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LETTER

Making a choice: initial fraction of inspired oxygen for resuscitation at birth of a premature infant less than 32 weeks gestational age

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Dear editor

As briefly noted by Abdel-Hady and Nasef in their 2012 publication in *Research and Reports in Neonatology*,[1] the best initial fraction of inspired oxygen (FiO_2) to use during resuscitation of preterm neonates <32 weeks gestational age (GA) has not been clearly elucidated. Most recent neonatal resuscitation guidelines leave the difficult choice of the actual FiO_2 in the hands of individual physicians. We believe that this letter, through review and discussion of the recent published literature, will aid physicians in this choice and confirm that, as per the opinion of Abdel-Hady and Nasef, the best present evidence-based choice for the initial FiO_2 for resuscitating preterm infants <32 weeks GA appears to be 30%. However, determination of the ideal initial resuscitation gas requires further research assessing both short-term and long-term outcomes.

The common clinical scenario of attending the birth of a premature infant brings up an important clinical question: in an infant born at <32 weeks GA (population), does the use of a low level of oxygen (≤30%, intervention) instead of a high level of oxygen (≥90%, comparison) as the initial FiO_2 for resuscitation result in adequate stabilization (outcome)? In order to answer this question, we sought recent randomized controlled trials (RCTs) examining the desired patient population, intervention, comparison, and outcome. We performed a PubMed search covering January 2008 until October 2013 using the following keywords: "oxygen" AND "resuscitation" AND "premature infant". Limits were: human species, English language, and age from birth to 23 months. Publications prior to January 2008 were excluded because of redundancy, lack of applicability, or outdated information being likely in these publications. We examined personal files and reference listings of the full-text articles for any additional publications. Our search yielded a total of 141 titles. We reviewed 44 abstracts and retrieved 21 full-text articles or conference proceedings for detailed review. We found four relevant RCTs[2–5] from the search and one additional RCT from our gray search[6] (Table 1).

Discussion

Term neonates and premature neonates born at ≥32 weeks GA should be resuscitated with room air in nearly all circumstances,[7] while there is no consensus on the ideal FiO_2 for resuscitation of preterm infants <32 weeks.[7–10] However, as recently as 2005,

