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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

An Insidious Threat for Cerebral Oxygenation: Neonatal Hypoglycemia

Beyin Oksijenasyonu için Sinsi Tehdit: Neonatal Hipoglisemi

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ABSTRACT

Purpose: Neonatal hypoglycemia (NH) is frequent in neonatology practice. This study aimed to evaluate the regional cerebral tissue oxygenation and cerebral blood flow in neonates who developed NH immediately after birth.

Methods: This prospective study included infants who developed NH (n=50) and the control healthy term neonates (n=50). Infants with NH are monitored in terms of continuous regional cerebral tissue oxygenation ($rcSO_2$) via near-infrared spectroscopy (NIRS) during the first 24 hours of life. Middle cerebral artery (MCA) blood flow was evaluated by doppler ultrasound at the first and 24 hours of life. The pulsatility index (PI) was measured to assess cerebral vascular resistance.

Results: The mean gestational age, birth weights and hemoglobin levels of infants were similar. The mean $rcSO_2$ was continuously higher and fractional tissue oxygen extraction (FTOE) was lower in infants with NH. The mean MCA PI values at the first and 24th hours of life were significantly higher in NH.

Conclusions: This study shows that cerebral perfusion was impaired in infants with NH. They had higher $rcSO_2$, lower FTOE values and increased PI compared to healthy term infants. We suggest that increased PI may reflect increased vascular resistance and higher $rcSO_2$ values associated with increased cerebral perfusion as a compensatory auto-regulatory response mechanism. Significantly lower FTOE values may dedicate decreased cerebral tissue oxygen extraction resulting from impaired cerebral perfusion even in the presence of auto-regulatory mechanisms. Therefore, even if they are asymptomatic, long term neurological outcomes should be followed in infants with NH due to impaired cerebral perfusion.

Keywords: Neonate, Hypoglycemia, NIRS, Cerebral Oxygenation, Cerebral Perfusion

ÖZ

Amaç: Neonatal hipoglisemi (NH) yenidoğan pratiğinde sık karşılaşılan bir durumdur. Bu çalışma ile doğumdan sonra NH gelişen yenidoğanlarda yaşamın ilk saatlerindeki serebral doku oksijenasyonu ve serebral kan akımının değerlendirilmesi amaçlanmıştır.

Yöntem: Prospektif yürütülen çalışmaya doğumdan sonra NH gelişen (n=50) ve gelişmeyen (n=50) yenidoğan bebekler dahil edildi. Her iki gruptaki bebeklerde yaşamın ilk 24 saati boyunca near-infrared spectroscopy (NIRS) ile devamlı bölgesel serebral doku oksijenasyonu ($rcSO_2$) ölçüldü. Yaşamın ilk saati ve 24.saatinde bebeklerin orta serebral arter (MCA) kan akımları Doppler ultrasonografi ile değerlendirildi. NH gelişen ve gelişmeyen gruplar karşılaştırıldı.

Bulgular: Bebeklerin ortalama gebelik haftası, doğum ağırlıkları ve hemoglobin düzeyleri benzerdi. NH gelişen ve gelişmeyen bebekler karşılaştırıldığında NH gelişen bebeklerde ortalama $rcSO_2$ değerleri anlamlı yüksek ve fraksiyone doku oksijen ekstraksiyon (FTOE) değerleri anlamlı düşük bulundu. Yaşamın ilk saatinde ve 24. saatinde ölçülen, vasküler direnci gösteren serebral doppler indeksleri (Pulsatilite indeksi:PI) de NH gelişen grupta anlamlı olarak yüksekti.

Sonuç: Bu çalışma ile NH gelişen yenidoğanlarda serebral dolaşımın ve oksijenasyonun bozulduğu gösterilmiştir. Hipoglisemi gelişen grupta yüksek ölçülen PI, serebral vasküler direncin arttığını göstermektedir. Bu grupta yüksek ölçülen $rcSO_2$ değerlerinin azalmış serebral akımı kompanse etmek için gelişen serebral otoregülasyon sonucu geliştiği düşünülmektedir. FTOE düzeylerinin düşük olması ise serebral otoregülasyon mekanizmalarına rağmen NH'de serebral dolaşımın ve serebral oksijenasyonun bozulduğunu düşündürmüştür. Bu nedenle asemptomatik olsalar dahi NH gelişen bebeklerin uzun dönem nörolojik gelişimlerinin takip edilmesi gerekmektedir.

