Oxygen administration for the resuscitation of term and preterm infants

Daniele Trevisanuto1, Camilla Gizzi2, Claudio Martano3, Valentina Dal Cengio1, Fabrizio Ciralli4, Flaminia Torielli5, Paolo Ernesto Villani6, Sandra Di Fabio7, Lorenzo Quartulli8 & Luigi Giannini9, on Behalf of Neonatal Resuscitation Study Group, Italian Society of Neonatology

Oxygen has been widely used in neonatal resuscitation for about 300 years. In October 2010, the International Liaison Committee on Neonatal Resuscitation released new guidelines. Based on experimental studies and randomized clinical trials, the recommendations on evaluation and monitoring of oxygenation status and oxygen supplementation in the delivery room were revised in detail. They include: inaccuracy of oxygenation clinical assessment (colour), mandatory use of pulse oximeter, specific saturation targets and oxygen concentrations during positive pressure ventilation in preterm and term infants. In this review, we describe oxygen management in the delivery room in terms of clinical assessment, monitoring, treatment and the gap of knowledge.

Keywords: Delivery room, neonatal resuscitation, oxygen supplementation

Introduction

Oxygen (O2) was discovered in 1604 by a Polish alchemist, Michal Sedzioj [1]. In 1777, O2 was first used by François Chausier in neonatal resuscitation [2].

The past decade has seen remarkable changes in attitudes to the use of O2 in the delivery room (DR). Although O2 represents a lifesaving milestone therapy in neonatal resuscitation, there has been recognition that newborn infants are susceptible to oxidative stress and that high O2 concentrations can be harmful to both preterm and term infants.

The aim of this article was to revise O2 management in the DR in terms of clinical assessment, monitoring, treatment and the gap of knowledge.

Clinical assessment

During the process of adaptation to extrauterine life, a normal newborn presents a period of cyanosis. In fact, O2 saturation gradually increases during the first minutes of life from intrapartum levels of 30–40% to physiologic postnatal levels of 95–100% [3]. This blood O2 value is reached approximately 10 minutes after birth so that oxyhaemoglobin saturation may normally correspond to 70–80% range for this period of transition [4–11], thus resulting in the appearance of a cyanotic colour of the skin.

Traditionally, the clinical assessment of colour was considered as a measurement of oxygenation and therefore O2 levels at birth were only established through direct skin observation. The 2005 International Liaison Committee on Resuscitation (ILCOR) Guidelines also confirmed this approach [12].

It has been recently demonstrated that the clinical assessment of skin colour as a measurement of oxygenation is imprecise and inaccurate. Indeed, some recent studies have demonstrated that this approach has an important interobserver and intraobserver variability. O'Donnell et al. [13] observed that clinicians often disagree whether or not an infant is pink; furthermore, they noticed that the saturation by pulse oximetry (SpO2), whereby observers declared infants to be pink was greatly varied, ranging from 10–100%. Besides this, the lack of cyanosis is a very poor indicator of the state of oxygenation of newborns [14] and, on the other hand, peripheral cyanosis is common and does not indicate hypoxaemia on its own [15].

As a result, assessing colour is not an accurate way to measure tissue oxygenation immediately after birth. Some studies have attempted to ascertain the best indicator for oxygenation and have recommended the use of pulse oximetry [4–16,17]. The 2010 the American Heart Association (AHA) Guidelines for Neonatal Resuscitation confirms this approach [14].

Monitoring

In October 2010, the ILCOR released new guidelines for neonatal resuscitation which expanded on the previous recommendations for the use of pulse oximetry during neonatal resuscitation [18]. Oximetry provides an objective continuous measurement of both the infant's oxygenation and heart rate (HR) and is, therefore, a...
Oxygen administration for the resuscitation of term and preterm infants

Tailoring \( \text{O}_2 \) administration in the DR

While administering \( \text{O}_2 \), the common goal is avoiding hypoxia and hyperoxia, particularly in extremely preterm infants that are at the most risk of harm from \( \text{O}_2 \) toxicity.

