Optimal oxygen saturation in premature infants

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There is a delicate balance between too little and too much supplemental oxygen exposure in premature infants. Since underuse and overuse of supplemental oxygen can harm premature infants, oxygen saturation levels must be monitored and kept at less than 95% to prevent reactive oxygen species-related diseases, such as retinopathy of prematurity and bronchopulmonary dysplasia. At the same time, desaturation below 80 to 85% must be avoided to prevent adverse consequences, such as cerebral palsy. It is still unclear what range of oxygen saturation is appropriate for premature infants; however, until the results of further studies are available, a reasonable target for pulse oxygen saturation (SpO2) is 90 to 93% with an intermittent review of the correlation between SpO2 and the partial pressure of arterial oxygen tension (PaO2). Because optimal oxygenation depends on individuals at the bedside making ongoing adjustments, each unit must define an optimal target range and set alarm limits according to their own equipment or conditions. All staff must be aware of these values and adjust the concentration of supplemental oxygen frequently.

Key words: Premature infant, Oxygen inhalation therapy, Oxygen saturation, Pulse oximetry

Introduction

The diseases associated with prematurity frequently require oxygen therapy as a main component of respiratory care. A number of recent studies have indicated that high oxygen saturation levels (above 93 to 95%) are detrimental to premature infants when compared with lower saturation levels (85 to 93%)1-6, and therefore, lower oxygen saturation targets have been recommended for the ongoing management of premature infants in the neonatal intensive care unit (NICU)7. Although many NICUs advocate a lower target range of oxygen saturation to prevent reactive oxygen species (ROS)-related diseases, such as retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD), the optimal upper and lower oxygenation limits must still be defined.

In this review, I will briefly review the currently available evidence for the use of lower oxygen saturation targets during the acute phase of premature newborn illness in many NICUs.

Historical aspects

Oxygen was first discovered in the 1600s by the Polish alchemist Sedziwoj, who did not publish his findings. Oxygen was then rediscovered by Scheele, followed by Priestly in the 1770s. Later, the French chemist Lavoisier renamed the compound oxygen8. In 1780, Chaussier used oxygen for the revival of “near-dead” infants9. In the 1930s, Hess, followed by Chapple, described the use of oxygen in
infants\(^{10}\). Specifically, Chapple's unit delivered 100% oxygen at 4 L/min, resulting in a fraction of inspired oxygen (FiO\(_2\)) of approximately 46% in the incubator. Today, a FiO\(_2\) of 46% is considered a high concentration of oxygen for premature infants.

### Oxygen toxicity

In the 1940s, Terry\(^{11}\) reported a novel type of blindness in premature infants; in 1951, Campbell\(^{12}\) first suspected a role for supplemental oxygen in the etiology of this new blindness termed retrolental fibroplasia, now called ROP. In 1952, Patz et al.\(^{13}\) confirmed a role for supplemental oxygen in the etiology of ROP using a randomized trial of 78 infants subjected to either high oxygen (100% oxygen in the incubator) or restricted oxygen (supplemental oxygen provided only during signs of desaturation). They found that 61% of infants in the high oxygen group developed ROP compared to 16% of infants in the restricted oxygen group. Their results suggested that excessive oxygen made an important contribution to the development of ROP. In a prospective study, Kinsey et al.\(^{14}\) followed 719 premature infants. They identified the significant risk factors of ROP as birth weight <1,200 g and length of exposure to supplemental oxygen. Oxygen concentration, while also a risk factor, was not as well correlated with ROP development.

Early studies suggested that prolonged supplemental oxygen use significantly contributed to ROP and that restricted oxygen use resulted in fewer deaths, decreased respiratory failure, and decreased lung disease compared to liberal oxygen use. As a result, many practitioners allowed infants to become too severely desaturated. Unfortunately, oxygen desaturation might increase the incidence of cerebral palsy (CP), despite decreasing the incidence and severity of ROP. A median duration of supplemental oxygen exposure of ≤2 days was associated with a 17.4% incidence of CP and an 8.7% incidence of ROP, whereas a median supplemental oxygen exposure of >10 days was associated with a 5.8% incidence of spastic diplegia but a 21.7% incidence of ROP. A median duration of supplemental oxygen exposure of <2 days was associated with a 17.4% incidence of CP and an 8.7% incidence of ROP. Recently, the SUPPORT study group\(^{15}\) reported 719 premature infants. They identified the significant risk factors of ROP as birth weight <1,200 g and length of exposure to supplemental oxygen. Oxygen concentration, while also a risk factor, was not as well correlated with ROP development.