Anahtar Kelimeler: Yenidoğan, Hipoglisemi, NIRS, Serebral Oksijenasyon, Serebral Perfüzyon

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INTRODUCTION

Glucose is the essential substrate for metabolism and the brain is the most vulnerable organ to hypoglycemia (1). Neonatal hypoglycemia (NH) is defined as plasma glucose concentration being below 47 mg/dL (2). Being late preterm, large for gestational age (LGA), small for gestational age (SGA) or being an infant of a diabetic mother (IDM) are defined as risk factors for NH by the American Academy of Pediatrics Committee on Fetus and Newborns in 2011 (2).

The brain is extremely vulnerable to plasma glucose level changes and hemodynamical deteriorations. Auto-regulatory mechanisms of the brain help to maintain adequate cerebral perfusion either by vasodilation or vasoconstriction (3). Changes in cerebral perfusion can be monitored by near-infrared spectroscopy (NIRS) and Doppler ultrasonography (4). NIRS is the most commonly used non-invasive spectroscopic method to evaluate regional cerebral tissue oxygenation ($rcSO_2$). The blood flow of tissues and serum hemoglobin (Hb) concentrations may affect NIRS measurement. The fractional tissue oxygen extraction (FTOE) can be calculated from $rcSO_2$ and oxygen saturation (SpO2). Cerebral blood flow can be evaluated by doppler ultrasonography of main cerebral arteries, mostly the middle cerebral artery (MCA). Angle-independent doppler indices such as the Pulsatility Index (PI) and Resistive Index (RI) have been used to evaluate the blood flow and the resistance of vessels. Increased PI and RI shows increased vascular resistance (5).

The aim of this study is to evaluate the changes in regional cerebral tissue oxygenation and cerebral blood flow within the first 24 hours of neonates who developed NH immediately after birth.

MATERIALS AND METHODS

This prospective observational study was conducted at the Kanuni Sultan Suleyman Training and Research Hospital and the Basaksehir Cam and Sakura City Hospital between April 2019 and September 2020, then, the research was reviewed and approved by the institutional review board (Approval no: 2019.03.78). Infants who were born late preterm, early term, LGA infants, SGA infants and infants of diabetic mothers were checked for plasma glucose levels and infants with plasma glucose below 47 mg/dL were included. Neonates with major chromosomal abnormalities and neonatal sepsis were excluded. A total of 100 neonates were sub-grouped as the study group (n=50) including neonates who developed NH and the control group (n=50) of term neonates with normoglycemia, after informed consent was obtained from parents.

Table 1: Demographical data of neonates

	Study group (n=50)	Control group (n=50)	p value
Gestational age (wk)	36.6 ± 1.8 (34-38)	37.8 ± 1.4 (37-39)	p>0.05
Birth weight (g)	2748 ± 785	3035 ± 614	p>0.05
Infants of diabetic mothers (%)	28	0	
† SGA infant (%)	8	0	
‡ LGA infant (%)	4	0	
Hb levels (g/dL)	17.6 ± 2.2	17.5 ± 2.4	p>0.05

† SGA: small for gestational age
‡ LGA: large for gestational age

Table 2: Plasma glucose levels within first 24 hours (mg/dL)

Plasma glucose level median (Range)	Study group (n=50)	Control group (n=50)	p value
0-1st hour	36 (28-45)	73 (51-121)	p=0.016*
3rd hour	87 (61-159)	86 (63-125)	p>0.05
6th hour	88 (52-137)	90 (55-150)	p>0.05
9th hour	72 (51-112)	70 (56-103)	p>0.05
12th hour	81 (65-148)	84 (62-118)	p>0.05
15th hour	83 (62-138)	87 (67-122)	p>0.05
18th hour	86 (67-112)	85 (69-96)	p>0.05
21st hour	82 (64-121)	84 (68-107)	p>0.05
24th hour	79 (63-103)	80 (67-97)	p>0.05

