Commentary on ‘Lower versus Higher Oxygen Concentrations Titrated to Target Oxygen Saturations during Resuscitation of Preterm Infants at Birth’

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Commentary

As well as concern that prolonged exposure to high concentrations of inspired oxygen during care in the neonatal unit may have adverse effects due to increased oxidative stress [1], it is postulated that even brief exposure to high oxygen concentrations during stabilisation immediately after birth may trigger pathogenic cascades for reperfusion and re-oxidation damage in very preterm infants [2]. Given this concern, clinical investigators have explored whether using lower versus higher oxygen concentrations for delivery room respiratory support for very preterm infants might affect mortality and morbidity. In a recently published Cochrane review, Lui and colleagues appraised and synthesised data from ten randomised controlled trials (914 infants in total) of lower versus higher fraction of inspired oxygen (FiO₂) for the stabilisation of preterm infants at birth [3]. The review authors prespecified ≥ 0.40 as the arbitrary level for “higher” FiO₂ and included only those trials that titrated the oxygen therapy to the infant’s target preductal oxygen saturation level (SpO₂) measured using pulse oximetry. All included trials were conducted within the past 15 years, but their methodological quality varied. Perfor-

mance bias due to lack of masking of clinicians and investigators was a key concern in most trials.

Meta-analysis of data did not show a difference in the primary outcome, the risk of mortality up to hospital discharge (risk ratio 1.05, 95% CI 0.68–1.63) (Fig. 1). There was no evidence of heterogeneity or funnel plot asymmetry to indicate possible publication bias. The review found only limited data on neurodevelopmental outcomes (3 trials). Meta-analyses of secondary outcomes did not show any significant differences in the incidence of neonatal morbidity that could be plausibly affected by oxidative stress including retinopathy of prematurity, necrotising enterocolitis, or bronchopulmonary dysplasia (risk ratio 0.91, 95% CI 0.72–1.14) (Fig. 2).

The review’s conclusion that there remains considerable uncertainty about whether lower versus higher delivery room FiO₂ has an important effect on mortality or morbidity in very preterm infants is reflected in international clinical practice guidelines [4]. Most guidelines, including the current International Liaison Committee on Resuscitation statement, suggest using a lower FiO₂ initially and titrating this to the infant’s SpO₂ to avoid exposure to additional oxygen without proven benefit [5].

Fig. 1. Lower versus higher inspired oxygen concentration. Mortality by near-term corrected age or discharge (latest reported).

Fig. 2. Lower versus higher inspired oxygen concentration. Chronic lung disease (36 weeks' postmenstrual age).

Guidelines accept that titrating and targeting oxygen administration is often difficult in acute situations in the delivery room, and acknowledge that, in real-life situations, most very preterm infants receive respiratory support with an FiO_2 bordering the arbitrary “lower” versus “higher” threshold. Concerns exist, however, that this ap-

proach may cause delays in achieving target SpO_2 levels that are associated with adverse outcomes [6]. This reinforces the Cochrane review’s conclusion that further large, high-quality RCTs that assess mortality, acute morbidity, and longer-term neurodevelopmental outcomes are needed to inform policy and practice.

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Cochrane Abstract

Background: Initial resuscitation with air is well tolerated by most infants born at term. However, the optimal fractional inspired oxygen concentration (FiO_2 – proportion of the breathed air that is oxygen) targeted to oxygen saturation (SpO_2 – an estimate of the amount of oxygen in the blood) for infants born preterm is unclear. **Objectives:** To determine whether lower or higher initial oxygen concentrations, when titrated according to oxygen saturation targets during the resuscitation of preterm infants at birth, lead to improved short- and long-term mortality and morbidity. **Search Methods:** We conducted electronic searches of the Cochrane Central Register of Controlled Trials (13 October 2017), Ovid MEDLINE (1946 to 13 October 2017), Embase (1974 to 13 October 2017) and CINAHL (1982 to 13 October 2017); we also searched previous reviews (including cross-references), contacted expert informants, and handsearched journals. **Selection Criteria:** We included randomised controlled trials (including cluster- and quasi-randomised trials) which enrolled preterm infants requiring resuscitation following birth and allocated them to receive either lower ($\text{FiO}_2 < 0.40$) or higher ($\text{FiO}_2 \geq 0.40$) initial oxygen concentrations titrated to target oxygen saturation. **Data Collection and Analysis:** Two review authors independently assessed the eligibility of studies for inclusion, extracted data and assessed methodological quality. Primary outcomes included mortality near term or at discharge (latest reported) and neurodevelopmental

disability. We conducted meta-analysis using a fixed-effect model. We assessed the quality of the evidence using GRADE. **Main Results:** The search identified 10 eligible trials. Meta-analysis of the 10 included studies (914 infants) showed no difference in mortality to discharge between lower ($\text{FiO}_2 < 0.40$) and higher ($\text{FiO}_2 \geq 0.40$) initial oxygen concentrations targeted to oxygen saturation (risk ratio [RR] 1.05, 95% confidence interval [CI] 0.68–1.63). We identified no heterogeneity in this analysis. We graded the quality of the evidence as low due to risk of bias and imprecision. There were no significant subgroup effects according to inspired oxygen concentration strata (FiO_2 0.21 vs. ≥ 0.40 to < 0.60 ; FiO_2 0.21 vs. ≥ 0.60 to 1.0; and $\text{FiO}_2 \geq 0.30$ to < 0.40 vs. ≥ 0.60 to 1.0). Subgroup analysis identified a single trial that reported increased mortality from use of lower (FiO_2 0.21) versus higher (FiO_2 1.0) initial oxygen concentration targeted to a lowest SpO_2 of less than 85%, whereas meta-analysis of nine trials targeting a lowest SpO_2 of 85–90% found no difference in mortality. Meta-analysis of two trials (208 infants) showed no difference in neurodevelopmental disability at 24 months between infants receiving lower ($\text{FiO}_2 < 0.40$) versus higher ($\text{FiO}_2 > 0.40$) initial oxygen concentrations targeted to oxygen saturation. Other outcomes were incompletely reported by studies. Overall, we found no difference in use of intermittent positive pressure ventilation or intubation in the delivery room; retinopathy (damage to the retina of the eyes, measured as

any retinopathy and severe retinopathy); intraventricular haemorrhage (any and severe); periventricular leukomalacia (a type of white matter brain injury); necrotising enterocolitis (a condition where a portion of the bowel dies); chronic lung disease at 36 weeks' gestation; mortality to follow up; post-natal growth failure; and patent ductus arteriosus. We graded the quality of the evidence for these outcomes as low or very low. **Reviewers' Conclusions:** There is uncertainty as to whether initiating post birth resuscitation in preterm infants using lower ($\text{FiO}_2 < 0.40$) or higher ($\text{FiO}_2 \geq 0.40$) oxygen con-

centrations, targeted to oxygen saturations in the first 10 min, has an important effect on mortality or major morbidity, intubation during post birth resuscitation, other resuscitation outcomes, and long-term outcomes including neurodevelopmental disability. We assessed the quality of the evidence for all outcomes as low to very low. Further large, well designed trials are needed to assess the effect of using different initial oxygen concentrations and the effect of targeting different oxygen saturations [see Ref. 3].