Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis

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Summary

Background **International consensus statements for resuscitation of newborn infants recommend provision of 100% oxygen with positive pressure if assisted ventilation is required. However, 100% oxygen exacerbates reperfusion injury in animals and reduces cerebral perfusion in newborn babies. We aimed to establish whether resuscitation with air decreased mortality or neurological disability in newborn infants compared with 100% oxygen.**

Methods **We did a systematic review and meta-analysis of trials that compared resuscitation with air versus 100% oxygen, using the methods of the Cochrane Collaboration. We combined data for similar outcomes in the analysis where appropriate, using a fixed-effects model.**

Findings **Five trials (two masked and three unmasked), consisting of 1302 newborn infants, fulfilled the inclusion criteria. Most babies were born at or near term in developing countries. In the three unmasked studies, infants resuscitated with room air who remained cyanotic and bradycardic were switched to 100% oxygen at 90 s. The masked studies allowed crossover to the other gas during the first minutes of life. Although no individual trial showed a difference in mortality, the pooled analysis showed a significant benefit for infants resuscitated with air (relative risk 0·71 [95% CI 0·54 to 0·94], risk difference –0·05 [–0·08 to –0·01]). The effect on long-term development could not be reliably determined because of methodological limitations in the one study that followed up infants beyond 12 months of age.**

Interpretation **For term and near-term infants, we can reasonably conclude that air should be used initially, with oxygen as backup if initial resuscitation fails. The effect of intermediate concentrations of oxygen at resuscitation needs to be investigated. Future trials should include and stratify for premature infants.**

Introduction

Rapid and complex physiological changes occur during birth. Usually, these changes are spontaneous and no intervention from health professionals is necessary. However, roughly 5–10% of newborn infants require some assistance to begin breathing in the first minutes after delivery.[1] The aim of resuscitation is to prevent death and adverse long-term neurodevelopmental sequelae. International consensus statements on resuscitation of the newborn infant[1,2] state that adequate ventilation is the key to success, and that if assisted ventilation is required, 100% oxygen should be delivered by positive pressure ventilation. Others have noted[3,4] that this recommendation is based mainly on precedent rather than sound evidence.

Concerns have been raised about the potential adverse effects of 100% oxygen.[5] Hyperoxia slows cerebral blood flow in term and preterm infants,[6] and exposure to even brief periods of 100% oxygen at delivery causes long-term reductions in cerebral blood flow in newborn preterm infants.[7] In addition, high concentrations of oxygen lead to generation of oxygen free radicals, which have a role in reperfusion injury after asphyxia.[8,9] Thus, air might be a more appropriate gas than 100% oxygen.[10] We aimed to establish whether resuscitation with air reduced the occurrence of death or neurological disability in newborn infants compared with 100% oxygen.

Methods

We undertook a systematic review and meta-analysis using the methods and software of the Cochrane Collaboration. Three authors assessed each article according to the following criteria: masking of randomisation and intervention, completeness of follow-up, and masking of outcome assessment. Independently, these authors extracted data from every trial, then compared results and resolved differences. Four trials measured failure of resuscitation for both the 100% oxygen and air groups.[13–16] Two unmasked studies[13,14] allowed infants allocated air to receive back-up therapy with 100% oxygen if they reached criteria for failure of resuscitation (remained cyanosed or bradycardic after 90 s of resuscitation). These two studies[13,14] also recorded the number of infants in the 100% oxygen group who reached the same failure criteria. Two masked studies[15,16] offered backup treatment with the alternative gas, at the clinician's discretion, if early clinical response to resuscitation was unsatisfactory, but one[15] reported that no infant in either group required backup therapy. Additional data provided by the author allowed us to measure rates of resuscitation failure in one trial[16] for all randomised infants.

Statistical analysis was done according to the guidelines of the Cochrane Collaboration.[18] Data for similar outcomes were combined in a meta-analysis where appropriate. For categorical outcomes, treatment

Search strategy and selection criteria

We searched PubMed from 1966–04 using the terms "resuscitation", "oxygen", and "infant"; and the Cochrane Controlled Trials Register using "resuscitation" and "infant". We searched Abstracts of the Society for Pediatric Research and the European Society for Paediatric Research from 1996–04, and found full-text articles on MEDLINE by searching for authors' names. Previous reviews were cross-referenced and personal files searched for additional references. No language restrictions were applied.

