Appropriate levels of oxygen saturation for preterm infants

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Although oxygen is probably the most common therapy delivered to small or sick newborns in the past 75 years, what constitutes appropriate oxygenation for these infants remains highly controversial. The lack of direct evidence, in the form of randomised trials, of the effects of different oxygen levels on meaningful, long-term outcomes has fuelled this controversy and contributed to the significant variation in practice currently seen. Conclusions drawn from the existing evidence regarding oxygen saturation levels for preterm infants include that retinopathy of prematurity rates may be reduced if lower saturation ranges are targeted in the early weeks of life. There is, however, no recent, good quality, trial information that has directly addressed this question. Retinopathy outcomes may also be improved if oxygen saturation is targeted higher in a subset of preterm infants with more severe eye disease in the post-acute phase. There is now direct evidence, from randomised trials, that routine higher oxygen saturation targeting in the chronic phase confers no short- or long-term growth or development benefits. Evidence is now mounting regarding the adverse pulmonary sequelae associated with routine higher, and thus longer, oxygen exposure. Information regarding oxygen saturation levels and early mortality is inconclusive. The major unanswered question that requires urgent resolution is the important long-term effects of targeting lower versus higher oxygen saturation ranges during the first days/weeks of a preterm infant’s life. Such an important clinical question can only be answered rigorously and definitively using the randomised trial methodology.

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Oxygen is probably the most common therapy that has been given to small or sick newborns in the past 75 years (1, 2). Despite this, what constitutes appropriate oxygenation for these infants remains highly controversial (3–7). The now well established association between high oxygen levels in the early days of life and retinopathy of prematurity (ROP) was first recorded by Campbell, in 1951 (8). Since then, many studies have tried to define what constitutes a safe level of oxygenation for preterm infants in order to maximise benefits such as growth and development, whilst minimising harms like death and ROP, with variable results. Interestingly, despite oxygen being an exceedingly common therapy or intervention given to newborn babies, there have been only a handful of studies which have used the methodology recognised as the best for achieving an unbiased assessment of the effect of an intervention – the randomised, controlled trial.

The lack of direct evidence of the effects of different oxygen levels on clinically meaningful, long-term outcomes has contributed to the significant variation in practice currently seen (9–11) and has fuelled the controversy surrounding the issue of what are the most appropriate levels of oxygen for preterm infants. Despite calls as long ago as 1977 by three eminent, but anonymous, commentators for large collaborative trials to resolve some of the issues of oxygen therapy (12), none have been forthcoming until very recently. Some clinicians favour generally “higher” oxygen saturation (SpO2) levels (for instance SpO2 ≥ 90%) whilst others target generally “lower” SpO2 levels (<90%) in either the acute, early days of life or later in infants who remain chronically oxygen-dependent. Both positions can be supported by ample, if mostly indirect, evidence. Until recently, information regarding the most appropriate oxygen saturation levels could only be derived from uncontrolled study designs, such as observational studies, reference data from healthy term infants and cohort studies.

‘Higher’ oxygen saturation levels

Physiological studies and animal work have consistently demonstrated that preterm infants with lower baseline saturations have more frequent oxygen desaturation episodes (13, 14) and increased oxygen consumption (15). In addition, observational studies
have suggested improved weight gain amongst infants on home oxygen (16, 17). The uncontrolled nature of these studies means that it is not known whether these associations are causal. It is also hypothesised that a persistence of subclinical hypoxia beyond term-equivalent age may predispose infants with chronic lung disease (CLD) to pulmonary hypertension (18–20). There are ample observational data from case control and cohort studies supporting the hypothesis that inadequate oxygenation contributes to poor long term development in CLD infants, including increased rates of neurological impairment and significant developmental delay (21–23).

There is no direct evidence of improved early survival if oxygen levels are kept higher, as the only three early trials that recruited infants from birth and collected mortality data showed no statistically significant difference in death rates between restricted and liberal oxygen administration (24). The resulting curtailment of oxygen therapy following those early trials due to the ROP sequelae, however, almost certainly caused a significant rise in the number of early neonatal deaths (25–27).

