OPTIMAL OXYGEN SATURATIONS IN PRETERM INFANTS: A MOVING TARGET

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Purpose of review

New evidence is emerging to address the continued uncertainty regarding the optimal range to target oxygen saturation levels in preterm infants.

Recent findings

A recently published systematic review summarized the existing evidence for currently used oxygen saturation targets in preterm infants and highlighted the paucity of randomized trials addressing this topic. It appears that higher oxygen saturation levels increase the risk of severe retinopathy of prematurity and pulmonary morbidities. However, data regarding the effects of various target ranges on early mortality and long-term neurodevelopmental outcomes is lacking. A collaborative group of investigators from five independent randomized trials was established to answer this question definitively. Although the final analysis will not be available until 2014, interim results from four of these trials revealed an increase in early mortality when the lower oxygen saturation range is targeted. At present it may be prudent not to target oxygen saturation levels below 90%. Whatever the optimal range, consistently maintaining the newborn's oxygen saturation levels within target proves an additional challenge for providers. Both technological advancements and optimized patient-caregiver ratios may be useful in achieving targeted oxygen saturation goals.

Summary

Defining and maintaining optimal oxygen saturations in preterm infants remains a challenge for clinicians caring for preterm infants. However, ongoing investigative collaborations may soon provide guidance.

Keywords

oxygen saturation, preterm infant, oxygen levels, neonate

Introduction

In a 2004 paper [1] written just before his death, Bill Silverman concluded that "there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants". For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP-blindness, chronic lung disease and brain damage) was, and remains to this day, unknown." Unfortunately, the uncertainty continues and the question of what is the optimal oxygen saturation range for preterm infants is a moving target.

Silverman entitled the aforementioned article "a cautionary tale about supplemental oxygen: the albatross of neonatal medicine" and indeed the oxygen story highlights the potential for unanticipated, adverse consequences when clinical practices are changed based only on anecdotal, observational and non-randomized evidence. In 1942, Wilson et al [2] observed that by giving preterm infants oxygen, the frequency and severity of periodic breathing was reduced. Despite cautionary caveats in that paper, the practice of administering unrestricted oxygen to preterm infants became widespread. By the early 1950s however, associations were beginning to emerge that linked high levels of inspired oxygen with a severe form of retinopathy of prematurity (known as retrolental fibroplasia). Three small randomized trials were performed in the mid 1950s (summarized in the Cochrane Systematic Review by Askie and Henderson-Smart) [3] which clearly linked unrestricted oxygen administration with severe retinopathy. Unfortunately, these trials did not report mortality or neurodevelopmental outcomes and/or did not randomize infants until after 48 hours of age. Hence, there was no information on how the restriction of supplemental oxygen would affect early death or disability rates. Despite this lack of evidence, widespread restriction of oxygen supplementation followed. It was subsequently estimated that for every infant whose sight was saved, there were 16 additional dead or disabled children as a result of this policy change [4].

Since that time there have been many observational, retrospective studies that have tried to determine on the optimal oxygen saturation range for preterm infants. However, very few sufficiently powered randomized trials have addressed this question directly. A large multination, collaborative effort is currently underway, with the goal of resolving this debate after sixty years of uncertainty.

What is the best range to target oxygen saturation levels in preterm infants?

Saugstad and Aune published a systematic review and meta-analysis in 2011 [5] that summarizes the current evidence regarding the effects of high versus low oxygen saturation targets in the first weeks of life in very low and extremely low birth weight infants. Their literature search highlighted the paucity of robust randomized controlled trial evidence directly addressing this question, with only three randomized trials being identified [6-8]. Seven other non-randomized (observational) studies were also identified as being appropriate for inclusion in the review [9-15]. The merits of combining randomized and non-randomized evidence in one meta-analysis may be questioned (albeit the summary effects of both types of evidence were displayed separately as well as combined). As is often seen, the treatment effects were more pronounced in the non-randomized studies.

The three randomized trials included in this review addressed the question of high versus low oxygen saturation targets in preterm infants; however, the BOOST [7] and STOP-ROP [6] trials did not randomize infants until approximately 32 and 35 weeks postmenstrual age respectively, whereas the SUPPORT trial [8] randomized infants at birth or soon thereafter. One might question whether it is thus appropriate to combine these trials in a meta-analysis as the effects of high and low target ranges may well be different in the early and later neonatal periods. Furthermore, the target ranges were quite different in the three trials. The SUPPORT trial randomized infants to a target oxygen saturation range of either 85-91% or 91-95% soon after birth. The two trials that randomized infants in the later neonatal period allocated infants to target ranges of 89-94% vs 96-99% (STOP ROP) or 91-94% vs 95-98% (BOOST). The authors did not include severe retinopathy of prematurity (ROP) or survival outcomes for the two trials that commenced the targeting intervention in the later neonatal period but did combine them with the early period SUPPORT trial in an assessment of bronchopulmonary dysplasia (BPD) outcomes.

