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Research Article

Regional Cerebral Oxygenation Variability Before, During and After Routine Clinical Practices in Preterm Newborns in Intensive Care

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Abstract

Introduction: Preterm newborns receive a large number of interventions during NICU stay; some are potentially damaging to the developing brain. Their possible deleterious effects on regional cerebral oxygen saturation ($rScO_2$) have not been well-defined.

Objective: To describe feasibility of routine noninvasive $rScO_2$ monitorization in NICU and assess effects of different NICU practices on $rScO_2$ in preterm infants.

Method: Proof of concept, descriptive study on 25-36 weeks' gestation infants in NICU. During the first 5 days, we assessed $rSCO_2$ for 5 minutes before a clinically necessary intervention (PRE), during (INTRA), and 5 minutes after (POST), without modifications of care protocols. Monitor used was O3® Regional oximetry (Masimo Corp, Irvine, Ca). Statistics: ANOVA for repeated $rSCO_2$ measures; post-hoc analyses using paired t tests with Bonferroni adjustment. Significance was set at < 0.05.

Results: There were 384 interventions analyzed in 37 preterm newborns with gestational age 31 ± 3.3 weeks and birth weight 1450 ± 667 grams. Seventy percent (269) of the $rSCO_2$ measurements were in infants receiving oxygen therapy. During the procedure INTRA $rSCO_2$ decreased by 2.21%, 95% CI of -1.67 to - 2.75 ($p < 0,001$). $rSCO_2$ changes were widely variable (extreme values between - 22% to + 14%). The worst $rSCO_2$ decreases occurred in the more immature infants with lower birth weight ($p < 0,001$). POST $rSCO_2$ values were statistically not different to PRE $rSCO_2$ but 46% did not show full recovery of their $rSCO_2$.

Conclusion: Most of the interventions in ill preterm infants induced $rSCO_2$ changes, with wide variability. Therefore, continuous $rSCO_2$ monitoring could be valuable to avoid regional cerebral hypoxia or hyperoxia in an individualized manner in order to improve patient safety.

Keywords: *Neonate; Interventions; Clinical Care; Regional Cerebral Oxygen Saturation*

Abbreviations

rScO2: Regional Cerebral Oxygen Saturation NIRS Near Infrared Spectroscopy; O2Hb: Oxygenated Hemoglobin; HHb: Reduced (Deoxygenated) Hemoglobin Spo2 Oxygen Saturation; NICU: Neonatal Intensive Care Unit NEC Necrotizing Enterocolitis PDA Patent Ductus Arteriosus

Introduction

Advances in prenatal and neonatal care have significantly improved neonatal survival, especially in infants born at < 32 weeks' gestation, but also in newborns with more gestational age who are severely ill. These improvements are due, at least in part, to a better understanding of neonatal diseases and physiology and to improvements of care for newborns. However, the incidence of morbidity and long-term neurodevelopmental disorders has not decreased [1-5]**.** Thus, brain injury is still relatively common in preterm infants and it is associated with a wide range of complications later in life, such as behavior, attention, cognitive, sensorimotor, or language disorders and epilepsy [1-4].

The developing brain is exquisitely sensitive to both hypoxemia and hyperoxemia. This has a major impact on increased long-term morbidity, neurodevelopmental abnormalities, and cerebral palsy. About 10% of preterm newborns with very low birth weight born in the USA suffer cerebral palsy later on in life [1] and this prevalence has not decreased despite advances in neonatal care.

Both the increasing number of preterm infants and the improvements in survival rates contribute to the numbers of affected infants with brain injury [4]. Improving the rates of long-term morbidity and permanent neurological sequelae is an outstanding debt in neonatal care.

Preterm infants as well as severely ill term infants admitted to neonatal intensive care units (NICU) need a vast number of different practices that, although they may be necessary and beneficial, some are known to have a high risk of being harmful to the developing brain [1, 6-21]**.**

There have been several publications regarding near-infrared spectroscopy (NIRS) during the neonatal period [22-38, 40-50]. NIRS brain oximetry provides continuous, non-invasive assessment of changes over time of hemoglobin (Hb) in brain tissue by determining the concentration of oxygenated Hb (O_2Hb) and deoxygenated or reduced Hb (HHb). It records the mixed-venous regional cerebral saturation ($rScO_2$), which represents the balance between tissue oxygen (O_2) input and demands. A good correlation between $rScO_2$, mixed venous saturation and cerebral blood volume has been demonstrated [13-14].