We assessed all potentially relevant published articles and abstracts for inclusion. To be included, trials had to meet four criteria:

- Study design—randomised or quasi-randomised controlled trial.
- Participants—term or preterm newborn infants requiring positive pressure ventilation at birth.
- Intervention—air versus 100% oxygen.
- Any of the following outcome measures—primary outcomes of death in the neonatal period or long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay—ie, IQ <2 SD on validated assessment instruments such as the Stanford-Binet intelligence scale); or secondary outcomes of signs consistent with hypoxic ischaemic encephalopathy,[11] time to establish regular respirations, time to establish heart rate >100 beats per minute, or Apgar scores at age 5 and 10 minutes. In addition to these criteria, which were defined in the protocol for *The Cochrane Library*,[12] the following outcomes were added after eligible studies had been examined: time to first breath of more than 3 minutes, heart rate at 5 minutes, developmental milestones at 18–24 months of age including walking and talking, and an assessment of "abnormal" by a paediatrician at 18–24 months.

effect was analysed by relative risk (RR), risk difference, and number needed to treat, with associated 95% CIs. For continuous outcomes, treatment effect was analysed by weighted mean differences with their 95% CIs. We used a fixed-effects model. We tested heterogeneity of results for all outcomes, and judged a p value less than 0·05 on χ^2 test to indicate significant heterogeneity.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our initial search identified abstracts from about 350 potentially eligible clinical trials and 12 review articles; however most were rejected (eg, animal studies, commentaries, guidelines, or non-randomised human studies). Ten full-text articles were reviewed and five trials, totalling 1302 infants, fulfilled inclusion criteria (table 1).[13–17] Allocation was quasi-random in three studies,[13,14,17] which allocated babies born on even dates to resuscitation with air and those born on odd dates to 100% oxygen: the authors were concerned that randomisation after birth might have delayed treatment and reduced the number of infants enrolled. Vento and others (2001)[15] described adequate generation of allocation sequence by random number assignment and the implementation of the allocated treatment by a nurse who was not involved in resuscitation. Computer-generated random numbers and sealed envelopes were used in another study.[16]

Two studies[15,16] masked the intervention by having a nurse who was not involved with resuscitation switch the hidden oxygen blender to either 21% or 100% oxygen. The other three studies[13,14,17] were not masked. Four studies[13–15,17] provided in-hospital outcome data for more than 90% of randomised patients. Vento and colleagues (2003)[16] excluded 45 (30%) of 151 randomised patients for the following reasons: failure to fulfil biochemical entry requirements; insufficient blood taken for analysis; switching to alternative treatment group; and loss of masking. The authors provided data for the outcomes death and failure of resuscitation for all randomised infants. We report other outcomes using the denominator of the remaining 106 infants. Three studies[13,14,17] included infants who were resuscitated with air, and who were later switched to 100% oxygen; infants in all studies were analysed by intention to treat. Vento and others (2001)[15] reported that all infants received only allocated treatment.

Saugstad and colleagues[19] attempted follow-up of infants in seven of ten centres that participated in the original study.[13] Of 331 eligible infants, 213 were assessed by a paediatrician between 18 and 24 months of age. No other trial reported long-term outcomes. Outcomes were assessed by investigators who were unaware of treatment allocation, in two trials,[15,16] but were assessed unmasked in the remaining three studies.

