The Use of Oxygen at Discharge: Is It Safe? Is It Effective?

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Oxygen is 1 of the most commonly used therapies in premature infants. Like all drugs, it can be both therapeutic and toxic.[1] In his 2004 commentary, "A Cautionary Tale About Supplemental Oxygen: The Albatross of Neonatal Medicine,"[2] Dr Silverman provided us with an important history lesson: what we believe to be true is not always true, and with great intent, we can do great harm. Over the last decade, clinical studies of oxygen dosing[3,4] and oxygen saturation targets[5] have only increased the intensity of Dr Silverman's message. Although recommendations regarding oxygen use in the delivery room and in the NICU have changed on the basis of clinical trials and careful analysis of the evidence,[3–7] the evidence regarding oxygen use after discharge is far less clear, and variation in practice is endemic.[8,9]

In their article "Home Oxygen and 2-Year Outcomes of Preterm Infants With Bronchopulmonary Dysplasia [BPD]," DeMauro et al[10] have added to our understanding of the efficacy and safety of this practice. Many clinicians believe that home oxygen therapy improves growth, reduces pulmonary complications, and promotes better neurodevelopmental outcomes, although none of these beliefs are supported by high-quality evidence. In this propensity score–matched cohort study, DeMauro et al[10] conclude that "postdischarge oxygen was associated with marginally improved growth and increased resource use but no difference in neurodevelopmental outcomes."

Growth is an important measure of infant well-being, particularly for prematurely born infants with BPD. The authors report a modest improvement in growth in the infants sent home on oxygen. However, in light of possible risks, we must ask if this modest growth benefit is clinically meaningful. Because there was no difference in the length *z* scores at 18 to 26 months ($P = .98$), the main driver for the reported growth difference is the differences in weight *z* score (0.11; $P = .05$). We can use this difference to estimate the potential improvement associated with home oxygen (*z* score difference $\times$ the reference SD at any given age). By using the World Health Organization growth standards at 24 months,[11] the reported weight *z* score difference of 0.11 translates to a 0.17-kg increase in boys and a 0.16-kg increase in girls. Although statistically significant, this small difference may be within error of the measurement. Importantly, this weight-gain difference was not accompanied by improvement in neurodevelopmental measures.

The findings by DeMauro et al[10] also raise concerns about the risks of supplemental oxygen after discharge in premature infants. At 18 to 26 months' corrected age, these children had significantly higher medical resource use. They received more medications for asthma or BPD, were more likely to be rehospitalized for a respiratory illness, and had more total hospitalizations. They were also more likely to have undergone tracheostomy after discharge. Although it may be tempting to attribute this to some

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unidentified or unmeasured confounding variables (altitude[12] and other site-specific health care practices[13]), previous clinical studies have revealed similar adverse effects of oxygen supplementation in the NICU.[14,15] The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity[14] trial revealed that using supplemental oxygen to achieve a higher oxygen saturation was associated with an increase in pneumonia and/or exacerbations of chronic lung disease. Askie et al[15] showed that infants in their higher oxygen saturation group had a significantly higher rate of dependence on supplemental oxygen at 36 weeks' postmenstrual age and a significantly higher frequency of home-based oxygen therapy. Both studies reveal that higher oxygen doses and prolonged exposure may cause harm.

Although DeMauro et al[10] correctly state that causality cannot be established with the study design, they have provided a critical service. Their results can be used to improve the design and safety of a more definitive prospective trial. For instance, the propensity-matched infants in this study could help identify a target trial population. As DeMauro et al[10] point out, there are some infants with more severe BPD for whom random assignment (to oxygen or not) may not be feasible or ethical. In addition, the reported differences in outcome measures between the 2 study groups can be used to calculate the sample size needed to assess a specific outcome in a prospective clinical trial. Assessing for the risk of being rehospitalized for a respiratory illness with an absolute risk difference of 10% would require 688 total patients, whereas detecting a 0.11 difference in weight *z* score at 24 months would require a much larger sample size of 3434 total infants (α = .05; β = .20).

Ultimately, the most compelling scenario for initiating a clinical trial is when equipoise exists on the basis of the possible risks and benefits from a given therapy in the absence of clear evidence in support of a specific approach. DeMauro et al[10] are to be congratulated for providing us the evidence and equipoise we need to design a meaningful clinical study. Once again, we are challenged to reevaluate our clinical beliefs and biases about the use of oxygen.[16] Now we must collaborate to design and implement a trial to help us determine which infants should receive oxygen after discharge. We look forward to seeing those results.

ABBREVIATION

BPD: bronchopulmonary dysplasia

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