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Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤ 32 weeks

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Short title: Oxygen to very low birth weight infants in the delivery room

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Abstract

Aim: The optimal initial fraction of oxygen (iFiO₂) for resuscitating/stabilising premature infants is not known. We aimed to study currently available information and provide guidelines regarding the iFiO₂ levels needed to resuscitate/stabilise premature infants of ≤ 32 weeks' gestation.

Methods: Our systematic review and meta-analysis studied the effects of low and high iFiO₂ during the resuscitation/stabilisation of 677 newborn babies ≤ 32 weeks' gestation.

Results: Ten randomised studies were identified covering 321 infants receiving low (0.21-0.30) iFiO₂ levels and 356 receiving high (0.60-1.0) levels. Relative risk for mortality was 0.62 (95% CI: 0.37-1.04, $I^2 = 0\%$, $p_{\text{heterogeneity}}=0.88$) for low versus high iFiO₂, for bronchopulmonary dysplasia it was 1.11 (95% CI: 0.73-1.68, $I^2 = 46\%$, $p_{\text{heterogeneity}}= 0.06$) and for intraventricular haemorrhage it was 0.90 (95% CI: 0.53-1.53, $I^2 = 9\%$, $p_{\text{heterogeneity}}= 0.36$).

Conclusion: These data show that reduced mortality approached significance when a low $i\text{FiO}_2$ (0.21-0.30) was used for initial stabilisation, compared to a high $i\text{FiO}_2$ (0.60-1.0). There was no significant association for bronchopulmonary dysplasia or intraventricular haemorrhage when comparing low and high $i\text{FiO}_2$. Based on present data, premature babies $\leq$ 32 weeks' gestation in need of stabilisation in the delivery room should be given an $i\text{FiO}_2$ of 0.21 to 0.30.

Key words: Resuscitation, very low birth weight infants, oxygen, mortality, morbidity

Key notes

- The optimal initial fraction of oxygen (FiO_2) for resuscitating/stabilising premature infants of $\leq$ 32 weeks' gestation is not known.
- Our analysis of 10 published studies covering 677 infants show that the results of starting with a low initial FiO_2 (0.21-0.30) were as good as starting with a high FiO_2 (0.6-1.0).
- Until more data from randomised trials are available, we suggest initiating resuscitation/stabilisation of these babies with a low (0.21-0.30) FiO_2 .

Introduction

Until 20 years ago, newborn resuscitation was not evidence based and newborn babies who needed ventilator support were provided with liberal doses of 100% oxygen. However, clinical studies (1) and meta-analyses (2,3) have clearly demonstrated that starting the

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resuscitation of term or near-term infants with air is just as effective as using 100% oxygen. More significantly, using air has been associated with a reduction in neonatal mortality compared to 100% oxygen (3). Therefore international bodies, such as the International Liaison Committee on Resuscitation (ILCOR) and the World Health Organization (WHO), now recommend using air to resuscitate term or near-term babies (4, 5).

The original studies covering resuscitation with air or pure oxygen focused mainly on term or near-term infants. Studies focusing on preterm infants have only been published more recently (6,7,8,9,10,11,12,13,14,15). However, all of these studies are small and do not enable us to draw any definite conclusions about the benefits of using low, rather than high, initial respiratory fraction of oxygen ($i\text{FiO}_2$) to stabilise the smallest babies who need ventilatory support in the delivery room.

Two meta-analyses and systematic reviews regarding premature infants resuscitated with air or oxygen supplementation have been performed. Saugstad et al analysed premature infants separately (3) and Brown et al recently published a systematic review of low versus higher oxygen concentration for delivery room stabilisation of preterm infants of less than 37 weeks' gestation (16).

A study by Vento et al of preterm infants between 24 to 28 weeks of gestation showed that reoxygenation with 30% oxygen, rather than 90%, reduced oxidative stress on day one, as assessed by the ratio of oxidised to reduced glutathione. The study also found that urinary markers of oxidative stress and oxidative damage to protein and DNA increased significantly

in the high-oxygen group in the first week after birth, compared to the low-oxygen group (10). A low $i\text{FiO}_2$ may reduce oxidative stress and injury and may, therefore, be beneficial. However, infants with immature lungs may have reduced pulmonary gas exchange requiring some supplemental oxygen. The ILCOR recommendations indicate that babies of less than 32 weeks need blended oxygen during resuscitation in the delivery room (4). We therefore performed a systematic review and meta-analysis of the available studies of babies with a gestational age of ≤ 32 weeks, who needed resuscitation/ventilator support in the delivery room and were treated with low or high $i\text{FiO}_2$.