*Mann-Whitney U test, p<0.05

Table 3: Regional cerebral oxygen saturations ($rScO_2$)within first 24 hours (%)

rScO2 (mean ± SD†)	Study group (n=50)	Control group (n=50)	p value
0-1st hour	82.5 ± 7.5	77.2 ± 7	p=0.03*
3rd hour	82.9 ± 6.5	77.2 ± 10.5	p>0.05
6th hour	81.6 ± 6.8	77.1 ± 9	p>0.05
9th hour	80.5 ± 8.1	77.8 ± 11.3	p>0.05
12th hour	80.8 ±6.30	75.9 ± 10	p=0.02*
15th hour	81.3 ± 7.2	76.7 ± 11.5	p>0.05
18th hour	81.1 ± 6.1	76.6 ± 11.5	p>0.05
21st hour	82.2 ± 6.2	77.4 ± 8.27	p=0.03*
24th hour	82 ± 5.9	70.7 ± 14.2	p=0.002*

*Mann-Whitney U test, p<0.05
† SD: Standard deviation

Table 4: Fractionized tissue oxygen extraction (FTOE) within first 24 hours (%)

FTOE (mean ± SD)	Study group (n=50)	Control group (n=50)	p value
0-1st hour	14.7 ± 7.8	20.5 ± 7.1	p=0.02*
3rd hour	14.6 ± 6.7	20.7 ± 11.6	p=0.03*
6th hour	15.9 ± 7.1	20.5 ± 9.3	p>0.05
9th hour	17.1 ± 8.5	19.3 ± 10.4	p>0.05
12th hour	16.7 ± 6.5	21.7 ± 10.3	p=0.02*
15th hour	16.2 ± 7.3	21.0 ± 11.9	p>0.05
18th hour	16.4 ± 6.2	21.2 ± 11.3	p>0.05
21st hour	15.7 ± 5.8	20.2± 8.5	p=0.04*
24th hour	15.1 ± 6.4	24.7 ± 8.5	p=0.003*

*Mann-Whitney U test, p<0.05

Infants who developed NH were immediately fed, and dextrose perfusion with a rate of 6 mg/kg/min was supplied if NH persisted. Continuous $rcSO_2$ was measured by NIRS from the first hour to 24th hours of life with an Invos Cerebral/Somatic Oximeter Monitor (Covidien, Mansfield, Massachusetts). The probe was placed at the middle of the frontal bone and regional tissue oxygenation was monitored continuously. The $rcSO_2$ values measured by NIRS and SpO_2 values detected by pulse oximeter were recorded and FTOE was calculated as; FTOE = (SpO2-rcSO2)/SpO2. Plasma glucose levels were monitored by glucometer with heel stick blood sample, from the first hour of life, for a 24 hour period, with 3 hour intervals at starvation. The blood flow of MCA was evaluated by doppler ultrasonography through the sphenoidal fontanel twice, at the first and 24 hours of life, with GE ultrasound by measuring the angel independent doppler indices such as PI and RI which reflect the vascular resistance. All these measurements were performed by the same neonatologist.

Statistical analyses were performed by IBM SPSS 22.0 (IBM SPSS for windows version 22, Armonk, NY, USA). The consistency of continuous variables to normal distribution was tested by Shapiro-Wilk test. Demographical data such as gestational age and birth weight were expressed as "mean ± standard deviation"; plasma glucose levels were expressed as "median (range)"; rcSO2, FTOE values, MCA Doppler PI and RI indices were expressed as "mean ± standard deviation". The Mann-Whitney U and Pearson's chi-square tests were used for appropriate comparisons between groups.

RESULTS

The mean gestational ages of infants were 36.6 ± 1.8 and 37.8 ± 1.4 weeks, the mean birth weights were 2748 ± 785 and 3035 ± 614 grams for the study and control groups; respectively (p>0.05). In the study group, 4 infants (8%) were SGA, 2 (4%) were LGA and 14 (28%) were IDM. Hemoglobin levels of both groups were similar (p>0.05). Demographical data of both groups are shown in Table 1. Plasma glucose levels were significantly lower in the study group within the first hour of life, at the NH diagnosis time point (p<0.05). Plasma glucose levels were reassessed at starvation with 3 hour intervals during first 24 hours of life. After dextrose was supplied to infants with NH, repeated plasma glucose measurements were

Table 5: † MCA Doppler ultrasonography indices

	Study group (n=50)	Control group (n=50)	p
MCA PI (0-1 hr)	1.45 ± 0.47	1.10 ± 0.04	p=0.002*
MCA PI (24th hr)	1.30 ± 0.38	1.06 ± 0.05	p=0.004*
MCA RI (0-1 hr)	0.82 ± 0.19	0.81 ± 0.03	p>0.05
MCA RI (24th hr)	0.85 ± 0.18	0.85 ± 0.02	p>0.05

*Mann-Whitney U test, p<0.05
† MCA: Middle Cerebral Artery

normoglycemic and similar between groups (p>0.05). Table 2 shows the plasma glucose levels of the groups.

