Increased Inspired Oxygen in the First Hours of Life is Associated with Adverse Outcome in Newborns Treated for Perinatal Asphyxia with Therapeutic Hypothermia

Hemmen Sabir, MD[1,4], Sally Jary, MSc[1,2], James Tooley, MRCPCH[2], Xun Liu, PhD[1], and Marianne Thoresen, MD, PhD[1,3]

Objective To assess whether increased inspired oxygen and/or hypocarbia during the first 6 hours of life are associated with adverse outcome at 18 months in term neonates treated with therapeutic hypothermia.

Study design Blood gas values and ventilatory settings were monitored hourly in 61 newborns for 6 hours after birth. We investigated if there was an association between increased inspired oxygen and/or hypocarbia and adverse outcome (death or disability by Bayley Scales of Newborn Development II examination at 18-20 months).

Results Hypothermia was started from 3 hours 45 minutes (10 minutes-10 hours) and median lowest P_{CO_2} level within the first 6 hours of life was 30 mm Hg (16.5-96 mm Hg). The median highest fraction of inspiratory oxygen within the first hour of life was 0.43 (0.21-1.00). The area under the curve fraction of inspiratory oxygen and Pa_{O_2} for hours 1-6 of life was 0.23 (0.21-1.0) and 86 mm Hg (22-197 mm Hg), respectively. We did not find any association between any measures of hypocapnia and adverse outcome ($P > .05$), but increased inspired oxygen correlated with adverse outcome, even when excluding newborns with initial oxygenation failure ($P < .05$).

Conclusion Increased fraction of inspired oxygen within the first 6 hours of life was significantly associated with adverse outcome in newborns treated with therapeutic hypothermia following hypoxic ischemic encephalopathy. *(J Pediatr 2012;161:409-16)*.

The new International Consensus on Cardiopulmonary Resuscitation guidelines for resuscitation of term newborns, published in 2010, recommend that resuscitation be initiated in air, rather than 100% oxygen.[1] Most newborns affected by perinatal asphyxia are born in poor condition, needing resuscitation and ventilatory support during their early minutes of life. These circumstances carry the risk of increased oxygen delivery during resuscitation and increased ventilation rates leading to hyperoxia and hypocarbia. Newborn cerebral blood flow (CBF) or relative changes in CBF velocities are very sensitive to rapid changes in P_{CO_2} levels, with a 25%-30% reduction in CBF or CBF velocity per kPa reduction in P_{CO_2}.[2,3] The low P_{CO_2} initiates cerebral vasoconstriction.[4] Reduced CBF means reduced oxygen delivery that may lead to cell death.[5] In noncooled term newborns, with hypoxic ischemic encephalopathy, hypocarbia was associated with adverse neurodevelopmental outcome.[6,7] In term newborns undergoing extracorporeal membrane oxygenation treatment, low P_{CO_2} also was associated with worse outcome.[8] In preterm neonates, hypocarbia induces white matter injury leading to long-term neurodevelopmental deficits including cerebral palsy.[9,10]

In addition, hyperoxia is associated with adverse outcome in the preterm and term newborns.[11-13] Hyperoxia causes oxidative stress,[14,15] inflammation,[16] and cerebral injury[14,17] and is directly associated with neonatal mortality.[11]

The aim of the current study was to examine the association of increased inspired oxygen and hypocarbia during the first 6 hours of life with neurodevelopmental outcome at 18 months in term newborns with neonatal encephalopathy treated with whole body hypothermia in a cooling center.

Methods

Anonymized retrospective data were analyzed with ethical permission (CH/2009/3091). Sixty-one term newborns (gestational age ≥36 weeks) who were born at (n = 37) or transferred to (n = 24) St Michael's Hospital, Bristol, United Kingdom within 6 hours of life between December 2006 and February 2010 were assigned for whole body hypothermia due to moderate

AUC	Area under the curve
Bayley II	Bayley Scales of Newborn Development II
CBF	Cerebral blood flow
F_{IO_2}	Fraction of inspiratory oxygen
MDI	Mental Development Index
PDI	Psychomotor Development Index
Tcs_{O_2}	Transcutaneous peripheral saturation

From the [1]School of Clinical Sciences, University of Bristol, and [2]University Hospitals Bristol, Neonatal Unit, St Michael's Hospital, Bristol, United Kingdom; [3]Department of Physiology, University of Oslo, Institute of Basic Medical Sciences, Oslo, Norway; and [4]Department of General Pediatrics and Neonatology, University Children's Hospital, Duesseldorf, Germany

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or severe neonatal encephalopathy. Newborns fulfilled the entry criteria for hypothermia therapy as used in the CoolCap trial[18] (Apgar score ≤5 and/or ongoing resuscitation at 10 minutes, abnormal blood gases with a pH <7.0 or base deficit ≥16 mmol/L as the immediate criteria for perinatal asphyxia, abnormal neurologic examination as the second criterion, and moderate or severe abnormalities on amplitude-integrated encephalography[19] or seizures as the third). Seizures were defined clinically or with amplitude-integrated encephalography (Cerebral Function Monitoring; Olympic Medical, Seattle, Washington).

The median time between birth and start of hypothermia treatment was 3 hours 45 minutes using whole body cooling with a manually regulated cooling mattress (Tecotherm, TS Med 200M; Inspiration Healthcare, Leicester, United Kingdom; n = 13) or a servo controlled cooling jacket (CritiCool; MTRE, Yavne, Israel; n = 48) to a rectal temperature of 33°-34°C.