Methods

This review only included strictly randomised studies of newborn infants with a gestational age of ≤ 32 weeks who were resuscitated in the delivery room with either a low (0.21-0.30) or high (0.6-1.0) $i\text{FiO}_2$. Studies with an $i\text{FiO}_2$ of between 0.31 and 0.59 have, therefore, not been included.

Search Strategy

The MEDLINE/PubMed, EMBASE and ClinicalTrials.gov databases and the Cochrane controlled trial register were searched up to 1 April 2013, using the index terms 'preterm' and 'resuscitation' and '21% oxygen'. We then repeated the exercise using the same words and the following oxygen percentages: 30%, 40%, 50%, 60%, 80% and 100%. In addition, we searched for relevant abstracts from the annual meeting of the Pediatric Academic Societies, the European Society of Paediatric Research and the European Association of Paediatric Societies. Reference lists of relevant articles were also scrutinised. The quality of the eligible

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trials was independently assessed by all authors and the extracted data were independently reviewed by the authors.

Outcome measures

In this meta-analysis and systematic review, the primary outcome was mortality, as defined in each study (Table 1). The secondary outcomes were bronchopulmonary dysplasia/chronic/lung disease, according to the definition of each study, and intraventricular haemorrhage $\geq$ grade 2.

Statistical analysis

We created a summary of the incidences of neonatal mortality, bronchopulmonary dysplasia (BPD) and intraventricular haemorrhage (IVH), comparing low and high iFiO₂.

We used random effects models, which take into account variation within and between studies (heterogeneity), to compute summary relative risks (RRs) (17). The average of the natural logarithm of the RRs was estimated and the RRs from each study were weighted by the inverse of their variance and then un-weighted by applying a random effects variance component, which is derived from the extent of variability of the effect sizes of the included studies. A two-tailed $p < 0.05$ was considered statistically significant. Heterogeneity between the studies was evaluated with Q and I^2 statistics (18). For the Q statistic, $p < 0.10$ was considered to indicate heterogeneity, as previously recommended (19). I^2 is the amount of total variation that is explained by variations between studies, for example I^2 of 25%, 50%

and 75% indicate low, moderate, and high heterogeneity, respectively. Publication bias was assessed with Egger's test (20).

Results

We identified 72 articles and six abstracts. Two seemingly relevant studies were not included. Harling et al (11) was excluded because infants were randomised to a low target that exceeded the one in our inclusion criteria, namely 50% oxygen in the low arm and 100% oxygen in the high arm. Ezaki et al (12) was excluded as it randomised babies of less than 35 weeks to a reduced oxygen group (titrating the $iFiO_2$ of 100% according to pulse oximeter readings between 90-95%) or 100% oxygen. Separate data on infants of less than 33 weeks' gestation were obtained from the authors, but this study was excluded because the infants in the low $iFiO_2$ group started with 100% oxygen.

Eleven randomised studies were initially included in this review. Of these, eight had been published as full papers (6,7,8,10,13,14,15,23) and three had been published as abstracts (21,22,24), but not in full before this paper was finalised. Because the data in reference 7 is duplicated in reference 10, we only included reference 10 in this systematic review and meta-analysis, leaving us with 10 randomised studies.

In addition, we identified three observational studies, one published as a full manuscript (9) and two as abstracts (25, 26). Data from the RESAIR 2 study (1,3) were not included because the study was not strictly randomised. The data from these four studies were not included in this systematic review.

Description of Studies

Table 1 summarises the basic information on the infants enrolled in the ten randomised studies included in this paper:

Lundstrøm et al (6) randomised 69 babies with a gestational age of < 33 weeks, enrolled from September 1991 to August 1993 in Copenhagen, to initially receive either 21% or 80 % oxygen in the delivery room. The primary outcome of this single centre study was cerebral blood flow two hours after birth. The study showed that 80% oxygen resulted in cerebral vasoconstriction when the babies were two hours old. If babies in the 21% group failed to normalise their heart rate one minute after birth, 30 to 40% oxygen was administered for the first minute and then increased by 10% for each subsequent minute, if needed. Limited data were available on the pulse oximetry applied to some of the babies. BPD was defined as oxygen requirement at 28 days. The study was not blinded.

