

# Optimal Oxygenation at Birth and in the Neonatal Period

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## Key Words

Childhood cancer · Newborn resuscitation · Room air · 100% oxygen · Extremely low birth weight infants · SaO<sub>2</sub>

## Abstract

**Background:** In recent years it has become clear that even a brief exposure to high oxygen concentration at birth and an oxygen saturation (SaO<sub>2</sub>) >93–95% in extremely low birth weight (ELBW) infants is more toxic than previously believed. **Objective:** To summarize and review clinical studies published to date either dealing with resuscitation of newborn infants with different oxygen concentrations or the use of high or low SaO<sub>2</sub> in the neonatal period of ELBW infants. **Results:** Three systematic reviews of five trials and seven individual studies including up to 2,011 newborn infants have shown that neonatal mortality is reduced by 30–40% if resuscitation is carried out with 21% instead of 100% O<sub>2</sub>. Room air resuscitation also leads to faster early recovery and need for shorter duration of resuscitation. Six studies of ELBW infants have shown that retinopathy of prematurity and chronic lung disease are significantly reduced if SaO<sub>2</sub> is kept <93–95% compared with higher saturations. Avoidance of fluctuations in SaO<sub>2</sub> also seems to be important. Two observational studies suggest a significant 2.5- to 3.5-fold increased risk of childhood cancer in infants resuscitated with

100% O<sub>2</sub> for a few minutes. **Conclusions:** To date there are sufficient data available to recommend that newborn resuscitation should not be carried out with 100% O<sub>2</sub>. In ELBW infants, SaO<sub>2</sub> levels should be kept between 85 and 93% or possibly between 88 and 95%, but should definitely not exceed 95%. Fluctuations should be avoided.

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## Introduction

Oxygen produced by photosynthesis started more than 2.3 billion years ago before the atmosphere changed from anoxic to become oxygen-rich. However, it is not more than 230 years since it was first described as an element by Priestly and Scheele, although alchemists probably already knew about it 150 years earlier [1].

Oxygen was quickly used as a drug to treat a number of conditions despite the fact that Priestly understood that too much oxygen may have detrimental effects. More than 200 years later we still do not know exactly how and why oxygen is toxic [2]. It has been understood from the early 1950s that oxygen is especially toxic to preterm infants and it has been identified as a risk factor for retinopathy of prematurity (ROP) and subsequently also a risk factor for chronic lung disease (CLD). However, only

in the last decade have we started to suspect that oxygen is perhaps more toxic than we believed to infants born near or at term [3]. It seems that even a brief exposure to oxygen at birth with a typical duration of only 3–10 min may trigger long-term effects in newborn infants.

The normal newborn and infant, at least during the first 6 months of life, seems to have an increased oxidative stress compared with later in infancy and in adult life [4]. The reason for this is unclear but it indicates that redox processes are important regulators of growth and development. They also may play an important role in the development of disease processes such as cancer that may strike the individual later in life. So far, only an association between childhood cancer and oxygen exposure at birth has been identified. However, whether oxygen given for resuscitation of newborn infants is associated with cancer or other diseases later in life beyond childhood has to date not been studied.

### Mechanisms

More than 50 years ago, Gerschman et al. [5] hypothesized that oxygen is toxic because it generates oxygen radicals. This hypothesis is now accepted; however, some of the mechanisms probably are complicated and today we know that there are a number of reactive oxygen and nitrogen species that may be toxic. Furthermore, we know that a number of systems may generate reactive oxygen species. It is more than 20 years since we discovered that reactive oxygen species are not only bad but also needed in regulation of normal biochemical and physiological processes. Oxygen radical systems play a role in regulating vascular beds such as the pulmonary circulation and the ductus arteriosus [6, 7].

