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Outcomes of oxygen saturation targeting during delivery room stabilisation of preterm infants

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Abstract

Objective—To determine the association between SpO_2 at 5 min and preterm infant outcomes.

Design—Data from 768 infants <32 weeks gestation from 8 randomised controlled trials (RCTs) of lower (≤0.3) versus higher (≥0.6) initial inspiratory fractions of oxygen (FiO_2) for resuscitation, were examined.

Setting—Individual patient analysis of 8 RCTs

Interventions—Lower (≤0.3) versus higher (≥0.6) oxygen resuscitation strategies targeted to specific predefined SpO_2 before 10 min of age.

Patients—Infants <32 weeks gestation.

Main outcome measures—Relationship between SpO_2 at 5 min, death and intraventricular haemorrhage (IVH) >grade 3.

Results—5 min SpO_2 data were obtained from 706 (92%) infants. Only 159 (23%) infants met SpO_2 study targets and 323 (46%) did not reach $SpO_2$80%. Pooled data showed decreased likelihood of reaching $SpO_2$80% if resuscitation was initiated with FiO_2 <0.3 (OR 2.63, 95% CI 1.21 to 5.74, p<0.05). SpO_2 <80% was associated with lower heart rates (mean difference −8.37, 95% CI −15.73 to –1.01, *p<0.05) and after accounting for confounders, with IVH (OR 2.04, 95% CI 1.01 to 4.11, p<0.05). Bradycardia (heart rate <100 bpm) at 5 min increased risk of death (OR 4.57, 95% CI 1.62 to 13.98, p<0.05). Taking into account confounders including gestation, birth weight and 5 min bradycardia, risk of death was significantly increased with time taken to reach $SpO_2$80%.

Conclusion—Not reaching $SpO_2$80% at 5 min is associated with adverse outcomes, including IVH. Whether this is because of infant illness or the amount of oxygen that is administered during stabilisation is uncertain and needs to be examined in randomised trials

INTRODUCTION

Preductal pulse oximetry (SpO_2) monitoring is now an integral component of delivery room stabilization of sick newborn infants.[1] SpO_2 is used to guide administration of fractional inspired oxygen (FiO_2) to achieve SpO_2 levels derived from healthy, spontaneously breathing full-term infants.[2] This is a relatively new practice. Prior to 2005, pure oxygen (FiO_2 1.0) was used for respiratory support of all newborn infants, regardless of gestation and SpO_2 was not consistently monitored.[3] Most delivery rooms, even in high resource countries, were not equipped to either blend oxygen or monitor SpO_2.[4]

In the 1990s, the Resair studies demonstrated that air (FiO_2 0.21) could be used instead of FiO_2 1.0 for resuscitating hypoxic, mature infants.[5,6] Using air, in fact, decreased oxidative stress, organ injury,[7] death[8] and encephalopathy.[9] Major changes in the use of oxygen for newborn infant stabilization subsequently ensued. Expert committees first suggested in 2005 that air could[10] or should[11] be used to resuscitate full-term infants. With the acquisition of transitioning SpO_2 data several years later from healthy term[2] and preterm[12] infants, guidelines then recommended that FiO_2 should be, first, initiated at low levels (air for term infants and 'judicious' amounts for preterm infants) to prevent rapid rise of SpO_2 and second, FiO_2 should be adjusted to meet healthy term infant SpO_2 thresholds.[2,12]

These SpO_2 recommendations were mostly applied to all infants, regardless of gestation.[13,14] However, the implications of these recommended SpO_2 thresholds on preterm infant outcomes are unknown and this is consistently acknowledged as one of the biggest knowledge gaps in clinical care of the sick preterm infant.[1,15–17] Prematurity is associated with both respiratory immaturity and anti-oxidant deficiency[18] that makes 'optimum' oxygen requirements difficult to balance. Using just air may cause hypoxaemia but conversely, using only FiO_2 1.0 will rapidly cause hyperoxaemia.[19]

Escrig *et al* first demonstrated that resuscitation with low levels of blended oxygen (eg, FiO_2 0.3) was feasible.[20] Vento *et al* then showed that this decreased biochemical oxidative stress when compared with the use of higher oxygen (eg, FiO_2 0.6).[21] In 2015, international committees that lower FiO_2 (≤0.3%) should be used for preterm resuscitation and that higher oxygen levels >0.65 should be avoided.[15–17] Over the last 10 years, a paradigm shift in the use of oxygen has evolved. In 2008, 50% of Australian and New Zealand perinatal centres used FiO_2 1.0 to resuscitate preterm infants.[4] In 2015, a survey of 630 clinicians from 25 countries found that only four clinicians would use FiO_2 1.0 and >70% would use FiO_2 <0.4. Furthermore, most would target SpO_2 thresholds of 'healthy term infants' or those at the lower percentiles of healthy preterm infants.[22]

Prospective acquisition of oxygen data from randomised controlled trials (RCTs) would take many years. Eight existing studies have been conducted to determine outcomes of preterm infants after resuscitation with either lower (<0.3) or higher (>0.6) initial FiO_2. A meta-analysis of this studies showed that FiO_2 did not influence death, major intraventricular haemorrhage (IVH) or bronchopulmonary dysplasia (BPD),[23] but the association between SpO_2 and outcomes have not been examined even though the Resair 2 study showed >20 years ago that failure to achieve a 1 min SpO_2 of 60% markedly increased the risk of death in asphyxiated term infants (OR 8.6).[24]

In this study, therefore, we obtained individual patient SpO_2 data from the eight RCTs[20,21,25–30] that have previously examined outcomes of premature infants <32 weeks gestation to compare outcomes of higher (≥0.6) versus lower (≤0.3) FiO_2 resuscitation strategies. We hypothesised that infants not reaching SpO_2 80% by 5 min would be at an increased risk of adverse outcomes, including death, major IVH or BPD, regardless of the initial level of FiO_2.