Escrig et al (7) published preliminary data from a two-centre prospective, non-blinded randomised study carried out in Valencia between 2005 and 2007. Babies with gestational ages of between 24 to 28 weeks were enrolled and there were 19 infants in the low oxygen group ($i\text{FiO}_2 = 0.30$) and 23 in the high oxygen ($i\text{FiO}_2 = 0.90$) group. Vento et al continued enrolment for another 13 months until 2008 and published data on 78 infants enrolled in both of these studies (10). Consequently, we used the data from Vento et al (10) in this review.

Indications for resuscitation were absence of spontaneous respiration > 1 minute, bradycardia < 60 beats per minute $\geq$ 2 minutes, hypoactivity and, or, hypotonia or ineffective ventilation as defined by auscultation and, or, lack of thoracic expansion. Preductal oxygen saturation (SpO_2) was provided at up to 75% at five minutes of life and 85% at 10 minutes of life. The FiO_2 in each group was titrated to attain the SpO_2 targets, with 60 to 90 seconds allowed for

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responses after each change. The levels were never changed more than 10% every 30 seconds. Primary outcome was neonatal death and BPD was defined as the need for oxygen supplementation at a postconceptional age of 36 weeks. If a heart rate of ≤ 60 beats per minute lasted > 30 seconds, the FiO_2 was switched to 100%. The FiO_2 in both groups was increased, and then decreased, in a stepwise manner, reaching 55% at five minutes of life. Significant differences in FiO_2 were only found during the first four minutes of life. There was no difference in heart rate between the groups.

Wang et al (8) performed a two-centre, prospective, randomised, blinded, controlled trial in California between 2005 and 2007 on 41 neonates with gestational ages of 23 to 32 weeks who received any resuscitation. The aim of the study was to test the theory that resuscitation initiated with air, and adjusted on the basis of SpO_2 levels, would be more effective than pure oxygen in achieving SpO_2 values similar to those of non-resuscitated transitioning neonates. The 18 infants in the low FiO_2 group started with 21% oxygen, which was increased in 25% increments if SpO_2 was $< 70\%$ at three minutes of life or $< 85\%$ at five minutes of life. If the heart rate was < 100 beats per minute at two minutes of life, or chest compressions were performed, 100% oxygen was given. Every resuscitated baby in the 21% group received an increase in FiO_2 by three minutes of life, with six moved directly to 100% and 12 receiving incremental increases. The high FiO_2 group started with 100% oxygen, with the FiO_2 decreasing after five minutes of life if the preductal pulse oximetry measured oxygen saturation (SpO_2) was $> 95\%$. Heart rates did not differ between the two groups during the first ten minutes of life, but SpO_2 was significantly lower in the 21% group than in the 100% group. BPD was defined as oxygen requirement at an adjusted age of 36 weeks.

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Rabi et al (14) conducted a single centre, prospective, blinded, randomised study in Calgary, Canada, between 2005 and 2007. The study included 106 infants of ≤ 32 weeks' gestational age, in need of resuscitation according to the 2005 ILCOR guidelines (27). The enrolled infants were randomised to three groups: 1) low FiO_2 , in which assisted ventilation was started with 21% oxygen, 2) moderate oxygen group, in which babies in need of assisted ventilation were initially given 100% oxygen and 3) high FiO_2 group, where a static concentration of 100% oxygen was provided during assisted ventilation. In the first and second groups, FiO_2 was adjusted in increments every fifteenth second if the SpO_2 was outside the target oximeter range of 85 to 92%, followed by smaller adjustments of 5% to 10% to maintain the SpO_2 within this target range. If the heart rate was lower than 100 beats per minute for longer than 30 seconds, or chest compression was needed, the FiO_2 was increased to 100% for the remainder of the resuscitation. The primary outcome was the proportion of resuscitation time spent in the target SpO_2 range of 85 to 92%. The secondary outcome measures were survival at discharge and BPD, defined as the requirement for additional oxygen at 36 weeks' corrected postnatal gestational age. In this study we combined data from the moderate and high groups into a single high group, as both these groups started with 100% oxygen.

