What is the Preferred Empiric Resuscitation Gas in Asphyxiated Infants?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the preferred empiric resuscitation gas in asphyxiated infants?*

The WHO Pocketbook of Hospital Care for Children recommends that in the resuscitation of the neonate to position the head of the baby in the neutral position and open the airway. The airway is then cleared if necessary and the child stimulated and repositioned. Bag and mask ventilation with oxygen (or room air if oxygen is unavailable) is commenced if the respiratory rate is too slow (less than 20) (Pocketbook chapter 3.6, page 48).

INTRODUCTION

Birth asphyxia or failure to establish breathing at birth accounts for approximately 4 million deaths a year worldwide [1]. 99% of these deaths occur in developing countries [1]. Birth asphyxia is closely associated with major neuro-developmental handicaps such as cerebral palsy, mental retardation, epilepsy and chronic diseases later in life [2]. Traditionally, 100% oxygen has been used to resuscitate all asphyxiated newborns irrespective of the severity of their condition. This practice largely reflects the concern that the poor tissue oxygen delivery, that is part of the fetal to neonatal transition, is exacerbated by problems at or during birth resulting in systemic and damaging oxygen deficiency [3]. Thus, the aim has always been to rapidly correct any oxygen debt in the expectation that this will prevent any damage. However, it has more recently been argued that the use of 100% oxygen may have adverse effects on breathing physiology, cerebral circulation and asphyxial tissue damage resulting from increased free oxygen radicals [3,7]. The choice of optimal resuscitation gas for asphyxiated newborns therefore remains controversial. This review therefore intends to answer the clinical question: What is the preferred empiric resuscitation gas?

METHODS

Potential studies for inclusion were identified through MEDLINE searches using Pubmed clinical queries. The searches were conducted using the following combination of terms: (air OR oxygen) AND newborn resuscitation.

Using the clinical filter for systematic reviews, 51 articles were found, 2 of which were relevant.

Under therapy, narrow specific filter, 41 articles were found (2 relevant).

Under prognosis, broad sensitive filter, 39 articles were found (2 relevant).

The titles and abstracts of all the retrieved articles were read and those with a comparison of air versus oxygen for resuscitation of asphyxiated newborns selected. The eligibility of the studies were assessed independently by two reviewers. The methodological quality of the individual articles were assessed using the Oxford CEBM LOE, which ranks the validity of evidence in a hierarchy of levels with systematic reviews as level 1 (strong evidence) and expert opinions as level 5 (weak evidence) [4]. Likewise, the grades recommendations were based on the SIGN grading system, which places weight on the quality and body of evidence [5].

Overall, 2 SRs, 2 RCTs, 3 Quasi-randomised trials, 1 Cohort Study and 1 Guideline were found; 2 studies (SRs) had a LOE of 1a, 5 were of level 1b evidence while 1 had a LOE of 2b (Table 1).

4 of the included studies [3,6,7,8] were analysed by a more recent SR [2]. Two of the selected SRs [2,9] reported the same data and analysis hence only one was included [2] [Tan 2004]. No RCT conducted after these SRs was found.

RESULTS

The studies assessed the following outcomes: mortality, longterm neurodevelopmental disability (cerebral palsy, motor/language milestones, 'abnormal development'), rates of HIE, Apgar score, time to establish regular respirations, arterial blood gases and resuscitation failures. Two studies [3,6] included only term infants. Four studies enrolled [7,8,10,11] term and preterm infants with a birth weight over 1 kg. Two studies [8,10] did not specify the proportion of included preterm infants.

Four studies [3,7,8,10] reported mortality as an outcome; none showed a statistically significant difference in mortality at latest follow up (all the 95% CIs crossed 1). However, a pooled analysis showed a significant benefit for babies resuscitated with air [RR 0.71 (0.54, 0.94), RD –0.05 (-0.08, -0.01), NNT 20, (12, 100)] [2]. Only one study [7] assessed this effect as a primary outcome.

One study [11] followed up a group of eligible infants from 18 to 24 months; the rates of cerebral palsy did not differ between the two groups [RR 1.34 (0.55, 3.24)]. The same study also reported no significant differences in rates of not walking [RR 1.03 (0.47, 2.25)], not talking [RR 2.68(0.69,10.44)] and 'abnormal development' [RR 1.56(0.76, 3.22)]. However, the follow up rate was low and no formal psychometric testing was done.