METHODS

Individual patient data were obtained directly from the authors of eight RCTs that initiated delivery room resuscitation with higher (>0.6) and lower (<0.3) FiO_2 in infants <32 weeks gestation.[202125–30] Four studies were excluded: authors uncontactable (1),[31] FiO_2 not titrated at birth (3).[32–34] No study examined FiO_2 between 0.31 and 0.59 (see table 1 and figure 1).

SEARCH STRATEGY AND DATA SOURCES

Databases (Medline/PubMed, EMBASE, ClinicalTrials.gov, Cochrane controlled trial registers) and meeting abstracts (Pediatric Academic Societies, European Society of Paediatric Research, European Association of Paediatric Societies) were searched from 1990 to 1 November 2016 using the index terms: preterm/resuscitation/oxygen. Reference lists of relevant articles were also scrutinised. Data were extracted and based on consensus between at least two investigators to resolve uncertainties. Studies published in abstract and full manuscript forms were included. Each study was cross-checked for duplication.

SPO_2 TARGETS

Three studies used oximeter downloads to obtain or to verify SpO_2 data[25–27] and the rest obtained data manually. SpO_2 targets were different for each study as were FiO_2 titration protocols. SpO_2 at 5 min was used as the primary outcome because earlier readings were not consistent. SpO_2 above or below 80% (lower limit of the most common expert committee 5 min SpO_2 recommendation (80%−85%)[13] was used as a dichotomous variable to determine influence on the primary outcomes of death before hospital discharge, major IVH (>grade 3)[35] and BPD (defined as the need for respiratory support or supplemental oxygen at 36 weeks postconceptional age).[36]

STATISTICAL ANALYSIS

Random effects models were used to account for variation within and between studies (heterogeneity) and to compute summary OR, mean differences (MD) and 95% CIs for dichotomous and continuous variables, where appropriate.[3738] Heterogeneity between studies was evaluated with I^2 statistics.[39] Publication bias was assessed with Egger's test[4041] and by funnel plot inspection. Categorical data were examined by the χ^2 test for proportions and expressed as number (%) and OR (95% CI). Parametric continuous data were examined with the two-sided Student's t-test. Logistic regression analysis using factors associated with death, IVH and BPD, including gestation, birth weight, gender, FiO_2, low heart rate (<100 bpm) were conducted to determine the influence of 5 min SpO_2 </>80% on the primary outcomes.[42–44] Cox regression analyses was used to determine HR to estimate the effect size of confounders between time to reach SpO_2 80% and death in infants with and without bradycardia (heart rate >100 bpm) at 5 min, using model predictors of: gestation, birth weight, male gender, 5 min heart rate <100 bpm, starting FiO_2 and mean SpO_2 at 5 min.

Analyses were performed with RevMan, V5 and SPSS (IBM) V22. A p value of <0.05 was considered to be statistically significant.

Ethics board approval and registration with clinical trial registries

All studies had been approved from the relevant ethics boards and were registered in approved clinical trial registries (details available from individual studies).

RESULTS

Study and patient characteristics

Study and patient characteristics are presented in tables 1 and 2. Data from 768 infants (369, 52% male) enrolled in eight studies were suitable for analyses. Of these, 191 were randomised to FiO_2 0.21, 189 to FiO_2 0.3,120 to FiO_2 0.6–0.65 and 268 to FiO_2 1.0. 5 min SpO_2 data were available from 706 (92%) infants. One study did not collect heart rate data.[29]

SpO_2 targets

At 5 min, 159 (23%) of the 706 infants reached SpO_2 targets for their individual study. Most infants either did not reach SpO_2 80% (323, 46%) or exceeded SpO_2 85% (297, 42%). SpO_2 was between 80% and 85% in 86 (12%) of infants. Figure 2 illustrates differences in SpO_2 for babies who were given either lower (≤0.3) or higher (≥0.6) initial FiO_2. Babies who were given lower oxygen were more likely to not reach SpO_2 80% (59.0% vs 32.2%, OR 2.63, 95% CI 1.21 to 5.74, I^2 73%, p = 0.01, figure 2A), took longer to reach SpO_2 ≥80% (MD 1.00, 95% CI 0.15 to 1.84), I^2 90%, p = 0.02, figure 2B) and had significantly lower SpO_2 at 5 min (MD −7.61, 95% CI −13.26 to −1.26, I^2 = 89%, p = 0.008, figure 2C) than babies given higher oxygen.

Characteristics of infants with SpO_2 below and above 80% at 5 min

Infants with SpO_2 <80% at 5 min were more premature and had lower birth weights than infants with SpO_2 >80%. They were also more likely to be given initial FiO_2 <0.3 (OR 3.08, 95% CI 2.26 to 4.19). There was no difference in FiO_2 administered at 5 min but mean SpO_2 (63.7% vs 91.8%) and heart rates (142.0 vs 148.7 bpm) were significantly lower in infants with SpO_2 <80%. Only two infants with SpO_2 >80% were bradycardic at 5 min (see table 3).