Nevertheless, an appropriate \( \text{SpO}_2 \) target below which \( \text{O}_2 \) therapy does more good than harm during resuscitation has not yet been determined, nor has the highest safe level of \( \text{SpO}_2 \). The AHA's 2010 Guidelines suggested target pulse oximetry levels at intervals after birth, under which the commencement of \( \text{O}_2 \) administration is recommended. The preductal \( \text{SpO}_2 \) target range is 1, 2, 3, 4, 5, and 10 minutes after birth are 60–65%, 65–70%, 70–75%, 75–80%, 80–85%, and 85–95%, respectively [26]. These values are close to the median values for infants who do not require resuscitation. In contrast, the ERC's newborn life support algorithm recommends starting \( \text{O}_2 \) at \( \text{SpO}_2 \) of 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, and 5 minutes after birth, respectively using values that are closer to the 25th percentile [27]. It is worth noting that in these recent 2010 guideline algorithms, the targeted \( \text{SpO}_2 \) range for the first 10 minutes after birth have been included without specifying the gestational age.

From a practical point of view, if the chosen target \( \text{SpO}_2 \) percentile is too low hypoxic damage may result, while if the target \( \text{SpO}_2 \) percentile is set too high, unnecessary \( \text{O}_2 \) treatment may be given. In this case, targets from both algorithms are sufficiently similar for practical use.

\( \text{SpO}_2 \) target ranges should also be used to titrate the ongoing fraction of inspired \( \text{O}_2 \) in the DR during neonatal resuscitation. \( \text{O}_2 \) blenders are now a standard of care in many DRs in developed countries, which help to set optimal oxygen concentration (\( \text{FiO}_2 \)) guided by \( \text{HR} \) and pulse oximetry. Moreover, Dawson's nomograms classified by gestational age may be very useful for the resuscitation team as they allow more accurate target \( \text{SpO}_2 \) to be established according to gestational age [11].

Before starting \( \text{O}_2 \) therapy, however, the clinical assessment of the infant is important. Many healthy, normally breathing infants do not appear pink until several minutes after birth and they do not need \( \text{O}_2 \), while an infant who is unresponsive, hypotonic, and bradycardic requires immediate assistance. Both ventilation and oxygenation form the cornerstones of neonatal resuscitation and \( \text{O}_2 \) treatment in a newborn infant will not be effective if the infant's lungs are not aerated. The AHA's 2010 guidelines suggest using continuous positive airway pressure (CPAP) if the infant is breathing, but has respiratory difficulty and/or in case of persistent cyanosis. If the infant is not breathing adequately, then intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure (PEEP) should be started [18]. Effective ventilation is also required before modification to \( \text{O}_2 \) therapy can be considered. It should not be forgotten that ventilation is the most relevant intervention during resuscitation, and that adequate ventilation improves air-blood interface \( \text{O}_2 \) exchange and reduces the \( \text{O}_2 \) load along resuscitation. Using pulse oximetry to determine the appropriate level of respiratory support and to guide the decision of whether or not to provide \( \text{O}_2 \) should, therefore, became an evidence-based practice. In Box 1, we report the delivery room \( \text{O}_2 \) administration recommendations of the Study Group on Neonatal Resuscitation-Italian Society of Neonatology.

\( \text{O}_2 \) for term infants

In 2010, the ILCOR supported the evidence of using of air instead of 100% \( \text{O}_2 \) in the DR for resuscitating asphyxiated term or near...
Box 1. Group of study on neonatal resuscitation–Italian Society of Neonatology. Delivery room O₂ administration recommendations

Suggested equipment: air/O₂ sources and blender; pulse oximeter; continuous positive airway pressure (CPAP) system; system for positive pressure ventilation (PPV).

- In all patients needing resuscitation at birth, apply pulse oximeter to the infant’s right hand or wrist, according to the procedures above described.
- In infants with cyanosis and/or labored breathing and heart rate (HR) ≥ 100 bpm: start CPAP and set optimal oxygen concentration (FiO₂) according to gestational age.
- In infants with HR < 100 bpm and/or apnea and or gasping: start effective PPV and set FiO₂ according to gestational age.
- If not clinical improvement, add O₂ titrating the FiO₂ to avoid hypoxic or hypoxic damage by guide of saturation by pulse oximetry (SpO₂) percentiles reference chart.