The only randomised trial that has directly assessed the effect of higher SpO₂ targeting on retinopathy outcomes, the STOP-ROP trial (28), found a small, but not statistically significant improvement in ROP progression when a saturation range of 96–99% was targeted in infants who had already developed pre-threshold ROP. The recently completed BOOST trial (29), which randomised extremely preterm infants to standard (SpO₂ 91–94%) or higher (SpO₂ 95–98%) oxygen saturation ranges, also found a reduction in the need for ablative retinal surgery in infants targeted at higher levels after 32 weeks postmenstrual age. These non-significant differences in ROP outcomes from the trial data contrast with many cohort and case-control studies (30, 31), animal models (32) and retrospective audits (33) that have consistently suggested substantial benefits of higher saturation targeting in reducing the progression of established ROP.

‘Lower’ oxygen saturation levels

The BOOST trial (29) found no significant differences in either short- or long-term growth measures or major developmental abnormality rates when higher versus lower SpO₂ ranges were targeted in post-acute, oxygen-dependent, preterm infants. Similarly, the STOP-ROP trial (28) assessed growth at three months corrected age as a secondary outcome and found no difference between the high and low range groups. A recent UK prospective cohort study (34) found that infants cared for in units that targeted a low SpO₂ range from birth were much less likely to have weights less than the third percentile at discharge compared with infants cared for in units targeting a high SpO₂ range. This study, however, found no difference in the cerebral palsy rates at two years between these groups of infants. All three studies found adverse pulmonary sequelae when higher oxygen levels were targeted including significantly more infants requiring prolonged assisted ventilation (34), remaining in oxygen at 36 weeks postmenstrual age (29, 34), requiring home oxygen (29), developing pneumonia or CLD exacerbation (28); or experiencing an adverse pulmonary event (defined as remaining on oxygen, steroids, diuretics, or in hospital at 3 months corrected age) (28).

Direct evidence for the beneficial effects of lower SpO₂ targeting on preventing, rather than treating established ROP, can only be drawn from three early trials which, when their data were meta-analysed in a Cochrane systematic review (24), showed a highly significant reduction in vascular retrolental fibroplasia in infants randomised to restricted rather than liberal oxygen exposure. Similarly the UK cohort study (34) found that lower saturation targeting from birth significantly reduced the incidence of threshold ROP. There have, however, been no randomised trials that have directly assessed the effect of lower oxygen saturation targeting from birth on ROP rates.

The effect on mortality of keeping SpO₂ lower from birth is more difficult to assess, as some early trials either did not enrol infants until after 48 hours of age or did not report mortality data. The available data show no difference in early mortality for restricted versus liberal oxygen exposure (24). Indirect evidence from the UK cohort study (34) revealed no adverse effect on survival to infancy when lower saturation ranges were targeted from birth. The two recent randomised trials assessing the effects of differing oxygen saturation targeting ranges for preterm infants in their chronic phase, STOP-ROP (28) and BOOST (29), found no significant differences in death rates, although both trials had little statistical power to assess this secondary outcome.

Conclusions

In preterm infants, ROP rates may be reduced if lower saturation ranges are targeted in the early weeks of life. ROP outcomes may also be improved if oxygen saturation is targeted higher in a subset of preterm infants with more severe eye disease in the post-acute phase. There is now direct evidence, from randomised trials, that routine higher oxygen saturation targeting in the chronic phase confers no short- or long-term growth or development benefits. Evidence, both direct and indirect, is now mounting regarding the adverse pulmonary sequelae associated with routine higher, and thus longer, oxygen exposure. There is inconclusive evidence regarding the effects on early mortality of targeting a lower SpO₂ range in the acute phase. The major unanswered question that now needs urgent
resolution is what are the important long-term effects of targeting lower compared with higher oxygen saturation ranges during the first days/weeks of an extremely preterm infant’s life (1, 3). Such an important clinical question can only be answered rigorously and definitively using the randomised trial methodology, a sample size of between two and four thousand infants would be required.

References
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