The Journal of Maternal-Fetal and Neonatal Medicine, 2012; 25(S3): 26–31

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2012.712344

Oxygen administration for the resuscitation of term and preterm infants

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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 (O_2) was discovered in 1604 by a Polish alchemist, Michal Sedziwoj [1]. In 1777, O_2 was first used by François Chaussier in neonatal resuscitation [2].

The past decade has seen remarkable changes in attitudes to the use of O_2 in the delivery room (DR). Although O_2 represents a lifesaving milestone therapy in neonatal resuscitation, there has been recognition that newborn infants are susceptible to oxidative stress and that high O_2 concentrations can be harmful to both preterm and term infants.

The aim of this article was to revise O_2 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, O_2 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 O_2 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 O_2 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 (SpO_2), 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 [4–9,16,17]. 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

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reliable tool for following the infant's foetal to neonatal transition and for titrating the concentration of supplemental O_2 in the DR, if required. Pulse oximetry is actually considered the optimal tool for monitoring SpO_2 in the DR. It provides an immediate and continuous display of SpO_2 and HR and does not require calibration [19].

The latest generation pulse oximeters can give measurements within 90 seconds when applied in the appropriate manner. The differences between the Masimo (Masimo, Irvine, CA) oximeter, the most studied machine in neonates, and other oximeters are likely to be ~2% and therefore not clinically relevant [11].

In order to obtain rapid, reliable data, the device should be applied in the following steps: (i) turn on the oximeter; (ii) apply the sensor to the infant's right hand or wrist; (iii) connect the sensor to the oximeter cable; and (iv) shield the sensor from light [20]. Sensor placed on the right hand or wrist reflects the SpO_2 of blood flow to the brain [17]. This approach has been studied using a Masimo (Masimo, Irvine, CA, USA) pulse oximeter, but has also been recently recommended for Nellcor (Nellcor OxiMax N-600) pulse oximeters [21].

In order to identify the physiological changes in preductal SpO_2 after birth and determine "normal" SpO_2 values for term and preterm infants, Dawson et al. recently defined reference ranges for SpO_2 values in the first 10 minutes after birth for infants who received no medical intervention in the DR. They studied 468 infants (25–42 weeks' gestation) and recorded 61,650 SpO_2 data points. The sensor (LNOP Neo Masimo SET, Masimo, Irvine, CA, USA) was placed on the right wrist and then connected to the oximeter monitor. Overall, it took a median of 7.9 minutes (interquartile range: 5.0–10 minutes) to reach a SpO_2 value of >90%, while SpO_2 values for preterm infants increased more slowly than those for term infants. Moreover, in the first 5 minutes after birth, infants born through caesarean section had significantly lower SpO_2 measurements than those delivered vaginally. Percentile charts for all infants, term infants of ≥37 weeks, preterm infants of 32–36 weeks and extremely preterm infants of <32 weeks were provided [11]. Dawson and colleagues' SpO_2 nomogram currently represents the best estimate of SpO_2 targets for term, but especially for preterm, infants during the first minutes of life [22].

The availability of reference ranges for SpO_2 has great relevance, but no randomized control trial (RCT) has defined the appropriate SpO_2 target ranges in the DR to date.

At any rate, pulse oximetry can be difficult to interpret because the correlation between SpO_2 and arterial O_2 tension (PaO_2) is dependent on the affinity of haemoglobin (Hb) to O_2 in differing physiologic circumstances. The composition of the neonatal Hb affects these values: the greater the amount of foetal Hb, the higher the SpO_2 for any given PaO_2 value [23]. Castillo et al. reported the relationship between actual PaO_2 and SpO_2 values in preterm infants and found that the mean PaO_2 level measured was 56 ± 14.7 mm Hg for SpO_2 values between 85 and 93%. Within this SpO_2 range, 86.8% of the samples had PaO_2 values of 40 to 80 mm Hg, 8.6% had values of <40 mm Hg, and 4.6% had values of >80 mm Hg. When the SpO_2 was >93% the mean PaO_2 was 107.3 ± 59.3 mm Hg with 59.5% of values >80 mm Hg [24].

In 2010, there are still differences between the AHA and the European Resuscitation Council (ERC) resuscitation algorithms about the preductal SpO_2 target ranges at 1, 2, 3, 4, 5 and 10 minutes after birth.

In infants with compromised circulation, reliable SpO_2 signals may not be available and decisions about the use of higher O_2 concentrations should be based on HR response to resuscitation manoeuvres [25].

Treatment

Tailoring O_2 administration in the DR

While administering O_2, the common goal is avoiding hypoxia and hyperoxia, particularly in extremely preterm infants that are at the most risk of harm from O_2 toxicity.

Nevertheless, an appropriate SpO_2 target below which O_2 therapy does more good than harm during resuscitation has not yet been determined, nor has the highest safe level of SpO_2. The AHA's 2010 Guidelines suggested target pulse oximetry levels at intervals after birth, under which the commencement of O_2 administration is recommended. The preductal SpO_2 target ranges at 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 O_2 at SpO_2 of 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, 5, and 10 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 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 SpO_2 percentile is too low hypoxic damage may result, while if the target SpO_2 percentile is set too high, unnecessary O_2 treatment may be given. In this case, targets from both algorithms are sufficiently similar for practical use.