Despite these methodologic concerns, the results of this review indicate that targeting lower oxygen saturation ranges significantly reduces the risk of severe ROP (from 20.9% to 9.5%) and BPD/lung problems (from 40.8% to 29.7%) in preterm infants. What remains unclear from the available evidence is whether this benefit comes at the expense of a potentially small, but important, increase in mortality. The effect on early mortality is particularly important and data from only two studies were included in the analysis of this outcome: the SUPPORT trial [8] and an observational study by Tin et al [9]. The results of that meta-analysis indicated that there is insufficient evidence on which to base any conclusive clinical or policy guidance at this time with regard to mortality outcomes.

It is timely then, that a collaboration has been formed that seeks to end this uncertainty and obtain definitive data regarding the benefits and harms of targeting either higher or lower oxygen saturation ranges in preterm infants from birth. The NeOProM Collaboration was initially established in 2003 [16] and formed a prospective meta-analysis collaboration that will address this question. The group published their study protocol in 2011 [17]. The need for a collaborative approach became apparent when sample size calculations revealed that in order to reliably detect a difference in death or major disability in survivors of as little as 4% (from a predicted baseline rate of 42%, increasing to 46%), approximately 5,000 infants would need to be randomized. No one trial group or funding agency had the ability to undertake such a large trial alone and in a timely manner. Hence, five trial groups (from the USA, UK, Canada, Australia and New Zealand) undertook to conduct their own individual trials, with very similar protocols, collecting common core outcomes, and have agreed to share the individual participant data from these trials once completed in a combined meta-analysis. The protocol for this endeavour, including the common key outcomes and overall analysis plan, were agreed prior to knowledge of any results of the individual trials being known. This method is known as prospective meta-analysis.

All trials in the NeOProM Collaboration [18-22] are recruiting infants born less than 28 weeks' gestation and enrolling them within 24 hours of birth. Infants are then randomly assigned to target either an oxygen saturation range of 85-89% or 91-95%. The assigned intervention is masked to parents, care givers and outcome assessors by the use of pulse oximeters that have been adjusted to display either 3% above or below the infant's actual saturation value within the 85-95% oxygen saturation range. The primary outcome of the NeOProM study will be a composite of death or major disability at 18-24 months corrected age. Several pre-specified secondary outcomes (including

retinopathy of prematurity, patent ductus arteriosus, necrotizing enterocolitis) and sub-group analyses (including gestational age, small-for-gestational-age, gender) have been identified. The prospective meta-analysis protocol allows individual trials within the collaboration to publish their own results first. Results of the final combined meta-analysis should be available by 2014.

While prospective meta-analyses collaborations such as NeOProM have particular advantages over large scale, international multicenter trials, significant challenges remain. For example, one of the NeOProM trials, SUPPORT [8], found unexpected results with regards to mortality. SUPPORT was a two-by-two factorial study design that randomized extremely preterm infants to one of two oxygen saturation targets ranges and to either early surfactant or CPAP. This trial had always planned to publish short term, in-hospital outcomes prior to ascertainment of longer term disability outcomes. These results, published in the *New England Journal of Medicine* in 2010 [8] revealed a small, but statistically significant increase in death before discharge (but not death by 36 weeks' postmenstrual age) in infants allocated to the lower oxygen saturation target range. The Data Monitoring Committees (DMCs) of the other ongoing NeOProM trials separately reviewed their interim data and found no reason to stop recruitment at that time [23]. At around the same time, an assessment of the calibration algorithm used to mask the Masimo oximeters in the NeOProM trials revealed an artifact that required an update of the trial oximeters' algorithm. This change of algorithm resulted in better separation of the oxygen saturation values observed in the two treatment groups within the UK trial [24]. All trial and non-trial Masimo oximeters were subsequently fitted with the revised algorithm.

In response to both these unexpected factors, the DMCs of the UK and ANZ BOOST II trials within the NeOProM Collaboration requested a safety analysis be undertaken of the available 'mortality to 36 weeks postmenstrual age' data in these trials and for this to be combined with the published SUPPORT trial mortality data. The resulting analysis of the combined 3,631 infants' data, published in a letter to the *New England Journal of Medicine* in April 2011 [25] showed a significantly increased survival to 36 weeks' postmenstrual age in the higher target group when using oximeters fitted with the new calibration algorithm (n=1,055 infants). As a result of these findings the two NeOProM trials that were still open to recruitment at that time (BOOST II Australia and UK) closed early on the recommendations of both their individual DMCs. The authors of this combined analysis warned however, that while it would currently be prudent not to target an oxygen saturation range of 85-89%, final recommendations cannot be concluded until information on the primary outcome of long term disability-free survival are presented on the full NeOProM cohort.

