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ARTICLE

Resuscitation outcomes of infants that do not achieve a 5 min target SpO_2 saturation

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Abstract

Objective To determine differences in the duration and level of resuscitation between infants that achieve a peripheral oxygen saturation (SpO_2) of 80% by 5 min compared with those who remain below 80% saturation.

Study design Infants < 32 weeks GA were analyzed. Pulse rate, SpO_2, airway pressure, and fraction of inspired oxygen were collected during the first 10 min of life.

Results Two hundred and eighty-four infants were analyzed of which 100 had $SpO_2 < 80\%$ at 5 min of life. Composite outcome of death and any IVH was greater in the <80% at 5 min group. These infants had lower heart rates and lower SpO_2 despite increased mean airway pressure and higher FiO_2 ($p < 0.001$).

Conclusion Infants <32 weeks GA that do not achieve a peripheral arterial saturation of 80% by 5 min of life experience more death or severe IVH. This association is amongst the strongest seen of any predictor of morbidity in the delivery room.

Introduction

Oxygen is the most commonly used therapy in very preterm infants. Despite this we know very little about how much oxygen is safe and effective at birth for the extremely low birth weight infant. Too much oxygen during the resuscitation of very preterm newborn infants has in the past been associated with death or organ injury. Excess oxygen may cause cerebral vasoconstriction [1, 2], resulting in decreased cerebral blood flow and brain damage, delay spontaneous breathing, also predisposing to brain damage, and generation of bursts of reactive oxygen species that overwhelm newborn's antioxidant capacity, causing severe oxidative stress and irreversible cellular injury [3, 4]. Likely due to these associations, as well as the increased risks of chronic lung disease, retinopathy, brain, heart, and renal injury, neonatal death and, later on, childhood leukemia found in term infants [5, 6], the vast majority of neonatologists responding to a survey by Oei et al. regarding use of oxygen in the delivery room would initiate oxygen for the preterm infant at or below a fraction of inspired oxygen (FiO_2) of 0.30, and target peripheral oxygen saturation (SpO_2) between the 10th and 50th percentiles of the reference range from Dawson et al. [7, 8].

More recent studies have cast doubt on an association between higher oxygen and these morbidities. The most recent trial (TO_2rpido) was stopped when infants <28 weeks who received room air resuscitation were found to have higher mortality compared with those given 100% oxygen [9]. This was also supported by retrospective data from the Canadian Neonatal Network that found an increase in death or severe neurologic injury (adjusted odds ratio: 1.36 [95% confidence interval (CI): 1.11–1.66]) when infants were resuscitated with <100% oxygen compared with 100% [10]. It is possible that room air or the use of low FiO_2 may result in hypoxia and delayed cellular damage. In animal studies, hypoxia has been associated with apoptosis and other irreversible cellular degeneration [11].

A post hoc exploratory analysis of the TO_2rpido trial found that children with a 5-min oxygen saturation <80% were more likely to die or have neurodevelopmental impairment (OR, 1.85; 95% CI, 1.07–3.2; $P = 0.03$) [12]. A subsequent meta-analysis of eight RCTs demonstrated an increase in short term outcomes including IVH in the same group [13]. This could be due to inadequate oxygen delivery in the first few minutes with lower starting FiO_2

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while providers are waiting for reliable SpO_2 data to appear. Prior studies have demonstrated that the majority of infants do not get a reliable SpO_2 signal until 2 min of life [14]. Subjects who failed to meet 80% threshold were three times as likely to have received a low initial FiO_2 (<0.30). It is unclear from these studies whether there were differences in the duration and degree of resuscitation in infants that achieved an SpO_2 of 80% by 5 min of life. We explored our own center's data in infants <32 weeks enrolled in prospective randomized delivery room trials. The primary hypothesis was that infants that did not achieve an SpO_2 of 80% would have a decreased amount of resuscitation as measured by FiO_2 or mean airway pressure (Paw).

Subjects/methods

This was a retrospective study from four delivery room trials [15–18] with recorded delivery room data (including heart rate, pulse oximeter, mean airway pressure, and FiO_2) included for analysis. The methodology and inclusion/exclusion criteria are published. The Sharp HealthCare Institutional Review Board approved all studies and parental informed consent was obtained on all subjects.

