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Outcomes of preterm infants following the introduction of room air resuscitation☆

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ABSTRACT

Background: After 2006 most neonatal intensive care units (NICUs) in Canada stopped initiating newborn resuscitation with 100% oxygen.
Methods: In this retrospective cohort study, we compared neonatal outcomes in infants born at ≤27 weeks gestation that received <100% oxygen ($OX_{titrate}$ group, typically 21–40% oxygen) during delivery room resuscitation to infants that received 100% oxygen (OX_{100} group).
Results: Data from 17 NICUs included 2326 infants, 1244 in the $OX_{titrate}$ group and 1082 in the OX_{100} group. The adjusted odds ratio (AOR) for the primary outcome of severe neurologic injury or death was higher in the $OX_{titrate}$ group compared with the OX_{100} group (AOR 1.36; 95% CI 1.11, 1.66). A similar increase was also noted when comparing infants initially resuscitated with room air to the OX_{100} group (AOR 1.33; 95% CI 1.04, 1.69). Infants in the $OX_{titrate}$ group were less likely to have received either medical or surgical treatment for a patent ductus arteriosus (AOR 0.53; 95% CI 0.37, 0.74).
Conclusions: In Canadian NICUs, we observed a higher risk of severe neurologic injury or death among preterm infants of ≤27 weeks gestation following a change in practice to initiating resuscitation with either room air or an intermediate oxygen concentration.

Introduction

Guidelines for oxygen use during newborn resuscitation have changed repeatedly over the past 10 years as new evidence regarding the perils of excessive oxygen exposure became available. In 2005, the International Liaison Committee on Resuscitation (ILCOR) published recommendations stating there was "insufficient evidence to specify the concentration of oxygen to be used

Abbreviations: AOR, adjusted odds ratio; CNN, Canadian Neonatal Network; FiO_2, inspired concentration of oxygen; ILCOR, International Liaison Committee on Resuscitation; NICU, neonatal intensive care unit; NRP, Neonatal Resuscitation Program; OX_{100} group, group of infants resuscitated with static concentration of 100% oxygen as per local policies; $OX_{titrate}$ group, group of infants resuscitated using oxygen titration as per local policies; OX_{21} subgroup, subgroup of $OX_{titrate}$ initially resuscitated with 21% oxygen; OX_{22-100} subgroup, subgroup of $OX_{titrate}$ initially resuscitated >21% oxygen; PDA, patent ductus arteriosus; SNAPII, score for neonatal acute physiology version II.

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at initiation of resuscitation", which implied that it was reasonable to continue the standard practice of giving 100% oxygen at the start of resuscitation.[1] Given mounting concerns about the dangers of hyperoxemia at birth, the Canadian Neonatal Resuscitation Program (NRP) Committee issued an amendment in 2006 to recommend that newborn resuscitation should begin with room air, regardless of gestational age.[2] The latest ILCOR recommendation, published in 2010, was updated to state that resuscitation of term infants should start with room air and that blended oxygen may be used for preterm infants.[3] However, the recommendation also specifies that, where blended oxygen is not available, resuscitation should be initiated with room air. The most recent Canadian addendum to the 6th edition of the NRP textbook states that resuscitation should be started with room air for infants born at ≥32 weeks gestation, while oxygen concentrations for infants born at <32 weeks gestation should be guided by local protocols.[4,5]

There is convincing evidence that 100% oxygen use in the delivery room can have far-reaching, clinically significant detrimental effects on outcomes for term infants.[6–8] Several smaller studies comparing low versus high oxygen concentrations for the resuscitation of preterm infants have been published.[6,8–17] These studies failed to show differences in clinically meaningful outcomes, perhaps due to small sample sizes, and as a result there are still many unanswered questions about the safety of using different oxygen concentrations during resuscitation of very preterm infants. Nearly all infants in the low oxygen groups in these studies required an increase in the inspired concentration of oxygen (FiO_2). While none of the studies showed differences in survival or severe injury, they did demonstrate high treatment failure rates for preterm infants initially resuscitated with 21–30% oxygen.