Improved control of oxygen saturation targeting

Despite the remaining uncertainty regarding the optimal range in which to target oxygen saturation values for preterm infants, there appears to be much interest in maximizing the time spent within the desired target ranged.. Achieving good compliance in keeping an infant within a target range appears quite difficult. In a 2012 paper, Van derEijk and colleagues [26] demonstrated that 0.7-5.2 manual adjustments of FiO_2 per hour per infant were performed in an attempt maintain target oxygen saturations. Importantly, despite this level of attention, oxygen saturation values were outside alarm limits for approximately half of the time. This was confirmed by studies from Sink et al [27] who observed that extremely preterm infants with a higher nurse:patient ratio (i.e. cared for by nurses with fewer assigned patients), and who had a lower postmenstrual age and more intensive respiratory support modes were more likely to be kept within the target oxygen saturation range. Importantly, this study demonstrated that targeted oxygen saturation levels were achieved only 16% of the time. Infants were noted to be hyperoxemic (SpO_2 98-100%) 22% of the time and the below the target range (SpO_2 <85%) 3.1% of the time.

Consequently, novel technologies are emerging that might automate FiO_2 control to achieve better oxygen saturation stability. Claure et al [28] conducted a multicenter crossover study of 32 ventilated preterm infants with a mean gestational age of 25 weeks at birth and aged approximately 27 postnatal days. These infants had been unstable in the previous 24 hours with frequent (≥ 4) spontaneous desaturation episodes ($SpO_2 \leq 80\%$). The infants were allocated, in random order, to two consecutive 24 hour periods of either usual care, including manual FiO_2 adjustment by staff, or FiO_2 adjustment via an automated system. The study was conducted under routine clinical care conditions, without the presence of any researchers, and in five different centers. The results demonstrate that when under automated FiO_2 control, infants spent significantly more time within the target SpO_2 range (SpO_2 87-93%) and less time in the hyperoxic range (SpO_2 >98%). However, they spent more time with SpO_2 levels in the 80-86% range compared to the manual control period. When in the "auto-control" period, infants' SpO_2 levels trended toward the center of the intended range; they had a lower overall median SpO_2 for the 24-hour period and less frequent high oxygen 'overshoots' after desaturation episodes. During manually controlled periods, infants remained near the upper limit of the intended range for significantly longer periods of time, resulting in an increased overall median SpO_2. The authors concluded that these results indicate a clinicians' preference for 'tolerating higher SpO_2 values'. Of interest however, is that even with auto control, infants only spent 40% of time in the intended range, which was nonetheless an improvement on the 32% of time spent in range during the manual adjustment period.

Oxygen saturation targets for preterm infants at delivery

The question of where to target oxygen saturation for preterm infants at delivery will not be covered in this article. Davis and Dawson comprehensively summarized the existing evidence on this topic in their April 2012 article in *Current Opinion in Pediatrics* [29]. Since that publication, Saugstad and colleagues have published a systematic review and meta-analysis [30] which summarized the longer term neurodevelopmental outcomes of infants (both term and preterm) resuscitated with either air or 100% oxygen. Although there were no differences seen in rates of abnormal development between the two groups, the high loss to follow-up and the marked heterogeneity in the criteria

used to assess neurodevelopmental outcomes preclude any definitive conclusions regarding long term outcomes. An accompanying commentary on this article by Shah [31] noted that the meta-analysis 'generated more questions than answers'.

Conclusions

The optimal oxygen saturations for preterm infants remains a moving target as uncertainty still exists as to the most appropriate range. Definitive evidence is currently being generated via data from five randomized trials that will be combined in a pre-planned prospective meta-analysis. Until that is available in 2014, it may be prudent to avoid targeting SpO_2 levels in the early neonatal period at <90% as there is a concern for increased mortality with these lower target levels. Even when more reliable evidence *is* available, it is conceivable that there may be both benefits and harms from targeting a particular oxygen saturation range and decision aids to assist clinicians may need to be developed. Whatever target range is chosen, it is challenging to maintain preterm infants within that range for more than 30-40% of the time. New technologies are being developed that may improve compliance with achieving oxygen saturation targets but other, less technologically complex strategies, such as having a higher nurse:patient ratio, may be just as effective. Targeting different oxygen ranges at various timepoints throughout the neonatal period (at delivery, early weeks, later period) may need to be considered once the currently emerging evidence is fully analysed.

Key points

- There are very few randomized trials that provide direct evidence regarding the optimal range in which to target oxygen saturation for preterm infants.
- Recent interim results from four ongoing randomized trials revealed an increase in early mortality when a lower range was targeted.
- At present it may be prudent not to target oxygen saturation levels below 90%.
- Consistently maintaining an infant's oxygen saturation within the targeted range represents an additional challenge.

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Conflicts of interest

There are no conflicts of interest to declare.

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