Table 1 Summary of findings in the five relevant randomized controlled trials

Reference	Population	Study type	Intervention	Titration method	Key outcomes	Results
Escrig et al[2,*]	Preterm neonates ≤28 weeks GA requiring resuscitation	Prospective, randomized controlled trial; blinded	LOG (30%, n=19) versus HOG (90%, n=23)	FiO_2 increased/decreased by 10% every 60–90 seconds based on HR and SpO_2 Goals: HR >100 at all times and a preductal SpO_2 rising towards 85% over first 10 minutes of life	Preductal SpO_2 at 10 minutes after birth	No significant difference between LOG (86.9%±2.5%) and HOG (88.7%±2.5%)
					Difference in preductal SpO_2 at 1, 2, 3, 4, 5, 10, 15, and 20 minutes after birth	No significant differences between LOG and HOG
					Ventilatory support in delivery room (eg, CPAP, intubation)	No significant difference between LOG and HOG
					FiO_2 in first 3 minutes of life	Significantly higher in HOG versus LOG ($P<0.01$)
					FiO_2 after first 3 minutes of life	No significant difference between LOG and HOG
Wang et al[3]	Preterm neonates ≤31 weeks GA requiring resuscitation	Prospective, randomized controlled trial; nonblinded	LOG (21%, n=18) versus HOG (100% for initial 5 minutes, n=23)	LOG: FiO_2 increased to 50% if preductal SpO_2 <70% at 3 minutes or <85% at 5 minutes; FiO_2 then increased by 25% every 30 seconds to reach target SpO_2 HOG: FiO_2 kept at 100% for the first 5 minutes, then weaned if preductal SpO_2 >95% Treatment failure: preductal SpO_2 <70% at 3 minutes of life, requiring an increase in FiO_2	LOG requirement of an increase in FiO_2 at or before 3 minutes of life	100% of infants required an increase in FiO_2 because all failed to meet the target with room air as the initial FiO_2
					Preductal SpO_2 at 2, 3, 4, 5, and 10 minutes of life	Significantly higher SpO_2 at all time points ($P<0.01$) in HOG although by 10 minutes of life, the mean SpO_2 in both groups was >85%
					Heart rate in first 10 minutes of life	No significant differences between LOG and HOG
					FiO_2 administered at 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 minutes of life	Significantly lower at all time points ($P<0.01$) up to 7 minutes in LOG; no significant differences between LOG and HOG at 8, 9, or 10 minutes
					Percent of neonates with preductal SpO_2 of >95% at 5 minutes	HOG ~57% versus LOG ~17% ($P<0.05$)
Vento et al[4]	Preterm neonates ≤28 weeks GA requiring resuscitation	Prospective, randomized controlled trial; nonblinded	LOG (30%, n=37) versus HOG (90%, n=41)	FiO_2 increased/decreased by 10% every 60–90 seconds based on HR and SpO_2 Goals: preductal SpO_2 of 75% at 5 minutes and 85% at 10 minutes	Percent of neonates reaching target preductal SpO_2 values of 75% at 5 minutes and 85% at 10 minutes	No significant differences between LOG and HOG; both groups reached the targets
					FiO_2 administered at 2, 3, 4, 5, and 10 minutes of life	Significantly lower at all time points ($P<0.01$) up to 4 minutes in LOG; no significant differences between LOG and HOG at 5 or 10 minutes
					Heart rate in first 10 minutes of life	No significant differences between LOG and HOG
					Preductal SpO_2 at 2, 3, 4, 5, and 10 minutes of life	No significant differences between LOG and HOG
					On FiO_2 of 21% on arrival at NICU	Significantly higher in LOG (76%) versus HOG (56%, $P<0.05$)

Rabi et al[5]	Preterm neonates ≤32 weeks GA requiring resuscitation	Prospective, randomized controlled trial; blinded	LOG (21%, n=34) versus HOG (100%, n=34)	FiO_2 increased/decreased by 20% every 15 seconds based on HR and SpO_2	Proportion of resuscitation time spent in target SpO_2 range**	No significant difference between LOG (16%) and HOG (21%)
				Goals: target preductal SpO_2 of 85%–92% Treatment failure: HR <100 beats per minute for >30 seconds	Time to reach target SpO_2 of 85%–92%	No significant difference between LOG and HOG (*P*=0.56); mean SpO_2 for each group was >85% by 5 minutes
					Proportion of infants in target SpO_2 range at 10 minutes	No significant difference between LOG (38%) and HOG (38%); there was also no significant difference at 5 minutes
					Proportion of infants with SpO_2 above 92% at 10 minutes	No significant difference between LOG (33%) and HOG (34%); there was also no significant difference at 5 minutes
					Proportion of infants meeting treatment failure criteria	No significant difference between LOG (24%) and HOG (9%)
Kapadia et al[6]	Preterm neonates ≤34 weeks GA requiring resuscitation	Prospective, randomized controlled trial; nonblinded	LOG (21%, n=44) versus HOG (100%, n=44)	FiO_2 increased/decreased by 10% every 30 seconds based on HR and SpO_2	Proportion of infants in LOG requiring an increase in FiO_2 to meet target SpO_2 range	All infants in LOG required an increase in FiO_2
				Goals: target preductal SpO_2 of NRP-recommended transitional goal saturations[7] Treatment failure: HR <60 beats per minute despite 30 seconds of effective PPV	Preductal SpO_2 at 2, 3, 4, 5, 6, 7, 8, 9, and 10 minutes of life	Significantly higher SpO_2 at 3–6 minutes of life (*P*<0.05) in HOG
					Proportion of infants with SpO_2 above 94% at 2, 3, 4, 5, 6, 7, 8, 9 and 10 minutes of life	Significantly higher at 2–10 minutes of life (*P*<0.05) in HOG
					Proportion of infants with SpO_2 below lower limit of target SpO_2 range at 2, 3, 4, 5, 6, 7, 8, 9, and 10 minutes of life	Significantly higher at 3–6 minutes of life (*P*<0.05) in LOG
					Proportion of infants meeting treatment failure criteria	No significant difference between LOG (0%) and HOG (0%)

