

Optimal Oxygen Saturation for Preterm Babies

Do We Really Know?

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Key Words

Oxygen saturation · Pulse oximetry · Infant, premature · Randomized controlled trials

Abstract

Oxygen is the most commonly used 'drug' in neonatal units as an integral part of respiratory support. It has also been known for half of the century that it is easy to damage the eyes of preterm infants by giving too much oxygen especially in the first few weeks of life. Despite this knowledge there is still a wide variation in approaches to oxygen monitoring within neonatal units. A randomized controlled trial conducted more than 50 years ago first made clinicians aware of 'oxygen toxicity' in preterm infants, but no other controlled trial has ever been conducted since to clarify how much oxygen infants really need, or what oxygen saturation level is optimal in caring these preterm babies. Perhaps time has come for clinicians to resolve this 'uncertainty' by well-designed randomized trials.

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Introduction

Oxygen must have been given to newborn babies more than any other medicinal product over the past 60 years [1], but uncertainty continues as to the most appropriate

ranges to maintain oxygen levels particularly for preterm infants, or a threshold value below which oxygen should be administered [2, 3]. There is still a wide variation in practice of oxygen monitoring and therapy in the neonatal units, and this issue remains controversial among clinicians [4].

Historical Perspective

Joseph Priestley [5], together with Karl Scheele and Antoine Lavoisier, can be credited with the discovery in 1774 that the air we breathe contains a mixture of dephlogisticated or 'vital air' and 'gas azote'. The use of oxygen for newborn infants was first experimented as early as 1780 by Chaussier [6] and the 'routine' use of supplemental oxygen in the care of small or preterm infants had its origin in the early 1940s, influenced by a report published by Wilson et al. [7] indicating that the irregular pattern of 'periodic' breathing commonly seen in infants of short gestation was largely abolished when they were given 70% oxygen or more to breathe. Although the authors were cautious enough initially to note that they had no proof that the regular 'normal' respiratory pattern was better for preterm infants than the periodic type of breathing, the widespread use of unrestricted oxygen crept in by the late 1940s as a result of belief and recommendation that oxygen was the most valuable single agent available for any newborn infant showing any

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evidence of respiratory failure, and that it should be used early and generously [8].

Oxygen toxicity in low-birth-weight or preterm infants was first reported more than 50 years ago by the Australian clinician Kate Campbell [9] who concluded that the normal oxygen environment of the newborn full-term infant is not normal for premature infants. More convincing evidence came within a year from Mary Crosse and Philip Evans in Birmingham, England [10] and from the results of a randomised trial started in 1948 by Arnall Patz in Washington [11] in which babies weighing less than 3.5 pounds were alternately assigned when 24 h old to care in high oxygen (65–70% for 4–7 weeks) or less than 40% oxygen for as short a time as possible (1–2 weeks). Seven of the 28 babies nursed in high oxygen developed stage 3–4 retinopathy, but none of the 37 nursed in as little oxygen as possible. Many studies since then have tried to define what constitutes the safe level of arterial oxygenation. The larger Cooperative trial, designed to replicate Patz's trial and completed in 1955 [12] was widely interpreted at the time as suggesting that oxygen was safe as long as the concentration given was not more than 40% [13]. The fact that babies in one arm of the trial had not only had more oxygen but also had it for much longer was almost entirely overlooked. So was the fact that some babies in the restricted exposure arm still developed eye damage. Even more seriously, it took some time for clinicians to realise that a policy of restricting oxygen exposure rather than restricting arterial oxygen levels almost certainly caused an increase in the number of early neonatal deaths [14–16].

Oxygen Monitoring Policies

Although the Cooperative trial [12] validated the hypothesis that excess oxygen exposure was at least one of the causes of retinopathy, it did not clarify how the administration could be optimized. Clinicians therefore started to look for ways of monitoring arterial oxygenation levels.

Indwelling arterial catheters were soon being widely used but no controlled trial has ever shown that their use reduces the risk of retinopathy [2]. The technology to continuously measure partial pressure of oxygen by transcutaneous method (TcPO₂) was introduced in the 1970s. Later on, one trial was conducted to see if this method could reduce the risk of excessive oxygen exposure [17]. There was no evidence that it did, although subsequent analysis of some of the information collected in this trial

suggested that retinopathy occurred more often when the transcutaneous reading reached or exceeded 80 mm Hg (10.7 kPa) in the first 4 weeks of life [18].

