Oxygen Treatment for Immature Infants beyond the Delivery Room: Lessons from Randomized Studies

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Without supplemental oxygen, extremely preterm infants often have low arterial oxygen tension (PaO_2) or arterial oxygen saturation (SaO_2) compared with older children. Until recently, oxygen was administered to these infants in the early weeks after birth, with little evidence to balance the risks and benefits. Five large randomized controlled trials of lower (85%-89%) vs higher (91%-95%) pulse oximeter saturation (SpO_2) targets with masking of group allocation now provide high quality evidence to guide practice and serve as a baseline for future research. It remains the case that restriction of supplemental oxygen in pursuit of reduced morbidities in this patient group carries a mortality risk that outweighs any other benefit. The evidence reiterates the need for caution against creeping change in practice. This review will summarize the evidence base for present approaches to titrating supplemental oxygen for preterm infants, provide deeper insights into the interpretation of the evidence from the recent trials, and identify some future challenges in improving care in this area.

Background

When oxygen therapy was introduced into neonatal care, oxygen tensions could not be measured and administration was guided by clinical judgement. High concentrations were often administered for prolonged periods. Trial evidence that several weeks of exposure to high concentrations of oxygen increased the risk of severe retinopathy of prematurity (ROP) prompted more restricted administration, and in the subsequent period, there was an increase in neonatal mortality and cerebral palsy. It has been estimated that oxygen restriction may have resulted in the death of 16 infants for each case of blindness that was prevented,[1] although other factors probably also contributed to the association.[2]

The development of blood gas analyzers, transcutaneous oxygen tension ($TcPO_2$) monitors, and pulse oximeter saturation (SpO_2) monitors allowed controlled oxygen therapy, with titration of oxygen to target values, but trials were not done to establish the optimal targets or monitoring technology. Clinical guidelines were developed from observational data and recommended that PaO_2 should be maintained between 50 and 80 mm Hg (6.7-10.7 kPa),[3] and later that SpO_2 should be targeted to 85%-95%.[4] PaO_2 and SpO_2 are not linearly related, and these ranges cannot be considered equivalent. The PaO_2 range associated with the SpO_2 range 85%-95% in oxygen dependent preterm infants in the first 2 weeks after birth is 28.5-67 mm Hg (3.8-8.9 kPa).[5] This indicates that the switch from $TcPO_2$ monitoring targeting a PaO_2 range of 50-80 mm Hg to SpO_2 monitoring targeting a saturation range 85%-95% ushered in a second era of unrecognized oxygen restriction, unsupported by trial evidence. Because these changes in practice occurred gradually and in parallel with reductions in mortality associated with increased implementation of antenatal steroid therapy and refinements to surfactant administration, any effect on mortality from changes in practice regarding oxygen supplementation during this period is unlikely to be identifiable in retrospect.

In the 1980s, it was increasingly recognized that oxidative stress is not only related to oxygenation. A number of other factors such as activities of antioxyenzymes,[6] free radical systems,[7] free iron,[8] and inflammation[9] all contribute to increased oxidative stress in the newborn. This created new interest concerning the optimal oxygen levels of the newborn and increased recognition that the optimal oxygen levels for premature infants may be different to those for older children and adults.

With wider use of SpO_2 monitoring, observational data suggested that targeting lower SpO_2 might reduce the risk of ROP without affecting the risk of mortality or cerebral palsy.[10-12] In the absence of evidence from controlled trials, Silverman argued that there had never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants.[13] At the turn of the century, the time was right for randomized controlled trials of oxygen targeting.

AAP	Academy of Pediatrics
BOOST	Benefits of Oxygen Saturation Targeting
BPD	Bronchopulmonary dysplasia
COT	Canadian Oxygen Trial
NEC	Necrotizing enterocolitis
NeOProM	Neonatal Oxygen Prospective Meta-Analysis
PaO_2	Arterial oxygen tension
ROP	Retinopathy of prematurity
SaO_2	Arterial oxygen saturation
SUPPORT	Surfactant Positive Pressure and Oxygenation Randomized Trial
$TcPO_2$	Transcutaneous oxygen tension
UK	United Kingdom

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STOP ROP and the First BOOST Trial

Two trials randomized convalescent preterm infants to higher vs lower SpO_2 targets. The Supplemental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity (STOP ROP) trial[14] randomized preterm infants with prethreshold ROP at 35 weeks of gestation to lower (89%-94%) vs higher (96%-99%) SpO_2 targets. The hypothesis was that a higher oxygen tension at this later stage could retard the progression of established ROP. There was a small but clinically unimportant effect on ROP progression. The higher SpO_2 target was associated with more adverse pulmonary events and a greater number of infants still receiving oxygen or diuretics or still hospitalized at 3 months of corrected age.

