Air versus oxygen for resuscitation of infants at birth

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Limited available data suggests that, compared with resuscitation with 100% oxygen, starting newborn resuscitation with room air is associated with a reduction in infant mortality. While room air is not associated with additional complications in the newborn, 100% oxygen should be available as backup for infants who remain persistently cyanosed.

RHL Commentary Pileggi Castro Souza C

1. INTRODUCTION

For a newborn, birth is a natural challenge that marks the transition from the intrauterine to extra uterine life. Most babies handle this transition well: 90% of them do not need any medical intervention for survival, but 5%–10% of newborns need some resuscitation. The interventions required may range from simple tactile stimulation to complex cardiopulmonary resuscitation. In 2005, WHO estimated that among 4 million neonatal deaths, 23% were directly caused by asphyxia and related complications (1).

Reducing mortality and long-term neurodevelopmental damage associated with birth asphyxia is the main purpose of an optimal neonatal resuscitation. Over time, strong recommendations from experts, textbooks and guidelines issued by health-care professional societies made 100% oxygen as the gas of choice for resuscitating newborns with asphyxia. However, this recommendation is not based on strong evidence and there is current uncertainty about the optimal concentration of oxygen that should be used during resuscitation. Indeed, some experiments using a high blood concentration of oxygen showed an increased risk of adverse neonatal effects in short- and long-term evaluations, especially in preterm infants.

The present Cochrane review aimed “to determine if the use of room air reduced the incidence of death or neurological disability when compared with the use of 100% oxygen in newborn infants requiring resuscitation”. It also sought to assess “whether resuscitation using room air, as compared with oxygen, resulted in decreased rates of hypoxic-ischemic encephalopathy, bronchopulmonary dysplasia or retinopathy of prematurity”. And finally the review compared “effects of room air versus oxygen on immediate clinical and biochemical responses to resuscitation” (2).

2. METHODS OF THE REVIEW

The authors planned to include all randomized or quasi-randomized trials that had studied term or preterm neonates requiring ventilation support at birth. The authors also planned to include trials comparing other levels of oxygen supplementation with either 100% oxygen or room air.

The primary outcomes considered were death and long-term neurodevelopmental outcomes at age 5 years. Secondary outcomes considered were consistent signs of hypoxic-ischemic encephalopathy, incidence of bronchopulmonary dysplasia, incidence of retinopathy of prematurity, time to establish regular respiration, time to establish heart rate > 100 beats per minute, Apgar scores at age five and ten minutes and results of
the first arterial blood gas analysis following resuscitation within the first 2 hours of life. In addition, some comparable outcomes were added after the eligible studies were examined.

The standard Cochrane search strategy was used to access the trials. Three authors independently identified the studies for inclusion, performed quality assessment and extracted the data. Discrepancies in the collected data were resolved by discussion between the reviewers.

The reviewers assessed the quality of primary evidence based on blinding of randomization, blinding of the intervention, completeness of follow-up and blinding of outcome measurements. The statistical analysis was done using the fixed-effects model. For categorical data, relative risk (RR), risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals (CI) were calculated. Continuous data were analysed using weighted mean difference (WMD).

3. RESULTS OF THE REVIEW

The authors provide the usual Cochrane tables of characteristics of included and excluded studies. Their extensive search found only five studies (two multicentre and three single-centre) with 1302 infants that fulfilled the inclusion criteria. Two studies included term newborns and three included term newborns and a small proportion of preterm infants with birth weight greater than 1 kg (24% of all infants). The inclusion criteria were homogeneous between the studies (infants were either apneic or had gasping respiration and/or were bradycardic with a heart rate less than 80 beats per minute).

Regarding the risk of bias, the reviewers found two studies with adequate allocation concealment and generation of allocation sequence. Some study authors were concerned about the fact that the process of randomization could represent a delay in the newborn receiving treatment; hence, they had opted for a quasi-randomization design. More than 90% of data on randomized newborns came from four studies. Only one study had post-randomized exclusion of 30% of newborns, but by contacting the authors of the original study, the review authors were able to retrieve data on intention to treat results of primary outcomes. Two studies were blinded for the intervention as well as the outcome measure.

Primary outcomes were fully presented in four trials. Pooled analysis of the trial data showed statistically significant reduction in mortality in the group allocated to room air (RR 0.71, 95% CI 0.54–0.94; RD -0.05, 95% CI -0.08 to -0.01; NNT 20. 95% CI 12–100).