Pulse rate, SpO_2, Paw, and FiO_2 were collected by a data acquisition system (BioPac MP50 and Acqknowledge 4.3.1). Data were obtained once the pulse oximeter was functional (from 2 min of life onward). Time of birth was considered as the time of the complete delivery of the infant. All infants were resuscitated by standard local practice following NRP guidelines, which included a starting peak inspiratory pressure of 20 cm/H_2O and positive end expiratory pressure of 5 cm/H_2O with a T-piece resuscitator. Initial FiO_2 was 30%. Data were collected at 200 Hz for the first 10 min of life. Pulse oximetry and heart rate outcomes were grouped by those that reached an SpO_2 target of 80% and those that did not. Subject clinical outcomes were collected from the medical record.

Available data from four prospective trials were collected as a convenience sample. Statistical analyses were performed using SPSS (v. 18). Data were first verified for accurate data entry, formats, coding, and missing observations. The largest and smallest values for each variable were reviewed for accuracy and plausibility. Each variable was also examined for variability and frequency distribution, skewness, and kurtosis. Data were subsequently evaluated using descriptive, univariate, and adjusted analyses. Multivariable analyses were conducted related to specific study aims. All significance tests were two-sided with a critical alpha level of 0.05. Comparison of demographic and subject characteristics was made using logistic regression, χ^2, or Fisher's Exact testing for dichotomous and categorical variables, Student's *t*-tests for comparison of means at each 1-min interval for continuous variables, and Mann–Whitney Wilcoxon Rank sum test was used as a nonparametric test for ordered categorical variables or for continuous variables failing to meet normal distribution assumptions.

Univariate and adjusted analyses between the dependent variable and each independent variable were carried out to examine the crude associations between variables using χ^2 or Fisher's Exact testing, analysis of variance, Mann–Whitney Wilcoxon Rank Sum test, linear regression, or logistic regression. Repeated measures analyses were carried out using generalized estimation equation modeling.

Table 1 Demographics

	$SpO_2 < 80$ ($n = 100$)	$SpO_2 \geq 80$ ($n = 184$)	*p* value
Gestational age, weeks	27.4 ± 2.6	28.0 ± 2.61	0.04
Birth weight, grams	882 ± 551	902 ± 568.7	0.70
Apgar 1 min, Median [IQR]	5 [3.7]	7 [5.7]	<0.001
Apgar 5 min, Median [IQR]	7 [6.8]	8 [7.8]	<0.001
Apgar 1 min <3	20 (20%)	21(11%)	0.049
Prenatal care	98 (98%)	183 (99%)	0.81
Antenatal steroids	98 (98%)	175 (95%)	0.13
Caesarean section	85 (85%)	168 (91%)	0.18
Male	53 (53%)	85 (46%)	0.83
Receipt of $MgSO_4$	90 (90%)	160 (87%)	0.33
Chorioamnionitis	38 (38%)	68 (37%)	0.81
PIH	19 (19%)	55 (30%)	0.05
PROM > 24 h	24 (24%)	35 (19%)	0.30

All data presented as means ± SD or even rates (%) unless otherwise noted

$MgSO_4$ receipt of antenatal magnesium sulfate, *PIH* pregnancy induced hypertension, *PROM* premature rupture of membranes, *IQR* interquartile range

Results

Two hundred and eighty-four infants were analyzed of which 100 had $SpO_2 < 80\%$ at 5 min of life. Demographics of the cohort are presented in Table 1. These infants had higher mortality, and/or were more likely to have any IVH than infants who achieved 80% by 5 min (Table 2). Analysis using the general estimating equation over the indicated minutes in the delivery room showed lower heart rates (2–6 min) and lower SpO_2 (3–10 min) despite increased mean airway pressure (4–10 min) and higher FiO_2 (5–10 min, $p < 0.001$, Fig. 1). There were no differences in the time to increase FiO_2 (Fig. 1).