Outcomes of infants with SpO_2 </> 80% at 5 min

Infants with 5 min SpO_2 <80% were more likely to die (OR 2.70, 95% CI 1.58 to 4.61) and develop IVH (OR 1.82, 95% CI 1.20 to 2.75) but there was no difference in BPD (OR 1.17, 95% CI 0.89 to 1.54), table 3. Logistic regression analysis was conducted to determine the association between SpO_2 <80% in the development of IVH, BPD and death. After taking confounders including gestation, birth weight, gender, FiO_2, low heart rate (<100 bpm) into account, SpO_2 <80% was associated only with an increased risk of IVH (OR 2.04, 95% CI 1.01 to 4.11, p = 0.04). Increasing gestation decreased the risk of all three primary outcomes (death OR 0.6 5, IVH OR 0.70, BPD OR 0.77). Bradycardia at 5 min was associated with increased risk of death (OR 4.57, 95% CI 1.62 to 13.98), table 4. Pooled patient data accounting for study differences showed that failure to achieve SpO_2 80% by 5 min increased the risk of bradycardia (8.9% vs 0.7%, OR 8.47, 95% CI 1.13 to 63.37, I^2 50%, p

= 0.04, figure 3A) and that babies with SpO_2 <80% had significantly lower heart rates than those with higher SpO_2 (MD −8.37, 95% CI −15.73 to −1.01, I^2 77%, p = 0.03, figure 3B). Furthermore, babies with 5 min SpO_2 <80% had an increased risk of death (OR 2.66, 95% CI 1.45 to 4.87, p = 0.02, I^2 0% (figure 4A) but not IVH (figure 4B) or BPD (figure 4C).

Association between time to attain SpO_2 >80% and risk of death

A Cox model of proportional hazards was developed to determine the relationship between time to reach SpO_2 >80% and death. No infant died during resuscitation. Increasing gestation (HR 0.76) and birth weight (HR 0.99) were associated with a decreased risk of death but bradycardia at 5 min (HR 4.17) and lower 5 min SpO_2 (HR 1.04) increased risk of death. Male gender and starting FiO_2 levels did not influence risk of death (see figure 5 and table 5).

DISCUSSION

In this study, we show that only 12% of preterm infants who were resuscitated with blended oxygen in eight RCTs reached the lower limit of expert committee SpO_2 (80%) at 5 min of age.[1] The implications of these recommendations on sick preterm newborn infants are unknown as they are predominantly derived from observational studies of healthy term and preterm infants.[12] Our study showed that babies who did not reach SpO_2 80% by 5 min were more premature, but also had lower heart rates. In univariate analyses, they were more likely to die before hospital discharge and to develop a major IVH. Risk of death was also increased with the time taken to attain SpO_2 80% but whether this was iatrogenic or due to inherent illness (eg, more severe respiratory pathology) cannot be determined from this study.

Nevertheless, we show that the relatively new practice of using blended oxygen and targeting SpO_2 requires urgent and careful evaluation in well-designed and sufficiently large randomised studies. Clinicians now accept lower oxygenation more readily than higher, primarily because of concerns of oxidative stress[22] but again, the implications of this practice on both short-term and long-term outcomes is unknown. Boronat *et al* showed no difference in 2-year neurodevelopmental outcomes after resuscitation with either FiO_2 0.3 or 0.6[45] and further evaluation of this concept is warranted after results from other studies, for example, the neurodevelopmental follow-up of babies enrolled in the Tor2pido study[25] is available.

It must be acknowledged, however, that outcomes of sick newborn infants are influenced by multiple factors and not only oxygenation. After accounting for confounders, low SpO_2 appeared to be important in increasing only the risk of IVH (OR 2.04) but not death (risk changed with gestation (OR 0.65), birth weight (OR 0.99) and bradycardia (OR 4.57)) or BPD (risk influenced by factors inherent to the patient, eg, gestation (OR 0.77), birth weight (OR 0.99) and male gender (OR 2.39)). Clinicians must therefore account for all these factors when stabilising preterm babies during the first critical few minutes of life. The practice of using blended FiO_2 to target SpO_2 is a relatively new method of resuscitation and definitive data about the outcomes of this practice are still being acquired. Adopting SpO_2 recommendations requires significant infrastructure changes that may be unfeasible in

resource-limited regions.[46] Therefore, fall-back safety measures that do not necessitate the use of additional equipment, for example, clinical assessment and heart rate auscultation, must be evaluated to ensure best patient outcomes.

We also caution that none of the RCTs was designed to examine infant outcomes in relation to target SpO_2. All but two studies[2930] were designed before the first recommended SpO_2 targets were published in 2010.[114] To date, there continues to be wide variability in SpO_2 recommendations. No international expert committee differentiates between term and preterm infants for SpO_2 recommendations and SpO_2 recommendations may vary by >20% between countries.[47] Further study to evaluate patient outcomes against differing SpO_2 targets is, as mentioned, greatly needed, considering the now almost ubiquitous nature of oxygen blending.

Currently, the only certain data point for oxygen administration during resuscitation is starting FiO_2. International expert committees recommend not using FiO_2>0.65 and to use lower FiO_2 (0.21–0.3) to initiate preterm resuscitation.[17] Note that no study has examined outcomes for initiation of resuscitation with FiO_2 0.4–0.58 or the impact of differing oxygen titration strategies. Pooled data from this study, however, shows that babies given lower (FiO_2<0.3) were more likely to have SpO_2 <80% (OR 2.63) and lower SpO_2 (MD −7.61) at 5 min and also need 1 min more to reach SpO_2 80% after birth. Lower SpO_2 was associated with lower heart rates which in turn increased the risk of death (OR 4.57), even after accounting for gestation and birth weight differences.

Whether infants were unable to reach threshold SpO_2 because of insufficient oxygen or illness cannot be determined by this study. Certainly, there was no difference in 5 min FiO_2 in infants with SpO_2 above or below 80% or in the starting FiO_2 level between babies with and without adverse outcomes after adjustment of confounders. There is increasing evidence that premature infants may be more susceptible to poor short-term outcomes with lower oxygenation strategies. Rabi *et al* showed that extremely preterm infants were at increased risk of death or neurological injury after Canadian resuscitation policies were changed from FiO_2 1.0 to titrated oxygen.[48] In an unplanned, post hoc analysis, the recently closed To2rpido study showed a marginally statistically significant increased risk of death (OR 3.9, p = 0.01) in babies <28 weeks gestation after initiation of resuscitation with air instead of FiO_2 1.0. Whether these strategies impact on long-term (including neurodevelopmental) outcomes are unclear and need evaluation.