Although three trials allowed recruitment of preterm infants, the mean[14,17] and median[13] gestational age in all three was 38 weeks. The air and 100% oxygen groups were well matched; there were no significant differences in baseline birthweight or gestational age. Additionally, the trials did not differ in the proportion of deliveries complicated by meconium, or in rates of caesarean section (data not shown). Most infants enrolled in the trials were moderately asphyxiated. Umbilical arterial pH values were reported in three trials,[13,15,16] with mean values between 7·02 and 7·12. Data were not available for outcome stratified for severity of asphyxia—ie, for umbilical arterial pH values less than or greater than 7·0. Other aspects of delivery-room treatment, including

	Ramji (1993)[17]	Ramji (2003)[14]	Saugstad (1998)[13]	Vento (2001)[15]	Vento (2003)[16]
Participants					
n	84	431	609	40	151
Inclusion criteria	Birthweight >999 g with apnoea, HR < 80 bpm, or both	Birthweight >1000 g with HR <100 bpm, apnoeic, or both, and unresponsive to stimulation.	Birthweight 999 g with apnoea or gasping, HR <80 bpm, or both	Term infants with apnoea, hypotonia, unresponsive to stimuli and HR < 80 bpm, or both	Birth weight >999 g Term infants with apnoea, hypotonia, unresponsive to stimuli, HR < 80 bpm, and pH <7·05
Air group					
Birthweight (g)	2410 (540)	2529 (629)	2600 (1320-4078)*	3380 (318)	3160 (240)
Gestational age (weeks)	38·4 (1·9)	37·9 (2·9)	38 (32–42)*	38·6 (1·7)	38·9 (1·6)
Umbilical arterial pH	..	..	7·11 (0·14)	7·11 (0·04)	7·09 (0·07)
Oxygen group					
Birthweight (g)	2410 (540)	2529 (629)	2560 (1303-3900)*	3190 (245)	3220 (168)
Gestational age (weeks)	38·1 (2·6)	38·1 (2·6)	38 (32–42)*	40·2 (0·8)	40·5 (1·1)
Umbilical arterial pH	..	..	7·12 (0·18)	7·09 (0·04)	7·02 (0·3)
Methodology					
	Quasi-randomised unmasked	Quasi-randomised unmasked	Quasi-randomised unmasked	Randomised, masked to caregivers and assessors of outcome	Randomised, masked to caregivers and assessors of outcome
Long-term follow-up					
	No	No	Yes (paediatrician at 18–24 months to assess cerebral palsy and developmental milestones)	No	No

Data are mean (SD) unless otherwise indicated. HR=heart rate; bpm=beats per minute. *Median (95% CI).

Table 1: **Study characteristics**

resuscitation devices used, response to meconium stained liquor, and criteria for endotracheal intubation, were adequately described in all studies and conformed to current international guidelines.

Table 2 and the figure show pooled results from the trials. We identified no significant heterogeneity for outcomes reported by more than one trial. Although no trial showed a difference in mortality at latest follow-up, the pooled analysis showed a significant benefit for babies resuscitated with air. The reduction in mortality during the first week of life in babies resuscitated with air was of borderline significance (table 2). One trial[13] assessed mortality in the first month of life; again there was a benefit from air, although it was not significant (RR 0·73 [0·51 to 1·05], risk difference –0·05 [–0·11 to 0·01]). No studies reported long-term developmental outcome with validated assessment methods as specified in our protocol.

The following post-hoc findings were identified after review of the studies. In a group of eligible infants followed up from 18 to 24 months, the rates of cerebral palsy did not differ between groups.[19] No formal psychometric testing was done, but motor and language milestones were assessed; the rates of not walking and not talking did not differ. Likewise, there was no significant difference in rates of abnormal development as assigned by the examining paediatrician. Failure of resuscitation in each group was included after the results of the studies were examined (ie, post hoc). The four trials[13–16] did not differ individually in this outcome, and pooled analysis showed no significant difference in the rates of failure of resuscitation between groups.

