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REVIEW ARTICLE

Evidence for oxygen use in preterm infants

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ABSTRACT

Aim: To review the evidence for optimal oxygen use in preterm infants.

Results: Clinicians have embraced lower saturation targets to minimize retinopathy of prematurity (ROP). Large randomized trials now have shown that while such targets reduce ROP, neonatal mortality is increased significantly.

Conclusions: Preterm infants should be resuscitated with blended oxygen (30–90%) targeted to avoid hyperoxia. Later, saturation management remains uncertain. Until ongoing trials and follow-up are complete, it is prudent to avoid saturation of 85–89%.

INTRODUCTION

Oxygen has been both a vital therapeutic tool and an agent of harm in Neonatal care. The recognition by Priestly, Scheele and Lavoisier that air contained the 'life giving' substance oxygen in 1775 led to the dissemination of oxygen use in medicine.

Such use included data from Wilson et al. (1) that administration of oxygen stabilized irregular respiratory patterns commonly seen in preterm infants. From such an observation in 1940, widespread administration of high concentrations of inspired oxygen became routine. It was not until Campbell in 1951 (2) suggested that the epidemic of blinding retinopathy was related to unrestricted oxygen administration and that levels that were normal for the full term infant were in fact toxic to the premature infant. Subsequent ground breaking randomized controlled trials of routine oxygen use vs. curtailed oxygen use confirmed the association (3). Unfortunately, the trial was misinterpreted to suggest that $FiO_2 > 40\%$ was unsafe and ushered in a tragic era of oxygen restriction that increased mortality. Curtailed oxygen use was estimated to lead to 16 deaths for every case of blindness prevented. Systematic trials of oxygen use have only been conducted within the last decade and will revamp much of what we know about optimal administration. In this review, we will focus on the preterm infant and evidence to support oxygen practices across three phases: resuscitation, early acute care and longer convalescent care.

Key notes

- There has been a trend of using lower oxygen saturation targets in extremely low gestational age infants to minimize retinopathy of prematurity (ROP) based largely on small uncontrolled series and retrospective reviews. Now, large randomized trials have shown that while such targets reduce severe ROP, mortality is increased significantly. Until current trials and follow-up are completed, it is prudent to avoid saturation targets <89%.

RESUSCITATION

Preterm infants have long been resuscitated in the delivery room with 100% oxygen although this practice is not evidenced based. High quality randomized trials in term infants have conclusively shown that room air is more effective than 100% oxygen in the resuscitation of term and

near-term infants (4–6). Increasing evidence demonstrates the harmful effects of even brief exposures to hyperoxia.

As a consequence of 100% oxygen resuscitation, preterm infants demonstrate increased markers of oxidative stress both in blood and urinary samples, markers which were later associated with the development of chronic lung disease (7–9). Two observational studies suggest hyperoxia is more likely to be present in infants leaving the delivery room resuscitated with 100% oxygen. Dawson et al. (10) found that resuscitation with 100% oxygen was not only associated more often with saturation exceeding 95% at 10 min of life but also led to a more rapid rise in saturation values. This association occurred in the presence of similar median saturation values and heart rates at 5 min of life among both groups. While 100% oxygen was deleterious, room air alone was not adequate for initial resuscitation in very low birthweight infants. Similar results were obtained by Stola et al. (11) in the evaluation of infants <1500 g who randomized infants to different supplemental oxygen strategies. In this study, more infants in their reduced oxygen group were found to have an oxygen tension <80 mmHg and lower saturation values upon admission to the neonatal intensive care unit (NICU). Moreover, they found that infants resuscitated with varying amounts of oxygen (but all <50% oxygen) maintained a lower oxygen requirement at 24 h of life compared to their hyperoxic controls.

In the first of two randomized clinical trials, Escrig et al. (12) compared the use of low (30%) vs. high (90%) fractions of inspired oxygen during delivery room resuscitation and assessed the time needed to achieve an oxygen saturation of 85%. In infants with a mean gestational age of 26 weeks, the use of 30% oxygen was as effective in resuscitation with similar time to reach the targeted oxygen saturation of 85% (low-oxygen group: 6.5 ± 1.1 min; high-oxygen group: 5.5 ± 0.7 min). In addition, there was no difference in measurements of body temperature and pH upon arrival to the NICU. However, infants resuscitated with 30% oxygen were more likely to be ventilated with room air ($p < 0.05$). Infants in the high-oxygen group were also noted to receive a greater volume of pure oxygen in the first 5 min of life and to have increased incidence of bronchopulmonary dysplasia and ROP compared to the low-oxygen group, although these differences did not reach statistical significance.

