

Commentary

Air or 100% oxygen for asphyxiated babies? Time to decide

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Abstract

Both experimental and clinical studies have demonstrated that room air is as efficient as 100% oxygen for newborn resuscitation and improves short-term recovery. The recent meta-analysis by Davis and colleagues in the *Lancet* includes five studies from the past 10 years where asphyxiated infants were randomised or pseudo-randomised to be resuscitated in room air or in 100% oxygen. A significant reduction in mortality was seen when infants were resuscitated in room air compared to 100% oxygen. It is astonishing that a brief exposure of only a few minutes to 100% oxygen may be so toxic to the newborn infant; this finding, however, is supported by increasing evidence from experimental work emphasising that resuscitation in 100% oxygen may be associated with an aggravation of cellular injury when compared with resuscitation in air. It is imperative that these findings are reflected in the new newborn resuscitation guidelines and that further research continues in this area of neonatal medicine. Key areas include defining the best resuscitation practice for the preterm infant, designing adequate multicentre, randomised and blinded studies of term newborn resuscitation with adequate outcome data, and pursuing intense experimental research into the mechanisms and prevention of injury from oxygen free radicals.

Around 5–10% of all newborn infants born worldwide require some degree of resuscitation at birth, ranging from simple stimulation to assisted ventilation. Defining the optimum technique for neonatal resuscitation is an extremely important challenge and has the potential to improve neonatal outcome globally. In the past two decades, neonatal research has established that, if assisted ventilation is required, room air is as efficient as 100% oxygen for newborn resuscitation. The meta-analysis published in the *Lancet* [1] goes further and suggests that mortality is lower in newborn infants resuscitated in room air compared with those resuscitated in 100% oxygen. One death would be prevented for every 20 babies resuscitated with air versus 100% oxygen. Several hundred thousand deaths might be prevented by avoiding 100% oxygen during resuscitation. It is astonishing that a brief exposure of only a few minutes to 100% oxygen may be so toxic to newborn infants. A brief review of the experimental, basic science and clinical literature on this

subject adds weight to this finding. It is imperative that newborn resuscitation guidelines are now revised.

The process of childbirth is accompanied by increased oxidative stress, as birth itself is a hyperoxic challenge. The fetus transfers from an intra-uterine hypoxic environment with a pO_2 of 20–25 mmHg to an extra-uterine environment with a pO_2 of 100 mmHg.

During the 20th century it became traditional to use 100% oxygen to resuscitate infants in hospitals because labour wards only had oxygen as a compressed gas [2,3]. It seemed logical and intuitive to reverse the anaerobic state as quickly as possible with 100% oxygen because 18–19 times more ATP is produced from glucose during aerobic metabolism than during anaerobic metabolism. However, following the discovery of the link between retinopathy of prematurity and the liberal use of supplemental oxygen therapy, controversy has surrounded the use of oxygen in neonatology [4,5].

There was considerable interest in the 1930s in the 'oxygen paradox' – the concept that tissue injury may be aggravated when 100% oxygen is administered following a significant period of hypoxia ischaemia. The link between oxygen and the generation of oxygen free radicals (OFRs) was an immense leap forward [6,7]. Following transient hypoxia ischaemia and reperfusion/reoxygenation, OFRs are generated by the xanthine oxidase system; their production is dependent on the tissue concentration of oxygen, hypoxanthine and other purines [8]. OFRs are cytotoxic because they have the ability to interact with and alter the principal components of cells including proteins, lipids, carbohydrates and DNA [9]. In addition, OFRs play an important role in apoptosis and necrosis [10]. Mammals have developed different mechanisms of protection against OFRs such as scavengers, repair agents, reduced glutathione, antioxidants and antioxidant enzymes (glutathione epoxidase, catalase, superoxide dismutase). The neonatal brain, in particular the preterm brain, is vulnerable to oxidative damage due to its high concentrations of

unsaturated fatty acids, its low concentration of antioxidants and the availability of redox-active iron [11].

Over the past 20 years the Norwegian group led by Ola Saugstad used the newborn piglet model to compare the *in vivo* effects of resuscitation with room air versus resuscitation with oxygen. Restoration of basic biochemical and physiological variables after hypoxia was shown to be as quick with reoxygenation with room air as with 100% oxygen [12]; furthermore, the production of OFRs was higher in leukocytes in the 100% oxygen group. In 2001, piglets with pneumothorax-induced asphyxia resuscitated in air were shown to have better short-term neurological outcomes than animals resuscitated in 100% oxygen [13]. Other studies show apparent increased brain injury (measured by cerebral leakage of glycerol) in conjunction with a reduced antioxidant capacity in cerebral tissue in animals resuscitated in 100% oxygen compared with those resuscitated in air [14].