In the one trial that reported time to onset of spontaneous respiration,[16] infants resuscitated with air breathed earlier than those resuscitated with 100%

	Studies	Air	100% oxygen	RR (95% CI)	Risk difference (95% CI)	Number needed to treat
Death at latest follow-up*	4[13,14,16,17]	70/616	107/659	0·71 (0·54 to 0·94)	–0·05 (–0·08 to –0·01)	20
Death in first week	4[13,14,16,17]	65/616	94/659	0·75 (0·56 to 1·00)	–0·04 (–0·07 to 0·00)	
Cerebral palsy	1[19]	9/91	9/122	1·34 (0·55 to 3·24)	0·03 (–0·05 to 0·10)	
Not walking†	1[19]	10/91	13/122	1·03 (0·47 to 2·25)	0·00 (–0·08 to 0·09)	
No words†	1[19]	6/91	3/122	2·68 (0·69 to 10·44)	0·04 (–0·02 to 0·10)	
Abnormal development	1[19]	14/91	12/122	1·56 (0·76 to 3·22)	0·06 (–0·04 to 0·15)	
Time to first breath >3 minutes	1[13]	28/284	60/321	0·53 (0·35 to 0·80)	–0·09 (–0·14 to –0·03)	11
5-minute Apgar score <7	1[13]	71/288	102/321	0·78 (0·60 to 1·00)	–0·07 (–0·14 to 0·00)	
HIE Sarnat grade[8] 2 or 3	3[13,14,17]	87/540	112/584	0·84 (0·65 to 1·08)	–0·03 (–0·07 to 0·01)	
Failure of resuscitation	4[13,15,16,17]	162/593	182/638	0·96 (0·81 to 1·14)	–0·01 (–0·06 to 0·04)	

Data are number. HIE=hypoxic ischaemic encephalopathy. NNT=number needed to treat (calculated for significant results). *Deaths reported in first week[14,16,17] or in first 28 days of life.[13] †In those followed-up at 18–24 months.

Table 2: **Results**

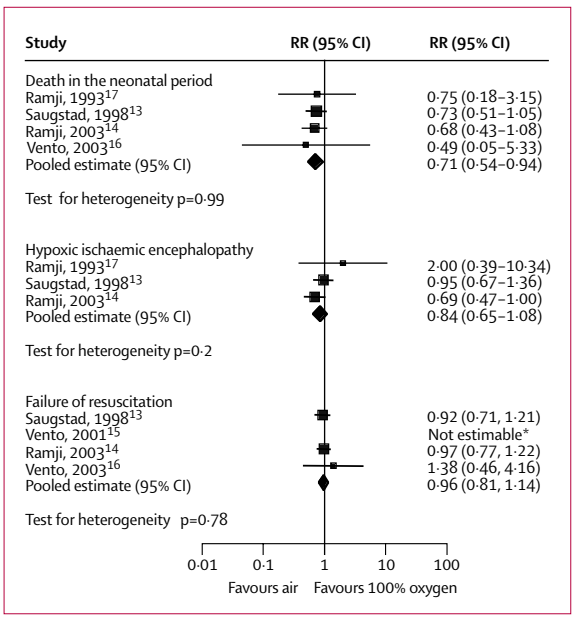

Figure: **Pooled analyses**
Relative risks assessed with fixed-effects model. *No events in either group.

oxygen (mean difference −1·5 minutes [−2·02 to −0·98]). Other short-term outcomes (time to first breath > 3 minutes and 5-minute Apgar score < 7) were better for those resuscitated with room air rather than 100% oxygen. Subgroup analyses based on gestational age or severity of asphyxia were not possible because the results of individual studies were not stratified for gestational age or umbilical arterial pH, respectively.

Discussion

One death would be prevented for every 20 babies resuscitated with air rather than 100% oxygen. No significant differences were recorded for outcomes of neurological disability. Resuscitation of adults and children is recorded as far back as biblical times,[20,21] but the use of 100% oxygen for this purpose is a recent notion.[22] Providing supplemental oxygen to a patient who has had hypoxia seems logical. This biological plausibility, exemplified by the opinion that "oxygen is vital, not just useful . . . one breath of oxygen is worth five breaths of air in this situation",[23] has underpinned such use in recent decades. More recently, the biological rationale for 100% oxygen has been challenged.[22]

