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Neurodevelopmental Outcome of Infants Resuscitated with Air or 100% Oxygen: A Systematic Review and Meta-Analysis

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Key Words

Air · Long-term follow-up · Neonatal resuscitation · Oxygen · Systematic review

Abstract

Background: The use of air for the initial resuscitation of newborn infants has been shown to reduce neonatal mortality. However, a precise estimate of the neurodevelopmental status upon follow-up of infants resuscitated in air is lacking. ***Objective:*** To perform a meta-analysis of all studies reporting resuscitation of newborn infants with air or 100% oxygen that included follow-up data. ***Methods:*** Bibliographic databases were searched. In addition, we estimated the effect of loss to follow-up on our analysis of abnormal neurodevelopmental outcome. ***Results:*** We identified 10 studies in which newborn infants had been randomly or quasi-randomly assigned to resuscitation with air or 100% oxygen. Three of these 10 studies had available follow-up data. A total of 678 infants were enrolled at centers that performed follow-up of these infants. Of these, 113 died, leaving 565 infants potentially eligible for follow-up. A total of 414 children were evaluated (73% of eligible children; 195 resuscitated with air and 219 with 100% oxygen). In the air group, 12.8% of infants had an abnormal neurodevelopmental outcome, compared with 10.5% in the 100% oxygen group [typical relative risk (RR) 1.24, 95% confidence interval 0.73–2.10]. This is consistent with an RR of abnormal development as low as 0.41 or as high as 2.28. ***Conclusions:*** Long-term follow-up did not detect any significant differences in these two groups regarding abnormal development. However, the results are imprecise and could be consistent with significant harm or benefit.

Introduction

The optimal oxygen (O_2) concentration for newborn resuscitation has been the subject of great debate [1]. We recently published an updated systematic review and meta-analysis of ten studies including 2,133 infants examining the effect of the use of air or 100% oxygen on important short-term outcomes including neonatal mortality and hypoxic ischemic encephalopathy (HIE) [2]. Neonatal mortality is significantly reduced in term or near-term infants resuscitated with air compared with those resuscitated with 100% oxygen, with the typical relative risk (RR) for neonatal mortality being 0.69 with a 95% confidence interval (CI) ranging from 0.54 to 0.88 in favor of resuscitation using 21% O_2. The number needed to treat

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to save 1 newborn life was 25. The studies included are fairly heterogenous both clinically and methodologically. For strictly randomized studies – all from European centers – the typical RR was 0.32 with a 95% CI of 0.12–0.84 in favor of air. There was also a tendency toward a lower risk of stage 2 and 3 HIE in the infants who had been resuscitated with air (typical RR 0.88, 95% CI 0.70–1.11) [2]. Resuscitation of term or near-term newborn infants with air therefore seems to lead to improved outcome in the neonatal period, including a 31% reduction in the risk of neonatal mortality, and may lead to less HIE when compared with the use of 100% O_2 [3].

In 2010, the International Liaison Committee on Resuscitation stated that 'in term infants receiving resuscitation at birth with positive pressure ventilation, it is best to begin with air rather than 100% oxygen'. Moreover, in preterm infants, oxygen needs should be titrated using a pulse oximeter, thus avoiding hyper- or hypoxemia [4].

In spite of reduced neonatal mortality with resuscitation with air, an important concern is the neurodevelopmental outcome of survivors of air resuscitation. Until now, long-term follow-up has only been published from the study by Saugstad et al. [5, 6]. That study showed no difference in psychomotor or neurosensory development between infants resuscitated in air and 100% O_2 at 18–24 months of age. However, the study included only 211 children and therefore had limited power to detect significant differences in outcome. To demonstrate any difference in neurodevelopmental outcome, there is a need for more and larger follow-up studies examining the long-term consequences of initiating resuscitation of depressed newborn infants with air.

To our knowledge, presently no prospective randomized trials comparing air resuscitation versus pure oxygen and no larger follow-up studies are under way. Therefore, our aim was to perform a systematic review of the available follow-up data and to model the uncertainty inherent to these analyses due to loss at follow-up.