Following publication of the Canadian NRP amendment in 2006, most neonatal intensive care units (NICUs) in Canada changed their local resuscitation practices for preterm infants and began using either room air or an intermediate concentration of oxygen (e.g., 30–40% oxygen) at the start of resuscitation. Our study objective was to determine if neonatal outcomes for infants born at ≤27 weeks gestation changed following this modification in practice.

Methods

Study design and population

In this retrospective cohort study, we included infants born at a gestational age of 23–27 weeks between 2004 and 2009 who were inborn at participating Canadian Neonatal Network (CNN) NICUs that stopped using a static concentration of 100% oxygen during resuscitation. To be included in the study, inborn infants must have been admitted to the NICU, or died prior to NICU admission despite resuscitation efforts. Infants were excluded from the study if they had severe congenital anomalies, were moribund or a decision was made to provide palliative care immediately after birth. Infants that were actively resuscitated and died before admission to the NICU were included in the analysis.

The CNN currently collects anonymized data from participating NICUs across the country according to a standardized protocol.[18] Briefly, data used in this study were collected from patients' charts by trained research assistants at affiliated sites according to standardized definitions and entered electronically into a data-entry program with built-in error checking. Data were collected until death or discharge from a level III NICU. Data collection at each site was approved by either the local research ethics boards or quality and data oversight committees.

To identify NICUs for inclusion in the study, CNN site investigators from all participating level III NICUs were invited to complete a brief online questionnaire regarding their local resuscitation practices and the date when they switched from starting resuscitation with 100% oxygen to using either 21% oxygen (room air) or an intermediate concentration. The questionnaire also requested details of other significant practice changes during the study period at each participating center. The answers to the questionnaires were used to assign infants to the study groups.

We compared outcomes for two groups. In the first group (OX_{100} group), we collected data for 2 years preceding the change in resuscitation policy at each NICU; during this period local resuscitation guidelines recommended using a static concentration of 100% oxygen. We included a 1-year 'washout' period to allow for the institution of practice changes. The washout period occurred at different times among the included sites and the outcomes from these washout periods were not included in the analysis. In the second group ($OX_{titrate}$ group) we collected data for 2 years following the stated change in local practices to starting resuscitation with <100% oxygen followed by titration of the oxygen concentration. In an a priori specified analysis we also compared outcomes between two subgroups of the OXtitrate group, infants who had resuscitation started with 21% oxygen (room air; OX_{21} subgroup) and those who had resuscitation started with a higher oxygen concentration of between 22 and 100% ($OX_{22–100}$ subgroup).

Outcomes

Our primary outcome was a composite outcome of severe neurologic injury or death at discharge from the NICU. Severe neurologic injury was defined as the presence of either grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia as per ultrasound or MRI.[19] Secondary outcomes included retinopathy of prematurity stage 3 or higher (highest stage in either eye) patent ductus arteriosus (PDA) requiring pharmacological and/or surgical ligation, bronchopulmonary dysplasia, necrotizing enterocolitis, and duration of mechanical ventilation.[20–23]

Statistical analyses

Continuous variables and categorical variables were compared between the two groups using Student's *t*-test and Pearson's Chi square test, respectively. Logistic regression models with or without adjustment for covariates were constructed for binary outcomes. Odds ratios and 95% confidence intervals were calculated. A Poisson regression model with and without adjustment for covariates was constructed for the continuous outcome of days on assisted ventilation. All models were adjusted by gestational age, gender, SNAP-II score, mode of delivery and site. The coefficient of maximum likelihood estimates and its 95% Wald confidence interval was calculated. Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

Results

Of the 27 participating CNN centers during the period of interest, 17 centers contributed data: 6 NICUs were not eligible as they continued resuscitation with 100% oxygen and 4 NICUs did not respond to the questionnaire. Data collection for the OX_{100} ($n = 1082$ infants) and $OX_{titrate}$ ($n = 1244$ infants) groups spanned 2004–2007 and 2006–2009, respectively. Details of the eligible infants and study flow are reported in Fig. 1. Of the 17 NICUs included in the study, 12 NICUs switched to initiating resuscitation with room air (OX_{21}) and 5 NICUs switched to initiating resuscitation with an intermediate oxygen concentration ($OX_{22–100}$). One NICU implemented its new resuscitation policy over 2 years and thus had a 2-year washout period for the purposes of this study. The other 16 NICUs introduced their new resuscitation