The major limitations of our study were its observational nature and the prolonged duration over which the studies were conducted. Knowledge, opinion and the capability of clinicians in SpO_2 targeting and FiO_2 titration would undoubtedly have changed considerably and may now influence clinical outcomes. Nevertheless, theresuscitation. results of our study show that randomised trials are urgently needed to evaluate the relatively new practice of oxygen blending and SpO_2 targeting in preterm infant stabilisation at birth.

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What is already known on this topic?

- Clinicians initiate preterm infant resuscitation with low levels of blended oxygen (FiO_2 <0.4) that is manipulated to meet SpO_2 derived from healthy term and preterm infants.
- This is now almost standard practice but whether clinicians are able to achieve recommended SpO_2 targets is unknown.

What this study adds?

- Almost half of preterm infants enrolled in oxygen titration studies did not reach SpO_2 80% at 5 min, and this was associated with increased risk of major intraventricular haemorrhage and bradycardia (heart rate <100 bpm).
- Bradycardia at 5 min increased risk of death by almost five times, suggesting that randomized trials to determine the consequences of oxygen titration and SpO_2 targeting strategies in preterm infants are urgently needed.

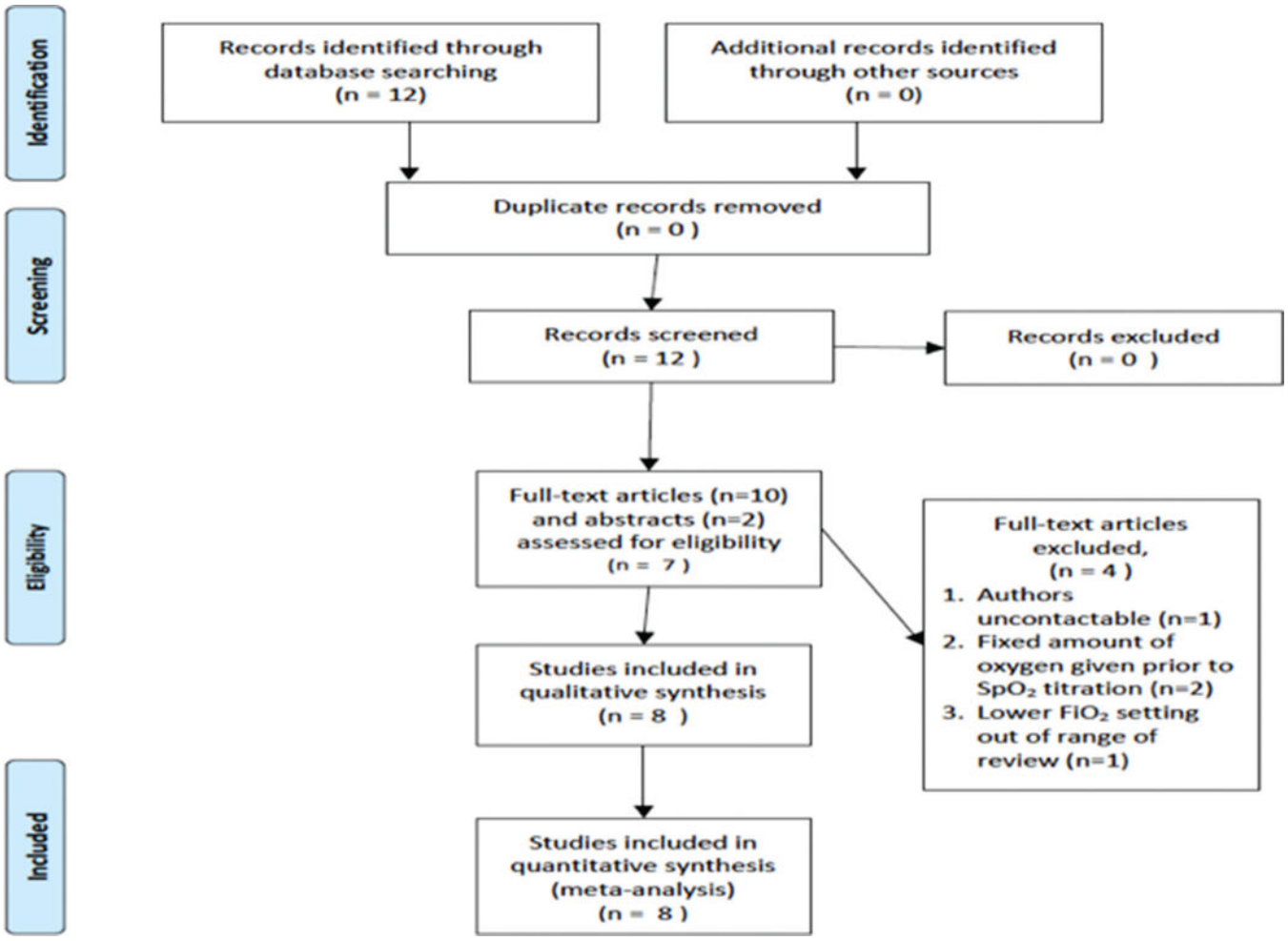

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

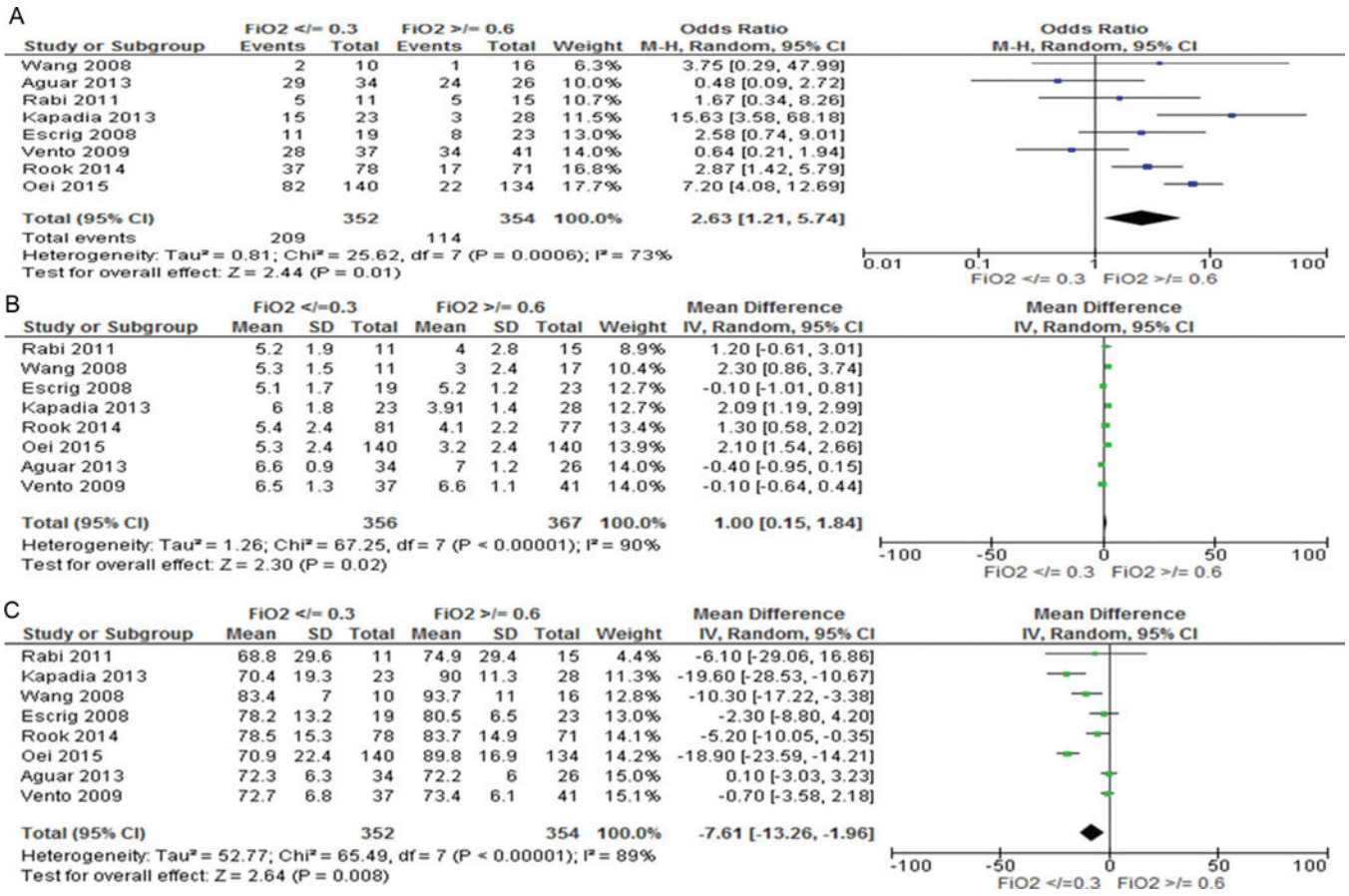

Figure 2.

5 min SpO_2 for infants given initial FiO_2 <0.3 or >0.6. (A) Number of infants in each group with $SpO_2$80%, (B) time to reach SpO_2 >80%, (C) mean difference in SpO_2at 5 min.