Seventy-one percent of newborns had umbilical cord gases recorded at birth followed by hourly blood gases. In 29% the first gas was capillary. These results and accompanying ventilation variables were collected from the intensive care sheets and original data output for the first 6 hours of life.

A total of 408 blood gas measurements were evaluated from birth to 6 hours of life and were analyzed at 37°C (Siemens, Rapidlab 1265; Siemens Healthcare Diagnostics, Erlangen, Germany), which is routine for clinical use. In this retrospective analysis, the blood gas results that were assessed during hypothermia were temperature corrected to 33.5°C using the formula as described by Austin et al.[20] A P_{CO_2} value of 36 mm Hg at 37°C would equate to 30 mm Hg at 33.5°C, and a Pa_{O_2} value of 120 mm Hg at 37°C would equate to 100 mm Hg at 33.5°C, respectively. Saturation of oxygen and pH were not temperature corrected as the temperature dependencies are negligible. The source of each blood sample was capillary (15%), venous (18%, including cord), or arterial (67%). In sicker newborns, more than one blood sample was available per hour. In these cases, the mean was calculated for the corresponding hour.

Hypocarbia was defined as P_{CO_2} <30 mm Hg for temperature-corrected values. In addition, the highest fraction of inspiratory oxygen (F_{IO_2}) was recorded in the first 6 hours of life from the intensive care sheets. An increased fraction of inspired oxygen was defined as F_{IO_2} >0.40. Transcutaneous peripheral saturation (Tcs_{O_2}) was available hourly for all patients. Data for F_{IO_2} and Tcs_{O_2} were available retrospectively within the first minutes of life and during transport. Whenever arterial blood samples were available (56 newborns), we analyzed the Pa_{O_2}. An abnormal high oxygen tension in the blood was defined as Pa_{O_2} >100 mm Hg.

Apgar scores at 10 minutes, sex, birth weight, need of resuscitation at birth, and mode of ventilation were recorded.

Poor outcomes were defined as death or severe neurodevelopmental disability in survivors. Surviving newborns (n = 50) were examined using the Bayley Scales of Newborn Development II (Bayley II)[21] at 18-22 months. We chose Bayley II at 18 months because all large cooling trials have examined the children at this time point.[22] Severe disability was defined as any of the following: a Mental Development Index (MDI) <70 and/or a Psychomotor Development Index (PDI) <70 on the Bayley II Scales (≥2 SDs below the mean) and/or bilateral cortical visual impairment with no useful vision and/or total deafness. Death was given a numeric value of 45 for display in the figures. For some subgroup analyses, we excluded newborns with persistent pulmonary hypertension, meconium aspiration, and congenital heart disease as they had abnormal oxygen requirement and could therefore lead to misinterpretation of the data. In total, this was relevant for 10 newborns, of whom 9 died.

Data Analysis

Data for P_{CO_2} at birth (umbilical cord vein [71%], capillary [29%]), P_{CO_2} after the first hour of life (arterial [41%], capillary [30%], and venous [29%]), and lowest P_{CO_2} within 1-6 hours of life were analyzed. For oxygen, F_{IO_2} within the first hour of life, Tcs_{O_2}, and Pa_{O_2} were analyzed. We recorded the P_{CO_2}, F_{IO_2}, Tcs_{O_2}, and Pa_{O_2} for the first hour separately. To avoid including the high P_{CO_2} value in the cord gas and immediate capillary gases, as well as the high oxygen levels during resuscitation, we calculated area under the curve (AUC) for P_{CO_2}, F_{IO_2}, Tcs_{O_2}, and Pa_{O_2} for hours 1-6 of life using the trapezium rule.[23] The results are presented as average unit per hour.

Linear regression analysis was performed on all 61 newborns with MDI and PDI as the dependent variables. Independent variables were P_{CO_2} within the first hour of life (including cord gases), lowest P_{CO_2}, AUC for P_{CO_2}, highest F_{IO_2}, AUC for F_{IO_2}, and AUC for Pa_{O_2}—all analyzed within the first 6 hours of life. Additionally, sex, Apgar at 10 minutes, source of blood gas, and birth weight were included as independent variables. A significance value of $P \leq .05$ was used when allowing independent factors to enter the regression to find potential relationships between the Bayley II results and the independent variables. SPSS 16 (SPSS Inc, Chicago, Illinois) was used. The "N − 1" χ^2 test[24] was used to compare values of F_{IO_2} and Pa_{O_2} with poor or good outcomes. All the data were normally distributed including the residuals.

Results

There were 35 boys and 26 girls. The mean ± SD gestational age and birth weight were $39^{+4} \pm 1^{+4}$ weeks and 3345 ± 615 g, respectively. The median (IQR) 10-minute Apgar score was 6 (0-10). Median age (IQR) of start cooling was 3 hours 45 minutes (10 minutes-10 hours). Fifty-five newborns needed resuscitation at birth and were mechanically ventilated while the blood gas measurements were taken. A total of 408 samples were examined, varying from 4 to 7 samples per individual. The sample sources where randomly distributed and we did not find a correlation between sample source, blood gas values, and outcome in individual newborns in the regression analysis ($P > .05$).

The median P_{CO_2} within the first hour of life was 39.7 mm Hg, the median lowest P_{CO_2} level within the first hour of life was 30.0 mm Hg, and the median AUC-P_{CO_2} for hours 1-6 of