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Clinical Usefulness of Regional Tissue Oxygen Saturation Monitoring Using Near-Infrared Spectroscopy in Neonates

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Objective: Recently, near-infrared spectroscopy (NIRS) has been introduced in the neonatal intensive care unit (NICU) to monitor the altered hemodynamic status causing cerebral hypoxemia or affecting mesenteric and/or renal oxygenation. This study aimed to reassess the clinical usefulness of NIRS and the correlation between regional O_2 saturation (rSO_2) and various physiological parameters in neonates.

Methods: Thirty-nine newborns, admitted in NICU from June 2019 to June 2020 and continuously monitored with NIRS (cerebral and renal) during the first 72 hours, were included.

Results: Among 39 newborns with a median gestational age of 33.9 weeks, and a median birth weight of 2,180 g, the median of the cerebral and renal rSO_2 were 84% (30%–95%) and 95% (45%–95%), respectively. Cerebral rSO_2 tended to increase over time since the time of delivery, while renal rSO_2 tended to decline, especially in preterm infants. Average of renal rSO_2 during 72 hours showed a statistically significant difference between term and preterm infants (P<0.05). Cerebral rSO_2 showed significant correlation with hemoglobin (r=0.35, P<0.05) and hematocrit (r=0.37, P<0.05). Renal rSO_2 showed significant correlation with capillary blood gas analysis such as pH (r=0.36, P<0.05), pCO_2 (r=-0.19, P<0.05), pO_2 (r=0.23, P<0.05), base excess (r=0.19, P<0.05), hemoglobin (r=0.33, P<0.05), hematocrit (r=0.32, P<0.05) as well as renal function indicator such as blood urea nitrogen (r=-0.50, P<0.05) and creatinine (r=-0.59, P<0.05).

Conclusion: We re-evaluated the clinical usefulness of NIRS in neonates by identifying trends and correlations of rSO_2 with clinical parameters. It is necessary to confirm its effectiveness through further study.

Key Words: Spectroscopy, Near-Infrared, Oxygen saturation, Newborn

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Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive, continuous, regional tissue oxygen saturation (rSO_2) monitoring technique that reflects the perfusion status and oxygenation status of underlying tissues at the bedside.[1,2] It represents the ratio of local oxygenated hemoglobin to total hemoglobin in the mixed arteries, capillaries, and veins passing under the sensor.[3,4] It can be helpful to detect improper tissue perfusion in advance, before irreversible cell or tissue damage occurs.

The NIRS devices have recently begun to be applied to newborns in the neonatal intensive care unit (NICU) and are being increasingly used.[5] Through several studies, researchers have noted the usefulness of monitoring cerebral or somatic rSO_2 with a significant cor-

relation with various conditions in neonate.[6] They found that rSO_2 was closely related to arterial mean blood pressure (BP), especially.[6] Moreover, in the first 6 hours after birth, cerebral oxygenation in healthy newborns was found to be correlated with routine monitoring parameters such as heart rates and respiratory rates, and oxygen saturation (SpO_2).[7]

NIRS monitoring can be applied for conditions with altered hemodynamic states causing cerebral hypoxemia such as hypoxic ischemic encephalopathy (HIE), congenital heart disease, hypoxic respiratory failure or pre-extracorporeal membrane oxygenation (ECMO), and prematurity with altered cerebral autoregulation.[8] Because of the hemodynamically significant patent ductus arteriosus (PDA), to apply NIRS monitoring for the first week of life should be suggested in the preterm infants under 29 weeks gestational age (GA).[9] Other conditions that are indicated in altered hemodynamics affecting mesenteric or renal oxygenation are shock, renal dysfunction, necrotizing enterocolitis and ECMO.[10] Potential applications of NIRS also include assessment of intraventricular hemorrhage (IVH), intra-operative management, and conditions such as anemia, hypoglycemia, seizures, PDA management, or metabolic disorders.[11,12] However, in Korea, there has been limited experience of applying NIRS to newborns.[10]

Our study aims to evaluate the clinical efficacy of cerebral/renal NIRS in term/preterm neonates through the correlation of oxygenation status measured by NIRS with the values of relevant physiological parameters estimated in blood tests, ultimately indicating the usefulness for NIRS in neonatal monitoring in NICU.

Methods

1. Study population

This was a retrospective study conducted on newborns admitted to the NICU of Gangnam Severance Hospital from June 2019 to June 2020. Thirty-nine neonates with NIRS monitoring within 72 hours after birth were included and patients whom the monitoring were applied after 72 hours were excluded. The study was approved by the Institutional Review Board (IRB) of Yonsei University Gangnam Severance Hospital. Need for written informed consent was waived by the IRB (approval number: 2021-3-128).