Babies ≥ 32 weeks’ gestation

- Start PPV with room air.
- If there is not an adequate response of HR (increase of 20 bpm) within 90 seconds Then.
- Add O₂ titrating the FiO₂ to avoid hypoxic or hypoxic damage by guide of SpO₂ percentiles reference chart.

Babies <32 weeks’ gestation

- Start PPV with FiO₂ at 30% until pulse oximetry provides an accurate signal and HR is in normal range.
- When reliable SpO₂ readings are available it seems reasonable to keep the newborn infants between the 10th and 75–90th centiles in the gestational age related chart, to avoid hypo- or hypoxia.
- If a baby is below the 10th centile, FiO₂ should be increased in 10% intervals every 30 seconds until SpO₂ is above the 10th centile (abrupt FiO₂ changes should be avoided to prevent pulmonary vessel constriction).
- If there is no improvement or the HR falls, adequacy of ventilation should be checked and FiO₂ increased as needed to achieve SpO₂ above the 10th centile.
- Conversely, if SpO₂ is above the 75th or the 90th centile (depending on the pre-established strategy) FiO₂ should be reduced by 10% at 30 seconds intervals until SpO₂ reaches pre-established safety limits.

All neonates

- If severe bradycardia (HR ≤ 60 bpm) lasts >30 seconds despite adequate ventilation, the FiO₂ should be switched to 100%.

The Journal of Maternal-Fetal and Neonatal Medicine

with a typical RR 0.32 (95% CI: 0.12–0.84). These strictly RCTs were all performed in Europe, mostly in Spain, suggesting that this finding was consistent in both developing and developed countries. The evidence-based treatment recommendation now states that: “In term infants receiving resuscitation at birth with PPV, it is best to begin with air rather than 100% O₂. If, despite effective ventilation, there is no increase in HR or if oxygenation (guided by oximetry) remains at unacceptable levels, the use of a higher concentration of O₂ should be considered.” The meaning of this adjustment is that, based on 814,000 asphyxia-related deaths per year [29], a mean of 252,000 (95% CI: 146,000–374,000) lives can be saved annually [28].

However, special attention should be given to severely asphyxiated newborns with an arrested or markedly depressed (HR <60 beats per minute, bpm) circulation. Although newborn piglets with cardiac arrest need similar times for the return of spontaneous circulation when either 21% or 100% O₂ is used [30], in newborns with compromised circulation, reliable SpO₂ signals may not be available and the HR response to the resuscitation manoeuvres should guide the higher O₂ concentrations to be used. Vento and Saugstad suggested that “in newborns with severe circulatory arrest (Apgar <1 at 1 minute), the HR response to the first ventilations even before obtaining a reliable reading from the pulse oximeter should determine O₂ use. When HR does not increase despite adequate ventilation, O₂ should be rapidly increased (as high as 100%) to attain a rapid return of spontaneous circulation” [31].

O₂ for preterm infants

Evidence from both RCTs and observational studies suggests that preterm infants can be successfully treated in the DR with less than 100% O₂. Given that even short-term exposure to excessive O₂ can generate reactive O₂ and nitrogen species that are associated with short and long-term morbidity [32], blended O₂ and air may be given “judiciously” to these infants.

To achieve this goal it is recommended that an air/O₂ blender and titrating gas admixture are used according to the readings of the pulse oximetry. Preterm infants should be then monitored for preductal SpO₂ and HR as soon as possible after birth and SpO₂ values should be maintained within a safety range in order to increase O₂ levels above foetal levels and avoid hypoxia. To date, there is limited data for very preterm infants to develop gestational age-specific normal SpO₂ ranges and preductal saturation values, according to Dawson’s nomograms (3), can be considered at the current time to be the “best guess at optimal SpO₂ targets in preterm infants” [33].

