Optimizing oxygenation of the preterm infant directly at birth: focus of future studies

To the Editor:

The optimal oxygen concentration during stabilization of extremely preterm infants at birth was recently discussed by Saugstad et al.[1] The authors comment on the findings of our randomized clinical trial, which compared commencing stabilization of extremely preterm infants with 100% vs 30% O_2.[2] With careful titration, commencing with 100% O_2 increased respiratory effort and did not increase the risk of hyperoxia.[2] Saugstad et al question the implication of these findings and recommend against initiating stabilization with 100% O_2. However, this recommendation is partly opinion-based and appears to overlook that the lung's oxygen exchange capacity gradually increases as the lung aerates.[3] Therefore, a higher oxygen pressure gradient is initially needed when the gas exchange regions are mostly liquid-filled. In a study cited by Saugstad et al, very preterm infants were resuscitated with either 90% or 30% oxygen, which produced identical changes in oxygen saturation levels.[4] This must have resulted from a large discrepancy in ventilation, lung aeration, or cardiac function between the 2 groups because the partial pressure of oxygen at the gas exchange surface will be ~670 mm Hg with 90% and ~210 mm Hg with 30% oxygen. Such a discrepancy has been observed previously because of a big difference (~20 cm H_2O) in the applied airway pressure support.[5] Saugstad et al also suggest that larger trials are warranted to demonstrate the effect of initial fraction of inspired oxygen (FiO_2) on neurodevelopmental outcomes. Although we do not disagree with this sentiment, this outcome is remote from the intervention and subject to a myriad of complicating factors that undermine the outcome. Thus, large trials with large sample sizes are needed that are both time- and cost-consuming. Perhaps we should acknowledge that an initial high FiO_2 improves respiratory effort and focus future studies on how to titrate FiO_2 optimally instead.

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Reply

To the Editor:

We agree with Dekker et al that their small, randomized trial did not show an increase in the risk of hyperoxia with the use of 100% oxygen.[1] We acknowledge that in this trial, respiratory effort was improved in the 100% oxygen group (as shown in the graphic abstract). We also agree that the gradient between PiO_2 (partial pressure of inspired oxygen), PaO_2 (partial pressure of alveolar oxygen), and PaO_2 (partial pressure of arterial oxygen) is high soon after birth and improves with time and emphasized this in Figure 3 of the commentary. In addition, we want to point out that there is a potential for significant discrepancy in the relationship between PaO_2 and preductal oxygen saturation (SpO_2) in neonates.[2]

The letter questions the discrepancy between SpO_2 achieved during the first few minutes in a previous study by Vento et al comparing 30% and 90% inspired oxygen[3] and the Dekker et al study comparing 30% and 100% oxygen.[1] The infants in the 90% arm of the Vento et al study were of lower gestational age (26.3 ± 1.3 vs 27.3 ± 1.9 weeks) and birth weight (902 ± 195 vs 1000 ± 291 g) and higher need for intubation (61% vs 0%) compared with the 100% arm of the Dekker et al study. By protocol, all infants <27 weeks of gestation in the Vento et al study requiring positive pressure ventilation were intubated. Identical pressures (5-8 cm H_2O) were used in the high

oxygen and low oxygen arms of the Vento et al study. The exact pressures used by Dekker et al were not mentioned but more efficient use of the mask ventilation with better seal might explain higher SpO_2 achieved in this study. Although an increase in alveolar PaO_2 is expected with 90% oxygen, presence of right-to-left shunts might attenuate the rate of increase in SpO_2. Finally, cord management differed between the 2 studies. These differences in study design and possible differences in efficacy of mask ventilation might have contributed to the differences in SpO_2 observed between the 2 studies. Similar to Kapadia et al,[4] Vento et al observed a reduction in bronchopulmonary dysplasia with the low oxygen strategy.

Dekker et al ask: should we recommend a change in guidelines to start with higher fraction of inspired oxygen ($FiO_2 \sim 1.0$) in extremely preterm infants based on a physiological sound but small, randomized trial of 44 infants and what is the optimal primary outcome of neonatal clinical trials evaluating resuscitation at birth?

Two systematic reviews conducted by the International Liaison Committee on Resuscitation Neonatal Task Force and Cochrane database prior to publication of the Dekker et al study concluded that the ideal FiO_2 for preterm newborns is still not known and no advantage of high vs low initial FiO_2 was demonstrated.[5,6] More studies evaluating this topic are needed to reach an evidence-based consensus. Recommending 1.0 FiO_2 for initial resuscitation for a short period during mask ventilation may be physiologically appropriate, but needs to be substantiated by a higher number of enrolled subjects and preferably by a systematic review.

There is considerable debate regarding the optimal primary outcome and endpoint for neonatal clinical trials in general and trials evaluating short-term measures in the delivery room. The use of death or neurodevelopmental impairment (NDI) at approximately 2 years has been considered the gold standard in many recent neonatal trials. We agree with Dekker et al that a large sample size will be needed for a short intervention during resuscitation to have an impact on death/NDI at 2 years. However, should we be implementing interventions that result in short-term transient improvements but do not influence mortality, morbidity (such as intraventricular hemorrhage or bronchopulmonary dysplasia) or long-term NDI? The Food and Drug Administration guidelines recommend clinical endpoints should be a direct measure of improved survival, a benefit that was detectable by the patient (improvement in symptoms or functional capacity) or decreased chances of developing a condition or disease complication that is itself apparent to the patient and is undesirable (https://www.fda.gov/media/84987/download).

The neonatal community needs more studies such as Dekker et al[1] so that appropriate systematic reviews can be conducted to enable International Liaison Committee on Resuscitation Neonatal Task Force to provide evidence-based recommendations for optimal initial oxygenation of extremely preterm infants that improve clinically relevant endpoints.

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Clarification of aOR calculation

To the Editor:

Foglia et al reported that changes in oxygen saturation (SpO_2) policies had no impact on the incidence of retinopathy of prematurity (ROP).[1] Their assertion is based on the finding of significant reduction of any ROP incidence during epoch 2 among the hospitals that did not change their SpO_2 policies as well as among those that did change their SpO_2 policies with aORs of 0.57 and 0.71, respectively, resulting in a nonsignificant interaction term for this outcome.

Table II of this report reveals that the magnitude of difference between aOR (0.57) and the unadjusted OR (0.97) is approximately 40% for any ROP among hospitals that did not change their SpO_2 policy. This degree of difference between adjusted and unadjusted ORs is not seen for any other