In the second randomized clinical trial, Wang and colleagues evaluated the time required to reach a targeted oxygen saturation using room air or 100% oxygen in infants <32 weeks' gestation (13–16). All infants initially resuscitated with room air failed to reach the desired oxygen saturation and subsequently required an increase in FiO_2 before 3 min of life. Moreover, the study noted significant differences in oxygen saturation in the room air group at 2, 3, 4, 5, 6, 7, 8, 9 and 10 min of life. The results of this study suggest that the initial use of room air may be inadequate for the resuscitation of preterm infants.

In a major step forward, Dawson et al. (17) defined for the first time the reference ranges for saturation values in infants, including preterm infants, during the first 10 min of life who did not require any resuscitation or oxygen in the delivery room. Of the 468 infants included in the study, 160 infants were <37 weeks and 39 infants were <32 weeks' gestation. The median saturation for preterm infants was 62% (range 47–72%) at 1 min, 86% (range 80–92%) at 5 min and 94% (range 91–97%) at 10 min. Saturation values were affected by the mode of delivery with infants delivered via caesarean section exhibiting significantly lower saturation measurements compared to infants delivered vaginally. The median time for preterm infants to achieve an oxygen saturation of 90% was 8.1 min (range 6.7–10.5 min).

In October 2010, treatment recommendations for the use of supplementary oxygen in preterm infants were released by the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science (18). The recommendations state that in preterm infants <32 weeks' gestation, 'initial use of air or 100% oxygen is more likely to result in hypoxaemia or hyperoxaemia, respectively, than initiation of resuscitation with 30–90% and titration to oxygen saturation'. The recommendations advise the use of blended oxygen and air in conjunction with pulse oximetry. However, if blended oxygen is not available, then resuscitation should proceed with air. For those infants between 32 and 37 weeks of gestational age, the committee was unable to recommend the appropriate strategy for oxygen administration because of the paucity of evidence in this group of infants.

The Neonatal Resuscitation Program released their recommendations for the resuscitation of preterm infants in 2010 (19). The guidelines state that though 'the ideal oxygen concentration for preterm infants is not known', using oxygen 'at either extreme (21% or 100%) may result in an oxygen saturation that is too low or too high'. The guidelines also recommend the use of pulse oximetry when supplemental oxygen, positive pressure ventilation or continuous positive airway pressure (CPAP) will be used. Preductal oxygen saturation targets based on the work of Dawson are recommended, which progressively increase over the first 10 min of life beginning at 60% and progressively increasing to 90% by 10 min of life.

ACUTE CARE

Neonatal clinical investigators pursued the study of optimal oxygen administration in preterm infants seeking to balance the benefits and risks. Observational data suggested that levels of oxygen saturation previously thought to be at the upper end of the normal range may increase the risk of ROP as compared with levels at the lower end of the normal range (20–22). In a survey of 144 neonatal intensive care units (NICUs), Anderson et al. (20) found the rate of retinal ablation surgery was increased among infants cared for in NICUs that used higher maximum target levels of oxygen saturation, as compared with infants in NICUs that used lower target levels. The rate of retinal ablation surgery was 1.4% in NICUs using target levels of <92%, 3.3% in NICUs using target levels of 92% or higher, and the rate was 5.6% in NICUs using target levels of 98%. In a retrospective study comparing outcomes at five NICUs, the incidence of severe

retinopathy requiring surgery was 27% in NICUs where the target saturation level was 88–98% and only 6% in NICUs where the target level was 70–90% (21). Rates of death and cerebral palsy did not appear to differ significantly. Chow and colleagues evaluated outcomes in three NICUs in the US and also found that lower oxygen saturation targeting reduced ROP (22). Taken together, these observational studies suggested that lower oxygen saturation targets might improve visual outcomes, yet the feasibility of maintaining infants in these targets, and the safety of these targets had not been rigorously tested.

In 2005, The Eunice Kennedy Shriver NICHD Neonatal Research Network performed the SUPPORT trial, a randomized trial using a 2×2 factorial design to compare oxygen saturation targets of 85–89% vs. 91–95% among 1316 infants who were born between 24 weeks and 27 and 6/7 weeks' gestational age (23). The primary outcome was a composite of severe ROP (defined as the occurrence of threshold retinopathy, the need for surgery or both) death prior to hospital discharge or both. Women with threatened preterm delivery were enrolled antenatally; thus, the group had an extremely high rate of antenatal steroid exposure (97%). The trial found competing outcomes with a significant reduction in ROP, but a significant worsening in death in the lower saturation group. The combined outcome of severe retinopathy or death was not different between the two groups (28.3% in lower saturation group vs 32.1% in higher saturation group; RR 0.90; 95% CI 0.76, 1.06). Death prior to discharge occurred more frequently in the lower saturation group 19.9% vs 16.2% (RR 1.27; 95% CI 1.01–1.60). In contrast, severe retinopathy among survivors was reduced significantly in the lower saturation group 8.6% vs. 17.9% (RR 0.52; 95% CI 0.37–0.73; $p < 0.001$). Bronchopulmonary dysplasia, defined by oxygen administration at 36 weeks, was reduced in the lower saturation group (37.6% vs 46.7%, RR 0.82 95% CI 0.72 vs 0.93). Subsequent analyses demonstrate that across both randomized arms saturations in excess of 96% were strongly associated with increased risk of ROP (24). DiFiore et al. (25) performed a detailed analysis of a nested sub-cohort at two sites which compiled saturation data every 2 s and demonstrated that infants randomized to the lower saturation targets had a significantly greater risk of intermittent hypoxia events. The mechanism by which such events may be detrimental may be either through repetitive hypoxia or through the relative hyperoxic stress associated with the re-oxygenation phase.