The optimal use of supplemental O₂ in very low birth weight babies was addressed in a series of recent trials. Escrig et al. studied 42 infants <28 weeks needing active resuscitation in the DR. The infants were randomized to receive either 90% or 30% O₂ as the initial resuscitation gas. FiO₂ was then adjusted according to the infant’s HR and SpO₂, in order to reach stable values of about 85% at 5–7 minutes in both groups. In accordance with the study protocol, every 60–90 seconds the fraction of inspired O₂ was increased in 10% steps if an onset of bradycardia was recorded (<100 bpm) or was decreased in similar 10% steps if SpO₂ reached values of >85%. As a result, no differences were observed between infants resuscitated with low or high O₂ concentrations in terms of the time needed to attain the target SpO₂ level, but those in the 30% group were exposed to less O₂ during the resuscitation [34]. Another clinical trial was then conducted by the same Authors to compare the clinical and biochemical consequences of using 2 different O₂ loads during
resuscitation. They found that lower exposure to $O_2$ at birth also caused lower oxidative stress and inflammation, a lesser need for $O_2$ and mechanical ventilation, and a lower risk of bronchopulmonary dysplasia (BPD) [35]. Similar results on oxidative stress were observed by Ezaki et al. [36].

Wang et al. randomized 41 infants of <32 weeks' gestation to receive 21% versus 100% $O_2$ as the initial resuscitation gas. A targeted approach to adjusting $FiO_2$ based on $SpO_2$ levels was used in the experimental (21%) group. If the targets of 70% at 3 minutes of life and 85% at 5 minutes of life were not achieved, the $FiO_2$ was increased at 25% increments. The $FiO_2$ was increased to 100% immediately for severe bradycardia. Infants in the control group were ventilated with 100% $O_2$ up to 5 minutes of life then $FiO_2$ was decreased if the $SpO_2$ was >95%. All 18 infants assigned to the experimental group required an increase of $FiO_2$ at or before 3 minutes of life. As a result, no infant could be successfully resuscitated with room air [37]. Likewise, Dawson et al. evaluated their unit's experience after changing from initiating resuscitation with 100% to 21% $O_2$. The practice of this unit was to change from 21% to 100% $O_2$ if the $SpO_2$ was <70% at 5 minutes of life, if HR was below 100 bpm after 60 seconds of ventilation or if chest compressions had been initiated. Of the 106 preterm infants given 21% $O_2$ from the start, 92% were given supplemental $O_2$ at some point during the resuscitation. The median $SpO_2$ for these infants at 2 and 5 minutes of life was 31% and 54%, respectively, and increased to 81% at 6 minutes of life, once 100% $O_2$ was administered. Conversely, the 20 infants evaluated before the practice change (resuscitated with 100% $O_2$) had median $SpO_2$ values of 84% and 94% at 2 and 5 minutes of life, respectively. The 8 infants out of 106 successfully resuscitated with 21% $O_2$ had a median $SpO_2$ of 71% and 87% at 2 and 5 minutes of life respectively [38].

Recently, an additional trial compared three different $O_2$ delivery strategies during resuscitation. In the ROAR study, Rabi et al. evaluated preterm infants at <32 weeks' gestation and randomized the 106 participants into one of the following groups: 100% $O_2$ throughout, 100% initial and titrated to $SpO_2$, or 21% initial and titrated to $SpO_2$. In the $O_2$ titrated groups, the $FiO_2$ was adjusted by 20% every 15 seconds to reach a target $O_2$ saturation range of 85–92%. Treatment failure was defined as a HR < 100 bpm for longer than 30 seconds. At the conclusion of the resuscitation process, both titrated groups were receiving similar $FiO_2$: 33% (range: 27–39%) and 36% (range: 27–45%). These values are consistent with those used at the conclusion of resuscitation in the Escrig and Wang trials. However, infants in the 100% initial and titrated to $SpO_2$, oxygen group spent a larger proportion of time in the target $SpO_2$ range while infants in the low $O_2$ group were eight times more likely to meet the criteria for treatment failure than those in the high $O_2$ group (24 vs 3%; $p = 0.022$). The three groups did not differ significantly in terms of the time taken to reach the target $SpO_2$ range [39].

Unfortunately none of these trials was actually powered to evaluate important long-term outcomes such as survival without significant neurodevelopmental disability. Two trials are currently being devised for this purpose [40]. The Targeted Oxygenation in the Resuscitation of Premature Infants and Their Developmental Outcome trial (T02RPIDO) is recruiting infants at <31 weeks' gestation to compare 100% $O_2$ and air as the initial gas for resuscitation, using $SpO_2$ targeting. For the air group, $FiO_2$ is increased if $SpO_2$ is <65% by 5 minutes, <80% at 5–10 minutes, and <85% thereafter. In the 100% $O_2$ group, $FiO_2$ is decreased when $SpO_2$ >92%. Furthermore, the Premature Infants Resuscitation with Oxygen or Air trial, currently in the planning stage, is a blinded comparison of a targeted $O_2$ strategy comparing the initial use of 21% $O_2$ and 90% $O_2$.