NIRS is based on the relative transparency of biological tissue to light. Neonatal brain tissue can be easily penetrated by light with wave length of 700-1,000 nm due to the thin overlapping layers of skin and skull. One of the two optodes sends light in the near infrared spectrum through brain tissue in a semi-curved form to a detector or receiver optode [13, 14]. O_2Hb and HHb absorb near infrared light at different wave lengths and this is used to calculate O_2Hb and HHb tissue concentrations according to the modified Beer- Lambert law [39]. The relationship between brain O_2Hb and HHb is expressed as $rScO_2$ and the addition of O_2Hb + HHb represents total Hb (THb), associated with cerebral blood volume. NIRS does not measure cerebral blood flow [40].

Reference $rScO_2$ values with SaO_2 values > 85% have been reported in several of the studies, with mean values between 61% and 75% (± 7 to ± 12%), but there exists wide variability in different publications. Additionally, it has been reported that respiratory assistance can affect cerebral hemodynamics, oxygenation [5,6] and cerebral circulation [7] and that the loss of variability in rScO2 can be a sign that identifies infants with severe cerebral impact after perinatal asphyxia [35]. However, the reproducibility of NIRS results has not been good [41].

The inconsistency within and, particularly, between patients and the limits of agreement have been found to be large. Hence, there is still a need for further validation and improved precision and there are dissimilarities in technical aspects among different devices(42-43), such as different algorithms, the source of emission of near infrared light, the number of wavelengths and/or the lower dispersion that can be among the causes of values that differ between different monitors and in different age ranges.

Due to the evolving use of NIRS-monitored $rScO_2$ in sick neonates, most companies making NIRS devices more recently developed pediatric and neonatal sensors. Lately, neonatal sensors were developed to be used in the first combined device (ROOT O_3 ® regional oximetry, Masimo, USA), for continuous non-invasive brain oxygenation monitoring with four wavelengths and special indices of variations of O_2Hb and HHb over time. These are the delta indices for total cerebral Hb (ΔcHbi), and for the two Hb components of $rScO_2$, ΔcHHbi and ΔcO_2Hbi. This device also allows users to simultaneously measure SpO_2, perfusion index and heart rate. The aforementioned and other differences between this and all other NIRS monitors in the market could be useful to provide important clinical information for the care of ill newborns in the NICU in real time (37, 44, 45).

Monitoring rScO2 may be able to identify early those NBs with alterations in regional cerebral oxygenation and detect potential changes that would occur in cerebral hemodynamics during and/or after a common clinical event, treatment or procedure. There are reports of alterations in cerebral oxygen metabolism during intubation, variations in CO2 [8-12], hypoxemia and hyperoxemia [36], nasogastric tube feeding [33]. Also, rScO2 has been used in delivery room resuscitation [46,47] and alterations in regional oxygenation have been reported in the presence of pathologies such as necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) [22-24,48,49]. However, the magnitude and/or variations in cerebral oxygenation during or after the implementation of frequent and routine clinical practices, interventions and procedures has not been well described in preterm infants in the NICU.

The objective of this proof-of-concept study is to explore the feasibility of rScO2 monitoring in two neonatal intensive care units and identify if different general practices or procedures performed during routine clinical care induce any changes in regional cerebral oximetry in preterm infants in NICU before 5 days of age. We seek to characterize rScO2 values and their variability in order to be able to perform a precise estimate of a sample size for a future multicenter study in which the aim will be to determine the impact of individual neonatal practices on neonatal cerebral oxygenation.

Methods

Descriptive and observational proof of concept study carried out in two NICU's in San Luis, Argentina between January and August of 2021.

