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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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Gregory P Moore[1–3]
Behdad Navabi[2]

[1]Department of Pediatrics, Division of Neonatology, Children's Hospital of Eastern Ontario, [2]Department of Obstetrics and Gynecology, Division of Newborn Care, The Ottawa Hospital General Campus, [3]Department of Pediatrics, University of Ottawa, Ottawa, ON, Canada



## 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 Publications prior to January 2008 were excluded because of redundancy, lack of applicability, or outdated information being likely in these publications.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,

Correspondence: Gregory P Moore
The Ottawa Hospital, General Campus, Division of Newborn Care,
Box 806, 501 Smyth Road, Ottawa, ON, Canada K1H 8L6
Tel +1 613 737 8561
Fax +1 613 737 8889
Email gmoore@cheo.on.ca

**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 $SpO_2$<br>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 $SpO_2$<br>HOG: $FiO_2$ kept at 100% for the first 5 minutes, then weaned if preductal $SpO_2$ >95%<br>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 $SpO_2$<br>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%<br>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]<br>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

Hesham Abdel-Hady
Nehad Nasef

Neonatal Intensive Care Unit, Mansoura University Children's Hospital, Mansoura, Egypt

Correspondence: Hesham Abdel-Hady
Neonatal Intensive Care Unit, Mansoura University Children's Hospital, Gomhoria, Street, Mansoura 35516, Egypt
Tel +200 0527 8051
Fax +205 0223 4092
Email hehady@yahoo.com

## 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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