2. Estimation of study variables

Monitoring of BP, HR and SpO_2 were started from at birth, and rSO_2 measurements were started within 72 hours of age. For NIRS monitoring, INVOS 5100C Cerebral/Somatic oximeter (Medtronic Minneapolis, MN, USA) was used, and the data was recorded every 5 seconds. NIRS sensors for cerebral rSO_2 monitoring were placed midline on the forehead to monitor the frontal lobe gray matter. Renal NIRS probes were placed on the back, between the costal margin and iliac crest, with the sensor lateral to the spine and reader tip wrapping around the flank.[13] SpO_2 and HR were monitored using a Nellcor pulse oximeter (Covidien, Boulder, CO, USA), with the neonatal sensor placed preductal (right hand). Measurements were recorded every 10 seconds and transferred to a personal computer through an RS-232 serial communication port. Data were collected simultaneously using dedicated software.

In addition, available data regarding the patients' clinical characteristics, capillary blood gas analysis, such as pH, pCO_2, pO_2, base excess, hemoglobin and hematocrit, and serum levels of blood urea nitrogen (BUN) and creatinine results were collected using electronic medical records.

3. Statistical analysis

Results are presented as the median and interquartile range for continuous variables and as percentages for categorical variables. Data were tested for normal distribution. Correlation between rSO_2 and physiological parameters was performed using Spearman's linear correlation analysis. Differences were considered significant at $P<0.05$. Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics of 39 neonates are summarized in Table 1. The median GA and birth weight of the included infants were 33.9 (28.9-38.6) weeks and 2,180 (1,260-3,005) g, respectively. There were 23 preterm infants (59.0%), and 20 infants (51.3%) with intubation in delivery room. These patients were applied

Table 1. Patient demographics (n=39)

Variable	Value
Gestational age (wk)	33.9 (28.9-38.6)
Birth weight (g)	2,180 (1,260-3,005)
Male	26 (66.7)
Cesarean delivery	23 (59.0)
Preterm	27 (69.2)
Apgar score at 1 min	4.5 (4.0-7.5)
Apgar score at 5 min	7.0 (6.3-8.8)
Surfactant	20 (51.3)
Disseminated in coagulopathy	32 (82.1)
C-reactive protein elevation	1 (2.6)
Intubation	20 (51.3)
Using epinephrine at delivery	1 (2.6)
Small for gestational age	3 (7.7)

Values are presented as median (interquartile range) deviation or number (%).

NIRS monitoring, due to the conditions with altered hemodynamic states.

Median cerebral rSO_2 was 84% (30%-95%) and median renal rSO_2 was 95% (45%-95%) during the first 6 hours after birth. On the other hand, median cerebral rSO_2 was 83% (15%-95%) and median renal rSO_2 was 94% (15%-95%) during the first 72 hours after birth.

Fig. 1 represents the tendency of tissue oxygen saturation within 72 hours after birth as a box-plot. The values of cerebral and renal rSO_2 during first 72 hours of life showed difference according to the postnatal age. Cerebral rSO_2 tended to increase over time since the time of delivery, while renal rSO_2 tended to decline, especially in preterm infants. Fig. 2 shows the difference in the tendency of rSO_2 within 72 hours after birth between term and preterm infants. Only mean renal rSO_2

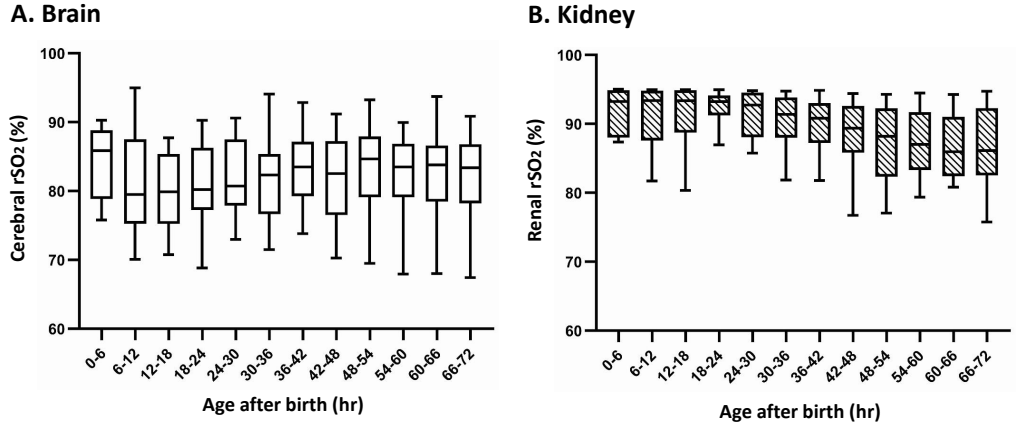

Fig. 1. Boxplots of the (A) cerebral and (B) renal rSO_2 within 72 hours after birth. Cerebral rSO_2 tended to increase over time since the time of delivery, while renal rSO_2 tended to decline.