We planned to study preterm infants 25 to 36 weeks' gestation who were relatively stable before 5 days of postnatal life in NICU. Infants with hemodynamic instability (i.e.: inotropic infusions, PDA, sepsis, severe anemia and other), an unstable rScO2 reading or a wide variability > 2%, congenital anomalies, identifiable etiologies of neurological dysfunction, like hypoxic ischemic encephalopathy (HIE), suspected genetic or metabolic disease and those who required resuscitation in the delivery room, were excluded. The inclusion of eligible subjects was related to the availability of the monitoring equipment in each unit and parental informed consent.

Cerebral oximetry was monitored using the O3® Regional oximetry device (Masimo Corp, Irvine, Ca) with ROOT using only neonatal sensors [Infant and Neonatal Adhesive Sensor < 10 kg].

The sensor was placed on the infant's skull following the manufacturer's guidelines. In all cases, the sensor was placed on the left side of the forehead and then it was connected to the monitor.

The following procedures performed in NICU were considered for inclusion. Interventions performed in the delivery room were not included in this study.

- Major interventions
  - Endotracheal intubation
  - Umbilical vein canalization
  - Peripheral insertion of a central venous catheter (PICC)
  - Exogenous surfactant
  - Endotracheal suctioning
  - Other invasive and painful procedures: lumbar puncture, venous, arterial or heel punctures, other.

- Minor interventions
  - Changes of infant's position from supine to prone and vice versa
  - Diaper changes
  - Diagnostic studies: x-rays, head ultrasound, echocardiography
  - Transfusion of blood products
  - Orogastric tube feedings
  - Intravenous administration of different drugs.

All nurses were previously trained in the use of the ROOT monitor. Additionally, care practices or procedures were uniformly standardized and there were no modifications or interference with routine NICU care for participating infants.

rScO2 was continuously measured. Recordings for this study were always started after a period of at least 60-90 seconds of stable displayed value and waves. We analyzed three different periods, as shown in figure 1: a) 5 minutes before the start of each intervention (PRE measurement), b) during the intervention (INTRA measurement) and c) 5 minutes after the end of the intervention (POST measurement). For INTRA measurements, we analyzed the lowest value detected during the intervention.

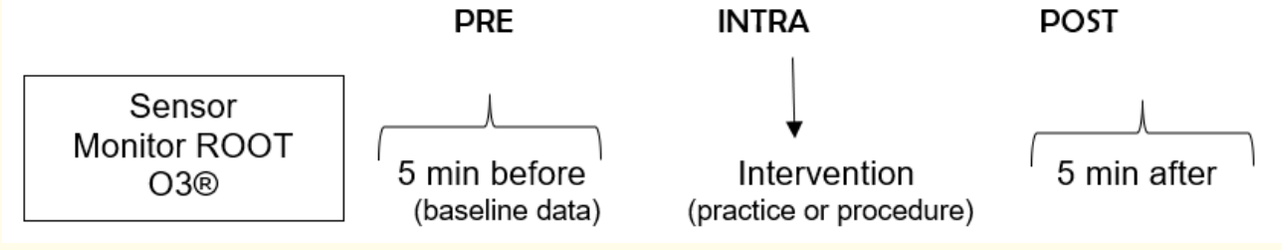

Figure 1: *Schematic representation of rScO2 recordings in NICU. PRE (before the intervention), INTRA (during) and POST (after).*

For the purposes of the analysis, we consider each intervention as the unit of study. More than one intervention and $rScO_2$ measurements in the same newborn could be included during the 5 days of the study**.** In order to avoid a possible residual effect from the previous intervention, the data was recorded and analyzed only if it was separated by more than 60 minutes from the preceding procedure. Thus, none of the data collected corresponded to consecutive interventions. The number of newborns enrolled and their demographic characteristics, including birth weight, gestational age, gender, mode of delivery, whether or not they receive oxygen therapy and type of respiratory support, such as cannula, CPAP or respirator, are described in results. The total number of interventions and the number evaluated in each individual newborn is also described.

Ethical considerations

The research was carried out in accordance with the principles of the Declaration of Helsinki and with the approval of the Clinical Research Ethics Committee of each center. Informed consent of the parents or guardians was obtained prior to inclusion in the study. Data obtained from the study was handled with absolute confidentiality and without patient identifiers.