See et al (21) published preliminary data of 36 infants from the TO_2RPIDO (Targeted Oxygen in the Resuscitation of Premature Infants and their Developmental Outcome) study. The aim of this on-going randomised multicentre study is to assess the effects on neonatal morbidities and mortality of starting the resuscitation of infants of < 31 completed weeks' gestation with either room air or 100% oxygen. Infants were enrolled from Australia, Malaysia, Singapore, Thailand and Qatar and data from 20 patients resuscitated with 21% oxygen and 16 patients resuscitated with 100% oxygen have been published in abstract form.

BPD was defined as needing oxygen at 36 weeks' post conceptional age and, or, respiratory support. The study was not blinded.

Armanian and Badiie (13) published a single centre, non-blinded study from Iran, carried out between 2009 and 2010. They randomised premature infants with gestational ages of between 29 to 34 weeks to receive initial oxygen concentrations of either 30% or 100% in the delivery room. The authors reported that 14 infants aged < 33 weeks were enrolled in the low oxygen group and a further 13 of the same age were enrolled in the high oxygen group. None of the infants died and there were no recorded cases of BPD or intraventricular haemorrhage.

Rook et al (23) organised a double blinded, randomised controlled single centre trial in Rotterdam, the Netherlands, comprising 193 infants with gestational ages from 26 5/7 to 30 3/7 weeks. Of these, 99 were initially supplemented with low $i\text{FiO}_2$ (0.30) and 94 with high $i\text{FiO}_2$ (0.65). The object of the resuscitation was to target preductal SpO_2 of 88 to 94% at ten minutes of life. Primary outcome was survival without BPD at 36 weeks' postmenstrual age. BPD was defined as babies who needed more than 30% supplemental oxygen at 36 weeks' postmenstrual age.

Kumar et al (22) from Buffalo, USA, randomised 11 Infants < 32 weeks' gestational age to 21%, 40% or 100% oxygen. The study was initially blinded, but after 10 minutes treatment it was unmasked and FiO_2 was adjusted to maintain SpO_2 85-95%. The intervention was complete when infants were transferred to the intensive care unit. Enrolment stopped after the 2010 resuscitation guidelines were published recommending lower FiO_2 (4), resulting in a very small study. In this review, we report results from the 21% and the 100% oxygen

groups. Mortality was noted before discharge and BPD was defined as oxygen requirement at 36 weeks' postconceptional age.

Aguar et al (24) from Valencia, Spain, randomised 60 infants < 30 weeks' gestational age to 30% and 60% oxygen in 2010 to 2012, following publication of the 2010 ILCOR guidelines (4). Caregivers in the delivery room and in the NICU were blinded to the level of FiO₂ during resuscitation. SpO₂ was continuously monitored and FiO₂ adjusted according to pulse oximeter readings and Dawson's nomogram (28). Mortality was noted before discharge and BPD was defined as oxygen requirement < 28 days of life.

Kapadia et al (15) from Texas, USA, conducted a single centre prospective non-blinded randomised controlled trial of 88 neonates from 24 0/7 to 34 6/7 gestational age who received any resuscitation. They were randomised to one of two strategies. The first was a limited oxygen strategy, where resuscitation was started with 21% oxygen and FiO₂ was adjusted to keep oxygen saturations in the interquartile range of preductal saturations, measured in healthy term infants following vaginal birth at sea level, as per the current Neonatal Resuscitation Program guidelines, USA (4). The second was a high oxygen strategy where resuscitation was initiated with 100% oxygen and adjusted to keep fixed goal saturations of 85 to 94%. We only included data from the preterm neonates of < 33 weeks' gestational age, who comprised 56 of the 88 infants in the study. BPD was defined as oxygen requirement at 36 weeks' postmenstrual age.