Discussion

In our study, we demonstrated that 35% of preterm infants initially resuscitated with 30% oxygen failed to reach an SpO_2 of 80% at 5 min of age. Low 5 min SpO_2 may also be due to the severity of illness (lower gestational age and 1 min Apgar score) or difficulty during resuscitation (prolonged intubations etc.). It is worrisome that we reproduced the association with a low 5-min SpO_2 reported by Oei et al. and an increase risk in death and severe IVH in these infants [13]. These similarities included the prolonged hypoxia and bradycardia noted in the first 10 min. However the FiO_2 separation does not occurred until 3 min of life between those who did and did not reach a saturation of 80% within 5 min. While there was no difference in the time to increase FiO_2, infants with an $SpO_2 > 80\%$ were at a lower FiO_2 at 5 min than those infants that had a $SpO_2 < 80\%$. It is unclear whether this difference was due to insufficient oxygen in the first 5 min or their severity of illness.

Table 2 Neonatal outcomes

	$SpO_2 < 80$ ($n = 100$)	$SpO_2 \geq 80$ ($n = 184$)	p value
Started on CPAP	63 (63%)	147 (80%)	<0.001
Received PPV	75 (75%)	112 (61%)	<0.001
Intubated	61 (61%)	67 (36%)	<0.001
CPR	2 (2%)	1 (<1%)	0.280
Mean time to FiO_2 change (seconds)	187 ± 96	175 ± 87	0.64
ROP	21 (21%)	11 (6%)	0.12
PDA	26 (26%)	37 (20%)	0.23
Any Grade IVH	24 (24%)	19 (10%)	<0.001
Severe Grade IVH	9 (9%)	6 (3%)	0.039
Death	16 (16%)	8 (4%)	<0.001
Severe IVH and/or death	21 (21%)	12 (7%)	<0.001

All data presented as means ± SD or even rates (%) unless otherwise noted

CPAP continuous positive airway pressure, *CPR* chest compressions in delivery room, *ROP* retinopathy of prematurity, *PDA* patent ductus arteriosus, *IVH* intraventricular hemorrhage

These results are surprising, as the clinical team had this saturation data available from 2 min of age and attempted to increase ventilation and FiO_2 but were still unsuccessful in achieving the target saturations.

In order to achieve target oxygen saturations, current guidelines recommend starting with a FiO_2 of 0.21–0.30 [19]. In order to increase oxygen concentration, oxygen, and air must be mixed using an oxygen blender, which is then sent to the newborn via the T-piece. Both bench and clinical studies have shown a clear delay when oxygen is manually increased on the blender and administration of the desired FiO_2 at the distal end. A recent study, by Dekker et al., demonstrated delays to reach the desired FiO_2 of 34 and 19 s in bench and real resuscitations of preterm infants, respectively [20]. Our FiO_2 data are collected from an