Notes: *The population in this study makes up a portion of the infants in the study by Vento et al.[4] The reported findings from this study provide readers with different clinical data of importance; **study was powered based on this primary outcome. No other study was specifically powered to assess any of their clinical outcomes.
Abbreviations: LOG, low-oxygen group; HOG, high-oxygen group; NRP, Neonatal Resuscitation Program; NICU, neonatal intensive care unit; CPAP, continuous positive airway pressure; HR, heart rate; GA, gestational age; PPV, positive pressure ventilation; SpO_2, oxygen saturation; FiO_2, fraction of inspired oxygen.

virtually all resuscitations for extremely low birth weight infants in the USA used 100% oxygen.[9]

The International Liaison Committee on Resuscitation (ILCOR) has stated that the initial use of room air or 100% oxygen is more likely to result in hypoxemia or hyperoxia, respectively, than initiation of resuscitation with 30% or 90% oxygen for preterm infants <32 weeks GA. ILCOR also recommends that resuscitation be performed with judicious use of blended oxygen and room air, ideally guided by pulse oximetry. Notably, the ILCOR[8] and American Heart Association recommendations[11] did not include the published results of three RCTs found in Table 1[4–6] due to their more recent publication dates. A recent meta-analysis outlines the limitations of the current data around the topic,[12] but does not provide clinicians with a practical conclusion on how to presently manage the use of oxygen in these resuscitations.

The science around this issue is evolving. A high FiO_2 leads to production of free radicals with the potential to extensively damage human cells.[13] A high FiO_2 may prolong time to spontaneous crying and breathing, increase oxygen consumption, decrease minute ventilation, cause atelectasis, or decrease cerebral blood flow.[13,14] At the same time, an overly low FiO_2 may result in various types of organ dysfunction, including neonatal encephalopathy.[13] The result of these data is physician uncertainty as to what is best for the premature infant they are resuscitating.

The determination of an appropriate oxygen saturation (SpO_2) target below which oxygen therapy does more good than harm during resuscitation of premature infants remains elusive; the highest safe SpO_2 remains unclear as well.[15] Preterm infants take longer than term infants to reach an SpO_2 of >85%.[16,17] Dawson et al report on SpO_2 levels in term and preterm infants (including 39 infants born at <32 weeks GA) that could guide post-delivery changes in the F_iO_2, but the infants studied were those that required no oxygen or assisted ventilation in the minutes after birth;[18] therefore, the reported SpO_2 levels may not be best for preterm infants of <32 weeks GA who actually require resuscitation. That said, these levels are recommended by the American Academy of Pediatrics' guideline for use when resuscitating even preterm babies,[7] and the European Resuscitation Council does not provide clearly recommended saturation targets for the preterm infant <32 weeks GA.[19,20] Based on a review of several publications, Finer and Rich[14] recommend: "initial SpO_2 following delivery can be assumed to be around 50% and increases by 5 to 6% per min for the very preterm infant. This will result in an SpO_2 of 65 to 70% at 3 min, 75 to 80% at 5 min and 85 to 90% by 7 to 8 min of age." All RCTs we reviewed (Table 1) considered an SpO_2 of ≥85% at 10 minutes acceptable, although one targeted an SpO_2 of ≥85% at 5 minutes in their low-oxygen group while accepting notably higher SpO_2 readings of >95% in the first 5 minutes of life in their high-oxygen group,[3] and one targeted an SpO_2 of 85%–92% as soon as SpO_2 readings were available,[5] which is usually by 1–2 minutes of life. Although the final determination of the ideal SpO_2 targeting remains elusive, an SpO_2 of 85%–94% at 10 minutes seems to be considered acceptable by most experts.