Statistical analysis

The information of each NB and the measurements were recorded in an ad hoc database. The characteristics of the population are presented using descriptive summary statistics and frequencies. The measurements at each stage (PRE, INTRA, and POST) are described as means and standard deviation, medians, and ranges for the different time points. We separated the interventions in the two groups previously described (major and minor) and compared them using t test for independent samples.

ANOVA test for repeated measurements was used to compare $rScO_2$ mean values in the three periods (PRE, INTRA and POST). Each subject was his or her own control. Prior to the comparisons, we confirmed a normal distribution and low frequency of possible outliers. The observed differences were evaluated by post-hoc analysis by performing paired t-tests and adjusting the p value by the Bonferroni method. The mean differences and their respective 95% CI were compared between the periods. A p value less than 0.05 was considered significant. R and STATA 12.0 software was used for statistical processing.

Results

There were 37 candidates eligible for this study and all were included. No infant had to be excluded due to unstable $rScO_2$ readings or technical issues of the sensor or monitor device. There were 384 interventions evaluated for changes in $rScO_2$ in the 37 preterm newborns admitted in NICU during the first 5 days of life. Their gestational age was 31 ± 3.3 weeks with birthweight of 1450 ± 667 grams; 62% were male infants and 97% were born by cesarean section. The number of evaluations of $rScO_2$ varied between two to eighteen in each of the preterm infants.

Table 1 describes the various interventions that were performed during the $rScO_2$ measurements; 78% corresponded to minor procedures or care practices and 22% were major interventions. In all cases, the 3 measurements (PRE, INTRA, and POST) could be recorded, suggesting that there were no difficulties in implementing $rScO_2$ continuous monitoring.

TYPE OF PROCEDURE OR INTERVENTION	N (% of total)
1. MINOR	298 (78)
Feeding	81 (21)
Diaper change	80 (21)
Change of position	86 (22)
Placement of OGT	11 (3)

Assessment of vital signs	7 (2)
X-Rays	5 (1)
Administration of IV medication	28 (7)
2. MAJOR	86 (22)
Umbilical catheter placement	8 (2)
PICC placement	6 (2)
ETT Suction	27 (7)
Intubation	6 (2)
Surfactant	5 (1)
Other painful procedure	34 (9)
TOTAL	384 (100)

Table 1: *Clinical interventions in which $rScO_2$ changes were evaluated.*

OGT: orogastric tube; PICC: percutaneous insertion of central catheter; ETT: endotracheal tube.

The infants were receiving oxygen therapy in 70% (n 269) of the $rScO_2$ measurements, 158 were on mechanical ventilation (41%), 28 on CPAP (7%) and 83 with nasal cannula (22%).

Table 2 and Figure 2 describe the $rScO_2$ values recorded in each of the measurement periods, globally for all the 384 procedures. ANOVA test for repeated measurements showed statistically significant differences (p = 0.017) between the $rScO_2$ PRE, INTRA and POST interventions (Table 2 and Figure 2). In the post-hoc analysis, performing paired t-tests and adjusting the p value by the Bonferroni method, we observed that the PRE and POST rScO2 values were not significantly different but there were differences between the PRE and INTRA $rScO_2$. When performing the interventions, the INTRA $rScO_2$ decreased on average by - 2.21% (± 5.39%) with 95% CI -1.67 to - 2.75, (p <0.001) as compared to PRE $rScO_2$. (Table 2 and Figure 2). The changes in $rScO_2$ when performing the procedure (INTRA rScO2) were highly variable in the whole group, with extreme values of change that ranged from -22% to + 14%. However, in 252 (65%) interventions, $rScO_2$ decreased (-1% to -22%). The preterm newborns in whom $rScO_2$ decreased had significantly lower gestational age and birth weight (30.5 ± 3.2 vs 32.1 ± 3.4 weeks and 1,371 ± 612 vs 1,698 ± 739 grams) (p <0.001). In 19 (6%) of the interventions there was no change in $rScO_2$ and in 113 (29%) $rScO_2$ increased (1% to 14%).