Primary outcome

A total of 677 patients in the 10 randomised studies were included, 321 in the low iFiO₂ groups and 356 in the high iFiO₂ groups. Mortality was 21/321 (6.5%) in the low oxygen

group and 35/356 (9.8%) in the high oxygen groups, giving a relative risk of 0.62 (95% CI: 0.37-1.04, $I^2 = 0\%$, $p_{\text{heterogeneity}}=0.88$) for low versus high FiO_2 (Figure 1). There was no evidence of publication bias ($p = 0.78$). Blinded studies (8,14,22,23,24) were analysed separately giving a RR for mortality of 0.55 (95% CI 0.28-1.05). The RR (95% CI) for the non- blinded studies (6,10,15,21) was 0.76 (0.33-1.77).

Secondary outcomes

There were no significant differences in BPD or intraventricular haemorrhage (grade 2-4) in the randomised studies when initial resuscitation was carried out using low or high FiO_2 . BPD incidence was 25.8% in the low group and 26.8 % in the high group. The summary RR for low versus high oxygen was 1.11 (95% CI: 0.73-1.68), $I^2 = 46\%$, $p_{\text{heterogeneity}}= 0.06$ for BPD (Figure 2). RR (95% CI) for BPD in the strictly blinded studies was 1.37(0.87-2.14) and in the non-blinded studies it was 0.70 (0.32-1.56). The incidence of intraventricular haemorrhage ($\geq$ grade 2) was 9.0% in the low group and 10.0% in the high group. Summary RR for low versus high oxygen was 0.90 (95% CI: 0.53-1.53), $I^2 = 8.7\%$, $p_{\text{heterogeneity}}= 0.36$) for intraventricular haemorrhage (Figure 3). There was no evidence of publication bias for either outcome. In the strictly blinded studies RR (95%CI) was 0.81 (0.32-2.05) and in the non-blinded studies it was 1.21(0.58-2.50)

Discussion

This systematic review and meta-analysis demonstrate no significant difference in mortality between low and high FiO_2 for the initial randomisation/stabilisation of newborn infants ≤ 32

weeks gestational age. However a trend towards lower mortality was observed in the low FiO₂ group, with a relative risk reduction of 38% (95% Confidence Interval 0.37-1.04).

In their recent review, Brown et al (16) identified six randomised controlled trials comprising 484 participating preterm infants < 37 weeks' gestational age. Low FiO₂ (21-50%) for the delivery room transition of preterm infants was compared to high FiO₂ (>50%). They found a significant reduction in mortality for the low oxygen group compared to the high oxygen group. However, when they only included strictly randomised studies, the relative risk for death was 1.00 (95% CI 0.45-2.24). Their review also included Harling's study in which 50% oxygen was used in the low arm (11) and therefore that was excluded from the present review. Our study included six more randomised studies (13,15,21,22,23,24) than Brown et al. Another main difference between the Brown et al study and our study is that we only reviewed babies < 33 weeks' gestational age.

Outcome regarding BPD and intraventricular haemorrhage seemed quite similar between low and high iFiO₂ groups, with relative risks of 1.00 and 0.90.

This review only included strictly randomized studies. As a result, we did not include three observational (9,25,26) studies and one pseudo randomised study (3). The observational studies included 875 infants in the low iFiO₂ group and 957 in the high iFiO₂ group, with mortalities of 6.7% and 13% respectively (RR 0.59, 95%CI 0.33-1.08). The pseudo randomised study also showed tendencies towards lower mortality in the low iFiO₂ group.

Larger studies are therefore needed and two large multicentre, randomised studies, TO₂RPIDO (Anz trials registry ACTRN12610001059055) and PRESOX (EudraCT Number 2011-005717-36) are underway. The TO₂RPIDO trial randomises babies < 31 weeks to 21% or 100% oxygen and the PRESOX trial randomises babies < 29 weeks to 21% or 60% oxygen. Both studies are planning long-term follow-up periods. However, until the data from these studies are available, clinical practice should be based on the best current evidence.