The aim of the first Benefits of Oxygen Saturation Targeting (BOOST) Trial[15] was to determine whether maintaining SpO_2 at a higher level in extremely preterm infants with a long-term dependence on supplemental oxygen improved their growth and neurodevelopmental outcomes. Infants who were born before 30 weeks of gestation and who remained dependent on supplemental oxygen at 32 weeks of gestation were randomized to lower (91%-94%) vs higher (95%-98%) SpO_2 targets. There were no advantages in terms of growth and development in the higher target range, and it prolonged the duration of oxygen supplementation and increased resource usage. The BOOST trial masked the caregivers to the SpO_2 target range allocation of the infants by using offset oximeters that were adjusted to read 2% higher or lower than the underlying measured value.

Neonatal Oxygen Prospective Meta-Analysis

The 2 studies described above did not randomize infants to different oxygen saturation targets until several weeks after birth. It, therefore, became important to study the effects of different oxygenation from soon after birth. For this reason, the Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaboration was launched.[16]

Five trials randomized preterm infants born before 28 weeks of gestation from the day of their birth to lower (85%-89%) vs higher (91%-95%) SpO_2 target ranges until the infants reached 36 weeks of postmenstrual age. Close to 5000 patients were enrolled. Outcome data up to at least 18-22 months have now been published from all of the trials.[17-22] The trials were prospectively designed to be very similar to permit meta-analysis. Two meta-analyses of the results, including the follow up outcomes have been performed.[23,24] The NeOProM individual participant data meta-analysis of the trials adds value in addition to the Cochrane review because of the enhanced ability to consider sub-group effects provided by the availability of individual participant data for the analyses.[24] There was not significant heterogeneity between trials for key outcomes (**Table I**).

The primary outcome of the meta-analyses—a composite of death or disability (blindness, deafness, cognitive impairment, or cerebral palsy) was not significantly different between groups. However, infants randomized to the lower (85%-89%) SpO_2 target range had significantly increased risk of mortality (risk difference 2.8%) and increased risk of necrotizing enterocolitis (NEC) (risk difference 2.2%). Infants randomized to higher (91%-95%) SpO_2 targets had a higher risk of ROP requiring treatment (risk difference 4.2%). Although these differences are modest, the lack of heterogeneity between trials and statistical significance, with large patient numbers make them likely to be reliable. There was no difference between groups in the risk of blindness, cerebral palsy, or deafness.

Assessing the effect of the intervention on bronchopulmonary dysplasia (BPD) is difficult. Because the protocols required one group to achieve higher SpO_2 readings than the other until 36 weeks, it is not surprising that significantly more infants randomized to higher SpO_2 targets required supplemental oxygen at 36 weeks of postmenstrual age (risk difference 5.9%). This estimate is biased by the protocols. To overcome this limitation, physiological tests were used in the Surfactant Positive Pressure and Oxygenation Randomized Trial (SUPPORT)[17] and BOOST-II United Kingdom (UK)[20] trials to determine the number of infants in each group who required supplemental oxygen at 36 weeks of gestation to achieve a SpO_2 of 90%.[25,26] If analysis is restricted to these 2 trials, the difference between groups in risk of BPD is smaller and not statistically significant (risk difference 2.4%, $P = .29$, **Table II**). Severe BPD (a requirement for positive pressure support or more than 30% oxygen at 36 weeks of postmenstrual age after receiving supplemental oxygen for at least 28 days) was reported in the Canadian Oxygen Trial (COT). This measure of more severe BPD was biased by protocol for the same reasons. It was observed in 31.8% of low SpO_2 target group infants and 33.1% of high SpO_2 target infants in the COT and was also not significantly different between groups (risk difference 1.3%, $P = .64$).

Table I. Meta-analysis of the NeOProM trials[23]

Outcomes	SpO_2 85%-89%	SpO_2 91%-95%	Risk ratio	95% CI	*P*	I^2	Risk difference
Death or major disability	1218/2380	1170/2374	1.04	0.98-1.10	0.18	27%	1.9%
Death	484/2433	418/2440	1.16	1.03-1.31	.012	0%	2.8%
Major disability	734/1903	752/1964	1.01	0.93-1.09	0.80	22%	0.2%
Severe ROP	214/2022	305/2067	0.72	0.61-0.85	<.001	69%	4.2%
NEC	277/2464	223/2465	1.24	1.05-1.47	.011	0%	2.2%
Blindness	25/1910	23/1965	1.13	0.65-1.97	0.66	0%	0.1%
Cerebral palsy	106/1910	107/1967	1.02	0.79-1.32	0.88	20%	0.1%
Deafness	65/1905	66/1964	1.02	0.73-1.43	0.91	0%	0%

BSID-III, The Bayley Scales of Infant and Toddler Development–Third Edition.
Major disability was any of cerebral palsy with Gross Motor Functioning Classification System level 2 or higher, BSID-III composite cognitive or language score <85, blindness, or deafness. Severe ROP was disease >stage 3 or requiring treatment by laser photocoagulation, cryotherapy, or bevacizumab treatment. Definition of NEC was defined differently between trials.

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