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Therefore, although excess oxygen can be toxic, insufficient oxygen is also harmful. Interestingly, both increased and decreased cellular oxygen levels result in the generation of ROS, and prolonged or extreme exposure to both excessively low and high oxygen levels may cause tissue damage\(^{17}\).

### The concept of optimal oxygenation

Normoxemia is not well defined for neonatal medicine. Nevertheless, on the basis of PaO\(_2\) (the partial pressure of oxygen in the blood at which the hemoglobin [Hb] is 50% saturated), saturation, and oxygen content, a partial pressure of arterial oxygen tension (PaO\(_2\)) of 40 mmHg should be adequate for tissue needs during early neonatal life, given normal Hb concentrations, cardiac output, blood flow, and cellular conditions. PaO\(_2\) values above 80 to 90 mmHg may be considered hyperoxemia\(^{18-20}\). Therefore, PaO\(_2\) values between 40 to 80 mmHg are considered optimal oxygenation in newborns.

### Oxygen saturation monitoring using pulse oximetry

In NICUs, monitoring of oxygenation is problematic, especially for sick premature infants whose oxygenation frequently fluctuate. Pulse oximetry is an advantageous approach to monitoring oxygenation, because it is noninvasive and continuous. In fact, in tiny premature infants, it difficult to draw sufficient arterial blood to measure the PaO\(_2\), and such measurements cannot be performed frequently even with indwelling arterial catheters. Continuous oxygen saturation monitoring using pulse oximetry has allowed for prompt and frequent titration of inspired oxygen concentration in order to maintain optimal oxygenation.

For ongoing management of infants in the NICU, a target oxygen saturation level of 85 to 93% has been recommended\(^{17}\). However, oxygen saturation values can be difficult to interpret, because the correlation between pulse oxygen saturation (SpO\(_2\)) and PaO\(_2\) depends on the affinity of Hb for oxygen in various physiologic circumstances. Clinical issues that may affect the proper functioning of pulse oximetry include significant hyperoxia, severe hypoxia, poor pulse pressure, presence of other Hb forms, electrical interference, optical interference, and motion\(^{21}\).

We have defined the relationship between PaO\(_2\) and SpO\(_2\) in premature infants for cases of hyperoxia. In 96 pairs of PaO\(_2\) and SpO\(_2\) measurements, a PaO\(_2\) of 43 to 79 mmHg on the oxyhemoglobin dissociation curve was associated with an oxygen saturation of 90 to 94% according to pulse oximetry. Within this SpO\(_2\) range, 100% of the samples had PaO\(_2\) values of 40 to 80 mmHg. When the SpO\(_2\) was ≥94%, the median (range) of PaO\(_2\) was 105 (65 to 172) mmHg with 73% of values >80 mmHg\(^{22}\). Previously, Castillo et al.\(^{23}\)
also reported that SpO2 values >93% are frequently associated with PaO2 values >80 mmHg, which may be a risk for some newborns receiving supplemental oxygen. As described above, pulse oximetry is not as useful for detecting hyperoxia; especially at oxygen saturations >94%, most infants are hyperoxic. On the other hand, Saugstad and Aune\(^{20}\) suggested that 85% saturation, which is the commonly accepted lower limit of optimal oxygenation, might be too low.

**Clinical studies on oxygen saturation targeting in premature infants**

Previous studies have suggested that the incidence and severity of retinopathy is lower in premature infants exposed to reduced levels of oxygenation compared to those exposed to higher levels of oxygenation\(^{1-3,6,25,26}\). However, the incidence and severity of ROP may also increase with exposure to hypoxia. Di Fiore et al.\(^{27}\) reported that infants with ROP requiring laser therapy had a higher incidence of hypoxicemic events. Therefore, therapeutic strategies to maintain optimal oxygenation in premature infants must minimize hypoxicemic episodes as well as hyperoxia.

