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Review

Oxygenation of Newborns

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Abstract: The last 20–30 years, the oxygen exposure of newborn infants has been substantially reduced. This is mainly due to a dramatic reduction in the use of oxygen in the delivery room in newborn infants in need of positive pressure ventilation (PPV) and the better control of oxygen saturation with clearly defined targets in immature infants in need of supplemental oxygen during treatment in neonatal intensive care units. Term and near-term infants in need of IPPV in the delivery room should start with a FiO_2 of 0.21. Between 28 and 31 weeks of gestation, an initial FiO_2 of 0.21–0.30 is generally recommended. For immature infants, a higher FiO_2 than 0.3 may be needed, although the optimal initial level is not defined. For all groups, it is recommended to adjust the FiO_2 according to oxygen saturation (SpO_2) and heart rate response. For immature infants, the combination of prolonged bradycardia and an SpO_2 not reaching 80% within 5 min of life is associated with a substantially increased risk of death. For immature infants beyond the delivery room, an SpO_2 target between 91 and 95% is recommended.

Keywords: delivery room; immature newborn; newborn infants; oxygen; resuscitation

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1. Introduction

Oxygen is one of the most critical components of life. Nature has taken billions of years to develop optimal atmospheric oxygen concentrations for human life, evolving from anaerobic conditions before reaching today's level of 20.95%. Life therefore evolved within an oxygen-poor atmosphere, and oxygen was primarily produced by photosynthesis as a waste product by prokaryotic, and later, eukaryotic organisms 3.5 billion years ago and by oceanic cyanobacteria a billion years after this. Photosynthesis by cyanobacteria soon led to the accumulation of atmospheric oxygen, which oxidized methane, a strong greenhouse gas, to carbon dioxide and water, which then reduced the greenhouse effect with subsequent planetary cooling. Approximately 2.3 billion years ago, a rapid increase in low atmospheric oxygen occurred, resulting in oxygen levels that at some stage were probably as high as 30%. During this period, life was able to develop antioxidant defenses as protection against hyperoxia and oxidative stress [1,2]. In fetal life, oxygen tension is low, and it seems that redox processes are of importance in regulating embryogenesis and fetal development [3].

Oxygen was described by Scheele as an element in approximately 1772. Although Priestly in his original article on oxygen in 1774 warned against the possible toxic effects of pure oxygen, it quickly became a ubiquitous medical treatment, including in newborn care [4]. Oxygen was applied in newborn resuscitation for about 200 years before the first critical appraisal of its safety occurred. With the introduction of the Apgar score in 1953 [5], oxygen was used routinely in many centers to "pink up" newborns in order to achieve a higher Apgar score. As late as in 1992, the American Heart Association guidelines for newborn resuscitation stated: "there is no reason to be concerned giving pure oxygen a brief period after birth" [6]. Moreover, within the field, there was a prevailing dogma that

if oxygen was not available at the initiation of resuscitation, attempts with air would be futile and were often withheld. Pure oxygen continued to be recommended in all newborn resuscitation guidelines until 1998, when the WHO first suggested air [7], and in 2010, ILCOR did the same [8]. However, previously, in the late 1970s, we questioned the necessity and safety of this practice [9]. There is now increased understanding of the potential toxicity of both too much and too little oxygen, especially for preterm and asphyxiated newborn infants, and of the potential lifelong impact of oxygen exposure, even for a few minutes after birth [10].

2. Methods and Materials

This is not a full systematic review. However, data were extracted from publications listed in Pubmed in the field of oxygenation of newborns in the delivery room, and oxygenation of immature infants beyond the delivery room. Systematic reviews and meta-analyses regarding these topics were identified.

3. Results

3.1. Oxygenation in the Delivery Room

Air for newborn resuscitation was tested in randomized and pseudo-randomized studies from the early 1990s. Meta-analyses in this field clearly show that when compared to 100% O_2, air reduces mortality by approximately 30% in term and near-term newborn infants [11,12]. A recent study in newborn hypoxic piglets applying Near Infrared Spectroscopy (NIRS) showed that reoxygenation improves splanchnic oxygenation; however, when applying 100% O_2, the intestine was exposed to hyperoxia [13].