$rScO_2$ (%)	Mean (SD)	Median (extreme values)	p value (ANOVA)
PRE *	72.08 (7.53)	72 (48-94)	0.017
INTRA*	69.78 (8.18)	70 (39-89)	
POST	71.75 (7.35)	72 (47-91)	

Table 2: *Comparison of PRE, INTRA and POST rScO2 for the 384 interventions evaluated*

** INTRA vs PRE: 95% CI -1.67 to - 2.75, (p <0.001).*

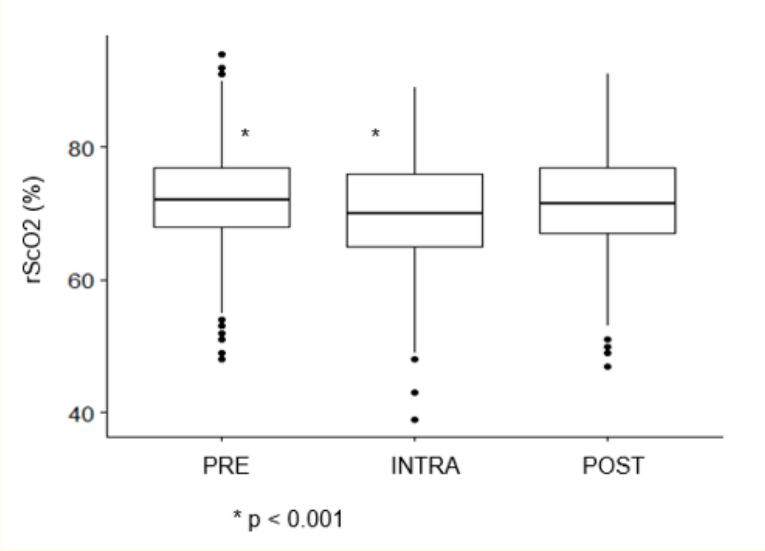

Figure 2: *Box plot: Distribution of rScO2 values before (PRE) during (INTRA) and after (POST) 384 interventions.*

Even though there was no statistical difference between POST and PRE $rScO_2$, in 177 (46%) interventions $rScO_2$ decreased -1% to -23% and there was no full return to PRE values in the 5 minutes analyzed post intervention.

We then analyzed separately the 298 minor interventions and compared them to the 86 major ones. There were no differences in rScO2 PRE, INTRA and POST intervention between the two groups as shown in Table 3. In both minor and major interventions, there were also statistically significant differences ($p<0.05$) between PRE and INTRA $rScO_2$ (Table 3).

rScO2 (%)	MINOR INTERVENTIONS (n 298)	MAJOR INTERVENTIONS (n 86)	p
PRE * **Mean (SD)** **Median (Range)**	71,85 (6,92) 72 (51-89)	72,90 (9,36) 73 (48-94)	NS
INTRA * **Mean (SD) Median (Range)**	69,76 (7,72) 70 (48 -87)	69,85 (9,67) 69 (39-89)	NS
POST **Mean (SD) Median (Range))**	71,47 (7,14) 72 (47 -88)	72,75 (8,01) 71 (55-91)	NS

Table 3: *No differences in $rScO_2$ between minor and major interventions (n 384).*

NS *not significant.*

** INTRA vs PRE: p <0.05.*

Discussion

In this prospective proof of concept two center study, the results show that it is feasible and simple to continuously measure rScO2 non-invasively with neonatal sensors in preterm newborns admitted to NICU utilizing a standardized procedure and recording in a prospective manner. The data could easily be incorporated into nursing and electronic medical records and rapidly identify if there are changes in cerebral oxygenation even during simple interventions like changing a diaper.

In 384 rScO2 determinations in relatively stable preterm infants < 5 days of age, mean value for rScO2 was 72%, showing that most had acceptable regional cerebral oxygenation. We found a statistically significant difference between these values and those recorded during the 384 interventions analyzed (INTRA rScO2). The differences between INTRA and PRE occurred both in minor and major interventions and even changing position or diapers caused variations in the rScO2. Lastly, cerebral oxygenation was found to be more labile in infants of lower gestational age and birth weight.