Oxygen saturation monitoring using pulse oximetry has gained widespread use in neonatal units since the early 1980s [19] due to its ease of use and lack of heat-related side effects, particularly in extremely preterm infants with sensitive skin, despite very little evidence of its effectiveness on clinically important outcomes [2]. However, no randomised trials have been attempted to assess whether oxygen saturation monitoring in itself could reduce the risks associated with oxygen exposure in the neonatal period.

How Much Oxygen Is Appropriate in the First Month of Life?

Variations in Practice of Oxygen Saturation Monitoring

There is no consensus as to what clinicians feel as 'safe' maximum and minimum saturation for a small baby in the first few weeks of life. A survey carried out in United States by Vijaykumar et al. [20] in the early 1990s showed that about 80% of the tertiary neonatal units would like to keep maximum saturation at least 95% or higher, and perhaps more worryingly, 13% did not have any upper limit at all. Figure 1 shows similar variation in monitoring policies in the United Kingdom obtained by a survey carried out in 2001 [21].

Evidence from Recent Observational Studies

Policy has varied as dramatically in the north of England in the last ten years as in any other part of the UK, and some fairly provocative findings were reported from a prospective observational study of every baby born alive before 28 weeks' gestation to a mother resident in the north of England in 1990–1994 [22]. Nasal CPAP was not at that time being used in the initial post-delivery management of babies as immature as this. The babies were born in, or referred for care to, one of five neonatal units where most care policies were fairly similar, but policy towards the monitoring of oxygen saturation varied widely. Survival rates, and survival rates without evidence of cerebral palsy at 18 months, were almost identical in the five units in the 295/568 babies of 23–27 weeks' gestation (52%) still alive a year after birth (table 1).

In one unit target fractional oxygen saturation (for definition, see 'Appendix') was 80–90% (with the lower alarm limit set to operate if saturation fell below 70%)

Table 1. Outcome at one year in all babies of 23–27 weeks' gestation born in 1990–1994 and its relation to minimum and maximum pulse oximeter alarm settings

Oximeter alarm settings	Number of babies admitted	One-year survivors (number and percentage)			
		number of survivors	median number of days on ventilator	cerebral palsy	threshold retinopathy
88–98%*	123	65 (53%)	21	11 (17%)	18 (28%)
85–95%	235	128 (55%)	16	20 (16%)	20 (16%)
84–94%	84	37 (44%)	15	6 (16%)	5 (14%)
70–90%	126	65 (52%)	7	10 (15%)	4 (6.2%)

* Nellcor pulse oximeter measurements (functional saturation). Other measurements are fractional saturation.

Target saturation was in the upper half of the accepted range.

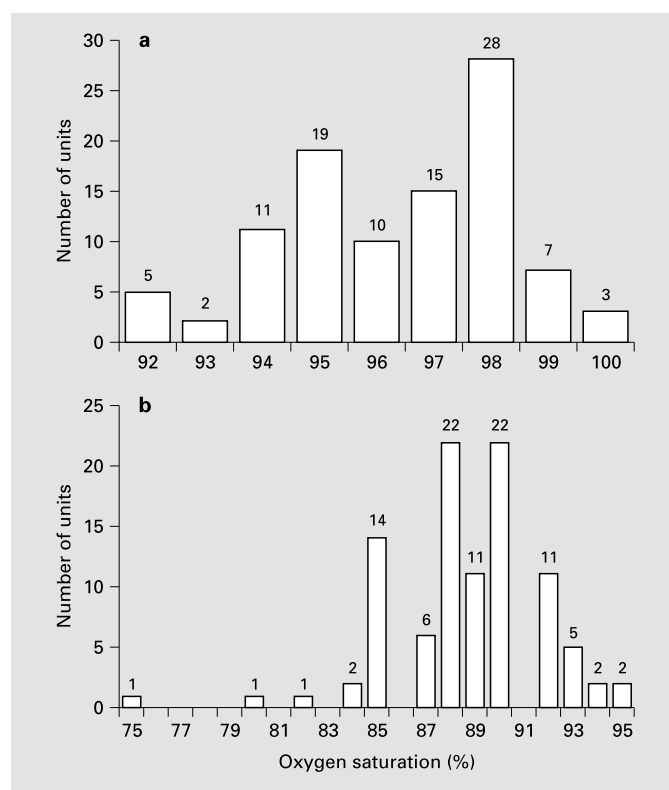


Fig. 1. Oxygen saturation monitoring policies in the UK. Results from a telephone survey of 100 units with 3 or more intensive care cots caring for babies of less than 28 weeks' gestation in 2001. High (a) and low (b) oximeter alarm settings. From Tin et al. [21], with permission.