The three studies [7, 8, 10] which reported rates of Hypoxic Ischaemic Encephalopathy (HIE) found no significant difference between the groups [RR 0.84 (0.65, 1.08), RD –0.01 (-0.06, 0.04)]. All the three studies allowed back up oxygen use for babies initially resuscitated using air. In addition, there was no blinding of interventions and outcome measurements in these studies.

Median Apgar scores at ages 5 and 10 minutes were not significantly different in three studies [3,6,10]. However, in one study [8], there was a significant difference (although small) in median (25th and 75th percentile) 5 minute Apgar scores favouring the room air group [8(7,9) vs 7 (6, 8), p=0.03)]. In one large multicenter study [7] there were significantly more infants with 5-minute Apgar score <7 in the oxygen group (31.8%) than in the room air group (24.8%), p=0.03); however, at 10 minutes, no such difference between the groups was found.

Three studies [3,6,7] reported that resuscitation with room air instead of oxygen favoured prompt initiation of sustained respiration pattern in the asphyxiated infant. In one study [7], time to first breath was significantly longer in the oxygen-resuscitated group compared to the room air-resuscitated group. The same study also reported that, in the oxygen group, 19.2% required >3 minutes to take the first breath compared with 9.9% in the room air group (OR=0.47; 95% CI=0.29-0.76). One study [8] reported no difference in the median time to first breath; 1.5 (1.0-2.0) min in both groups (p=0.59).

Arterial blood gases at 10 to 15 minutes of life was reported by three studies [3,7,8]; in one of the studies [3], pure oxygen caused hyperoxemia (pO2, 126.3 ± 21.8 mm Hg) that did not occur with the use of room air (pO2, 72.2 ± 6.8 mm Hg). The same study also reported a lower level of pCO2 in babies randomised to room air (46.4±6.8 mm Hg) compared to those in the oxygen group (49.5±5.3 mm Hg). In the other two studies [7,8], the differences in base deficit were not statistically significant.

5 studies [3,6,7,8,10] reported failure of resuscitation as a post hoc analysis (after the results of the studies were examined); there was no individual difference in the rates of failure in resuscitation in 4 of these studies [3,6,7,10] and the pooled analysis also showed no significant difference between the groups in this outcome [RR 0.96 (0.81, 1.14), RD –0.06, 0.04)]. In one study [8], 6 out 42 infants allocated to room air reached failure criteria. However, this trial did not report this outcome for babies allocated to the oxygen group.

DISCUSSION

Resuscitation using air significantly reduced mortality compared with oxygen; one death would be prevented for every 20 babies resuscitated with air rather than oxygen. However, in cases of resuscitation failure, back up oxygen was provided for some babies initially allocated to room air. Thus, there is a possibility that some subgroups of infants could benefit from resuscitation with oxygen supplementation.

The evidence on similarity of neurodevelopmental outcomes between the two groups is not conclusive. This is because of methodological weaknesses of the only study that reported this effect (low follow up rates, lack of masking of assessors, and absence of psychometric testing). Furthermore, this effect was not assessed as a primary outcome.

Room air resuscitation was shown to have a number of short term benefits; RAR infants seemed to recover more quickly as assessed by Apgar scores, time to first breath and onset of a sustained pattern of respiration. In addition, the use of 100% oxygen was shown to cause hyperoxia and alterations in cerebral circulation.

Main weaknesses of the studies, apart from their small numbers, were low follow up rates [11], and lack of blinding of interventions/outcome measurements [7,8,10]. The studies also included few low birthweight/premature infants and therefore the results cannot be extrapolated with confidence to this group.

SUMMARY

Based on the findings of this review, resuscitation of asphyxiated newborns can be done with room air just as efficiently as with oxygen (grade A evidence). However, back up oxygen should continue to be made available to babies initially resuscitated with air in case of resuscitation failure. In addition, room air resuscitation was shown to significantly reduce mortality compared with oxygen. However, the effect on preterm infants was not conclusive. Thus, there is need for future trials to specifically explore the optimal resuscitation gas for this subset of asphyxiated newborns. Likewise, the limited evidence on neurodevelopmental outcomes in favour of babies resuscitated with room is insufficient and warrants confirmation by larger long term follow up studies.

