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S100B protein and near infrared spectroscopy in preterm and term newborns

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TABLE OF CONTENTS

1. ABSTRACT

Cerebral monitoring constitutes an emerging issue in perinatal medicine. Near Infrared Spectroscopy (NIRS) monitors brain oxygenation status in sick infants although data in healthy infants are lacking. The present study investigates whether NIRS parameters change according to gestational age and correlate with S100B protein. We recruited 64 healthy newborns (weeks' gestation: 30-42 wks) in which we performed in the first 6-hours after birth routine clinical, radiological and laboratory variables, cerebral oxygen saturation (rSO_2), fractional cerebral tissue oxygen extraction (FTOE) values and S100B urine assessment. rSO2 and FTOE correlated (R=-0.73; R=0.51; P less than 0.01, for both) with gestational age. Highest rSO2 and the lowest FTOE peaks (P less than 0.001) were found at 30-33 wks. From 34 wks onwards, rSO2 progressively decreased and FTOE increased reaching their lower dip/peak (P less than 0.001) at 38-39 weeks. A significant correlation between S100B and NIRS parameters (rSO2: r=0.77; FTOE: r=-0.69; P less than 0.01) has been found. The present study shows that NIRS parameters and S100B protein correlation may be of help in brain function monitoring.

2. INTRODUCTION

An emerging issue in perinatal medicine is the early detection of cerebral distress in infants complicated by chronic/acute perinatal hypoxia that constitutes one of the major causes of mortality and morbidity (1,2). Despite accurate postnatal monitoring, the post-insult period is crucial, since brain damage may be at a sub-clinical stage, or its symptoms, hidden by the effects of NICU's therapeutic strategies and radiological assessment, may still be silent (3,4). Another priority is the knowledge of the timing of hypoxic insult (2,3) with respect to future measures of prevention: data in experimental models and in humans suggest that the time-window for successful therapeutic performance is restricted to the first 6-12 hours from birth. In this respect, standard monitoring procedures such as imaging techniques, neurophysiology evoked potentials (5-7) and EEG (8,9) show technical and diagnostic limitations. On this light, near-infrared spectroscopy (NIRS) has been recently proposed among potential prognostic tool for brain monitoring offering useful information on cerebral hemodynamics, oxygenation, (10-13), based on patterns' changes in oxygenation of hemoglobin (14-16). In preterm and term

sick newborns NIRS has been shown to offer useful information on cerebral oxygenation as well as on cerebral oxygen extraction (17).

S100B protein (S100B) is an acidic calcium-binding protein of the EF-hand family, characterized by the most common calcium-binding motif of a helix-lop-helix structure (18). The protein is concentrated in the nervous system, its half-life is about 1-2 hours, and it is eliminated mainly by the kidneys (19,20). Elevated (micromolar) S100B concentrations are a consolidated marker of brain damage and/or hypoxia in adult, in children and in animal model whilst at nanomolar concentrations S100B acts as a cytokine with a neurotrophic effect (19, 21-24). S100B, regulates several cellular functions (cell-cell communication, cell growth, cell structure, energy metabolism, contraction and intracellular signal transduction) (19). Among biological fluids, urine appears to be the most suitable, since it can be collected easily and sampling can be repeated without risk for the newborn (19). However, data on possible correlation between a brain oxygenation monitoring parameter such as NIRS and a brain hypoxia/damage well-established biochemical marker such as S100B is to date lacking.

The purpose of the present study was to investigate whether changes in cerebral oxygenation and in cerebral oxygen extraction are related with S100B protein urine levels, in healthy preterm and term newborns.

3. MATERIALS AND METHODS

3.1. Population

From January to December 2007 we recruited, at our tertiary NICU centre, 64 newborns from consecutive singleton physiological pregnancies, whose deliveries were between 30 and 42 weeks' gestation. Gestational age was determined by clinical data and by a first trimester ultrasound scan. Appropriate growth was defined by the presence of ultrasonographic signs (when biparietal diameter and abdominal circumference were between the 10^{th} and the 90^{th} centiles) according to the normograms of Campbell and Thoms (25) and by post-natal confirmation of a birth weight between the 10^{th} and 90^{th} centiles according to our population standards after corrections for the mother's height, weight and parity and the sex of the newborn. According to gestational age at birth we classified infants admitted to the study in term (n=32) and preterm (n=32) groups. All infants admitted to the study fulfilled all the following criteria: no maternal illness, no signs of fetal distress, pH more than 7.2 in cord blood or venous blood, Apgar scores at 1 and 5 minutes more than 7. All newborns were in normal clinical condition and showed no overt neurological syndrome at the discharge from the hospital (Table 1).