In the newborn the most important pro-oxidative factors seem to be oxygen itself, inflammation and a reduced intracellular defense (especially in preterm infants). Some of these infants also are exposed to free iron that may further promote oxidative stress. The most important antioxidative factors are glutathione, uric acid, bilirubin and the antioxidant enzymes that predominantly are intracellular [for details and review, see 8].

The redox balance therefore should not be changed artificially until we know exactly any short- and long-term consequences of such a change. Today we know that use of pure oxygen for resuscitation at birth induces inflammation in the lungs, heart and brain. Metalloproteinases and cytokines are activated. Free radical production increases and antioxidant defense is reduced, for ex-

ample in the brain and the lungs [9]. Brain injury assessed by glycerol in microdialysate in the brain of newborn piglets seems also to be greater after use of 100% compared with 21% O<sub>2</sub> [10]. In humans, myocardial and renal injuries are increased in those resuscitated with 100% compared with 21% O<sub>2</sub> [11]. Oxidative stress is increased during the whole neonatal period in babies who needed resuscitation and were exposed to a few minutes of 100% O<sub>2</sub> at birth [12, 13].

This new insight into the significance of oxidative stress in the newborn period has led to new interest and research activity especially regarding the optimal oxygen saturation (SaO<sub>2</sub>) for extremely low birth weight (ELBW) infants and what FiO<sub>2</sub> one should use for newborn resuscitation. So far, the association between use of oxygen and childhood cancer has not triggered much interest among pediatric oncologists, although it has been suggested that the most efficient way to limit childhood cancer is to reduce oxygen exposure during resuscitation at birth [14].

### Oxygen for Newborn Resuscitation

To date, three meta-analyses and systematic reviews of resuscitation of newborn infants with room air or 100% oxygen have been published [15–17]. They report outcomes of >2,000 newborn infants enrolled into randomized or quasi-randomized studies. Odds ratios (OR) for neonatal mortality favoring room air vary from 0.57 to 0.63 with adjusted relative risks of about 0.70. Thus all these reviews show that use of 21% O<sub>2</sub> for newborn resuscitation dramatically and significantly reduces neonatal mortality compared to conventional resuscitation with 100% O<sub>2</sub>. Table 1 summarizes the main results of these studies. In the most recently published meta-analysis [17], not only neonatal mortality but also first-week mortality was reduced in those resuscitated with room air. Figure 1 shows OR with 95% confidence intervals (CI) for both first- and fourth-week mortality from this study [17].

There is no difference in the risk of developing hypoxic ischemic encephalopathy between groups of infants resuscitated with 21 or 100% O<sub>2</sub>. However, those given 21% O<sub>2</sub> took their first breath 30 s earlier than those given 100% O<sub>2</sub>, having a significantly higher heart rate at 90 s and a higher 5-min Apgar score. Their duration of resuscitation was also shorter [16, 17]. Few data are available for preterm infants and these studies are ongoing.

**Table 1.** Newborn resuscitation with 21% or 100% O<sub>2</sub>: risk of neonatal death

Group (first author)	RR or OR (95% CI)	Enrolled n	Studies n
Tan, 2004 [15]	RR 0.71 (0.54–0.94)	1,302	5
Saugstad, 2005 [16]	OR 0.57 (0.42–0.78)	1,737	5
Rabi, 2007 [17]	OR 0.63 (0.43–0.92)	2,011	7