once the baby was more than 2–3 h old. Such a policy was sustained for all babies thought to need supplemental oxygen until retinal vascularisation was complete. In another unit target functional oxygen saturation (for definition, see 'Appendix') was 94–98% (with the lower alarm set to

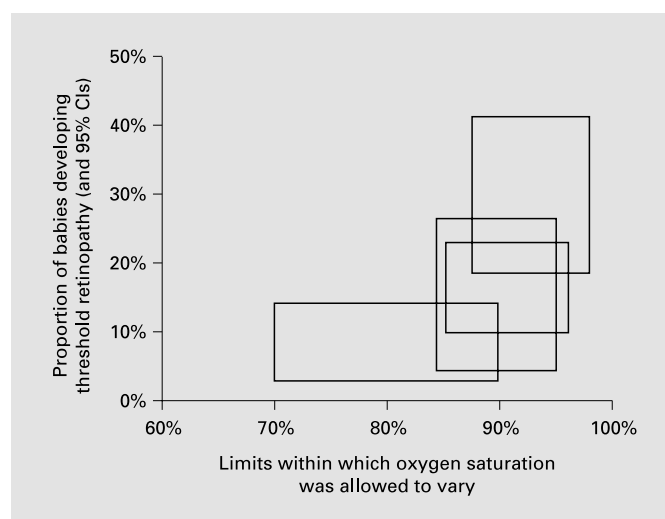
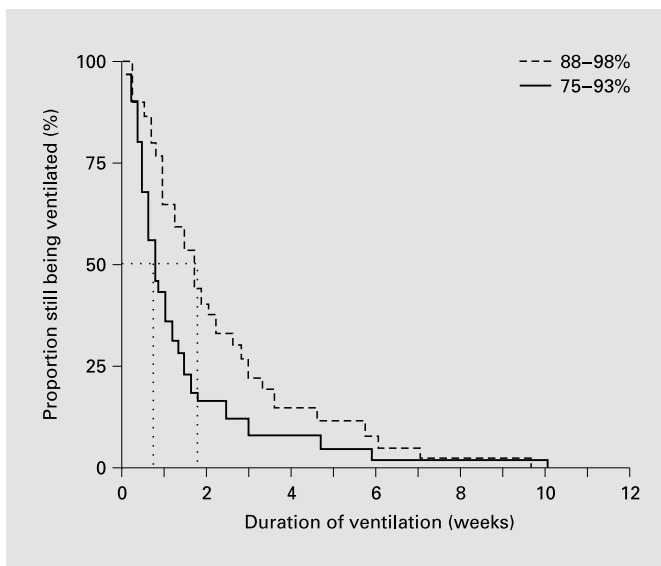


Fig. 2. The relation between the limits within which oxygen saturation was allowed to vary and the proportion of 1-year survivors who later developed severe (grade 3+) retinopathy of prematurity; a comparison of four policies. Staff aimed to keep saturation in the upper half of the allowed range. Reproduced with permission from BMJ Publishing Group [22].

operate at 88%). The other units had intermediate policies. Careful, uniform, ophthalmological review of all the survivors showed that retinopathy severe enough to merit treatment with cryotherapy occurred in 6.2% (95% CI 1.7–15%) of the babies in the unit with oximeter alarm setting 70–90%, and in 28% (95% CI 17.3–40%) in the unit with alarm setting 88–98% (fig. 2). No child from the first unit, but four from the latter unit became blind. The units employing intermediate policies for target oxygen saturation had 'threshold' retinopathy rates in the middle of this range.

Table 2. Summary of recent observational studies showing the potential benefits of lower SpO₂ targeting

Reference	Study group	Oxygen saturation ranges compared	Survival	Chronic lung disease	Retinopathy (stage 3–4)	Retinopathy (treatment)
Tin (2001) [22]	≤27 weeks' gestation	low: 70–90% high: 88–98%	53% 52%	18% 46% p < 0.001	6% 27% p < 0.001	
Sun (2002) [23]	≤1,500 g	low: ≤95% high: >95%	83% 76%	27% 53% p < 0.0001	10% 29% p < 0.0001	4% 12% p < 0.0002
Anderson (2002) [24]	≤1,500 g >2 weeks old	low: ≤92% high: >92%			2.4% 5.5% p < 0.001	1.3% 3.3% p < 0.0001
Chow (2003) [25]	500–1,500 g	low: 85–93% high: 90–98%	88% 81%		2.5% 12.5% p < 0.01	0–1.3% 4.4% p < 0.001

**Fig. 3.** The length of time babies of 24–27 weeks' gestation were ventilated in 1995–1996 (when the upper and lower oximeter alarms were set at 98 and 88%) and in 1998–2000 (when the alarms were set at 93 and 75%). From Tin et al. [21], with permission.