Exclusion criteria were: multiple pregnancies, intrauterine growth retardation, gestational hypertension, diabetes and infections, fetal malformations, chromosomal abnormalities, perinatal asphyxia, and distocia.

The study protocol was approved by the local Ethics Committees and the parents of the subjects examined gave informed consent.

3.2. Monitoring of cerebral oxygenation using NIRS

For non-invasive monitoring of cerebral hemodynamics and oxygenation, transcranial NIRS was used (INVOS 5100). A self-adhesive transducer that contained the light-emitting diode and 2 distant sensors were fixed on the left parietal side of the neonatal skull (26,27). For assessment of cerebral oxygenation, rSO2 was calculated from the differential signal obtained from these 2 sensors, expressed as the venous-weighed percentage of oxygenated hemoglobin [oxygenated hemoglobin/total hemoglobin (oxygenated hemoglobin + deoxygenated hemoglobin)] (28). For investigation of the balance between oxygen delivery and oxygen consumption, a relative FTOE measurement can be formulated as a ratio: (SaO2-rSO2)/SaO2. An increase in FTOE reflects an increase of the oxygen extraction by brain tissue, suggesting a higher oxygen consumption in relation to oxygen delivery. Conversely, a decrease of FTOE suggests less utilization of oxygen by brain tissue in comparison with the supply (17,28).

Data in the preterm and term healthy newborns were continuously recorded at 1-minute interval. For S100B protein correlation, bearing in mind protein's half-life (about 1-hour) (20) we calculated the median of 1-hour interval before and after S100B assessment.

3.3. Standard monitoring parameters

Heart and respiratory rates, oxygen saturation monitoring were assessed in the first 6-hours after birth by a Masimo Datascope Radical (Masimo Corporation, Irvine, CA, USA) at a 1 minute interval in the two studied groups and recorded by MetaVision ICU X-Edition software (*i*-MDsoft Ltd., Tel Aviv, Israel). In all infants admitted to the study standard laboratory investigation was performed and results are reported in Table 1.

3.4. Statistical analysis

S100B concentrations and NIRS parameters are given as median and 25°-75° centile. Data were analyzed for statistically significant differences between groups by t-test and Mann-Whitney U two-sided test when not normally distributed. Comparison among sub-groups, when corrected for different gestational age periods, were analyzed for statistically significant differences by Kruskal-Wallis one-way ANOVA and multiple comparisons was performed using Dunn's Method. Comparison between proportions was performed with Fisher's exact test. The correlation among NIRS parameters, gestational age and monitoring parameters was assessed by linear regression analysis. Statistical significance was set at P less than 0.05.

4. RESULTS

Perinatal characteristics in preterm and term healthy newborns are shown in Table 1. According to admission criteria, age and weight at birth, the incidence of caesarean section were significantly different (P less than

Table 1. Neonatal outcomes and laboratory parameters in healthy preterm and term newborns. Data are expressed as mean +/- SD

	Preterm Group n= 32	**Term Group n=32**
Age at birth (weeks)	32.1 +/- 2.3	40.1 +/- 1.6[1]
Birthweight (g)	1,845 +/- 266	3,269 +/- 199[1]
Apgar score at 1st min	8 +/- 2	9 +/- 1
Apgar score at 5th min	9 +/- 1	8 +/- 1
Male/Female (n°)	17/15	16/16
Red blood cell count (10^6/mm^3)	3.89 +/- 0.4	4.01 +/- 0.1
Hemoglobin (g/dL)	13.5 +/- 0.3	13.9 +/- 0.3
Hematocrit rate (%)	41.1 +/- 2.4	41.7 +/- 1.6
Venous blood pH	7.34 +/- 0.3	7.35 +/- 0.2
Partial venous CO_2 pressure (mmHg)	50.1 +/- 5.2	48.9 +/- 8.5
Partial venous O_2 pressure (mmHg)	38.1 +/- 3.9	39.7 +/- 5.8
Base excess	1.5 +/- 0.2	1.9 +/- 1.1
Na^+ (mmol/L)	139 +/- 3	140 +/- 3
K^+ (mmol/L)	4.5 +/- 0.2	4.5 +/- 0.1
Ca^{++} (mmol/L)	1.11 +/- 0.07	1.12 +/- 0.3
Plasma glucose (mmol/L)	4.3 +/- 1.2	4.2 +/- 1.1
Urea (mg/dl)	36.2 +/- 4.2	39.1 +/- 3.6
Creatinine (mg/dl)	0.86 +/- 0.13	0.89 +/- 0.11
Urine Gravity	1010 +/- 5	1012+/- 4