Concerning Apgar score, all included studies presented only medians values, which rendered pooled analysis unfeasible. One study presented the proportion of newborns with Apgar score of less than seven at 5 minutes of birth, which suggests a trend in favour of the room air group (RR 0.78, 95% CI 0.60–1.00; RD -0.07 95% CI -0.14 to 0.00). In blood gas analysis within the first two hours of life, presented in three trials, there was no statistical difference in the pH observed between the room air and 100% oxygen groups. Otherwise, a significant lower pCO2 and pO2 were observed in babies randomized to room air (respectively: WMD -2.13 mmHg, 95% CI -4.08 to -0.18; and WMD -37.09 mmHg, 95% CI -41.99 to -32.19).

The time to start of spontaneous respiration was reported in one trial, which showed statistically and clinically significantly shorter median time to first breath in the room air group compared with those resuscitated with 100% oxygen (WMD -1.5 minutes ; 95% CI -2.02 to -0.98). Another trial reported the proportion of infants spontaneously breathing at three minutes with room air, which was significantly reduced among babies that received room air compared with those who received 100% oxygen (RR0.53; 95% CI 0.35–0.80)

A post-hoc analysis of data on failure of resuscitation was conducted. There was no significant difference in the rates of failure of resuscitation between the room air and 100% oxygen groups (four trials RR 0.96%, 95% CI 0.81–1.14; RD -0.01 95% CI -0.06 to 0.04).
Other comparisons in this systematic review were statistically not significant and some outcomes (such as bronchopulmonary dysplasia and retinopathy of prematurity) were not referred to in the original trials.

**Additional evidence**

Since the publication of the systematic review, three new randomized controlled trials that compared the use of room air and 100% oxygen for neonatal resuscitation have been published. In a study involving newborns weighing 1000 g or more, Bajaj, found no differences in the incidence of hypoxic ischemic encephalopathy (HIE) or death before discharge, and, as well, no differences in other adverse outcomes (3). In a trial that evaluated resuscitation of asphyctic neonates, Vento et al. concluded that use of room air causes less oxidative stress and damage to the heart and kidneys than 100% oxygen (4). In another study of resuscitation of preterm neonates aged <32 weeks, Wang et al. found that pulse oxygen saturation was significantly lower in the room air group from 2–10 minutes, but heart rates did not differ between groups in the first 10 minutes of life and no differences in other outcomes were found (5).

4. **DISCUSSION**

4.1 **Applicability of the results**

Starting newborn resuscitation with room air was not associated with any adverse effects. Moreover, resuscitation with room air was found to be associated with a reduction in infant mortality compared with resuscitation with 100% oxygen. On the one hand, some methodological limitations and small sample sizes in the included studies reduce the overall strength of the conclusions of the review, but on the other hand more recent studies lend support to the conclusions. Another issue with regard to the comparison of 100% oxygen with room air, which is especially relevant to under-resourced settings, is the relative higher cost of 100% oxygen. Thus, considering that 100% oxygen is still widely used for newborn resuscitation (more for historical reasons rather than the intervention being truly evidence-based), this gas should be available as backup in case of failure of the initial resuscitation with room air.

A recent well-controlled randomized clinical trial demonstrated the beneficial effects of titrating the concentration of oxygen using pulse oximetry during resuscitation of preterm infants. In this trial, avoiding excessive use of oxygen, was associated with less oxidative stress and the authors of that study recommended the use of pulse oximetry to reduce inspired oxygen in the resuscitation of asphyxiated premature infants (6). The use of oximetry in all childbirths probably represents an ideal situation that may not be implementable in all settings. On the other hand, validated clinical signs should be used to guide the start use of high concentration of oxygen, if needed.

4.2 **Implementation of the intervention**

After birth, for all babies, the assurance of thermal control is the first step to a successful resuscitation. A rapid evaluation of the clinical condition must direct the care provider to assessment of the need for ventilation support. The initial resuscitation should be initiated with room air, but supplementary oxygen must be provided if positive-pressure ventilation is indicated or when there is no appreciable improvement in skin colour after 90 seconds of life (7).

4.3 **Implications for research**

The above recommendations are based on small trials with some methodological limitations. The trials could not address several key questions: Is there a way to isolate the effects of delivery-room oxygen in a newborn with asphyxia? Could the long-term side-effects be attributed only to the first offer of oxygen? Is it possible that, in the extra-uterine life of a preterm baby, other co-interventions, confounders or effect modifiers could have played a role in the long-term outcomes? Could the methodological limitation, including the small sample size of the included trials, have biased the results? Hence, overall, the evaluation of the effectiveness and short- and long-term complications related to high concentrations of oxygen used for resuscitation in the
delivery room was inconclusive, regardless of setting. Weaknesses in the current evidence point to the need for larger, well-designed trials. The systematic review also needs to be updated with recently published studies.

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References

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