Abbreviations

SR: Systematic Review
RCT: Randomised Controlled Trial
CEBM LOE: Center for Evidence Based Medicine Levels of Evidence

Authors' contributions

ON was responsible for conducting the literature searches, reviewing articles, assessing their quality, drafting and finalising the manuscript.

ME conceived of the idea for the review and was responsible for reviewing articles, assessing their quality, drafting and finalising the manuscript.

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REFERENCES

1. Lawn JE. et al. 4 million deaths: when? where? why? The Lancet 2005;365:891-900.

2. Tan A. et al. Air versus oxygen for resuscitation of infants at birth (Review). 2004 The Cochrane Database of Systematic Review.

3. Vento M. et al. Oxidative stress in asphyxiated term infants resuscitated with 100% Oxygen. Journal Pediatrics 2003;142(3): 240-246.

4. Philips B. et al. Oxford centre for evidence-based medicine levels of evidence (May 2001). Available from: http:cebm.net/levels_of_evidence.asp#top

5. Habour R. et al. A new system for grading recommendations in evidence based guidelines. British Medical Journal 2001;323:334-336

6. Vento M. et al. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 2001 107:642-647.

7. Saugstad O. et al. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The resair 2 study. Pediatrics 1998; 102(1).

8. Ramji S. et al. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. Pediatric Research 1993;34(6):809-812.

9. Davis P. et al. Resuscitation of newborn infants with 100%oxygen or air: A systematic review and meta-analysis. Lancet 2004. 364: 1329-1333.

10. Ramji S. et al. Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: A multicentric clinical trial. Indian Pediatrics 2003; 510-517.

11. Saugstad O. et al. Resuscitation of newborn infants with 21% or 100% oxygen: Follow-up at 18 to 24 months. Pediatrics 2003;112: 296-300.

Table 1. Characteristics of included studies

Citation Design	Country Setting	Inclusion Criteria	Sample Size	Intervention	LOE
Ramji et al [10] Quasi-randomised	India Teaching Hospitals	Asphyxiated babies Weight>1000grams Heart Rate<100/min Apnea unresponsive to suction No abnormalities	431	*Room air group; RAG (n=210)* Asphyxiated neonates born on even dates given room air *100% oxygen group, OG (n=221)* Asphyxiated neonates born on Odds date given 100% oxygen	**1b "-"**
Vento et al [3] RCT	Spain Hospital Obstetric Ward	Asphyxiated babies Term	151	*RAG; n=51*, given room air *Oxygen group; n=55*, given 100% oxygen	**1b**
Vento et al [6] RCT	Spain Hospital Outpatient Clinic Obstetric Ward	Asphyxiated Term Apneic, unresponsive to stimuli Bradycardic	40	Room air (n=19) or 100 % oxygen (n=21) via IPPV with bag and mask at 30 bpm	**1b**
Saugstad et al [11] Cohort	Multicentre Hospitals	Asphyxiated infants Weight> 999g Heart rate<80 bpm Apnea/gasping No abnormalities	213	Follow up between ages 18 and 24 months of 213 children enrolled in Saugstad *et al*, 1998 study: 91 (62%) had been resuscitated with 21% oxygen and 122 (69%) had been resuscitated with 100% oxygen	**2b**
Saugstad et al [7] Quasi-RCT	Multicentre Hospitals	Asphyxiated infants weight >999g Heart rate <80 bpm Apnea/gasping No abnormalities	609	Quasi-randomised by date of birth (even= room air, odd= 100% oxygen) Room air group, n=288 100% oxygen group, n=331	**1b "-"**
Ramji et al [8] Quasi-randomised	India Hospital	Birth weight > 999g apnea Heart rate< 80 bpm	84	Neonates allocated to be resuscitated with either room air (n=42) or 100% oxygen (n=42)	**1b "-"**

IPPV: Intermittent Positive Pressure Ventilation
LOE: Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001)