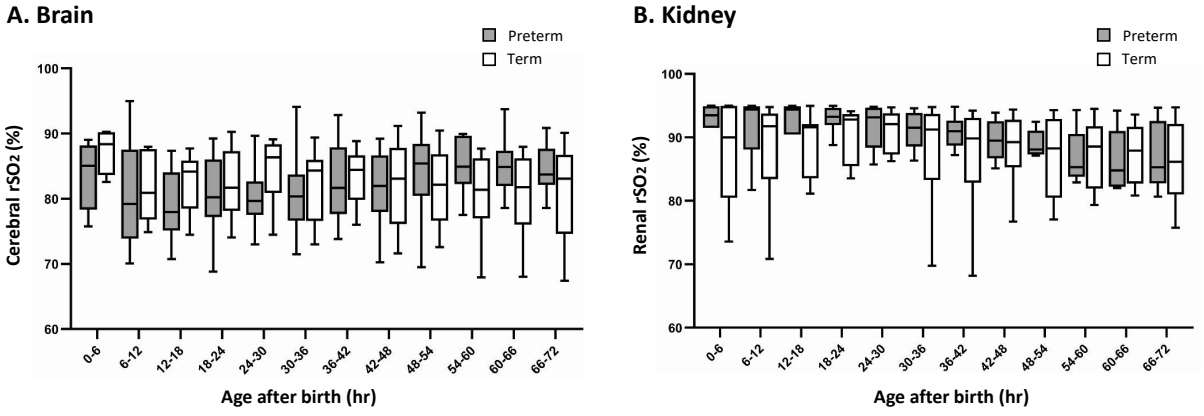

Fig. 2. Trends of (A) cerebral and (B) renal rSO_2 within 72 hours after birth in term and preterm infants. During first 72 hours of life, cerebral rSO_2 tended to increase, while renal rSO_2 tended to decrease in both term and preterm infants. Average renal rSO_2 showed a significant difference between term and preterm ($P<0.05$).

Table 2. Correlation between cerebral/renal rSO_2 and parameters of laboratory test

Regional O_2 saturation	Cerebral rSO_2		Renal rSO_2	
	Coefficient	*P*-value	Coefficient	*P*-value
pH	0.047	0.475	0.355*	<0.001
$PaCO_2$	-0.033	0.617	-0.188*	0.004
PaO_2	0.115	0.079	0.226*	<0.001
Base excess	-0.019	0.778	0.194*	0.003
Hemoglobin	0.352*	0.000	0.329*	<0.001
Hematocrit	0.366*	0.000	0.318*	<0.001
Blood urea nitrogen	-0.126	0.585	-0.503*	0.020
Creatinine	0.165	0.474	-0.591*	0.005

*$P<0.05$.

showed a significant difference between term and preterm ($P<0.05$).

Table 2 shows the results of correlation between tissue oxygenation saturation and parameters of laboratory test. Cerebral rSO_2 showed significant correlation with hemoglobin and hematocrit. Renal rSO_2 showed significant correlation not only with the levels of parameters estimated blood gas analysis, such as pH, pCO_2, pO_2, base excess, hemoglobin and hematocrit, but also with renal function indicators such as BUN and creatinine.

Discussion

This study confirmed that NIRS is clinically useful in monitoring the newborn, since the use of invasive procedures for neonates should be restricted to minimal. Improper tissue perfusion and oxygen delivery can be fatal or induced irreversible tissue damage in neonates. Thus, early detection is necessary. We found that cerebral and renal rSO_2 correlated significantly with the blood gas results and renal function indicators, promising to indicate the accurate oxygenation in the deep tissues.

In 1985, a human cerebral oximetry studies using NIRS was first published.[4] Since 2001, there have been various studies regarding the potential applications of NIRS in the NICU.[14] However, the use of NIRS in NICU in Korea has only recently started, after the coverage by the Korean National Health Insurance since 2018.[15] Thus, there are only few studies for the application of NIRS in neonates in Korea.[10]

There has been no precise definition of the reference value of rSO_2. Pichler et al.[16] reported reference ranges of cerebral rSO_2 and fractional tissue oxygen extraction (FTOE) in healthy preterm and term neonates during the first 15 min after birth showing median of cerebral rSO_2 as 41% (23%–64%) at 5 minutes of age and 77% (63%–89%) at 15 minutes of age, respectively. Among 12 stable premature infants of 29 to 34 weeks of gestation, cerebral and renal rSO_2 ranges during the first week after birth corresponded to 66% to 83% and 64% to 87%, respectively.[13] In a study of 26 healthy term neonates during rest and feeding in the first few days of life, average cerebral rSO_2 was 77.9% and renal rSO_2 was 86.8%.[17] Our rSO_2 data were presented as averages over 6-hour intervals, and a total of 14 newborns began monitoring within the first 6 hours after birth. It showed in accordance with other studies.