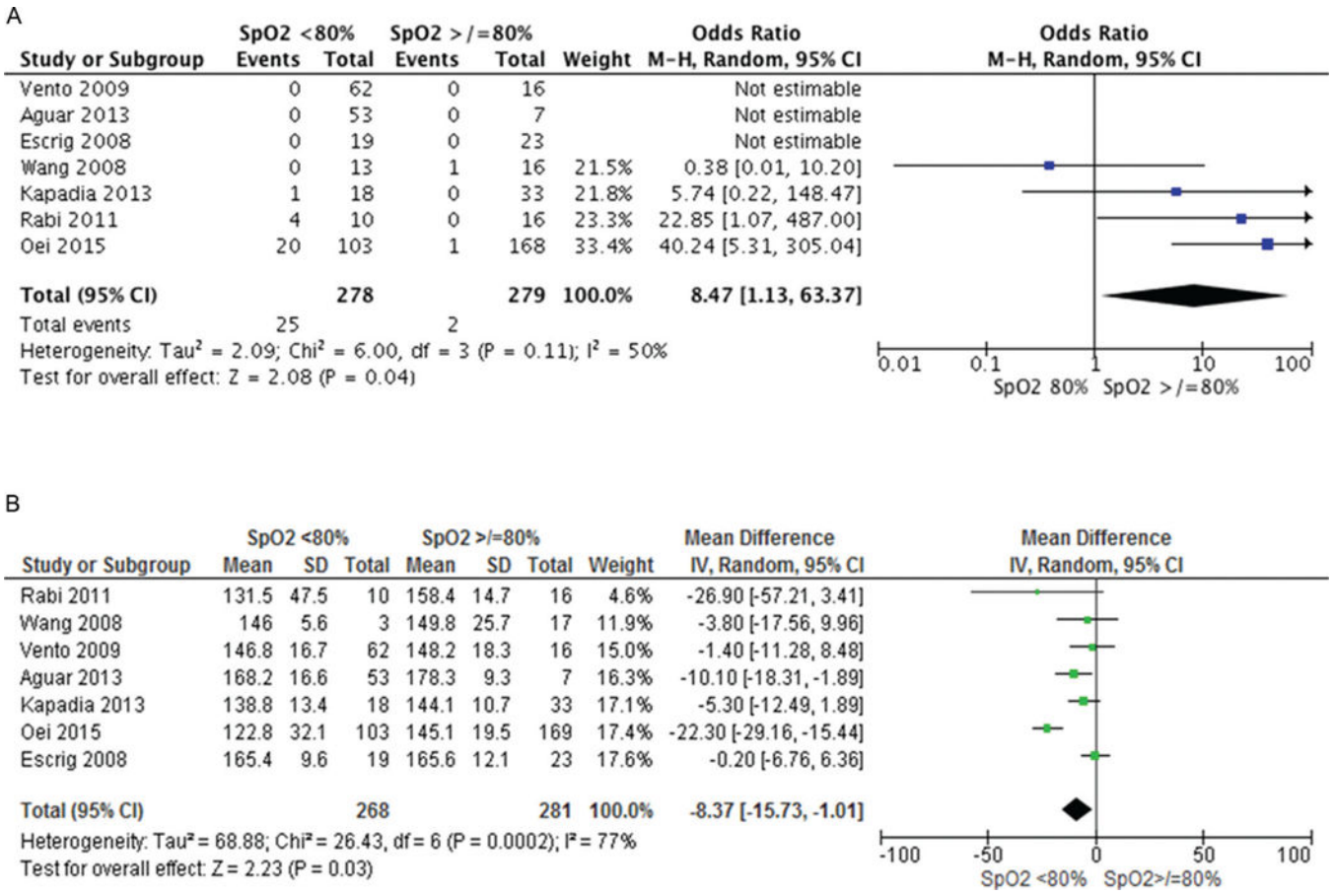

Figure 3.

Heart rate (HR) differences between infants with SpO_2 </>80% at 5 min. (A) Infants with HR <100 bpm at 5 min, (B) mean HR at 5 min.

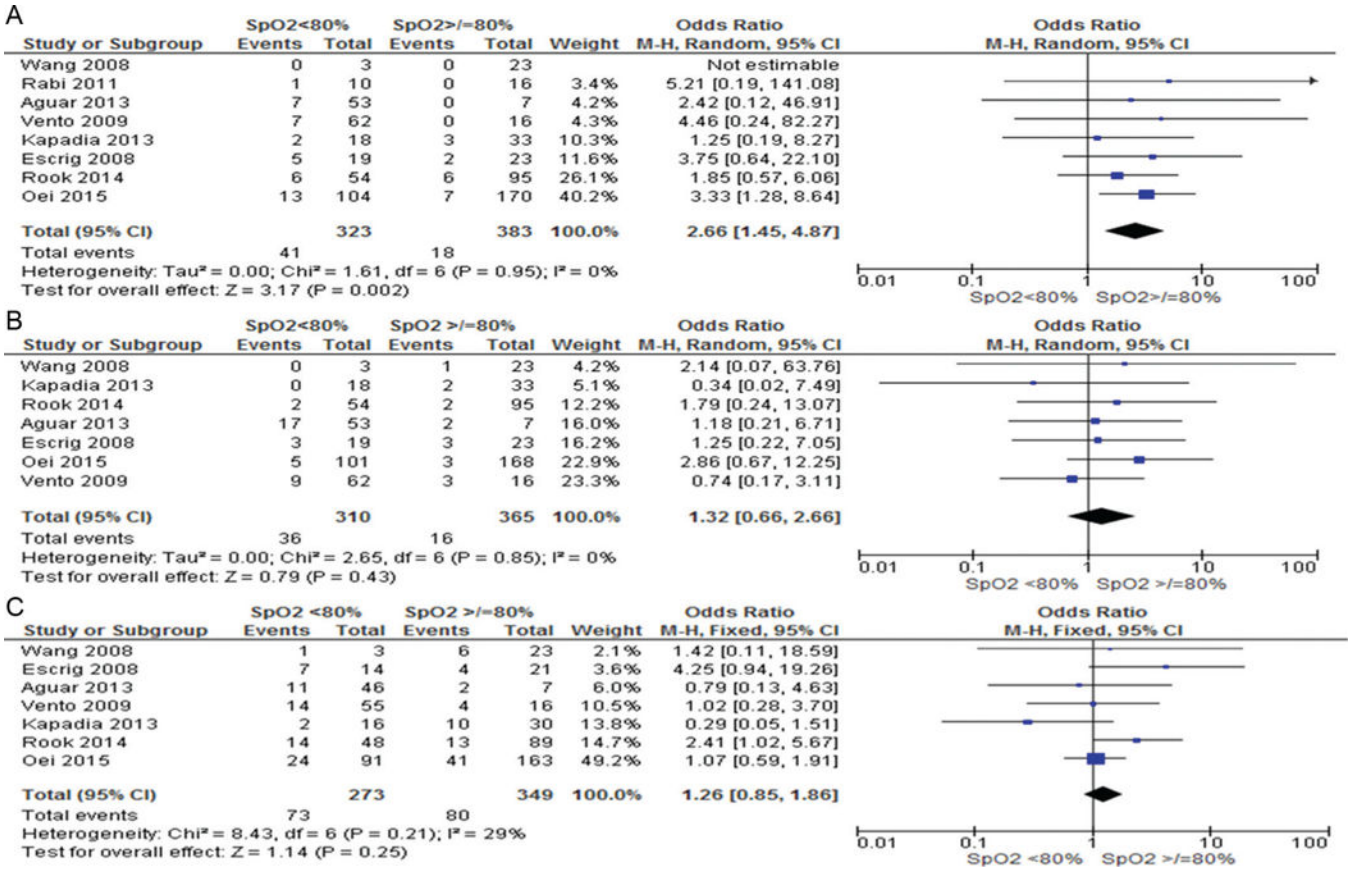

Figure 4.

Risks of death, intraventricular haemorrhage and bronchopulmonary dysplasia in infants with 5 min SpO_2</>80%.