SpO_2 target ranges should also be used to titrate the ongoing fraction of inspired O_2 in the DR during neonatal resuscitation. O_2 blenders are now a standard of care in many DRs in developed countries, which help to set optimal oxygen concentration (FiO_2) guided by 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 SpO_2 to be established according to gestational age [11].

Before starting 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 O_2, while an infant who is unresponsive, hypotonic, and bradycardic requires immediate assistance. Both ventilation and oxygenation form the cornerstones of neonate resuscitation and 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 (PPV) with positive end-expiratory pressure (PEEP) should be started [18]. Effective ventilation is also required before modification to 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 O_2 exchange and reduces the 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 O_2 should, therefore, became an evidence-based practice. In Box 1, we report the delivery room O_2 administration recommendations of the Study Group on Neonatal Resuscitation-Italian Society of Neonatology.

O_2 for term infants

In 2010, the ILCOR supported the evidence of using of air instead of 100% 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 O_2 administration recommendations

Suggested equipment: air/O_2 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 (FiO_2) according to gestational age.
- In infants with HR < 100 bpm and/or apnea and or gasping: start effective PPV and set FiO_2 according to gestational age.
- If not clinical improvement, add O_2, titrating the FiO_2 to avoid hyperoxic or hypoxic damage by guide of saturation by pulse oximetry (SpO_2) 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 O_2 titrating the FiO_2 to avoid hyperoxic or hypoxic damage by guide of SpO_2 percentiles reference chart.

Babies <32 weeks' gestation

- Start PPV with FiO_2 at 30% until pulse oximetry provides an accurate signal and HR is in normal range.
- When reliable SpO_2 readings are available it seems raisonable to keep the newborn infants between the 10th and 75–90th centiles in the gestational age related chart, to avoid hypo- or hyperoxia.
- If a baby is below the 10th centile, FiO_2 should be increased in 10% intervals every 30 seconds until SpO_2 is above the 10th centile (abrupt FiO_2 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 FiO_2 increased as needed to achieve SpO_2 above the 10th centile.
- Conversely, if SpO_2 is above the 75th or the 90th centile (depending on the pre-established strategy) FiO_2 should be reduced by 10% at 30 seconds intervals until SpO_2 reaches pre-established safety limits.

All neonates

- If severe bradycardia (HR ≤ 60 bpm) lasts >30 seconds despite adequate ventilation, the FiO_2 should be switched to 100%.

term newborn infants [18]. Air undoubtedly offers clinical advantages as a shorter time to first breath or cry, which tends towards a reduction of the risk of severe hypoxic ischaemic encephalopathy and decreased mortality. Saugstad et al. reviewed 10 trials comparing the use of 21% versus 100% O_2 and reported that the relative risk of mortality was lower when 21% O_2 was used with a typical RR 0.69 (95% CI = 0.54–0.88) [28]. These studies, however, have received frequent criticisms as some of them were quasi randomized with patient allocation by day of birth and many were performed in the developing world where the overall mortality is higher than in developed countries. Analysis of the studies that were all strictly randomized as opposed to quasi randomized showed that the reduction in mortality risk remained significant 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% O_2. 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 O_2 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% O_2 is used [30], in newborns with compromised circulation, reliable SpO_2 signals may not be available and the HR response to the resuscitation manoeuvres should guide the higher O_2 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 O_2 use. When HR does not increase despite adequate ventilation, O_2 should be rapidly increased (as high as 100%) to attain a rapid return of spontaneous circulation" [31].

O_2 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% O_2. Given that even short-term exposure to excessive O_2 can generate reactive O_2 and nitrogen species that are associated with short and long-term morbidity [32], blended O_2 and air may be given "judiciously" to these infants. To achieve this goal it is recommended that an air/O_2 blender and titrating gas admixture are used according to the readings of the pulse oximetry. Preterm infants should be then monitored for preductal SpO_2 and HR as soon as possible after birth and SpO_2 values should be maintained within a safety range in order to increase O_2 levels above foetal levels and avoid hyperoxia. To date, there is limited data for very preterm infants to develop gestational age-specific normal SpO_2 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 SpO_2 targets in preterm infants" [33].

The optimal use of supplemental O_2 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% O_2 as the initial resuscitation gas. FiO_2 was then adjusted according to the infant's HR and SpO_2 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 O_2 was increased in 10% steps if an onset of bradycardia was recorded (<100 bpm) or was decreased in similar 10% steps if SpO_2 reached values of >85%. As a result, no differences were observed between infants resuscitated with low or high O_2 concentrations in terms of the time needed to attain the target SpO_2 level, but those in the 30% group were exposed to less O_2 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 O_2 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 (TO_2RPIDO) 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

much supplemental O_2 should be used when there is persistent bradycardia (i.e. HR < 60 bpm) that does not respond within 30–45 seconds to effective ventilation? What is the effect of administering room air as compared to supplemental O_2 during circulatory arrest on restoring cerebral blood flow and/or subsequent brain injury? What should the optimal SpO_2 target be for supplemental O_2 delivery when a baby has evidence of compromise? Should the targets be different for premature versus term infants?" [50].

Conclusions

In conclusion, the recommendations for O_2 management in the DR 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 O_2 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.

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