Saugstad and Aune\(^{20}\) compared the outcomes of infants with high (SpO2 94 to 100%) or low (SpO2 70 to 95%) oxygen saturation targeting. The RR in favor of low SpO2 was 0.42 (95% CI, 0.34 to 0.51; \(P=0.25\)) for severe ROP, 0.73 (95% CI, 0.63 to 0.86, \(P=0.003\)) for BPD, and 1.12 (95% CI, 0.86 to 1.45; \(P=0.13\)) for mortality. When the randomized trial was analyzed separately, the RR (95% CI) was 0.48 (0.34 to 0.68) for severe ROP, 0.79 (0.64 to 0.97) for BPD/lung problems, and 1.27 (1.01 to 1.60) for mortality. The low oxygen saturation approach reduced severe ROP by 50% (i.e., from 20.9 to 9.5%) and BPD/lung problems by 25% (i.e., from 40.8 to 29.7%). In this meta-analysis, no difference in mortality was found; however, this result was based on only 2 studies including 1 observational study. The only randomized study\(^{26}\) reported that a target range of oxygen saturation of 85 to 89% increased mortality of lower oxygen saturation targets; however, more randomized studies are required to draw proper conclusions regarding mortality.

**Automated adjustment of supplemental oxygen**

Even with an optimal oxygen saturation range established, maintaining this range of oxygenation is difficult for the frequently fluctuating, sick, premature infants. A prospective, observational analysis compared the percent of time within, above and below the target oxygenation range between 2 groups with different target ranges. For group 1, the target oxygenation range was 90 to 95%; the percent of time within, above, and below this range was 57.7±9.8, 15.4±10.6, and 26.9±9.7%, respectively. For group 2, the target oxygenation range was 88 to 94%; the percent of time within, above, and below this range was 59.4±12.4, 14.0±9.4, and 26.6±10.2%, respectively. The percent of time within and above the goal range was similar for both groups. However, the percent time with SpO2 <80% increased significantly for group 2 (4.0±2.7 vs. 1.9±1.4%, \(P<0.001\)). This demonstrated that the percent of time spent within the goal range was <60% and that the risk of hypoxemia increased when the lower limit of the target range was less than 90%\(^{20}\).

A timely response to a preterm infant’s changing need for supplemental oxygen is necessary to minimize exposure to unnecessarily high levels of supplemental oxygen or to periods of hypoxemia. However, busy circumstances in NICUs make it difficult for caregivers to dedicate the full attention required for immediate manual adjustment of FiO2 according to the oxygen saturation displayed on the monitor. One promising new alternative is to provide automated adjustment of supplemental oxygen based on targeted pulse oximetry readings\(^{28}\). A recent multi-center crossover study on automated control of inspired oxygen in ventilated preterm infants demonstrated that automated FiO2 adjustment improved maintenance of the intended SpO2 range (87 to 93%), led to reduced time with high SpO2, and achieved more frequent episodes with SpO2 levels between 80 to 86%\(^{29}\).

SpO2 measurement is ideal for automated FiO2 control because of its continuous and noninvasive nature. However, there are many factors affecting the reliability of SpO2 readings in premature infants, and decreased accuracy of SpO2 measurements during automated FiO2 control can lead to inadvertent hypoxemia or increase exposure to unnecessarily high FiO2. In order to minimize this problem, an automated FiO2 system requires proper setup. Furthermore, automated FiO2 should not be used in cases of any conditions that impair SpO2 reliability.

**Conclusion**

Based on the evidence reviewed above, and until the results of further studies are available, a reasonable SpO2 target for premature infants is approximately 90 to 93% with an intermittent review of the correlation between SpO2 and PaO2\(^{27,22-25}\). However, it is difficult to define an absolute upper and lower limit due to differences in monitor
accuracy and differences in the bias, accuracy, and precision of the equipment. These equipment differences may be more pronounced during unstable conditions and at lower SpO2 values. In conclusion, oxygen saturations must be carefully monitored in premature infants to prevent frequent desaturation as well as unnecessary hyperoxia. To achieve this goal, each NICU should establish an optimal target range with alarm limits set according to their specific equipment or conditions. All staff should be aware of the target values and be dedicated to adjusting the concentration of supplemental oxygen frequently.

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