Methods and Patients

We searched for studies reporting the long-term outcome of depressed newborn infants resuscitated at birth with either 21% O_2 (air) or 100% O_2. The methods used in this search were identical to the methods used in our previously published systematic overviews [1, 7].

Selection Criteria

Only trials utilizing random or quasi-random patient allocation methods were selected for inclusion. Trials were included from both technically developed and less developed settings. Criteria for inclusion of 'depressed' newborn infants for resuscitation were identical to those of our previously reported systematic review [2]. Most typically, these infants had apnea and a heart rate of <80–100 bpm immediately after birth and before 1 min of age. Studies included newborn infants regardless of gestational age or birth weight. Published and unpublished data were included if verified by the primary authors of the original studies.

Search Strategy

Relevant databases including Medline/PubMed, Embase and The Cochrane Controlled Trials Register were searched until December 2010 using the index terms 'newborn resuscitation', 'follow up' or 'oxygen' or 'room air'. The Medline/PubMed search specifically used the search strategies ('resuscitation'[MeSH Terms] OR 'resuscitation'[All Fields]) OR ('oxygen'[MeSH Terms] OR 'oxygen'[All Fields]) OR (room[All Fields] AND ('air'[MeSH Terms] OR 'air'[All Fields])) AND (follow[All Fields] AND up[All Fields]) AND (Randomized Controlled Trial[ptyp] AND 'infant'[MeSH Terms]), as well as using the advanced search function based on the recommendations of Haynes et al [8], i.e. ('resuscitation'[MeSH Terms] OR 'resuscitation'[All Fields]) AND Therapy/Narrow[filter] AND 'infant'[MeSH Terms].

Expert informants were consulted, and abstracts, conference and symposia proceedings were also searched. All authors performed separate independent searches and were in complete agreement with regard to the studies identified and which articles and abstracts should be included.

The search in Medline/PubMed resulted in the identification of 12 publications, 1 of which represented follow-up of a clinical trial [5, 6]. The search of Embase and The Cochrane Database of Systematic Reviews yielded no additional information. By contacting the first author of the 10 studies published to date regarding resuscitation with air or 100% oxygen, we were able to get follow-up data at the age of 1–2 years from 2 additional studies [9, 10]. Ten of the 12 identified studies have been described in table 1 of our previous publication [2]. The 2 other studies [11, 12] investigated preterm infants. Wang et al. [11] used sealed envelopes to randomize babies <32 weeks to 21 or 100% oxygen. Dawson et al. [12] performed a prospective observational study in babies <30 weeks resuscitated with either 21 or 100% oxygen. These studies were not included because they included premature infants only and do not report follow-up data.

Description of Included Studies

Saugstad 1998 (Resair 2 Study)

The Resair 2 study was a multicenter study that enrolled 609 infants (288 were resuscitated with air and 321 with 100% oxygen) [5]. Infants were enrolled from 10 centers in India, Egypt, Estonia, the Philippines, Norway and Spain. The study was not blinded. Infants were allocated to air or 100% O_2 resuscitation in a quasi-random fashion according to even or odd birth dates. Seven centers enrolling 410 patients in the original study participated in the follow-up study performed when the infants were 18–24 months of age (not corrected for prematurity) [6]. In total, 323 of the 410 infants were eligible for follow-up (excluding 79 deaths, of which 76 were neonatal and 3 post-neonatal deaths; parental informed consent for participation in the follow-up study had not been obtained in 8 of the remaining infants, leaving 323 eligible for follow-up). Of these 323 eligible infants, 213 (66%) were followed up, 91 in the air group and 122 in the 100% O_2 group (62% of all eligible infants resuscitated with air and 69% of those resuscitated with 100% oxygen). Babies with a birth weight >1,000 g were included, but the age of follow-up was not corrected for prematurity. Mean (5th, 95th percentiles) birth weights in the 21 and 100% O_2 groups were 2,650 g (1,490, 4,240) and 2,800 g (1,560, 4,300), respectively. Mean (5th, 95th percentiles) gestational ages were 38 weeks (32, 42) and 39 weeks (33, 42) in the 21 and 100% O_2 groups, respectively. The follow-up assessment was blinded. The primary outcome was psychomotor development and neurosensory status. Outcome was cerebral palsy and/or mental delay according to a clinical assessment at 18–24 months of age [6].