Table 1 details the few small RCTs that compare commencing with a low FiO_2 (21%–30%) versus high FiO_2 (90%–100%) during resuscitation of preterm infants (particularly those ≤31 weeks GA). One RCT likely had a single 32-week GA infant based on their inclusion of preterm neonates ≤32 weeks and their final population having a mean GA of 29 (95% confidence interval 28–30);[5] another included infants at 32–34 weeks GA.[6] Various titration methods were used (see Table 1 for details); of note, sudden FiO_2 alterations (over 10% every 30 seconds) may result in constriction of the pulmonary vasculature.[4] In the two RCTs[2,4] comparing 30% versus 90% as the starting FiO_2 in infants ≤28 weeks GA, saturations were similar in both groups at all times, but the high-oxygen group had greater exposure to oxygen,[2] more signs of oxidative stress, more ventilation days, and prolonged oxygen supplementation,[4] with no noted benefits from the higher oxygen exposure. Two of the three RCTs comparing room air with 100% oxygen[3,5] had a higher treatment failure rate (as defined by the studies and noted in Table 1) in their room air groups (only statistically significant in one[3]), suggesting that room air is likely not the best initial FiO_2 choice in this population. The other recent RCT comparing room air with 100% oxygen[6] demonstrated that all babies initially resuscitated with room air required an increase in FiO_2 to reach the targeted preductal saturations, again suggesting room air is perhaps not the best initial FiO_2 choice. In this study, there was no difference in treatment failure (as defined by the study and noted in Table 1) between the groups, but this may have been due to the inclusion of more mature infants at 32–34 weeks GA; importantly, the study was underpowered, particularly for those infants <29 weeks GA, for any clinical outcomes given that the primary outcome was a laboratory-based measurement of oxidative stress. Several upcoming RCTs are using room air as one of their comparison groups and may help determine if, indeed, it should not be used as the initial gas for resuscitation.[15] Another upcoming

RCT will compare 30% and 65% as the initial gas for resuscitation.[21]

We have reviewed the most recent and relevant evidence for clinical oxygen use in the resuscitation of infants born at <32 weeks GA. The heterogeneous outcomes assessed in each respective study hamper any meta-analysis of the RCTs.[12] Based on our review of these few small RCTs, the best approach at the present time seems to be initiating resuscitation with an initial FiO_2 of 30% and titrating oxygen up or down based on the preductal pulse oximetry. The oxygen should also be titrated if the HR remains <100 despite 30 seconds of effective positive-pressure ventilation. The FiO_2 should be titrated to match the current recommended "minute by minute" preductal SpO_2 targets from the American Heart Association[7,11] or the original evidence-based data.[15,18] Additionally, should cardiac output fail to improve (ie, heart rate <60 beats per minute) despite adequate ventilation and chest compressions become necessary, the FiO_2 should immediately be increased to 100% based on current recommendations.[7]

In closing, room air may be acceptable as the initial resuscitation gas, but present data suggest it inadequately stabilizes SpO_2 levels or the heart rate of infants <32 weeks GA. Given the equivalent stabilization of these infants on 30% or 90% FiO_2 as the initial resuscitation gas, an FiO_2 of 30% appears to be the better choice given the risks of high oxygen exposure. Determination of the ideal initial resuscitation gas and SpO_2 targets requires further high quality research assessing both short-term and long-term outcomes.

Disclosure

The authors declare no conflict of interest in this work.