Published studies show that 90 to 100% of the very and extremely low birth weight infants whose resuscitation was initiated with 21% or 30% oxygen needed additional oxygen (7,8,9,10). However, the heart rates were very similar in the high and low oxygen groups during the first ten minutes of life and the FiO₂ was only different between the groups during the first four to six minutes of life. In spite of this brief period of difference in oxygen load, Vento et al (10) found that when the babies of < 29 weeks were resuscitated with 90% rather than 30% oxygen, they had significantly increased markers of oxidative stress during the first days of life and significantly higher markers of inflammation for more than one week. Kapadia et al (15) also found that preterm infants resuscitated with a high oxygen strategy of a 100% initial oxygen concentration, had higher markers of oxidative stress on admission to the neonatal intensive care unit than infants resuscitated with a low oxygen strategy of 21% initial oxygen concentration. No increased oxidative stress was observed by Rook et al in babies < 32 weeks given 65% rather than 30% oxygen (23). Lundstrøm et al found infants stabilised in the delivery room with 80% oxygen had a lower cerebral blood flow two hours after birth than those stabilised with 21% oxygen (6). An exposure to 80 to 90% oxygen for a few minutes only seems therefore to trigger long-term effects in small babies. It should be noted that during the first studies (6,7,8) no reference ranges for SpO₂ during the first minutes after birth were available. Therefore FiO₂ was adjusted according to a fixed value of SpO₂ at

a predetermined time point. These days, FiO_2 can be adjusted in a more relevant and physiologic manner, thanks to new dynamic reference values for SpO_2 immediately after birth (29) and pulse oximetry, and this potentially reduces oxidative stress.

The studies included in this review differed in target oxygen saturations and how oxygen was adjusted during the initial resuscitation. It is possible that this resulted in differences between the total oxygen exposure infants received during different studies.

The data from this systematic review suggest that it is reasonable to adopt a low initial FiO_2 approach with 21% to 30% oxygen until more data from larger studies are available.

Furthermore, when starting with low oxygen, FiO_2 should be adjusted according to the patient's needs. These should be primarily assessed by heart rate response, and preferably by pulse oximeter as well, to try and avoid exceeding 60-65% oxygen. Although initial FiO_2 should probably be low, the optimal starting point and the optimal way to adjust FiO_2 is not known at present.

None of the included studies include long-term, follow-up data. Such information is of the utmost importance before firm conclusions can be drawn regarding the optimal iFiO_2 for newly born infants with a gestational age of ≤ 32 weeks in need of resuscitation at birth.

The data presented here are insufficient to determine whether an initial approach using high or low oxygen affects important outcomes of preterm infants ≤ 32 weeks' gestational age. That is why larger prospective randomised trials are needed.

In conclusion, until data from larger studies, including long-term follow up, is available, the best information to date is that newborn babies with gestational ages of 32 weeks or lower in need of stabilisation/ventilation at birth, should initially be given 21-30% O₂. FiO₂ should then, ideally, be dynamically adjusted, according to SpO₂ changes measured by pulse oximetry, to reach preductal SpO₂ targets (30). The ideal preductal oxygen saturation targets for these small infants are still not known

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Table 1

Basic characteristics of the included and excluded randomised studies. according to the initial inspiratory fraction of oxygen (iFiO₂) employed for resuscitation in the delivery room.

Study	Blinded	GA weeks	Low iFiO ₂	High iFiO ₂	Mortality Definition
Included studies					
Lundstrøm (6)	No	24-32	0.21	0.80	Before discharge
Vento (10)	No	24-28	0.30	0.90	< 28 days
Wang (8)	Yes	23-32	0.21	1.0	< 28 days
Rabi (14)	Yes	≤ 32	0.21	1.0	Before discharge
See (21)	No	< 31	0.21	1.0	Before discharge
Rook (23)	Yes	<32	0.30	0.65	< 36 weeks' post conceptional age
Armanian (13)	No	29-34	0.30	1.0	Not specified
Kumar (22)	Yes	<32	0.21	1.0	< 28 days
Aguar (24)	Yes	<30	0.30	0.60	Before discharge
Kapadia (15)	No	<35	0.21	1.0	Before discharge
Excluded studies					
Harling (11)	No	<31	0.50	1.0	Not specified
Ezaki (12)	Yes	<35	unknown	1.0	Not specified

GA: Gestational age

Only enrolled infants with a gestational age < 33 weeks are included in this review from studies referenced 12,13 and 15

Table 2

Primary and secondary outcome in included randomised studies comparing low (0.21-0.30) versus high (0.60-1.00) initial inspiratory fraction of oxygen (FiO₂)