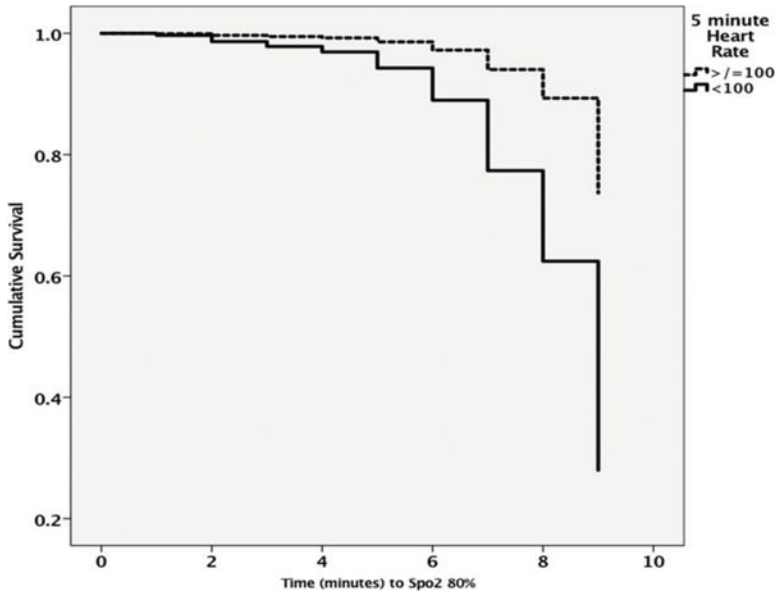

Figure 5.

Cumulative risk of death with time taken to reach SpO_2 80%. Note higher risk of death in infants with heart rates <100 bpm at 5 min (also see table 5 for HRs associated with each confounder).

Table 1

SpO_2 targets and FiO_2 strategies from individual studies

Study	Enrolment period/location	Gestation (weeks)	FiO_2	SpO_2 targets	5 min SpO_2 study targets: Detected	Not met	Met	Overshot
Wang *et al*[26]	2005–2007 USA	23–32	0.21 vs 1.0 n=31	► FiO_2↑ to aim for SpO_2 <70% at 3 min or <85% at 5 min ► FiO_2↓ if SpO_2 was >95% any time ► $FiO_2$1.0 given if heart rate was <100 bpm at 2 min or CM needed ► Time 0 not stated	26 (84%)	3 (10%)	9 (29%)	14 (45%)
Escrig *et al*[20]	2005–2007 Spain	≤28	0.3–0.9 n=42	► FiO_2 adjusted by 0.1 every 30 s to aim for a SpO_2 of 75% at 5 min and 85% at 10 min ► $FiO_2$1.0 given if heart rate ≤60 bpm >30 s ► Time 0 not stated	42 (100%)	18 (43%)	1 (2%)	23 (55%)
Vento *et al*[21]	2007–2008 Spain	≤28	0.3–0.9 n=78	Procedure as per Escrig *et al*[22]	78 (100%)	47 (60%)	29 (37%)	2 (3%)
Rabi[27]	2005–2007 Canada	≤32	0.21 vs 1.0 n=26	► FiO_2adjusted by 0.2 every 15 s to aim for SpO_2 85%–92% ► 5%–10% changes made to maintain SpO_2 within target range ► $FiO_2$1.0 given if heart rate was <100 bpm for >30 s or CM needed	26 (100%)	13 (50%)	6 (23%)	7 (27%)
Aguar *et al*[28]	2010–2012 Spain	<30	0.3 vs 0.6 n=60	► FiO_2adjusted according to internationally recommended SpO_2 targets ► Time 0 not stated	60 (100%)	53 (88%)	7 (12%)	0
Rook *et al*[29]	2008–2012 The Netherlands	26+5–32	0.3 vs 0.6 n=193	► FiO_2adjusted to target SpO of 88%–94% at 10 min of age ► FiO_2decreased if SpO_2 was >94% ► Time 0=at cord clamping	149 (77%)	87 (45%)	39 (20%)	23 (12%)
Kapadia *et al*[30]	2010–2011 USA	24–34	0.21% vs 1.0 n=51	► Only infants <32 weeks included ► Time 0 not stated ► $FiO_2$0.21 group given extra oxygen if HR <100 bpm after effective ventilation, lower limit of term infant SpO_2 (5 min	51 (100%)	18 (35%)	4 (8%)	29 (57%)

Study	Enrolment period/location	Gestation (weeks)	FiO_2	SpO_2targets	5 min SpO_2study targets			
					Detected	Not met	Met	Overshot
				80%–85%) not reached. FiO_2 1.0 if HR <60				
				► FiO_2 adjusted 10% every 30 s to maintain SpO_2 in IQR				
				► $FiO_2$1.0 group had oxygen reduced by 0.1 q30s to meet SpO_2 85%–94%				
Oei *et al*[25]	2009–2014 Australia	<31+6	0.21 vs 1.0 n=287	► FiO_2increased by 0.1 if SpO_2 was <65% before 5 min or <80% after 5 min	274 (96%)	104 (36%)	64 (22%)	106 (37%
	Malaysia			► FiO_2decreased by 0.1 if SpO_2 >95%.				
	Qatar			► FiO_2increased to 1.0 if heart rate <100 bpm or SpO_2 <65% at 5 min or if CM was required				
				► Time 0=at cord clamping				
Total			768		706 (92%)	343 (49%)	159 (23%)	204 (29%)

CC, cord clampling; CM, cardiac massage; FiO_2, fraction of inspired oxygen; HR, heart rate; NS, not stated; SpO_2, pulse oximetry.