There was wide-ranging variability in the changes that occurred in INTRA rScO2 compared to the PRE rScO2. In one extreme, the intervention decreased the rScO2 by 22% in one infant, and on the other extreme, rScO2 increased by 14% in one infant, but a majority of interventions led to a decrease in rScO2.

Furthermore, even though there was no statistically significant difference between PRE and POST intervention rScO2 values, rScO2 remained below the PRE value for at least 5 minutes in almost half of the interventions in this study.

In order to evaluate the practices described in methods, in this pilot study we chose to exclude infants receiving dopamine and transfusions, and those with HIE and PDA, as it has been shown that all of them can affect rScO2 [19-24,26,28-30,35,38,48-50]. We also chose not to evaluate transfusion of red blood cells changes as it has been described that a low rScO2 could improve with transfusions and as well as cFTOE [25-30,50].

As mentioned, there is evidence that the developing brain is very vulnerable and that many practices can be associated with alterations in its development and maturation [1]. For example, pain and its treatment [31,32], feedings with orogastric tube [33], the use of post natal dexamethasone [15-18] and many others can negatively affect the developing brain by diverse mechanisms which may be of significance long term.

Cerebral hypoxia is not desirable and, similarly, avoiding hyperoxia can positively influence long- term cognitive and motor outcome of extremely premature babies [36,37]. Treatment guided by cerebral NIRS oximetry has the potential to decrease the risk of death or survival with neurologic complications in preterm infants [51-53]. SafeBoosC III trial evaluates the effects of treatment guided by cerebral oxygenation monitoring versus treatment as usual. One of the publications [52] describes the detailed statistical analysis plan for the main publication, with the aim to prevent outcome reporting bias and data-driven analyses. Another recent publication [53] comments on the benefits and harms of clinical care with access to cerebral NIRS monitoring versus clinical care without cerebral NIRS monitoring in children and adults across all clinical settings and that it is difficult for randomised clinical trials to capture a sufficiently large number of events to evaluate the clinical effect of cerebral NIRS monitoring, when focusing on specific clinical settings [53]. When rScO2 drops below a predefined hypoxic threshold an intervention should be considered. The problem, as previously mentioned, this threshold value differs between different brands of instruments. Additionally, as another potential confounder, it has recently been found that keeping the adhesive cover on an INVOS neonatal sensor results in lower measured rScO2 values [54]. At the hypoxic threshold, this is more than 3% (from 60.3% to 63.8%), and therefore, if clinicians keep the cover on the INVOS sensor, they need to be aware of this difference [54].

In summary, this proof-of-concept study is different from previous studies as it compared the impact of 384 interventions on rScO2 values on the same infant, using O3® Regional oximetry device (Masimo Corp, Irvine, Ca) with ROOT using only neonatal sensors. We

found that there is significant variability in cerebral oxygenation in relatively stable preterm infants in NICU secondary to diverse routine clinical practices or interventions performed in the NICU. This supports the need for individualized continuous monitoring of regional cerebral oxygenation in high-risk NICU infants to alert clinicians at the bedside to prevent deleterious episodes of regional hypoxia or hyperoxia of any origin.

The limitations of the study are the small number of babies included and the inability to assess in detail risk factors of vulnerability. The findings, however, provide preliminary information and open an opportunity for larger prospective studies with adequate sample size calculations to assess the negative impact of specific practices on $rScO_2$ and to identify factors that have the greater influence in altering regional cerebral oxygenation. This would be of value in early individual detection and prevention or correction of repeated episodes of cerebral hypoxia and hyperoxia associated with clinical interventions. Modifying individual clinical practices in real time that may seriously affect neonatal cerebral oxygenation will be important to increase patient safety.

Furthermore, this tool could be found valuable to aid in prognosis and long term follow up of morbidities and delayed neurodevelopment. We are now initiating a multicenter multinational study with the aim of increasing the understanding of these issues.

Conflict of Interest

Augusto Sola MD holds a part time position as VP for Medical Affairs at Masimo (Neonatology, Education).

The rest of the authors declare no conflict of interest.

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