

Oxygen therapy in the newborn period represents a challenge

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Oxygen is one of the most widely used drugs in medicine, and especially so in the newborn period. In many cases, oxygen supplementation is needed and is life-giving, but we are also aware of its toxic effects. In spite of this, we still do not know exactly what is the correct way to administer this drug.

It is a problem that oxygen was introduced, e.g. for newborn resuscitation, without the support from data collected from scientific studies. Today it has become increasingly clear that extreme care should be exercised when administering oxygen to any newborn infant, even for a brief period.

It is a potent drug with long-lasting adverse effects. Today we need to define the correct dose and duration of oxygen therapy, both for term and for premature babies after birth and the optimal oxygen concentration during resuscitation.

The following two questions will therefore be addressed: What is the **1)** optimal oxygen saturation limits for preterm infants with extremely low birth weight, and **2)** optimal oxygen concentration for newborn resuscitation.

Oxygen

Oxygen was probably discovered and described already in 1604 by Polish alchemist Sendivogius, who heated nitre and released what he called aerial nitre. Sendivogius described this substance as "*the Elixir of life without which no mortal can live*". This was approximately 170 years before Scheele and Priestly, who up to now have been honored as the discoverers of oxygen [1].

After the experiments of Scheele, Priestly and especially Lavoisier, oxygen quickly came into use in adult medicine. When oxygen was introduced in newborn medicine almost 100 years ago, no critical questions seemed to be raised. When the relation between retinal damage (retinopathy of prematurity = ROP) and high oxygen in premature infants was detected more than 50 years ago, this resulted in a more careful approach regarding oxygen supplementation in these babies.

In spite of this, the optimal oxygen saturation in which we should nurse such babies is still not known.

Even fewer questions were raised regarding the use of

oxygen for resuscitation of the newborn. Even as recently as a decade ago, the American Heart Association stated that a brief exposure of 100 % oxygen around birth does not represent any risk.

But today we are slowly beginning to understand that this might not be so. Both clinical and experimental studies in the past decade have brought this field forward, and more clinical studies are now planned.

While awaiting the results and conclusions of these studies we may still draw some conclusions regarding the use of oxygen in the newborn period.

Oxygen saturation in extremely-low-birth-weight infants
Five studies have so far systematically investigated the effects of high or low oxygen saturation in the postnatal/neonatal period of extremely-low-birth-weight infants. These studies all have different designs, but some general conclusions may still be drawn. All of them equivocally indicate that high oxygen saturations give more ROP stage 3-4 and more pulmonary problems.

The article by Tin *et al* [2] investigated infants with gestational age between 23 and 27 weeks and compared outcome in those nursed in NICUs using high (88-98 %) saturation limits with those nursed in low (70-90 %) saturation limits. In the high-saturation group there were four times more severe ROP (27 vs. 6 %) and more than two times more chronic lung disease (46 vs. 18 %).

The high-saturation group needed twice as many days in oxygen and on ventilator; in addition, growth was poorer in this group compared with the low-saturation group. Survival and rate of handicap did not differ between the groups.

Askie *et al* [3] studied < 30-week infants, but they were not randomized to a standard (90-94 %) or a high (95-98 %) SpO_2 until the postconceptional age of 32 weeks. There were no differences in growth or severe ROP; however, those in the high-saturation group had significantly more chronic lung disease.

A survey from USA by Anderson *et al* [4], a study from Chow *et al* [5], and an abstract by Sun *et al* [6], including infants having a birth weight ≤ 1500 g, confirmed Tin's data that there is significantly more severe ROP in the high-saturation group.

Chow's data also confirmed how important it is to avoid fluctuations in SpO_2 with high peaks during e.g. procedures such as routine suctioning.

It is impressive to see how efficiently these authors were able to reduce severe ROP by strict control of saturation peaks and intensive teaching of the whole staff.