In view of the importance of resuscitation of newborn infants, the fact that only five controlled trials could be identified that compared air and 100% oxygen is surprising. Several reasons could explain the scarcity of studies. First, 100% oxygen has been uncritically accepted for many decades; questioning its effectiveness and safety is therefore difficult. Randomised trials are difficult to undertake in the setting of acute and unpredictable events such as neonatal resuscitation. The scarcity of evidence epitomises the wider problems in the discipline of neonatal resuscitation. Although gathering the evidence might be difficult, we should remember the potential for harm when interventions are adopted or rejected without rigorous assessment. Indeed, the short history of neonatology is littered with such instances; the best known is the epidemic of blindness caused by unrestricted oxygen therapy for apnoea of prematurity and the increased mortality after its subsequent restriction.[24]

The finding that air significantly reduces mortality compared with 100% oxygen is a powerful argument for its use in resuscitation. However, caution should be exercised in application of this result. Most infants in our analysis were recruited in developing countries where antenatal and perinatal care, resuscitation equipment, and perinatal mortality rates differ from those in developed countries. Can the results be applied to hospitals in countries with more resources? The effect of each strategy on long-term development remains unclear because of methodological limitations of the one study[19] that followed up children into infancy (ie, low follow-up rates, lack of masking of assessors, and absence of formal psychometric testing). The use of backup oxygen for babies allocated air has important implications for the applicability of the results of this review. Although the number of babies with failed resuscitation did not differ between groups, 168 (27%) of 635 allocated to room air in the five trials received backup treatment with 100% oxygen.

Despite these limitations, clinicians must decide how to resuscitate newborn infants on the basis of best available evidence. Existing guidelines are based on expert opinion, which is derived from an understanding of oxygen therapy that is now decades old. Biological plausibility and expert opinion are ranked bottom of the hierarchy of evidence used in development of treatment recommendations. Clinicians and expert committees now have to deal with evidence from higher up this hierarchy—derived mainly from quasi-randomised trials.

A reasonable conclusion from the evidence is that, for term and near-term infants in the delivery room, air should be initially used for resuscitation, with oxygen as backup if initial resuscitation fails. Monitoring of oxygen saturation during neonatal resuscitation and titration of oxygen delivery to meet an infant's needs has been suggested, and these strategies seem logical. Kattwinkel[25] cautioned against "moving from one extreme to the other"—ie, from 100% oxygen to air. He suggested that particularly severely asphyxiated infants might require supplemental oxygen and that pulse oximetry could facilitate rapid restoration of normal oxygen status. Along similar lines, Milner[3] recommended 30–40% oxygen as a reasonable compromise. Further investigation of the feasibility of techniques for monitoring of oxygen-saturation in the delivery room is necessary. In addition, the optimum saturation values for term and preterm infants in the

first minutes of life have yet to be established. Definition of severity of asphyxia in terms of clinical signs, Apgar scores, and umbilical blood gases is difficult. Subgroup analysis based on severity of initial asphyxia was not possible in this review. It is unclear whether infants at high risk of pulmonary hypertension—ie, those with meconium aspiration syndrome, fulminant sepsis, and severe asphyxia—respond differently to different oxygen concentrations. Future trials should stratify and report separately the results for this important subgroup. Recommendations for practice in developing countries could be different. Scarce resources might lead to the choice of air for resuscitation, and we have found no evidence of harm from this practice.

Preterm infants as immature as 27 weeks' gestation were included in some studies in our analysis;[13,14,17] however, numbers enrolled were small and subgroup analysis was not possible. Preterm infants might be at increased risk of the adverse effects of hyperoxia compared with babies born at term.[26,27] There is insufficient evidence on which to make recommendations for this subgroup. Researchers should be encouraged to build on existing trials to address this important issue. Large-scale trials can be undertaken in the delivery room, with random allocation and masked to caregivers. Future trials should include and stratify preterm as well as term infants, investigate the role for intermediate concentrations of oxygen, and ensure long-term neurodevelopmental follow-up as part of the primary outcome.

Contributors

A Tan wrote the protocol with assistance from P G Davis and A Schulze. A Tan, P G Davis, and C P F O'Donnell did the literature search and took data from eligible trials. P G Davis prepared the report with the assistance of the other authors.

Conflict of interest statement

We declare that we have no conflict of interest.

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