Study	Death		BPD		IVH	
	Low	High	Low	High	Low	High
Lundstrøm (6) *	2/34	6/35	5/34	2/35	2/34	1/35
Vento (10) *	4/37	3/41	6/37	13/41	7/37	5/41
Wang (8) *	1/18	1/23	7/18	3/23	2/18	0/23
Rabi (14)	1/34	3/72	18/33	41/69		
See (21)**	1/20	1/16	4/20	3/16	0/20	0/16
Rook (23)**	6/99	10/94	23/99	14/94	8/99	10/94
Kumar (22) **	0/5	1/6	3/5	1/6	1/5	0/6
Aguar (24)	4/34	7/26	10/34	6/26	11/34	8/26
Armenian (13)	0/14	0/13				
Kapadia et al (15) **	2/26	3/30	3/26	11/30	4/26	6/30
Total	21/321	35/356	79/306	91/340	24/239	30/245
%	6.5	9.8	25.8	26.8	10.0	9.0

Abbreviations

BPD: bronchopulmonary dysplasia; IVH: intraventricular haemorrhage.

*IVH > grade 2 **IVH ≥ grade 2

Legends to figures

Figure 1

Random effects forest plot with summary relative risk (RR) and 95% confidence intervals of mortality and the combined values comparing the use of low (0.21-0.30) versus high (0.60-1.00) initial inspiratory fraction of oxygen for resuscitation/stabilization of preterm infants ≤ 32 weeks' gestational age in the delivery room. $RR < 1$ favours low oxygen

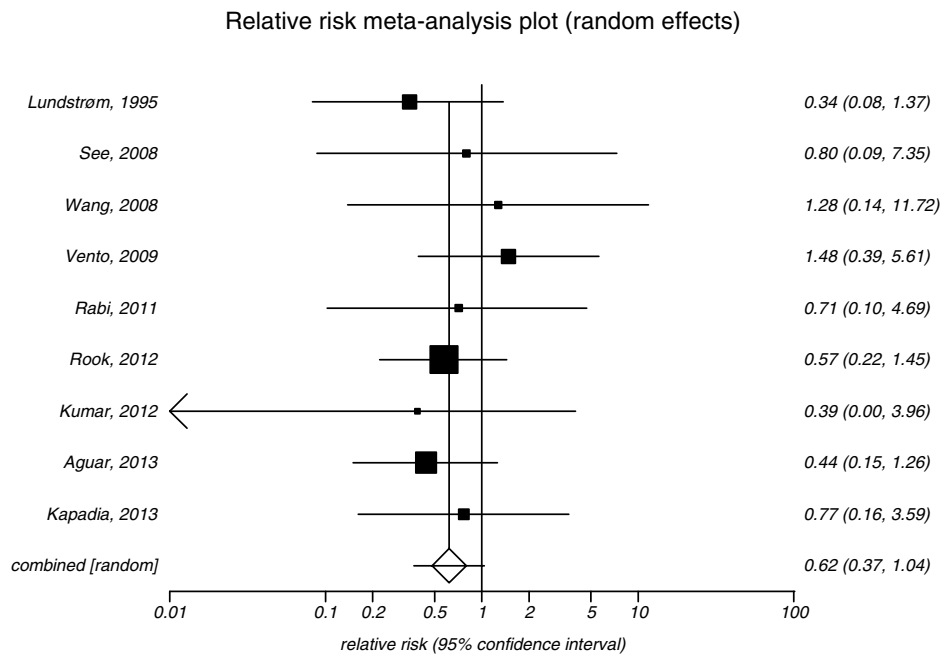
Figure 2

Random effects forest plot with summary relative risk (RR) and 95% confidence intervals of bronchopulmonary dysplasia (BPD) and the combined values comparing the use of low (0.21-0.30) versus high (0.60-1.00) initial inspiratory fraction of oxygen for resuscitation/stabilisation of preterm infants ≤ 32 weeks' gestational age in the delivery room. $RR < 1$ favours low oxygen