The value of cerebral/renal rSO_2 showed a significant difference according to postnatal age and GA.[16] Over the first 5 days after birth in 26 healthy term infants, average cerebral rSO_2 tended to decrease, and renal rSO_2 showed no change.[17] In a large cohort of preterm infants, the mean cerebral rSO_2 during the first 72 hours of life ranges from 62% to 71% depending on a postnatal age, with a positive association between cerebral rSO_2 and GA.[18] In our study included infants with 29 to 42 weeks GA, average cerebral rSO_2 tended to increase, while average renal rSO_2 tended to decrease in both preterm and term infants. The cerebral rSO_2 in preterm infants lower than in term infants in the early part of 72 hours of life, and then it increases toward the latter part of 72 hours, showing higher than in term infants. Similar to previous studies, cerebral rSO_2 tended to decrease in term infants, and increase in preterm infants.

In a study with 734 preterm infants, the lower threshold of cerebral rSO_2 was established as 55% in the first 3 postnatal days.[19] They reported that a total 20% of time spent with rSO_2 of <55% in the first postnatal 72 hours was associated with death or unfavorable cognitive outcome at 24 months of age.[19] If brain oxygenation in premature infants is not optimized during the first 2 weeks after birth, neurodevelopmental outcomes are poor.[20] Because the differences in rSO_2 between adult, pediatric, and neonatal sensors was 10% to 14%, the lower threshold for cerebral rSO_2 could be set at approximately 65% when using neonatal sensors.[19,21] In our study using NIRS with the neonatal sensor, most of the neonates experienced

with cerebral rSO_2 below 65%, but none of those neonates spent more than 20% of time in cerebral rSO_2 below 65%. One of them spent a total 15.5% of time spent with rSO_2 of <65%, and it was the longest time in our study. Considering that the neonates were not monitored by NIRS throughout the first 72 hours of life, follow up of their neurodevelopmental prognosis is required to corroborate the results of previous study.[22]

The significant correlation between cerebral and somatic tissue specific SO_2 and FTOE with measured vital sign parameters, such as arterial oxygen saturation, HR and respiratory rate, especially mean BP is well established.[6,7] However, there are few articles on their correlations with the physiological parameters evaluated by blood tests. Our study demonstrated that renal rSO_2 has a positive correlation with pH, PO_2, base excess, hemoglobin, hematocrit and a negative correlation with PCO_2, BUN, and creatinine. Contrary to expectations, our study showed that cerebral rSO_2 has a positive correlation with only hemoglobin and hematocrit. Therefore, our study is in the first to confirm the relationship between the values of physiological parameters estimated by blood tests and rSO_2 in Korean neonates. In a previous study for 27 preterm infants, correlational analyses revealed hematocrit was directly related with raw data of cerebral and renal rSO_2 (r=0.418 and r=0.436, both P<0.01).[23] Similar findings were noted in our study. There were significant positive correlations between hematocrit and cerebral or renal rSO_2, respectively (r=0.366 and r=0.318, both P<0.05).

Various studies have showed the relationship between tissue specific rSO_2 and immediate postnatal adaptation, HIE, PDA and IVH[24]; however, these were not evaluated, and hence could not be confirmed in our study, because it was limited to 72 hours after birth. In a previous study included 38 infants less than 32 weeks GA, consisting of 18 with and 20 without respiratory distress syndrome (RDS), it has been reported that there was no difference in the pattern of rSO_2 with or without RDS.[24,25] Likewise, there was no significant difference between groups with and without surfactant in our study when only preterm infants were included.

This study has several limitations. First, sample size was small, so it is difficult to generalize the findings. Second, in this study, severe cases with life threatening condition were not included, indicating a selection bias. The newborns hospitalized during that period were not seriously ill. Third, due to the retrospective nature of the study, further randomized prospective studies with larger sample size will be needed to confirm the findings of this study.

Non-invasive continuous rSO_2 monitoring has the clinical usefulness in neonates by identifying trends and correlations of regional tissue oxygen saturation with postnatal age, GA and laboratory tests. Further studies with a large number of neonates are required to reach a consensus on the uniform interpretation of the results and to develop universally applicable reference values.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Authors' Contributions

Conceptualization: SHL, SML; Data curation: SJY, JHL; Formal analysis: SHL; Methodology: SHL, SJY, JHL; Writing-original draft: SHL; Writing-review & editing: MSP, HSE, JES, JHH, SML.

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