Bajaj 2005

The study by Bajaj et al. [9] was a single-center study conducted in India between April 2001 and June 2002. Infants were eligible for the resuscitation study if they had a birth weight ≥1,000 g with apnea or gasping respiration and/or a heart rate <100 bpm requiring positive pressure ventilation after the initial steps of basic resuscitation. The study was not blinded. Infants were allocated to air or 100% O_2 in a quasi-random fashion according to the date on which they were born. Those infants born on even dates were resuscitated with 100% oxygen (n = 97) and those born on odd dates were resuscitated with air (n = 107). The primary outcome, death at discharge or HIE, was noted in 41% of infants in the air group and 43% in the oxygen group (not significant). Seventeen infants died in each group in the neonatal period.

An organized follow-up at 1 year of age (corrected for prematurity) was performed using the Amiel-Tison method and Baroda Development screening test (Modified Bayley Scale of Infant Development) [13]. In the air and 100% O_2 groups, 90 and 80 surviving children were eligible for follow-up, respectively. Of these infants, 13 (14%) and 10 (13%), respectively, were lost to follow-up, leaving 77 infants in the air group and 70 in the 100% O_2 group for follow-up. Mean (SD) birth weight and gestational age were 2,550 g (522) versus 2,411 g (572) and 39.2 weeks (1.9) versus 38.1 weeks (2.9) in the air and 100% O_2 groups, respectively. There were 14 premature infants in the air group and 13 in the 100% O_2 group.

Infants who scored less than 97% were defined as neurologically abnormal.

Toma 2006

The study by Toma et al. [10] includes follow-up data from a Romanian study. Term newborns in need of resuscitation at delivery (at least bag and mask ventilation) were randomized to be resuscitated with air (n = 27) or 100% O_2 (n = 27). Mean (SD) birth weights were 3,340 g (776) in the 21% O_2 group and 3,174 g (648) in the 100% O_2 group. Mean (SD) gestational ages were 38.6 weeks (2.2) and 38.0 weeks (2.1), respectively. The study was not blinded. The Bayley Infant Neurodevelopmental Screen was performed at 3–4 months, 5–6 months, 7–10 months and 11–15 months. In addition, age at head control and walking was noted. The neurodevelopmental assessment at 11–15 months is presented in this analysis. Infants were considered to have an abnormal neurodevelopmental outcome if they were scored as high or moderate risk.

Outcome Measures and Statistics

The primary outcome was any abnormal neurodevelopmental outcome including either cerebral palsy and or mental or motor retardation/delay/disability in survivors at the age of evaluation (only 3 post-neonatal deaths were registered, all in the first study, 2 of which were in the air group and 1 in the 100% O_2 group). The assessment and definition of abnormal neurodevelopmental outcome differed between the studies and was defined for each of them. Follow-up data for the studies by Bajaj et al. [9] and Toma et al. [10] were obtained directly from the authors.

For the dichotomous outcomes, the results were expressed as RR with the 95% CI. The pooled estimates of the RR of various outcome measures were calculated using a fixed effect model. Heterogeneity was evaluated by visual inspection and the $[I]^2$ statistic [14].

Several approaches were used for the meta-analysis calculations comparing abnormal outcome with air compared to 100% oxygen across the three studies. For the complete case analysis, missing data were excluded. In addition, two extremes for imputation were used, one imputing all missing cases to favor air and the other imputing all missing cases to favor 100% oxygen. Pooled estimates of RR and 95% CIs were calculated for each analysis, using the inverse variance weighting method of Woolf [15]. The interval for the best/worst analysis was calculated as the extremes from the best- and worst-case scenarios. Following the method of Gamble and Hollis [16], uncertainty intervals were calculated from the best/worst cases for each study. These were then pooled using the inverse variance weighting method to obtain a pooled uncertainty interval.

Results

Of the 547 infants eligible for follow-up in these 3 studies, a total of 414 infants (76%) were followed, 195 of whom were resuscitated with air and 219 with 100% O_2.

