OXYGEN USE IN INITIAL RESUSCITATION OF PRETERM INFANTS

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New European Resuscitation Guidelines from 2010 for initial resuscitation of term infants in the delivery room recommend use of room air instead of 100% oxygen. For preterm infants currently there is not enough data to conclude what is the most appropriate initial fraction of inspired oxygen needed for initial resuscitation. Delivery room must be equipped with oxygen blender and saturation monitor. Increasing oxygen concentration in resuscitation/stabilization of preterm infants should be titrated according to clinical and oxygen saturation responses.

Descriptors: PRETERM INFANTS, INITIAL RESUSCITATION, OXYGEN

Room air for resuscitation of term infants

Use of supplemented oxygen used during neonatal resuscitation has been never validated in prospective controlled trials. A review of 6 randomized trials that compared use of room air (RA) and 100% oxygen reported that RA was associated with a significant lower mortality compared to 100% oxygen (13% vs 8%, P=0.0021) (1). Despite the fact that results were similar to Cochrane review from 2005, the conclusion of the Cochrane review was still inconclusive saying there is not enough data to support either use of RA over 100% or vice versa. Results from different studies continuously revealed positive effects from RA:

- earlier initiation of spontaneous breathing;
- reduced mortality rate;
- no increase in neurodevelopment delay (2, 3).

Based on current knowledge many neonatal units all over the world slowly shifted to use of RA or at least lowered starting fraction of oxygen in resuscitation of term infants during past ten years. Finally, in 2010 new European Resuscitation Guidelines have been published. The new recommendations say that in term infant’s air should be used for resuscitation at birth; and only if, despite effective ventilation, oxygenation (ideally guided by oximetry) remains unacceptable, use of a higher concentration of oxygen should be considered (4).

How much oxygen is enough for resuscitation/stabilization of preterm infants?

The survival of extremely low birth weight (ELBW) infants has increased steadily over past years although mortality in the delivery room and during first 12 hours for ELBW is still high. Data from the Vermont Oxford Network compared to data from Neonatal intensive care unit (NICU) in Maternity Hospital Ljubljana are shown in Table 1, Table 2 and Figure 1.

In NICU Maternity Hospital Ljubljana delivery room (DR) oxygen is used only in 43% of infants with GA 22 to 29 wks whereas in VON database it is used almost in 91%. There is also much higher percentage of infants without any medical intervention in DR (56% vs 6.7%). Contrary to opinion that very preterm infants need intensive resuscitation support after birth, the study from O’Donnel et al showed that the majority of extremely preterm infants cried (69%) and breathed (80%) without any medical intervention (5). Despite less aggressive management in DR the outcome measures in the NICU Maternity Hospital Ljubljana show more favorable results compared to VON database, especially in the much lower percentage of bronchopulmonary dysplasia (BPD).

Golden hour-oxygen effect

Intrauterine PaO₂ levels in the fetus are in the 15-30 mm Hg (2-4 kPa) range resulting in fetal SpO₂ levels of 45% to 55%. After delivery these levels will rise to 50-80 mmHg (6.7-10.7 kPa) (6). During resuscitation with 100% oxygen, the SpO₂ may increase to >80 mmHg (>10.7 kPa) within 5 minutes of birth in some of these infants (7, 8). Many morbid conditions associated with extreme immaturity are aggravated by an excess of free-radicals occurring in infants who are intrinsically deficient in enzymatic antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase (9-11). Low plasma antioxidant activity at birth in premature infants was
an independent risk factor for mortality (12). Further more, in preterm animals it was established that they are unable to upregulate deficient antioxidants (13). During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. BPD and neurological impairment are two major long term morbidities in ELBW. Pulmonary oxygen toxicity with enhanced inflammatory cytokine response to oxygen is believed to be a major contributor to the development of BPD (14-16). The brain is also adversely affected by reoxygenation injury, and such conditions may also help explain the underlying pathogenesis of periventricular leucomalacia (17). Mickel et al showed that reoxygenation with high oxygen concentrations after global brain ischemia caused increased lipid peroxidation and mortality in Mongolian gerbils (18). There are new preliminary data that also suggest that higher SpO₂ in the first four hours after birth in VLBW infants may be associated with lower impulse control and attention skills in the elementary school age period (19).

Saturation levels during first ten minutes of life in term and preterm infants

Healthy neonates are poorly saturated immediately after birth. In the study from Altuncu et al median SpO₂ values in the first, fifth and tenth minutes were 71, 92, and 98% in vaginal deliveries and 70, 79, and 96% in caesarean deliveries, respectively (20). Dawson et al have recently reviewed saturation measurement during first 10 minutes of life from 2 centers for 160 preterm infants and 306 term infants (Figure 2, Figure 3 and Figure 4). The study documents 3rd to 97th percentile changes in preductal SpO₂ after birth for term and preterm infants with no medical interventions. These findings can be used to monitor changes in SpO₂ and to titrate oxygen treatment in the DR (21).