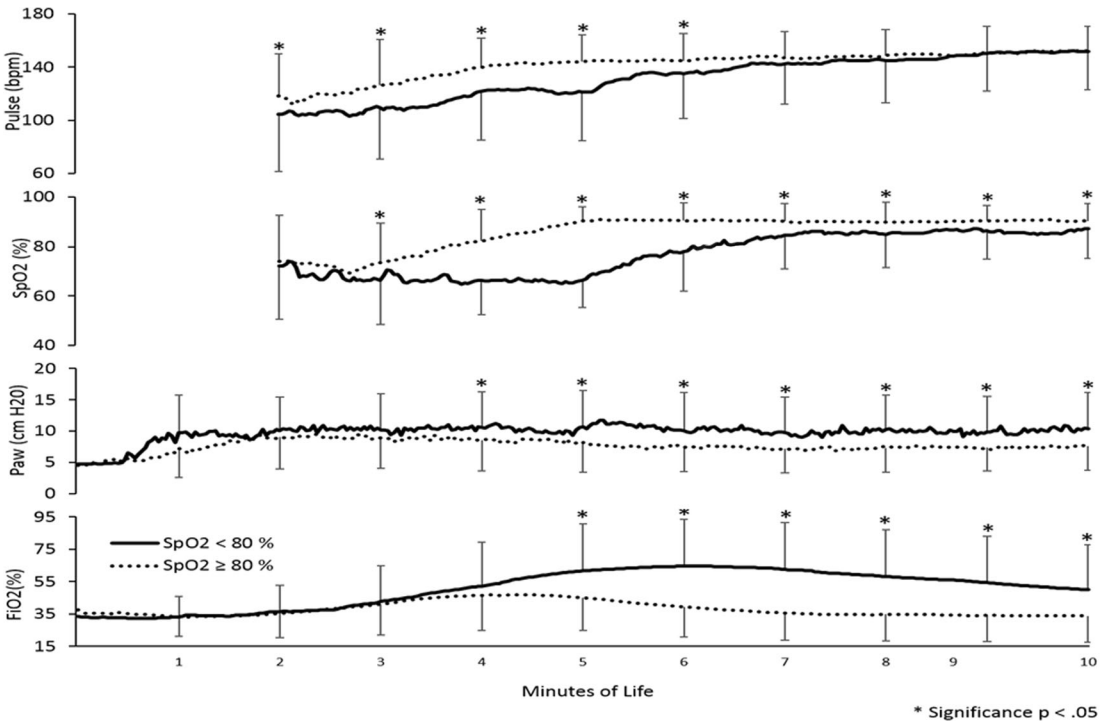

Fig. 1 Vital signs and respiratory support in the delivery room (up to 10 min of life). Solid line denotes SpO_2 of 80%

analyzer the output of which reflects the delay from the time of increasing the FiO_2. While starting on lower FiO_2 or air and titrating up may seem logical, when one accounts for delayed cord clamping, time to place the oximeter, titrating the FiO_2, and then the time it takes to reach the infant, it may be that current practice provides too little oxygen to hypoxic infants to improve their SpO_2 by 5 min. It may be logical to start with significantly higher FiO_2 and titrate lower. The TO_2rpido trial compared the initial use of 100% with room air and their results may reflect the potential benefit of this practice.

There are now meta-analyses for the preterm infant comparing the use of lower versus higher initial FiO_2 in the delivery room [5, 21]. The most recent meta-analysis for preterm infants <28 weeks GA, by Lui et al., shows no difference in mortality to discharge between lower ($FiO_2 < 0.4$) and higher ($FiO_2 \geq 0.4$) initial FiO_2 targeted to oxygen saturation (risk ratio 1.05, 95% CI 0.68–1.63). In an post hoc analysis of survival in infants <28 weeks, the TO_2rpido trial demonstrated a difference in survival of 22% versus 6% for room air and 100%, respectively. Long-term outcome for the survivors in this trial showed no difference in the primary outcome of death or NDI in infants <32 weeks resuscitated in 100% compared with those in room air. A post hoc analysis of subjects reaching 80% at 5 min showed that infants who did not reach the target were more likely to die or have neurodevelopmental impairment [12].

The major limitations of our study were its observational nature and 5-min peripheral oxygenation targets were not a prespecified outcome in the trials that included these infants. Strengths of this study include an expanded variable dataset including mean airway pressure and inspired oxygen allowing a better capture of the extent of resuscitation provided.

The use of higher concentrations of oxygen for the initial resuscitation of the ELBW infants may lead to decreased death and severe IVH as well as other morbidities. A number of approaches should be tested, such as the use of higher initial FiO_2, including 100% oxygen, the brief use of 100% oxygen—i.e., for 1 min after birth, and better targeting as soon as the oximeter is functional, and if below expectation, more aggressive increase in FiO_2 may be warranted. We speculate that with the use of delayed cord clamping, there will be further delays in measuring the SpO_2 and increased difficulties in delivering higher FiO_2 in the short interval between oximetry function and 5 min of postnatal life.

Despite increasing FiO_2 and ventilation, 35% of infants in this cohort were unable to achieve a saturation of 80% at 5 min of life. This same group also had increased risk for mortality and intraventricular hemorrhage. There is an urgent need for the evaluation of the 5 min SpO_2 as a prognostic indicator for the ELBW infant and for randomized trials to compare the use of higher initial FiO_2 with current practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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