Figure 3

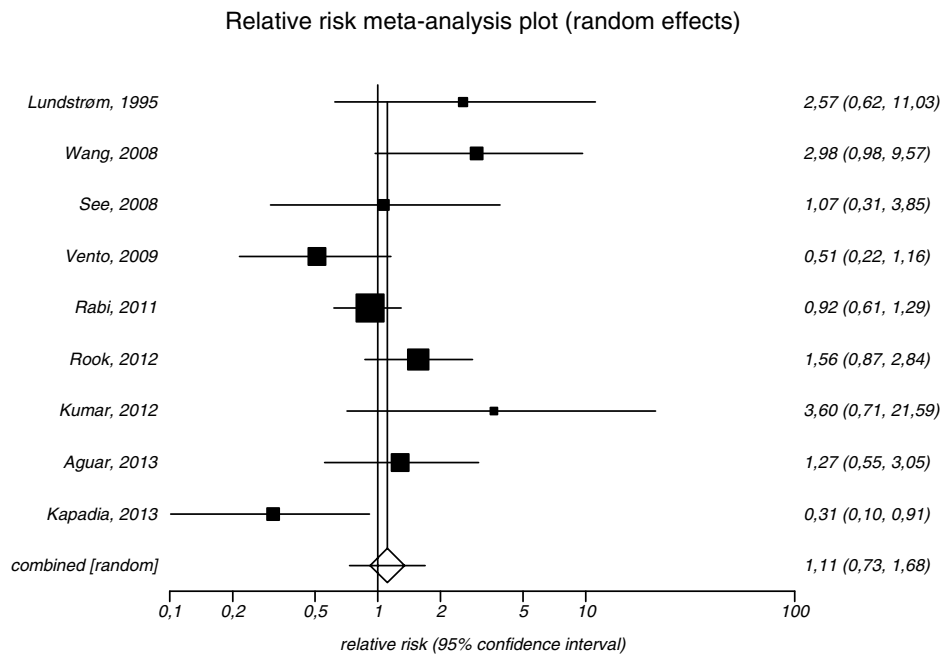
Random effects forest plot with summary relative risk (RR) and confidence intervals of intraventricular haemorrhage (IVH) and the combined values comparing the use of low (0.21-0.30) versus high (0.60-1.00) initial inspiratory fraction of oxygen for resuscitation/stabilisation of preterm infants ≤ 32 weeks' gestational age in the delivery room. $RR < 1$ favours low oxygen

Figure 1. Mortality



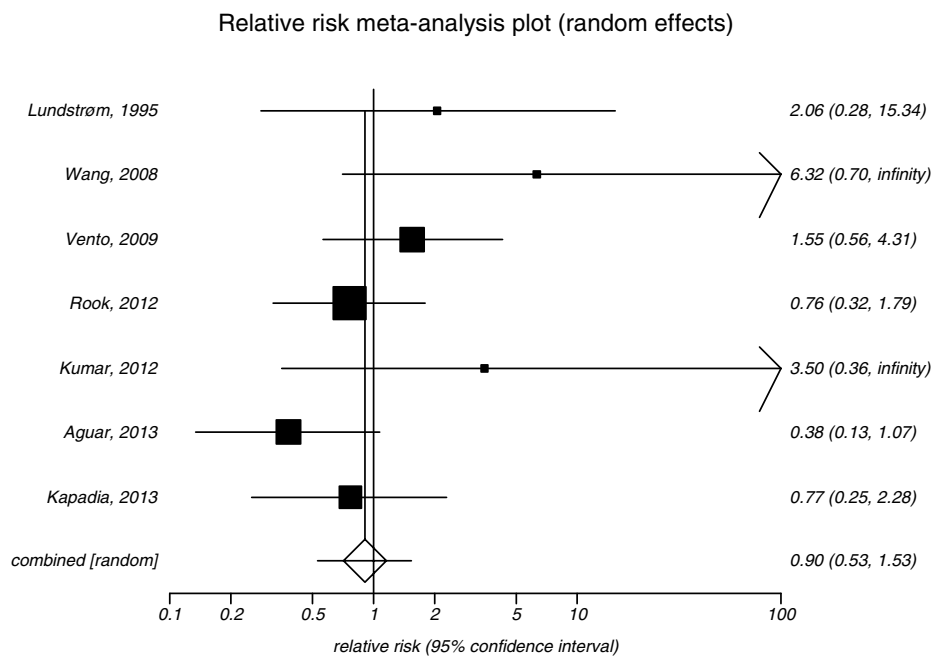
RR < 1 favours low oxygen

Figure 2. Bronchopulmonary dysplasia (BPD)



RR < 1 favours low oxygen

Figure 3. Intraventricular haemorrhage (IVH)



RR < 1 favours low oxygen