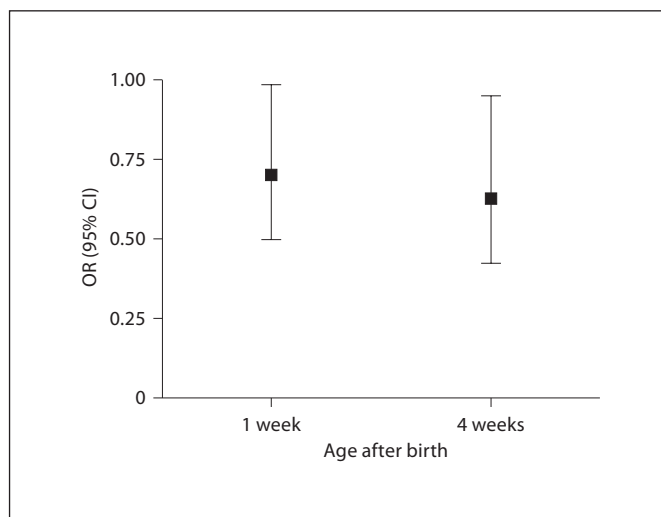
Odds ratio (OR) or relative risk (RR) with 95% CI for neonatal mortality of three systematic reviews studying the effect of resuscitation of newborn infants with 21% or 100% O<sub>2</sub>. Values <1 show significant benefit of 21% O<sub>2</sub>.

### Optimal SaO<sub>2</sub> in the Postnatal Period for ELBW Infants

At least six studies [18–23] and a couple of abstracts have now studied effects of high or low arterial SaO<sub>2</sub> in ELBW infants. Most of these data were recently reviewed [24]. No difference in survival has been found. However, the incidences of both ROP and CLD are significantly reduced in infants with SaO<sub>2</sub> levels kept between 85 and 93% versus those with >92–95%. In one study it was shown that strict control of SaO<sub>2</sub> limits and avoidance of its fluctuations virtually eliminated the need for treatment of ROP in the low saturation group [20]. One recent prospective study shows a significantly lower mental developmental index in those ELBW infants with high vs. low SaO<sub>2</sub> [25]. There is however still a lack of randomized controlled trials although these are now in progress.

### Oxygen at Birth and Cancer

Two large studies, one from Sweden and one from the USA, have shown a significant association between oxygen exposure during resuscitation at birth and childhood cancer. In the Swedish study by Naumburg et al. [26], resuscitation with 100% O<sub>2</sub> using a face mask and bag immediately after birth was significantly associated with an increased risk of childhood lymphatic leukemia (OR 2.57, 95% CI 1.21–6.82). If the ventilation lasted for 3 min or more the OR was 3.5 (95% CI 1.16–10.80). In the study from the USA by Spector et al. [27], a hazard ratio of 2.9 (95% CI 1.46–5.66) for any childhood cancer developing at age <8 years was found when oxygen exposure at birth for resuscitation lasted 3 min or longer.



**Fig. 1.** Meta-analysis of neonatal mortality for seven studies including 2,011 infants resuscitated with 21 or 100% O<sub>2</sub>. Odds ratio (OR) <1 favors 21% O<sub>2</sub>. Adapted from Rabi et al. [17].

### Conclusion

Today there is clear evidence that use of high oxygen concentrations at birth for term or near-term babies and in the postnatal course of the most immature infants significantly increases mortality and morbidity. Therefore I believe that there are sufficient data to warn about the use of high oxygen concentrations in these circumstances. In a recent Swedish study it was also shown that early recovery was faster in newborn babies resuscitated with 40% compared with 100% O<sub>2</sub> [28]. Some animal data, however, strongly indicate that even 40% O<sub>2</sub> may have detrimental effects.

In clinical practice this means that use of 100% O<sub>2</sub> should no longer be routine for newborn resuscitation [29]. Several national and local guidelines now recommend starting with 21% O<sub>2</sub> and adding supplementary oxygen if the infant is not responding adequately within 90 s [30]. SaO<sub>2</sub> normally increases from around 60–70% at 1 min of age to 90% within 5–10 min of life [31]. So far this is the best and closest ‘guess’ of which SaO<sub>2</sub> one should aim for immediately after birth. However, for pre-term infants, especially those <1,000 g, no data are available. SaO<sub>2</sub> for ELBW infants should until further evidence is available not exceed 93–95% and fluctuations should be avoided. In this way both CLD and severe ROP should be reduced quite dramatically without long-term sequelae. This is a cheap and simple way to reduce newborn mortality and morbidity.

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