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EDITORIAL

The twofold NICU challenge: avoiding hypoxia and hyperoxia

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From the earliest days of Neonatology as we know it today, the risks and benefits of oxygen therapy were at center stage. It is remarkable that so many decades later this issue remains at the fore, focused primarily on the population of extremely preterm infants. Areas of active investigation include optimizing oxygenation in the delivery room, during the first days of life when the stage is set for potentially initiating lung injury, and during subsequent weeks when intermittent desaturation events may need intervention. Meanwhile, there is increasing evidence that adverse respiratory and neurodevelopmental outcomes are inextricably interwoven.[1] It would appear highly likely that oxygenation is part of that linkage.

Our colleagues from Helsinki have provided interesting new information that links oxygenation patterns in the first 3 days of life with brain imaging and neurodevelopmental outcome data.[2] Their first observation, which might be anticipated, is that early lower oxygen saturation (SaO_2) and lower arterial oxygen tension (paO_2) levels were associated with more white matter injury on magnetic resonance imaging at term and more neurodevelopmental problems at 2 years. Interestingly, the separation in initial mean SaO_2 values between infants who did and did not exhibit white matter injury at term was very modest (92.8 vs 93.8%). While these values coincide with currently widely employed SaO_2 targets, they represent relatively low paO_2 values (low-to-mid 50 mmHg range). There is a greater difference in percentage of time infants were exposed to inspired O_2 fraction (FiO_2) >21% (approximately 70 vs 45% of time in the presence vs absence of white matter injury, respectively). This may be mechanistically relevant as we discuss later.

The other observation which may not have been anticipated was that a slightly higher SaO_2 and lower FiO_2 were associated with abnormal brain imaging at term via magnetoencephalography. This technique employs sensory stimulation during imaging in order to map brain activity by recording magnetic fields produced by naturally occurring electric currents in the brain. It has been proposed to reflect cortical somatosensory processing. Given the relatively small sample size in this observational cohort, these data might be considered hypothesis generating. However, it is tempting to speculate that the findings from this imaging technique could contribute to our understanding of a possible role for oxidant stress in the later, more subtle, developmental coordination disorders to which former preterm infants are predisposed.[3]

In the human fetus at around 24 weeks of gestation, glial maturation and synaptogenesis are far from complete, making neuronal development potentially vulnerable from hyperoxia as well as hypoxia. Rodent studies have shown that hyperoxia leads to neurodegeneration triggered by oxidative stress and inflammation. Poor ability to handle oxidative stress leads to cell death of pre-oligodendrocytes, giving a body blow to myelination. Combined with neuronal loss, the damage could be lifelong. Not surprisingly, the end result of aberrant oxygenation could be behavioral and cognitive impairment in addition to motor disability. As neonatologists, we need to pay close attention to the perils of hyperoxia-induced brain damage along with that caused by hypoxia. We also need to remember that both the brain and lung are exposed in utero to much lower levels of oxygen tension.

The percentage of time with early desaturation/bradycardia events was twofold higher in infants who subsequently exhibited white matter injury. These events only increase with advancing postnatal age and their higher incidence at a lower baseline SaO_2 has been clearly documented.[4] Poets and colleagues, from the Canadian Oxygen Trial, have demonstrated an association between intermittent hypoxic episodes and late death or neurodevelopmental disability at 18 months.[5] The ongoing National Institutes of Health-sponsored multicenter Pre-Vent Study should further inform as to the association between such episodes and adverse outcomes.[6]

Rantakari and colleagues provide ample evidence in their manuscript for a link between adverse respiratory and neurodevelopmental outcomes, and their data suggest that early oxygenation may provide an important link. What is the mechanism for such a causal relationship? Neonatal rodent models have demonstrated that an experimental proinflammatory intrapulmonary stimulus may generate a proinflammatory cytokine message response in the brainstem mediated via neural afferents originating in the lung.[7] Therefore, one cannot exclude the possibility that the higher FiO_2 to which the lungs of the white matter-injured infants (with lower SaO_2 levels) were exposed triggered an adverse lung-to-brain signal. Multiple neural and supportive elements may be injured by suboptimal oxygenation. For example, neonatal rodents exposed to hypoxia exhibit abrupt changes in brainstem extracellular matrix formation.[8]

Recently published data in extremely preterm infants have demonstrated an association between duration of ventilatory support, imaging evidence of smaller brainstem volumes, and white matter abnormalities, as well as adverse preschool motor outcomes.[9,10] Thus, ventilatory support, even in the first 3 days, may have been a contributor to the findings of Rantakari in their current study, especially given that the infants with brain injury had more respiratory distress syndrome and bronchopulmonary dysplasia and presumably more ventilatory support. Nonetheless, the authors have reinforced the key role that oxygenation plays in the lung-to-brain dynamic. They may well be the first investigators to simultaneously provide both static and dynamic neonatal brain imaging in extremely preterm infants at term, an important step in the quest to optimize longer-term outcomes of high-risk neonates. Protecting the immature brain from both deficiency and excess of oxygen is the need of the hour!

AUTHOR CONTRIBUTIONS

Each author has met the *Pediatric Research* authorship requirements.

ADDITIONAL INFORMATION

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