For newborn infants < 32 weeks of gestational age, the data are less clear. It seems 21% or 30% oxygen may safely be applied for infants between 28 and 32 weeks. For immature infants ($\leq$28 weeks of gestational age), a higher initial FiO_2 seems to be needed [14–16]. The optimal level is, however, not known [17]. A recent study showed that appropriate adjustments of FiO_2 are far more important than which initial FiO_2 is chosen [18]. For this reason, many investigators in this field would recommend starting out with 30% O_2 for infants < 29 weeks GA and titrate FiO_2 according to the development of oxygen saturation measured using pulse oximetry (SpO_2). The target for titration should be SpO_2 80–85% within 5 min of life [19] and the avoidance of bradycardia. A combination of hypoxemia (SpO_2 < 80%) and bradycardia (heart rate < 100 bpm) $\geq$ 2 min during the first 5 min of life is associated with an increased risk of death, 18-fold compared to normoxemia and heart rate < 100 bpm [20].

3.2. Oxygenation beyond the Delivery Room

Immature infants < 28 weeks GA have been particularly studied. The so-called Neoprom study consisting of five individual studies from the USA, the Canada, UK, New Zealand, and Australia tested the effect of lower (85–89%) versus higher (91–95%) SpO_2 target from birth to corrected term age in 4911 infants. The lower target group had higher mortality (19.3% vs. 16.2%), relative risk (RR) 1.41, and 95% confidence intervals (CI) 1.14–1.74, higher severe necrotizing enterocolitis (RR 1.25, 95% CI 1.05–1.49), but lower retinopathy of prematurity with RR 0.74 (95% CI 0.59–0.92) than the higher target group [21–23]. Most guidelines therefore recommend an SpO_2 target of 91–95% with very close alarm limits [24].

3.3. Present Practice

A recent survey by Sotiropoulos et al. [25] demonstrated that in moderate to late preterm infants, most units initiated respiratory support in the delivery room with an FiO_2 0.21 (43%) or 0.3 (36%) but only 45% titrated FiO_2 to target SpO_2. Most (89%) considered heart rate as a more important indicator of response than SpO_2. Almost all (96%) supported the need for well-designed trials to examine oxygenation in moderate–late preterm delivery room resuscitation. The survey demonstrated that most clinicians seem to resuscitate

moderate–late preterm infants with a lower initial FiO_2, but there is a hesitance to target SpO_2 or titrate FiO_2. Most consider heart rate as a more important indicator of infant response than SpO_2 [25]. In low-income countries, the lack of oxygen blenders makes it more difficult to follow such guidelines [26]. Further, a recent survey regarding guidelines showed that the SpO_2 target at 5 min varied considerably, between 70 and 90% [27].

3.4. New Technology

Delayed cord clamping leads to a higher and more rapid increase in SpO_2 in the first few minutes after birth [28–30]. The published target ranges for SpO_2 the first 10 min of life are based on early cord clamping [31]. New curves therefore need to be developed based on delayed cord clamping. Most extremely premature infants have respiratory instability that can manifest as frequent episodes of intermittent hypoxemia. Although caregivers target clinically recommended ranges of SpO_2, the consistent maintenance of these ranges is not always achieved. The excessive administration of supplemental oxygen combined with limited staff resources increases exposure to SpO_2 levels outside of the desired range. In this population, exposure to hyperoxemia and prolonged episodes of intermittent hypoxemia have been associated with damage to the eye and lung and impaired neurodevelopment. To improve SpO_2 targeting, various systems for the automated control of inspired oxygen have been developed and are commercially available at an increasing rate. There are no follow up data on the impact of these automated FiO_2 adjustment systems on mortality or morbidity [32–34]. However, the method has potential to improve outcomes for preterm neonates with their inherent respiratory instability.

4. Conclusions

Term and near-term infants in need of positive pressure ventilation at birth have an approximately 30% reduction in mortality rate when this procedure is initiated with air instead of pure oxygen. For preterm infants < 32 weeks of gestational age, there seems to be an agreement amongst clinicians that there is a need for more large and robust clinical trials examining oxygen use in general for immature infants but also for moderate–late preterm resuscitation. Further, there is a need to focus on the titration of FiO_2 as much as the initial FiO_2 chosen and examine the long-term neurodevelopmental outcomes in particular [17,18].

For oxygenation beyond the delivery room, we do not have solid data except for immature infants with gestational age < 28 weeks GA. A high-SpO_2 approach (target between 91 and 95%) is preferred.

In the last 10–15 years, the oxygen exposure—and probably also oxidative stress—of newborn infants has been dramatically reduced. This may be reflected in improved health in adulthood. Long-term follow-up is highly needed to shed light on the issues related to the oxygenation of newborns. The studies summarized in this review have contributed to dramatic changes in the clinical handling of newborn babies, resulting in significantly lower mortality and morbidity rates.

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