

Oxygen Redux

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The groundbreaking work of Dr Ola Saugstad and colleagues^{1,2} led to a reappraisal and more judicious use of oxygen in term infants. Of course, this led to questioning the appropriate fraction of inspired oxygen (F_{IO_2}) to use in the initial resuscitation of preterm infants. Preterm infants are particularly vulnerable to free radical-associated conditions and oxidative stress; the use of high oxygen load during resuscitation has been associated with increased oxidative stress, chronic lung disease, and prolonged need for oxygen and respiratory support.³ The 2015 International Liaison Committee on Resuscitation (ILCOR) Neonatal Resuscitation Guidelines recommend that for preterm infants <35 weeks' gestation, resuscitation begins at a lower oxygen concentration (0.21–0.30) and not be higher than an initial oxygen concentration of 0.65.⁴

Trials data comparing resuscitation with lower or higher oxygen have yielded mixed results and do not fully support the ILCOR recommendation. The largest randomized controlled trial undertaken to date, the To2rpidio Trial comparing room air versus 100% oxygen, was terminated because of failure to enroll adequate subjects, in part because investigators no longer felt comfortable randomizing infants to 100% oxygen.⁵ Surprisingly, a post hoc subgroup analysis of infants <29 weeks' gestation found a significantly higher mortality in the group resuscitated with room air. Oei and colleagues⁶ incorporated these recent data in a meta-analysis of 8 randomized trials in which preterm infants ($n = 504$) were resuscitated with either low (defined as <0.3) or high (defined as

≥ 0.6) F_{IO_2} . In this updated analysis, there was no difference in the risk of bronchopulmonary dysplasia, intraventricular hemorrhage, or retinopathy of prematurity. Importantly, there was no increase in risk regarding overall mortality (typical relative risk, 0.99; 95% confidence interval, 0.52–1.91).

Few studies have reported neurodevelopmental follow-up of infants enrolled in previous randomized trials. In this issue of *Pediatrics*, Boronat and colleagues^{7–9} report the follow-up from 2 previous trials of lower versus higher F_{IO_2} . A total of 253 infants were recruited and 206 (81.4%) completed follow-up. No differences were seen in mortality and perhaps more importantly, no differences were demonstrated in neurodevelopmental outcomes at 24 months. The investigators are to be applauded for doing comprehensive follow-up of infants enrolled in their trials. However, the results leave us with as many questions as answers.

Although the ILCOR guidelines are described as being informed by “moderate” evidence, the fact is that there is currently no evidence to support the use of a lower versus a higher initial F_{IO_2} in the resuscitation of preterm infants. As noted previously, the largest and most recent trial reported better outcomes in the most premature infants receiving 100% oxygen.⁵ This study was not included in the ILCOR evidence review, because it appeared just after the committee met and made its recommendations. Evidence from observational studies cast additional concern regarding the use of lower F_{IO_2} . In a retrospective cohort study of the Canadian Neonatal

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Network, infants ≤ 27 weeks' gestation born after implementation of policies curtailing the use of 100% oxygen for initial resuscitation had an increase in severe neurologic injury or death.¹⁰

A strict interpretation of the current report of Boronat and colleagues⁷ does not, as the authors note, support the use of either lower or higher F_{IO_2} during stabilization of extremely preterm infants in the delivery room. The imprecision reflected in the broad confidence intervals tells us that we could be doing great harm or great good based on the choice of the initial oxygen as we initiate resuscitation.

At present, there are a number of questions that need to be addressed in addition to the choice of initial F_{IO_2} . The suggested pulse oxygen saturation targets are taken from preterm infants who did not need resuscitation,¹¹ and no published study to date has evaluated the infants' outcomes based on their ability to reach or exceed such targets compared with those who did not. There have been no studies evaluating other potential targets. None of the neonatal studies in this area have had >300 infants enrolled, and many of the studies have taken years to recruit even these limited samples of infants.

What are the barriers to completing such research successfully in a timely fashion? Trials that have required antenatal consent, as is required for delivery room interventions, have been found to enroll slowly and yield nonrepresentative groups for analysis.¹² Yet, waiver of consent cannot be obtained on ethical grounds because these trials comparing initial oxygen concentrations, which are different than the current standard concentrations, are judged to represent more than "minimal risk" in that they may well affect important outcomes, such as mortality or neurodevelopment.

The reality is that we need to test the boundaries of current practice in ways that are expedient and ethically appropriate. Although

novel trial designs, such as cluster randomized trials, might hold the possibility of studying large numbers of infants in an expedient fashion, such trials still represent difficult ethical issues of waiver and later "opt out" withdrawal. Newer approaches will need to be taken for responsible ethical research in this fragile population, and we believe that parents of previous preterm infants should play a significant role in helping to determine what level of risk is ethically acceptable to allow the determination for the best evidence-based practice. Indeed, it is possible at present that infants managed by using current recommendations may be at a higher risk than infants managed with higher initial oxygen concentrations.

ABBREVIATIONS

F_{IO_2} : fraction of inspired oxygen
ILCOR: International Liaison Committee on Resuscitation

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