Is room air sufficient for resuscitation of ELBW infants?

The first prospective dual center randomized trial was performed by Wang et al (22). Newborns below 32 weeks of gestation were randomized to initiation of resuscitation with RA or 100% oxygen. Target saturations were 75% at 3 minutes and 85% at 5 minutes of life. When target SpO₂ was not achieved, inspiratory fraction of oxygen (FiO₂) was increased in steps of 0.25. When severe bradycardia was present, FiO₂ was immediately switched to 1.0. Because every patient in the RA group required oxygen by 3 minutes of age and at 5 minutes SpO₂ were significantly lower (<80%) in RA group, authors concluded that resuscitation with RA is not recommended for very preterm infants.

In an observational study Dawson at al measured SpO₂ and heart rate in two groups of infants with GA <30 wks after 10 minutes of resuscitation either with room air or 100% oxygen. Results were similar to Wang's study. Majority of very preterm infants received supplemental oxygen if air was used for the initial resuscitation. Of the infants resuscitated with 100% oxygen, 80% had SpO₂ ≥95% after 5 minutes of life (19.10). The strategy of starting the resuscitation with 100% oxygen followed by titration of FiO₂ was the most effective at maintaining SpO₂ in the target range (24).

The ROAR study (RA versus oxygen administration during resuscitation of preterm infants) combined 3 different strategies. One group was resuscitated with 100% oxygen, and two other groups received 100% oxygen or RA as initial gas, which was then titrated according to SpO₂. The aim of the study was to achieve SpO₂ between 85% and 92% by the end of resuscitation. The strategy of oxygen delivery was very similar (23).

In a prospective, randomized trial Escrig at al randomly assigned infants below 28 weeks of gestation who required active resuscitation to the low-oxygen group (FiO₂ 30%) or the high-oxygen group (FiO₂ 90%) (25). Oxygen delivery was titrated regarding saturation value and heart rate. The fraction of inspired oxygen in the low-oxygen group was increased stepwise to 45% and that in the high-oxygen group was reduced to 45% to reach a stable SpO₂, of approximately 85% at 7 minutes in both groups. No differences in mortality rates in the early neonatal period were detected. They concluded that resuscitation can be safely initiated for extremely low gestational age neonates with low FiO₂ (approximately 30%), which then should be adjusted to the infant's needs, reducing the oxygen load to the neonate. Vento et al (26) in prospective, randomized study in infants of 24 to 28 wks of gestation compared 30% to 90% oxygen at the start of resuscitation and a targeted SpO₂ strategy during resuscitation. The 30% group had shorter duration of oxygen treatment (6 days vs. 22 days; p <0.01), mechanical ventilation (13 days vs. 27 days; p <0.01), and had a lower incidence of BPD at discharge (15.4% vs. 31.7%; p <0.05). Markers of oxidative stress in blood and urine were significantly increased in the 90% oxygen group. They also established that concentrations of isofurans, ortho-tymosine and 8-hydroxy-2deoxyguanosine (on day 7) significantly correlated with development of BPD.
Large, randomized, blinded, prospective studies to establish the most appropriate initial fraction of inspired oxygen

Before further recommendations about the most appropriate initial fraction of inspired oxygen

Conclusions drawn from the published studies about the use of oxygen in resuscitation of preterm infants are (27):

- Preterm infants need some oxygen for the resuscitation/stabilization immediately after birth.
- Exposure to excessive amount of oxygen increases oxidative stress.
- Increased oxygen concentration should be titrated according to clinical and SpO₂ responses.
- In newborns with severe circulatory arrest, the heart rate response to the first ventilations before obtaining a reliable reading from pulse oximeter should guide oxygen use. When the heart rate does not increase despite adequate ventilation, oxygen should be rapidly increased to attain a return of spontaneous circulation.
- Extremely low gestational age newborns should be monitored for predural SpO₂ and heart rate immediately after birth when possible; delivery room must be equipped with oxygen blender and saturation monitors. Reliable reading of saturation obtained simultaneously in neonatal critical situ-uations differs by the type of the pulse oximeter used, being significantly faster with Masimo Signal Extraction Technology. This may permit better adjustments of inspired oxygen aiding in the prevention of damage caused by unnecessary exposure to high or low oxygen (28).

The plan for both trials is to enroll over 1200 infants. In US based trial, infants from 23 to 29 weeks will be randomized either to low oxygen group (21% oxygen) or high oxygen group (90% oxygen). The FiO₂ will be increased or decreased in 0.1 increments to maintain the SpO₂ level between 65% and 85% for the first 10 minutes. Both trials include neurodevelopmental follow up at 2 years.

LITERATURE


Sažetak

PRIMJENA KISIKA U POČETNOM OŽIVLJAVANJU NEDONOŠČADI

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Deskriptori: NEDONOŠČAD, POČETNO OŽIVLJAVANJE, KISIK