The BOOST II Trial Data Safety and Monitoring Committee was informed of the SUPPORT results and performed a scheduled interim analysis that led them to terminate trial enrolment in the UK and Australian cohorts. (The New Zealand cohort had completed enrolment. The Canadian cohort DSMC found no reason to curtail enrolment.) Prespecified stopping criteria were based on a threshold of a survival difference exceeded 3 standard deviations with a 99.73% confidence interval. The analysis detected an 8.5% reduced mortality in the higher saturation arm (RR 1.65 (99.73% CI 1.09–2.49, $p = 0.003$) (26,27).

The increased mortality found in these trials parallel older findings of increased mortality found when oxygen was restricted in the 1950s and 1960s. The combined risk difference in the oxygen restriction trial was 4.9% in the oxygen restricted group which is eerily similar to the 3.7% increased mortality found in the SUPPORT trial. The trade-off of reduced severe ROP with increased mortality indicates that approximately one extra death for every two cases of severe retinopathy was prevented. Several additional trials are ongoing using saturation targets identical to the SUPPORT trial with a planned prospective individual patient meta-analysis (28). Together, these will more completely inform the search for optimal oxygen saturation targets. However, moving these targets into practice can be challenging. Targets must be attainable and avoid the unintended consequence of alarm fatigue (staff desensitization to alarms that occur frequently). Laptook demonstrated that attempts to tighten oxygen target ranges 80–96% vs 88–94% led to similar amounts of time in target, but increased the per cent of time <80% saturation (1.9% vs 4.0%). These are a real barrier to optimizing neonatal care (29,30).

Successful implementation of targeted oxygen saturation may be directly linked to nursing staffing levels (31). This has major implications for nursing staffing levels for NICU patients. Acuity has long been gauged by cardiorespiratory status alone. NICUs may also need to consider the degree of retinal maturity to guide our staffing patterns. The development of automated devices for titrating oxygen may improve the ability to maintain tight oxygen targets. Until further data are available, including 2-year neurodevelopmental outcomes, clinicians should exercise caution in using a low saturation algorithm to avoid unintended mortality.

CONVALESCENT CARE

There has been a long standing interest in preventing ROP by strictly limiting oxygen exposure. Most studies have focused on infants beyond 32 weeks postmenstrual age. Flynn et al. (32) were among the first to use transcutaneous oxygen monitors to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent arterial or capillary sampling; however, for subgroup of infants >1100 g, there was a decrease in the incidence of ROP.

The STOP–ROP trial randomized infants with established prethreshold retinopathy and saturation <94% to two ranges of saturation (89–94% vs. 96–99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of saturation was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD (33).

The BOOST I Trial compared saturation ranges of 91–94% vs. 95–98% in 358 infants of <30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received

oxygen for a longer period after randomization (median, 40 days vs. 18 days; $p < 0.001$) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy (34). They reported that additional oxygen supplementation did not improve survival, growth or the occurrence of cerebral palsy at 18–24 months.

Chen analysed the above studies and other non-randomized studies published prior to 2009 in a systematic review and found that the ideal oxygen saturation target might vary by the period of use (35). They analysed studies as early or late defined as prior to or after 32 weeks postmenstrual age. They concluded that prior to 32 weeks' PMA, low-oxygen saturation (70–96%) reduced ROP [RR 0.48 (95% CI 0.31–0.75)]. After 32 weeks' PMA, high–oxygen saturation (94–99%) was favoured [RR 0.54 (95% CI 0.35–0.82)]. Of course, these studies did not include the SUPPORT or BOOST II studies and its finding of increased mortality. Thus, the optimal oxygen targeting strategy remains elusive. The conclusion of the two ongoing trials and the planned prospective patient level meta-analyses together with 2 year outcomes should bring clarity to a long muddied field.

CONCLUSIONS

Preterm infants should be resuscitated with blended oxygen (30–90%) targeted to achieve a gradual increase in saturation over the first 10 min of life while avoiding hyperoxia. Later saturation management remains uncertain. Until the ongoing trials and neurodevelopmental follow-up are available, it may be prudent to avoid saturation targets of 85–89%. It is possible that saturation targets that maximize disability-free survival may vary depending on the postmenstrual age of the infant.

CONFLICTS OF INTEREST

The author has declared no potential conflicts.

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