The important findings to emerge from three clinical studies are that room air is as effective as 100% oxygen for resuscitation of the newborn [15–17] and may be superior to 100% oxygen in terms of both physiological and pathological effects. A new and surprising finding was that the use of 100% oxygen delayed the time to first breath and cry compared with the room air [15–17], and infants resuscitated with room air required less time of ventilation to achieve a regular respiratory pattern compared with those resuscitated with 100% oxygen. In addition, resuscitation with 100% oxygen had long-term effects on oxidative stress (oxidation of blood glutathione) up to 4 weeks following birth, whereas those resuscitated in air did not [17]. Oxidative stress may also induce DNA damage; this could explain why an association has been seen between delivery room oxygen exposure and later childhood lymphatic leukaemia [18].

The recent systematic review and meta-analysis published in the *Lancet* [1] combining data from five clinical trials [15–17,19,20] that compared resuscitation with air versus 100% oxygen demands that we re-examine our current practice and guidelines. Although no individual trial included in this meta-analysis was adequately powered to show a difference in mortality, the pooled analysis of 1302 infants (randomised or pseudo-randomised) showed a significant benefit for infants resuscitated with air (relative risk, 0.71; 95% confidence interval, 0.54–0.94). A second meta-analysis involving the same five studies but with different inclusion criteria found a similar reduction in neonatal mortality with room air resuscitation, even in those with an Apgar score <4 at 1 min [21]. In their last consensus statement published in 2000 [22], the American Academy of Pediatrics along with the American Heart Foundation and the International Liaison Committee for Resuscitation recommended the use of 100% oxygen during positive pressure ventilation as "... data is insufficient to justify a change ...". In the next year we are expecting new guidelines

from the International Liaison Committee for Resuscitation – it is time to change.

Many questions, however, remain unanswered.

What is the optimal concentration of oxygen for resuscitation of asphyxiated infants? Is it the same for infants who are mildly asphyxiated as for those who are severely asphyxiated? Further trials are needed that stratify the severely asphyxiated subgroup. If the main aim is to achieve normal levels of blood oxygen throughout and beyond the resuscitation period, routine use of the pulse oximeter in the labour ward will be needed to tailor oxygen delivery to each infant.

Can the results of the meta-analyses be applied generally? Most infants in the meta-analyses were recruited in developing countries where antenatal and perinatal care, resuscitation practices and perinatal mortality rates differ from those in developed countries.

Do resuscitation practices make a difference to neuro-developmental outcome – this has not been addressed and will be difficult to address accurately as detailed follow-up is required on a large scale. Future trials must include detailed neurodevelopmental outcome scores at 18–24 months.

How should we resuscitate the preterm infant? The preterm brain is likely to be even more vulnerable to the adverse effects of hyperoxia compared with infants born at term due to the extreme vulnerability of the pre-oligodendrocyte to oxidative stress, the very low antioxidant levels in the preterm brain and excess free iron due to the commonly associated intraventricular haemorrhage. There is insufficient evidence at present, however, to make any recommendations for resuscitation of preterm infants.

To resolve these important questions, further clinical trials are needed; it may not be ethical to include a comparison of air versus 100% oxygen, and a midpoint such as 50% oxygen may be required. Intense and detailed experimental studies are also required to facilitate a clearer understanding of mechanisms of damage. These studies must be correlated with detailed brain histology.

It is more than 200 years since oxygen was discovered by the English clergyman and amateur chemist, Joseph Priestly. At the time Priestly warned against oxygen, saying: "... the air which nature has provided us may be as good as we deserve". The recent meta-analyses [1,21], taken in the context of two decades of translational research, strongly suggest that our practice of resuscitating term infants who need positive pressure ventilation in 100% oxygen should be avoided in most cases. Room air appears to be safe. The discovery that mortality is lower in asphyxiated infants resuscitated in room air is a tremendous advance in neonatal medicine and newborn resuscitation guidelines and practice need to be revised globally.

Competing interests

The author(s) declare that they have no competing interests.

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