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Table 2

Patient demographics

Gestation (weeks)	n	5 min SpO_2				Male gender	Died	IVH >grade 3*	BPD†
		Detected	<80%	80%–85%	>85%				
23	2	2 (100%)	2 (100%)	0	0	1 (50%)	1 (50%)	0	1/1 (100%)
24	47	44 (94%)	30 (68%)	7 (16%)	7 (16%)	19 (43%)	14 (32%)	6/43 (14%)	14/49 (48%)
25	80	73 (91%)	42 (58%)	10 (14%)	21 (29%)	40 (55%)	17 (23%)	13/70 (19%)	33/53 (62%)
26	112	105 (94%)	55 (52%)	17 (16%)	33 (31%)	57 (54%)	13 (12%)	14/101 (14%)	43/88 (49%)
27	103	99 (96%)	52 (52%)	13 (13%)	34 (34%)	53 (54%)	5 (5%)	11/94 (12%)	24/90 (27%)
28	148	135 (91%)	72 (53%)	12 (9%)	51 (38%)	67 (50%)	5 (4%)	6/121 (5%)	18/117 (15%)
29	94	89 (95%)	25 (28%)	11 (12%)	53 (60%)	53 (60%)	4 (5%)	2/86 (2%)	14/85 (17%)
30	84	75 (89%)	18 (24%)	7 (9%)	50 (67%)	37 (49%)	0	0	3/75 (4%)
31	98	84 (86%)	27 (32%)	9 (11%)	48 (57%)	38 (45%)	0	0	3/84 (4%)
Total	768	706 (92%)	323 (46%)	86 (12%)	297 (42%)	365 (52%)	59 (8%)	52/675 (8%)	153/622 (25%)

*675 infants had a head ultrasound performed.

†Excludes deceased infants.

BPD, bronchopulmonary dysplasia[35]; IVH, intraventricular haemorrhage; SpO_2, pulse oximetry.

Table 3

Characteristics and outcomes of infants with 5 min SpO_2 above or below 80%

	5 min SpO_2 <80%	5 min SpO_2≥80%	OR or mean difference	95% CI
Gestation (weeks)	27.1 (1.9)	28.2 (1.9)	−1.03	−1.37 to 0.74 *
Birth weight (g)	988 (297)	1100 (325)	−111	−157 to 65.2 *
Male gender	170 (47%)	195 (53%)	0.93	0.69 to 1.26
Starting FiO_2 <0.3	209 (59%)	254 (41%)	3.08	2.26 to 4.19 *
5 min status				
FiO_2	0.56 (0.23)	0.55 (0.26)	1.28	−2.42 to 4.99
SpO_2 (%)	63.7 (15.2)	91.8 (6.2)	−28.1	−29.7 to 26.4
HR (bpm)	142.0 (30.5)	148.7 (19.5)	−6.7	
HR <100 bpm †	25/278 (9.3%)	2/263 (1%)	12.8	
Short-term outcomes				
Dead	41/323 (13%)	18/303 (5%)	2.70	1.58 to 4.61 *
IVH ≥grade 3 ‡	36/310 (12%)	16/365 (4%)	1.82	1.20 to 2.75 *
BPD §	73/273 (27%)	80/349 (23%)	1.17	0.89 to 1.54

* p<0.001,

** p<0.05

† 557 infants had both SpO_2 and heart rate detected at 5 min.

‡ Head ultrasound data were obtained on 675 infants

§ Excludes deceased infants

BPD, bronchopulmonary dysplasia; FiO_2, fractional inspired oxygen; HR, heart rate; IVH, intraventricular haemorrhage; SpO_2, pulse oximetry.

Table 4

Adjusted regression analysis of factors associated with death, severe (≥grade 3) intraventricular haemorrhage and bronchopulmonary dysplasia

Factor	Died			IVH >grade 3			BPD		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Gestation	0.65	0.49 to 0.86	0.02 **	0.70	0.52 to 0.93	0.01 **	0.77	0.64 to 0.94	0.01 *
Birth weight	0.99	0.99 to 1.00	0.03 **	0.99	0.99 to 1.00	0.62	0.99	0.99 to 0.99	<0.001 *
Male gender	1.07	0.55 to 2.07	0.84	1.29	0.69 to 2.42	0.42	2.39	1.46 to 3.90	0.001 *
5 min SpO_2 <80%	1.57	0.74 to 3.34	0.24	2.04	1.01 to 4.11	0.04 **	1.55	0.93 to 2.57	0.09
5 min HR <100	4.57	1.62 to 13.98	0.005 *	0.69	0.14 to 3.29	0.9	0.88	0.19 to 4.08	0.87
Starting FiO_2	0.67	0.34 to 1.33	0.26	1.23	0.65 to 2.31	0.53	1.11	0.68 to 1.81	0.67
Model	0.09		<0.001 *	0.10		<0.001 *	0.35		<0.001 *

Data are expressed as adjusted OR, 95% CI.

* p<0.001.

** p<0.05.

BPD, bronchopulmonary dysplasia; bpm, beats per minute; FiO_2, fractional inspired oxygen; HR, heart rate; IVH, intraventricular haemorrhage; SpO_2, pulse oximetry.

Table 5

HRs associated with risk of death, IVH and BPD, accounting for time taken to reach SpO2 >80% (see figure 5)

Factor	Died		
	HR	**95% CI**	**p Value**
Gestation	0.76	0.60 to 0.96	0.019 **
Birth weight	0.99	0.99 to 0.99	0.01 **
Male gender	1.01	0.55 to 1.86	0.97
5 min HR <100 bpm	4.17	1.20 to 14.48	0.02 **
Starting FiO_2	0.67	0.35 to 1.28	0.22
SpO_2 5 min (%)	1.04	1.01 to 1.07	0.004 **

Data are expressed as adjusted OR, 95% CI

* p<0.001

** p<0.05

BPD, bronchopulmonary dysplasia; bpm, beats per minute; FiO_2, fractional inspired oxygen; HR, heart rate; IVH, intraventricular haemorrhage; SpO_2, pulse oximetry.