saturation target range have a greater mortality risk than infants born AGA, we recommend adherence to the recent Guidance for the Clinician from the American Academy of Pediatrics for both infants born SGA and AGA.[12] The authors of this statement concluded that "a targeted oxygen saturation range of 90%-95% may be safer than 85%-89%, at least for some infants." Importantly, target ranges should not be equated with oximeter alarm settings. The American Academy of Pediatrics Guidance suggests an "upper alarm limit of approximately 95% while the infant remains on supplemental oxygen" and a lower alarm limit "somewhat below the lower target, as it must take into account practical and clinical considerations, as well as the steepness of the oxygen saturation curve at lower saturations."[12] After the present analyses by Di Fiore et al,[6] we may want to add to this guidance that infants born SGA deserve heightened vigilance and careful titration of supplemental oxygen to avoid episodes of intermittent hypoxemia as much as possible. ■

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