[1]P less than 0.01

Table 2. rSO_2 and FTOE values, S100B urine concentration (microg/L) in normal preterm and term newborns in the first 6 hours from birth. Data are shown as median and interquartile ranges

Gestational Age at Recording wks	**rSO2**			**FTOE**			**S100B (microg/L)**		
	Median	25°	75°	Median	25°	75°	Median	25°	75°
30-33	89	85	92	0.28	0.21	0.35	2.28	1.65	2.88
34-37	81	76	84	0.25	0.14	0.33	1.12	0.55	1,66
38-41	72	64	79	0.14	0.07	0.15	0.14	0.07	0.15

0.001, for all) in the two groups. No differences (P more than 0.05, for all) were shown for Apgar score at 1' and 5' minutes and gender distribution. Standard laboratory investigation performed at admission to the unit were superimposable (P more than 0.05, for all) in the two groups (Table 1). No overt neurological syndrome was observed in the two groups and all newborns were discharged from hospital in good clinical conditions.

4.1. rSO2 and FTOE recordings

NIRS values at different gestational age of recordings are reported in Table 2. rSO2 pattern showed its highest peak in the early phases of the third trimester, between 30-33 wks, when rSO2 values were significantly higher than other periods of recording (P less than 0.001, for all). From 34 wks onwards, rSO2 progressively decreased reaching its lower dip (P less than 0.001, for all) at 38-41 weeks. rSO2 correlated with gestational age (r=-0.73; P less than 0.01), with heart (r= 0.68; P less than 0.01) and respiratory (r=-0.61; P less than 0.01) rate, and with SaO2 values (r=-0.71; P less than 0.01).

Data on FTOE values at different gestational ages are reported in Table 2. FTOE pattern showed its dip in the early phases of the third trimester, between 30-33 wks, when FTOE values were significantly lower than other periods of recording (P less than 0.001, for all). From 34 wks onwards, FTOE progressively increased reaching its highest peak (P less than 0.001, for all) at 38-41 weeks if compared to earlier periods. A significant correlation between FTOE and gestational age was found (r=0.51; P less than 0.01).

4.2. S100B measurements

S100B was detectable in all examined urine samples. S100B was significantly higher in the pre-term group, peaking in the earliest weeks of gestation, and progressively decreasing near term, being at the limit of sensitivity in the term group (P less than 0.001) (Table 2). A significant correlation between S100B urine levels and gestational age was observed in all the newborns considered (r=-0.76; P less than 0.01). Moreover, a significant correlation between S100B and NIRS parameters (rSO2: r=0.77; P less than 0.01; FTOE: r=-0.69; P less than 0.01) has been found (Figure 1, Panel A, B).

5. DISCUSSION

The present study shows that in healthy infants cerebral oxygenation status, evaluated by NIRS parameters (i.e. rSO2 and FTOE), changes in a gestational age manner and correlated with a brain constituent, such as S100B protein, known to be a consolidated marker of brain hypoxia and damage. Furthermore, a correlation with standard monitoring parameters such as oxygen saturation and heart and respiratory rates has been found.

The correlation among cerebral oxygen status, and S100B protein constitute the first observation in this setting, and may offer useful information to physicians about newborn's adaptation in the early phases after birth.

NIRS parameters were significantly higher in preterm than in term infants: the finding may be related to different hemodynamic patterns and oxygenation status according to earlier gestational ages (29,30) as well as to different oxygen extraction of the brain tissue (i.e. FTOE patterns) (31) and in hemoglobin changes during gestation (32). Another explanation resides in the fact that "in late-preterm" the central nervous system development (i.e.