From these studies it seems that saturation should be kept ≤ 92 %. It also seems clear from these and other studies that fluctuations in SpO_2 should be avoided. The saturation peaks in relation to suctioning or bagging should therefore be avoided. Careful teaching of the staff – doctors and, not least important, nurses – is needed in order to achieve this.

What about the children who have a high saturation in spite of breathing room air? It is today common that even among the most immature infants supplementary oxygen is not needed, and still $SpO_2 > 95$ % often is seen. This may be a negative consequence of the introduction of extremely potent and efficient therapies such as antenatal corticosteroids and postnatal surfactant therapy.

In one recent investigation such infants were studied separately with respect to development of severe ROP. These children progressed to threshold ROP to a lesser extent than babies deliberately nursed in a high saturation [7]. Such healthy babies, for some reason, seem to be less vulnerable, at least when it comes to developing severe ROP.

Resuscitation

Several animal studies and five clinical studies have demonstrated that hypoxic newborn subjects may be resuscitated with ambient air. If this is the case, it represents a step forward since it simplifies the resuscitation procedure and also reduces the costs.

Becoming independent of the oxygen-tank resuscitation can be carried out wherever a birth takes place merely by using a mask coupled to a self-inflating bag.

Many places in the world newborn resuscitation was previously not even initiated if oxygen was not available, because it has been considered absolutely necessary for this procedure.

The WHO took a brave and important step forward in 1998 when they stated that room air can be used for basic resuscitation of the newborn. It also represented a leap forward when the American Heart Association/American Academy of Pediatrics in their guidelines of 2000 underlined that resuscitation should be carried out with ambient air if oxygen is not available.

Data accumulated recently from studies with hypoxic newborn animals now strongly indicate that room air is not only equal to pure oxygen for resuscitation; it even causes less injury to several organs such as lung, myocardium and brain.

The following is known from studies in newborn hypoxic piglets [8]:

- Resuscitation with pure oxygen increases the concentration of reactive oxygen species both in the lung and the brain, in contrast to resuscitation with room air, which does not produce such elevations.
- Brain injury is augmented when assessed by increase in glycerol and metalloproteinases in the brain and by histologic changes. Some of the same biochemical changes are also found in the lung and heart.
- Short-term neurologic recovery is poorer in animals resuscitated with oxygen compared with ambient air.

That the lungs are affected by inhaling pure oxygen might be possible to understand, however, that the heart and brain are affected as well is more astonishing and perhaps more concerning.

In human infants needing resuscitation at birth it has been shown that pure oxygen triggers an increased oxidative stress at least four weeks after birth [9]. A

recent meta-analysis including 1737 infants resuscitated either with 21 % or 100 % oxygen has given the dramatic finding that neonatal mortality is reduced 40 % in the 21 % group (OR 0.57 (95 % CI 0.40-0.80)).

Further, short-term recovery is also faster in these infants since heart rate at 90 sec and Apgar score at 5 min are significantly higher. Time to first breath is significantly shorter, in median 0.5 min in room-air-resuscitated infants [10].

Another concerning finding has been that newborn babies exposed to pure oxygen for only 3-10 min after birth have a significantly increased risk of developing childhood leukemia (for review, see [8]).

Conclusions and recommendations

In extremely-low-birth-weight infants, SpO_2 should not exceed 92-93 % the first weeks after birth, and strict controls to avoid peaks are imperative. Many units now recommend that limits be between 88 and 92 %. Whether SpO_2 values should be different the first 1-2 weeks of life compared with the following weeks is not known.

More and more centers have stopped using 100 % oxygen for newborn resuscitation. For instance, in Sweden the guidelines state that resuscitation should begin with 40 % O_2 . Pure oxygen should definitely be avoided for routine and basic newborn resuscitation, and room air seems to be superior for newborn resuscitation.

However, oxygen as backup should be available and used if the infant does not recover quickly (90 sec).

Any extra oxygen given should be titrated according to the normal SpO_2 . The first 3-5 min of life, median SpO_2 is < 90 %, and at this age a newborn infant is not supposed to be pink. Optimal resuscitation would therefore require saturation measurements.

References

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