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Authors' reply

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Dear editor

We compliment Moore and Navabi for their updated report on evidence-based choice of the initial fraction of inspired oxygen (FiO_2) for resuscitation of premature infants <32 weeks gestation. These infants often need respiratory support and oxygen supplementation immediately after birth, and adequate oxygenation is essential because both hypoxia and hyperoxia can have detrimental effects.[1,2]

Moore and Navabi correctly point out that studies in preterm infants failed to define the optimal initial FiO_2 during resuscitation. A recent meta-analysis[3] of six randomized controlled trials (RCTs)[4–9] concluded that there is not sufficient evidence to affirm that the use of lower or higher initial FiO_2 in the delivery room for preterm babies confers important benefits or harm. Moreover, none of these trials[4–9] was actually powered to evaluate important long-term outcomes such as survival without significant neurodevelopmental disability. Until further evidence becomes available, we still believe that the best approach is to initiate a resuscitation with an FiO_2 of 30%, thereafter, FiO_2 should be titrated according to the pulse oximetry oxygen saturation (SpO_2) readings with changes in 10% intervals performed every 30 seconds to allow babies cardio-respiratory response.

Oxygen blenders and pulse oxygen saturation monitors should be used to achieve the balance of administering the FiO_2 based on the infant's needs. Using pulse oximetry to guide oxygen therapy in the delivery room is not evidence-based practice. However, the American Heart Association (AHA)[10] and the European Resuscitation Council (ERC)[11] guidelines advise preductal SpO_2 targets for the first 10 minutes after birth, without specifying the gestational age. These targets are based on observational studies of healthy infants not requiring any intervention during their resuscitation.[12] The AHA guidelines advise a narrow SpO_2 target range close to the median values for infants who do not require resuscitation (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), while the ERC guidelines prescribe single value SpO_2 targets (SpO_2 of 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, 5, and 10 minutes after birth, respectively) these values are closer to the 25th percentile. Recently a group of experts have suggested that the use of the 10th and 50th percentile SpO_2 curves of Dawson's nomograms,[12] as the SpO_2 target range may be more appropriate.[13] 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.[12] It is worth noting that the available SpO_2 targets are based on observational studies of healthy infants not requiring any intervention during their resuscitation, in a recent study it has been shown that preterm babies and especially females receiving positive pressure and air attain higher saturations earlier than those spontaneously breathing.[14] Meanwhile, resuscitation team must control the SpO_2 adequately, and follow the targets with as little deviation as possible. Recently it was demonstrated that the resuscitation team could effectively maintain SpO_2 values within a specific target range during transition using Transitional Oxygen Targeting System (TOTS) plots which record real-time SpO_2 values in relation to 10th and 50th percentile SpO_2 curves.[15]

Further appropriately-sized RCTs are needed to define the best initial FiO_2 and the appropriate SpO_2 range in the delivery room. These trials should measure not only short term but also long-term outcomes. The Targeted Oxygenation in the Resuscitation of Premature Infants and Their Developmental Outcome trial (TO2RPIDO)[16] is recruiting infants at ≤31 weeks' gestation to compare 100% oxygen 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% oxygen group, FiO_2 is decreased when SpO_2 >92%. The Study of Room Air Versus 60% Oxygen for Resuscitation of Premature Infants (PRESOX),[17] will use targeted oxygen saturation levels over the first 15 to 20 minutes of life to compare a low (21%) and a higher initial oxygen (60%) level for the resuscitation of preterm infants <29 weeks gestation, and will be large enough to evaluate short term outcomes of survival without oxygen at 36 weeks and survival without retinopathy of prematurity, and the long term outcome of survival without significant neurodevelopmental impairment at 2 years of age.

To summarize, resuscitation in room-air or 100% oxygen is not recommended for preterm neonates <32 weeks gestation. The FiO_2 of 30% apparently enhances successful transition, lowers the oxygen exposure, and diminishes the risk of oxidative damage. The FiO_2 should be titrated according to SpO_2 values. Further RCTs are needed to define the best initial FiO_2 and the appropriate SpO_2 range in the delivery room for preterm infants. These trials should measure not only short term but also long-term outcomes.

Disclosure

The authors report no conflicts of interest in this communication.

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