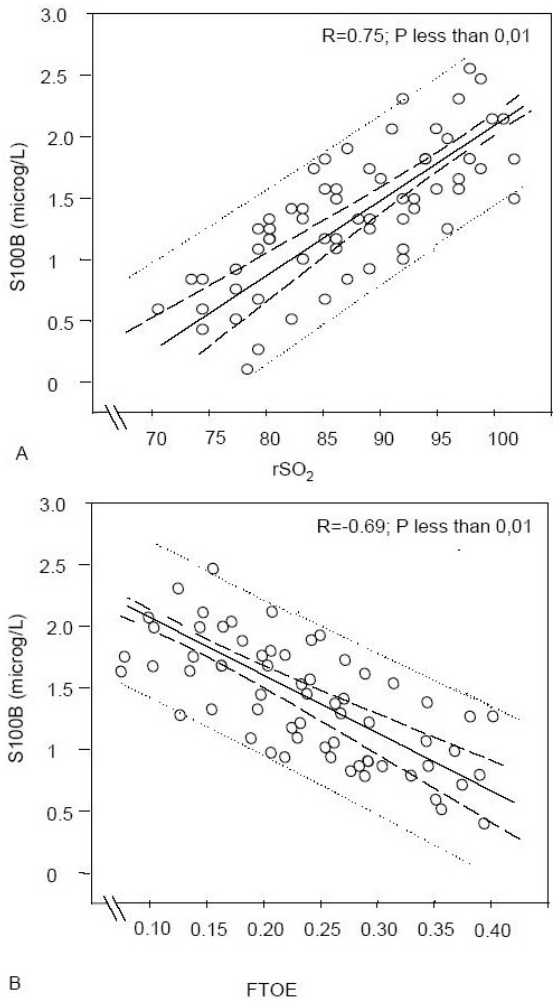

Figure 1. S100B (microg/L) correlations with rSO2 (Panel A), and with FTOE, (Panel B). There was a positive significant correlation between S100B and rSO2 (r=0.77; P less than 0.01) and a negative correlation between S100B and FTOE (r=-0.69; P less than 0.01).

synaptogenesis, dendritic arborization and axonal elongation) is particularly active and brain weight and volume may increase up to one third of the total amount (33-37).

S100B pattern changes according to gestational age as previously reported (19,23,24) in urine and in different biological fluids. Experimental models and humans data showed that the protein, at nanomolar concentrations, acts as a cytokine with a neurotrophic effect (19): therefore, the higher S100B levels in preterm infants could be a final consequence of the increased concentration of the trophic factor when brain maturation processes are more active. The progressive decrease in S100B urine levels near term could reflect a reduced release of the trophic factor at a later stage of fetal-neonatal brain maturation. Another explanation lies, in part, in the different blood-brain barrier permeability and cerebral circulation patterns (23). The hypothesis is based on: i) hemodynamic adaptive mechanism due to the anatomical and functional changes occurring in spiral arteries in the third trimester of pregnancy; ii) modifications in cerebral and umbilical blood flow from early third trimester to term (29,30).

The correlation between NIRS parameters and S100B protein warrants consideration. Data in animal, in humans and herein reported, show that rSO2 and S100B are both: i) gestational age dependent; ii) correlated with hemodynamic modifications involving brain blood barrier permeability that can occur during physiological CNS development or damage (17,19,24,25); iii) increased under pathological conditions, such as acute/chronic hypoxia (16,17,19,24). This latter point need further consideration. S100B has been shown to be early activated (within 15 minutes) in fetuses and infants complicated by perinatal asphyxia and adverse outcome (high sensitivity, specificity and predictive value) (38-40). Conversely, NIRS role at this stage has to be fully elucidated. The most suitable explanation resides in the fact that combined increase in rSO2 and decrease in FTOE reflect a less utilization of oxygen of brain tissue as a result of neuronal cell death and decrease in uptake of oxygen by the brain (17). In adults with stroke, increased rSO2 values have been shown in the damaged region suggesting that injured or dead neurons consume little or no oxygen. (41). Similarly, in animals developing extensive brain damage, decreased oxidative metabolism secondary to energy failure, delayed neuronal cell death and less utilization of oxygen, from 24 hours up to 48-72 hours after insult have been shown (42,43). Energy failure pattern was also confirmed in newborns complicated by severe birth asphyxia and adverse outcome (44) characterized by increased rSO2 and decreased FTOE (17). All together, the present findings support that the combined use of a biochemical brain function marker and of a non-invasive parameter may be of help in sick-infants brain monitoring. This especially refers for the first 6-12 hours from birth, that are known to constitute the useful time-window for therapeutic strategies performance. Therefore, the possibility to screen at birth by S100B assessment high risk cases and to perform a S100B longitudinal monitoring (half-life 1 hour) associated with continuous NIRS recording is not so fairly remote. Their assessment can be of help for brain function monitoring and at the same time physician can have the opportunity to verify the effectiveness of risky therapeutic strategies (mechanical ventilation, brain cooling, sedation) performed in NICU.

In conclusion, the present data showing first the correlation among S100B protein, rSO2 and FTOE, suggest that combined biochemical and non-invasive monitoring can constitute a tool potential for CNS monitoring in healthy and sick infants. However, further investigations are needed aimed to establish accurate research protocols to include in clinical practice.

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Abbreviations: rSO_2: cerebral oxygen saturation; FTOE: fractional cerebral tissue oxygen extraction; NIRS: near infraread spectroscopy.

Key Words: NIRS, Prematurity, Brain Oxygenation, Brain Damage, Cerebrovascular System

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