In the unit where target oxygen saturation was 80–90%, half of the 65 long-term survivors were managing without ventilatory support by seven days, and without supplemental oxygen by 30 days. In the unit where target oxygen saturation was 94–98%, these milestones were achieved by half the survivors in 21 and 72 days, respec-

tively. Neurodevelopmental outcome was similar at 18 months (no child was lost to follow-up) [22].

When the results of this analysis first became known, the unit that had been maintaining its functionally calibrated oximeter alarm settings at 88–98% modified its practice, and lowered these settings to 75 and 93%. In the years 1995–1996, before the change in policy, half of the surviving babies of 25–27 weeks' gestation were ventilated for more than 13 days. In the years 1998–2000 inclusive, half the babies were weaned from ventilatory support by the time they were 5 days old, even though there had been no other change in unit policy during this time (fig. 3) [21]. This within-unit change over time is comparable to the between-unit difference seen in 1990–1994, strengthening the suggestion that accepting a lower target saturation may make it possible to halve the time it takes to wean babies from ventilatory support.

Observational studies from United States, published after the North of England study, also showed the potential short-term benefits of targeting lower oxygen saturation in the early life of preterm babies [23–25] (table 2).

Upper Saturation Limit

There is, unfortunately, no controlled trial evidence with which to shape policy. The observational study from the north of England [22] suggests that the risk of retinopathy increases when fractional oxygen saturation is allowed to exceed ~90% in the first few weeks of life, a figure in line with an earlier observational study [18] suggesting an increase when transcutaneous partial pressure reached or exceeded 80 mm Hg (as shown in fig. 4, frac-

tional oximeter readings above 92% can be associated with partial pressures of 80 mm Hg or more [26, 27]). Nevertheless, only a controlled trial can ever establish whether some unrecognised factor other than the difference in target oxygen saturation was responsible for the observed difference in incidence of retinopathy and difference in duration of ventilatory support and requirement of supplemental oxygen.

Lower Saturation Limit

If there is uncertainty as to what constitutes the safe upper limit for fractional oxygen saturation, there is even greater uncertainty as to what constitutes the lower safe limit. The North of England observational study [22] was too small to address this issue, but it did suggest that a more permissive approach to minor hypoxia may, like a permissive approach to hypercapnia, reduce the need for ventilatory support, the consequential risk of chronic lung disease, and the associated health care costs. The levels discussed here are all higher than the retina, and the brain, would normally experience during fetal life.

How Much Oxygen Is Appropriate for Babies over a Month Old?

Evidence from Recent Randomized Controlled Studies

Two trials have recently been conducted to see whether it is better to keep arterial oxygen saturation high in very preterm babies when they are more than a few weeks old. The American STOP-ROP trial [28] recruited 649 babies with a mean gestational age of 25.4 weeks and mean age of entry into the trial was about 35 weeks' postmenstrual age. This study carried out between 1994 and 1999 showed that keeping fractional oxygen saturation above 95% slightly reduced the number of babies with pre-threshold retinopathy who went on to develop disease severe enough to require retinal surgery. However, benefit was only seen in those without evidence of 'plus disease' (dilated and tortuous vessels in at least two quadrants of the posterior pole) at recruitment (32 vs. 46%). More unexpectedly the higher oxygenation target significantly increased the number in hospital, in oxygen, and on diuretics at a postmenstrual age of 50 weeks. Significant pulmonary deterioration after recruitment (13.2 vs. 8.5%) was only seen in those with more than average evidence of chronic lung disease at trial entry. The higher oxygenation target did not improve growth or the eventual retinal outcome as assessed 3 months after the expected date of delivery [28].