Combined Outcome

For the analysis of the combined outcome measure of death or abnormal neurodevelopmental outcome, the 1998 study by Saugstad et al. [5] evaluated a total of 402 infants. Of these, 179 were in the air group with 32 deaths and 14 abnormal outcomes (26%) and 223 in the 100% O_2 group with 47 deaths and 12 abnormal outcomes (26%).

In the 2005 study by Bajaj et al. [9], death or abnormal neurodevelopmental outcome was diagnosed in 23 infants (17 deaths and 6 abnormal neurodevelopmental outcomes) out of 107 (21%) in the air group and 22 (17 deaths and 5 abnormal neurodevelopmental outcomes) out of 97 (23%) in the 100% O_2 group.

The study from Romania (Toma et al. [10], 2006) had no neonatal mortality; however, 5 out of 27 infants in the air group (19%) and 6 out of 27 in the 100% O_2 group (22%) were considered to have an abnormal neurodevelopmental outcome.

Table 1. Abnormal neurodevelopmental outcome in infants evaluated in the three studies comparing air and 100% oxygen

Study	Air			100% oxygen		
	eligible	evaluated	abnormal	eligible	evaluated	abnormal
Saugstad et al. [5] (2003)	147	91	14 (15.4)	176	122	12 (9.8)
Bajaj et al. [9] (2005)	90	77	6 (7.8)	80	70	5 (7.1)
Toma et al. [10] (2008)	27	27	5 (18.5)	27	27	6 (22.2)
Total	264	195	25 (12.8)	283	219	23 (10.5)

Figures in parentheses represent percentages.

Table 2. Meta-analysis of studies with follow-up data: RR for abnormal outcome in evaluated infants (air compared to 100% oxygen)

Study	Abnormal outcome		Missing	Relative weight	RR	95% CI
	air	100% oxygen				
Complete case analysis						
Saugstad et al. [5] (2003)	14/91 (15.4%)	12/122 (9.8%)	34%	54%	1.56	0.76–3.22
Bajaj et al. [9] (2005)	6/77 (7.8%)	5/70 (7.1%)	14%	21%	1.09	0.35–3.42
Toma et al. [10] (2008)	5/27 (18.5%)	6/27 (22.2%)	0%	25%	0.83	0.29–2.41
Pooled					1.24	0.73–2.10

Table 3. Meta-analysis of studies with follow-up data: RR for abnormal outcome (air compared to 100% oxygen) using the best-/worst-case scenario

Study	Abnormal outcome		RR	95% CI
	air	100% oxygen		
Extremes favoring 21% oxygen				
Saugstad et al. [5] (2003)	14/148 (9.5%)	66/176 (37.5%)	0.25	0.15–0.43
Bajaj et al. [9] (2005)	6/90 (6.7%)	15/80 (18.8%)	0.36	0.14–0.87
Toma et al. [10] (2008)	5/27 (18.5%)	6/27 (22.2%)	0.83	0.29–2.41
Pooled			0.33	0.22–0.50
Extremes favoring 100% oxygen				
Saugstad et al. [5] (2003)	70/147 (47.6%)	12/176 (6.8%)	6.98	3.94–12.37
Bajaj et al. [9] (2005)	19/90 (21.1%)	5/80 (6.3%)	3.38	1.32–8.63
Toma et al. [10] (2008)	5/27 (18.5%)	6/27 (22.2%)	0.83	0.29–2.41
Pooled			4.09	2.63–6.38

Poor Outcome

Table 1 shows the number of infants enrolled and available for follow-up, as well as the number of infants actually followed. In the complete case analysis, none of the individual studies report a significant difference in the risk of abnormal neurodevelopmental assessment [Saugstad (2003): RR 1.56, 95% CI 0.76–3.22; Bajaj (2005): RR 1.09, 95% CI 0.35–3.42; Toma (2008): RR 0.83, 95% CI 0.29–2.41]. The meta-analysis conducted as a complete case analysis does not demonstrate any statistically significant

Table 4. Summary of RR estimates and intervals for abnormal neurodevelopmental outcome