Given that the long-term consequences of such differences in oxygenation are not known, it seems likely that neither 21% nor 100% will be optimal. These studies on the use of $O_2$ in preterm infants during the transition to extrauterine life suggest that most preterm infants require supplemental $O_2$ to achieve expected oxygenation levels within the first 20 minutes of life. An initial low amount of oxygen supplementation (25–30%) apparently enhances successful transition, lowers the $O_2$ load, and diminishes the risk of $O_2$-derived damage and inflammation.

**Gap of knowledge**

Clinical studies [28,41,42] and practice [43] seem to lead towards resuscitation of term infants with room air. However, this evidence come from RCTs with potential limitations including study design (quasi randomized trials), setting (some of them were conducted in developing countries), and characteristics of enrolled patients (the majority of patients suffered from a mild–moderate asphyxia) [28,41,42].

While term babies can be effectively and safely resuscitated in room air, the choice has not always a clear cut-off. Animal models of severe asphyxia show an uncertain or no supremacy of one strategy over the other [44–46]. These studies used different asphyxia models and endpoints, making any comparison almost impossible. However, cumulative experimental findings suggest that with persistent bradycardia (i.e. HR < 60 bpm not responding to effective ventilation) an increase in supplemental $O_2$ is warranted. HR response and, when detectable, $SpO_2$ would determine the $O_2$ supplementation.

Studies in preterm infants failed to define the optimal $O_2$ concentration for these babies. Since preterm infants have immature $O_2$ scavengers, they have the highest risk to be negatively affected by excessive oxygenation and consequent formation of reactive $O_2$ species [47,48]. From a theoretical point of view, $O_2$ at birth may contribute to the development of a variety of preterm birth complications. In experimental and clinical settings, hyperoxia has been associated with serious injury to the developing brain, lung, myocardium and kidney [32,49]. On the other hand, a few studies [39] raised some concerns about room air resuscitation in these premature babies since the vast majority needed some $O_2$ to recover during resuscitation. 100% $O_2$ resuscitation was associated with increased markers of inflammation and BPD rate [35]. Based on this evidence, resuscitation guidelines state that “in preterm infants at <32 weeks' gestation, the initial use of air or 100% $O_2$ is more likely to result in hypoxia or hyperoxia, respectively, than initiation of resuscitation with 30% or 90% $O_2$ and titration to $SpO_2$”.

As 100% $O_2$ should be avoided, guidelines recommend that “blended $O_2$ and air may be given judiciously and ideally guided by pulse oximetry […]”. If a blend of $O_2$ and air is not available, resuscitation should be initiated with air [14].

Given the unlikelihood that the consequences of 90% $O_2$ will differ from 100% $O_2$, leaving such a wide range of $O_2$ concentration open may be harmful to the babies. Efforts should be directed towards an $O_2$ “finding dose” to start neonatal resuscitation as effectively and safely as possible, especially in those babies who are more fragile such as preterm infants and severely asphyxiated babies.

A recent paper by Perlman et al. evaluated the “gap of knowledge” on neonatal resuscitation. In their opinion, the most relevant questions on $O_2$ administration at birth remain: “How
Conclusions
In conclusion, the recommendations for O₂ management in the NR have changed greatly: colour is no longer recommended as a useful indicator of oxygenation, pulse oximetry provides accurate information on both oxygenation and HR, resuscitation of term and very preterm infants should be started with room air and a fraction of inspired O₂ between 30 and 90%, respectively following physiological saturation targets. There is a gap of knowledge in the field that needs to be explored further.

Acknowledgement
The authors are responsible for the research contained herein, they have participated in the concept and design, drafting or revising of the manuscript, and have approved the manuscript as submitted.

Declaration of Interest: The authors declare no conflict of interest.

References