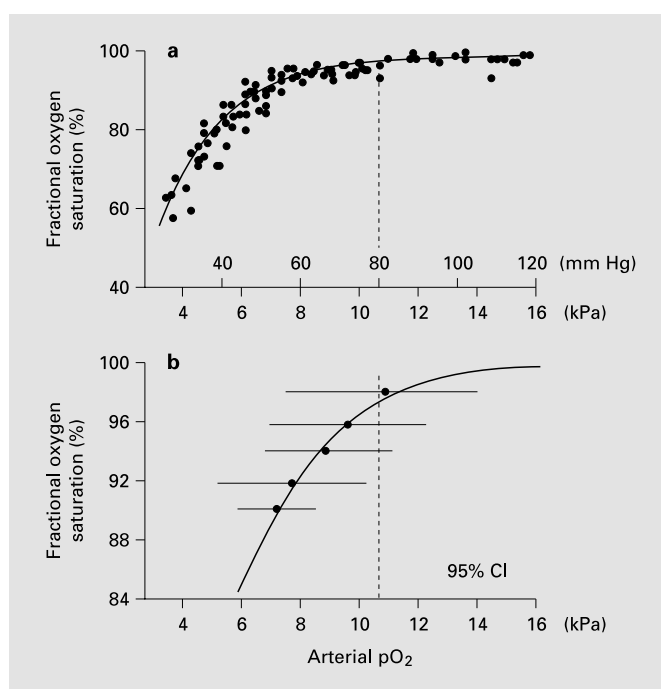


Fig. 4. a The relation between fractional oxygen saturation measured with a pulse oximeter, and arterial partial pressure in mm Hg and kPa. The dashed line marks the transcutaneous PO_2 above which there was an increased risk of retinopathy in the study reported by Flynn et al. [18] in 1992. **b** The bars show the range within which 95% of all measures of partial pressure varied when the oximeter read 90, 92, 94, 96 and 98% in the study reported by Brockway and Hay [27]. Note that pulse oximeters calibrated to display functional saturation produce readings about 2% higher than those reflecting fractional saturation. Reproduced from Neonatal Formulary, with permission from BMJ Books.

The Australian BOOST (Benefit Of Oxygen Saturation Targeting) trial has just been reported [29]. There was no evidence that growth and developmental outcome of babies of less than 30 weeks' gestation at birth who were still oxygen dependent at a postmenstrual age of 32 weeks was improved by keeping their functional oxygen saturation in the high 90s. This randomized, double-blind, multicentre study recruited 358 babies between 1996 and 2000; collaborating units had different policies with regard to optimum oxygenation in the period immediately after birth (as in the STOP-ROP trial), but all monitored saturation using a pre-specified Nellcor N-3000 pulse oximeter after recruitment for as long as supplemental oxygen was deemed necessary. Trial oximeters were specially modified to keep functional saturation in the range 91–94% or 95–98%, depending on allocation at entry, while displaying a figure in the range 93–96%.

This finding contradicts the substantial body of observational evidence suggesting that higher oxygen targeting can improve growth [30], ameliorate sleep pattern abnormalities [31] and reduce desaturation episodes [32].

Resolving the Uncertainty

Perhaps the time has come to admit our ignorance (for more than half a century) of how to optimize the delivery of supplemental oxygen to the very preterm baby, and agree to use the tool best suited to addressing that uncertainty, viz. a randomized controlled trial.

A trial, provisionally known as POST-ROP, is being planned to attempt to fill this evidence gap by assessing the effects of targeting lower saturation in early life of preterm babies. The POST-ROP trial aims to enroll babies of less than 28 weeks' gestation (since gestation rather than weight is the best predictor of serious morbidity including retinopathy) and randomize them within a few hours of birth to a target oxygen saturation range of either 85–89% or 91–95%. This intervention will continue until 32 weeks postmenstrual age or until they are stable in room air. The recent BOOST trial [29] successfully used masked oximeters in order to ensure double blinding of treatment allocation. The POST-ROP trial plans to use a similar study design that entails the use of Masimo Radical pulse oximeters whose display values will be offset by either +3% or –3%. Caregivers will then be asked to target an enrolled infant's saturation in the blinded target range of 88–93%. Whilst this technique appeared to be well ac-

cepted by BOOST trial participants, the feasibility of using this method in more acutely ill infants needs to be carefully piloted to ensure the cooperation of both parents and staff. Masimo oximeters employ Signal Extraction Technology (SET) and appear to significantly reduce false positive alarm rates [33] which should also enhance staff acceptance of the study oximeters. Primary outcome in the POST-ROP trial is severe retinopathy needing retinal surgery, death and survivors with severe disability (pre-defined), with several clinically important secondary outcomes.

Conclusion

Collaboration across three continents helped Kate Campbell identify the cause of retinopathy in the preterm baby [9]. It seems likely that similar collaboration to mount a large and well-designed randomized trial will be required a second time to optimise the use of oxygen – a product capable of doing great harm as well as great good.

Appendix

$$\text{Fractional SaO}_2 = \frac{\text{HbO}_2}{\text{HbO}_2 + \text{Hb}} \times 100$$

$$\text{Functional SaO}_2 = \frac{\text{HbO}_2}{\text{HbO}_2 + \text{Hb} + \text{HbCO} + \text{Met Hb}} \times 100$$

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