Method	Pooled RR	Interval
Complete case	1.24	0.73–2.10
Extreme favors air	0.33	0.22–0.50
Extreme favors 100% O_2	4.09	2.63–6.38
Best/worst case		0.22–6.38
Uncertainty		0.41–2.28

Intervals are 95% CIs for RR or uncertainty-type intervals.

difference in the risk of abnormal developmental follow-up (typical RR 1.24, 95% CI 0.73 to 2.10; $[I]^2$ 0%; table 2). Heterogeneity of the 3 studies, as measured by $[I]^2 = 0.0$, was not significant. Since this term is zero, which implies that between-study variability is not greater than within-study variability, the fixed-effects model is appropriate.

Best- and Worst-Case Scenario

Given the large number of infants lost to follow-up, it seemed sensible to model the data using a 'best-case/worst-case scenario' in order to gain understanding of how imprecise the estimate might be. The 'extreme favoring air' codes all infants not seen in follow-up who received air as having a normal neurodevelopmental assessment and all infants not seen in follow-up who received 100% oxygen as abnormal; the 'extreme favoring 100% oxygen' codes the infants in the opposite fashion. This analysis gives the extreme estimates of effects (table 3). In the analysis using the extremes favoring air, the potential for great benefit is seen (typical RR 0.33, 95% CI 0.22–0.50), whereas the analysis using the extremes favoring 100% oxygen suggests the potential for great harm (typical RR 4.09, 95% CI 2.63–6.38). A more conservative and realistic estimate of the uncertainty can be derived using the methods of Gamble and Hollis [16]. This estimate suggests that we still have great uncertainty regarding the effect of using air for resuscitation, with the 95% CI for the risk of abnormal neurodevelopmental assessment ranging from 0.41 to 2.28 (table 4).

Discussion

A growing body of evidence from animal and clinical studies supports the use of air for initial resuscitation regarding short-term outcomes [2, 17, 18]. The presented data do not demonstrate any statistically significant difference in abnormal neurodevelopmental outcome in infants resuscitated with air compared with 100% oxygen. The three follow-up studies summarized and reviewed in this article all have weaknesses. Only one of the resuscitation studies was strictly randomized. The number of patients evaluated is relatively small, and follow-up varied from informal assessment to more formal testing. Most of the babies were recruited from low-income countries with higher mortalities and morbidities than in high-income countries. It should be kept in mind that a 30% reduction in the risk of neonatal mortality has been found for infants resuscitated with air versus 100% O_2 [2, 3]. Despite the higher survival rate for infants resuscitated with air, there was no statistically significant increased risk for abnormal neurodevelopmental outcome in surviving children. By contrast, Klinger et al. [19] showed that one or more hyperoxic episodes in the first 2 h of life resulted in a significantly worse outcome at 18 months of follow-up. If hyperoxia was combined with hypocapnia, the outcome became even worse, giving a 4-fold greater odds ratio of an impaired outcome at the age of 18 months.

The present study found a nonstatistically significant difference in poor outcome between children resuscitated with air and 100% oxygen. However, by using the best-case/worst-case scenario, we found that RR in air-resuscitated infants varied between a reduction of poor outcome by 2/3 to a 4-fold increase. This undoubtedly indicates a need for more long-term follow-up studies after high versus low oxygen for resuscitation of term newborns. However, because the International Liaison Committee on Resuscitation in its recent guidelines recommends to initiate resuscitation of term and near-term infants with air, it is not likely that additional information will be obtained regarding follow-up after air or 100% oxygen resuscitation. Future studies should perhaps therefore be designed comparing lower versus higher oxygen concentrations using pulse oximetry in the delivery room and titrating oxygen needs according to the development of SpO_2 as previously published [20] and as recently shown for extremely preterm infants [11, 12, 21, 22].

In conclusion, follow-up data at 12–24 months of age are now available from 414 newborn infants resuscitated with either air or 100% O_2. No statistically significant difference between the groups was found regarding abnormal neurodevelopmental outcome; however, the estimates are imprecise and warrant further study to fully understand the implications of this approach to resuscitation.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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