The $rcSO_2$ values that were measured with 3 hours intervals were continuously higher in the study group, and significantly higher at 1st, 12th, 21st and 24th hours of life (p<0.05). The $rcSO_2$ values are detailed in Table 3. FTOE values showing cerebral tissue oxygen use were continuously lower in the study group, and significantly lower at 1st, 3rd, 12th, 21st and 24th hours of life (p<0.05). FTOE values are shown in Table 4.

The mean MCA PI at the first and 24th hours of life was significantly higher in the study group (p<0.05). There were no significant differences between the mean MCA RI measurements in both groups (p>0.05). The values for doppler indices are detailed in Table 5.

DISCUSSION

In this present study, cerebral oxygenation and cerebral blood flow (CBF) of infants who developed NH at early stages of life were evaluated. The $rcSO_2$ values were continuously higher in infants who developed NH, and significantly higher at 1st, 12th, 21st and 24th hours of life compared to control group (p<0.05). Along with this, FTOE values were continuously lower in the study group, which were significantly lower at 1st, 3rd, 12th, 21st and 24th hours of life compared with the control group (p<0.05). The mean MCA PI values which reflect the vascular resistance at the first and 24th hours of life were significantly higher in the study group (p<0.05).

NH is an important clinical condition which can adversely affect neurological and developmental prognosis. After birth; there occurs a physiological, transient, asymptomatic decrease in plasma glucose levels, as low as 30 mg/dL (2, 6). During this physiological hypoglycemia period, the newborn uses other energy sources like fatty acids and ketone bodies (2). If these other energy sources are deficient, adverse neurological effects may be more prominent. Incidence of serious adverse neurological outcome due to NH is reported as 0.13-0.44% and 1-5.5% for term and preterm infants, respectively (2, 7).

Boluyt et al (8) conducted the first systematic review of neurodevelopmental outcomes after NH in 2006. They reported that NH has an inconclusive effect on neurodevelopment. Kaiser et al (9) reported that infants who developed NH have lower literacy and math scores in later life. It is also reported that specific cognitive deficits including a two to three-fold increased risk of visual-motor impairment at 2-5 years and a two-fold increased risk of literacy and numeracy problems at 6-11 years of age (10). Neurological outcomes of infants with asymptomatic hypoglycemia still remain unclear. Even if a clear glucose concentration for hypoglycemia is well defined in neonates, such as being below 47 mg/dL, the threshold level that causes neurological negative effects is still a debate (2).

The brain is an important organ with its own autoregulation ability. When CBF is compromised, brain vessels dilate and vascular resistance decreases to maintain adequate cerebral perfusion. Hypoglycemia is an important clinical status in which cerebral autoregulation takes significance. Pryds and Vannucci reported that, low plasma glucose levels will lead to a lower glucose supply to the brain and CBF increases up to two or three folds as a compensatory mechanism to supply adequate glucose to the brain (11, 12). Epinephrine is secreted as a counterregulatory hormone in a state of hypoglycemia. Chandran et al (1) related the increase in CBF during hypoglycemia with increased epinephrine that leads to an increase in cardiac contractility and cardiac output, thus the CBF.

NIRS and MCA Doppler ultrasound gives information about cerebral oxygenation and perfusion. Schwarberger et al (3) reported that higher hemoglobin levels and increased blood flow both result in higher regional oxygen saturations. In our study group, the $rcSO_2$ measurements were higher than in the control group, and there was no significant difference in terms of Hb levels in both groups. Higher rcSO2 values in the study group thought to be a result of increased CBF which is suggested to be a result of cerebral autoregulatory mechanisms. FTOE shows oxygen consumption of tissues and is calculated by using arterial oxygen saturation and $rcSO_2$ (13). Lower cerebral FTOE values in the study group were interpreted as impaired blood flow and decreased oxygen consumption of cerebral tissue.

The general assumption is that, neonates with asymptomatic hypoglycemia are at low risk for neurological negative effects. In contrast with this, Burns (14) and Kinnala (15) showed, even moderate asymptomatic hypoglycemia is related with structural brain abnormalities. Lucas et al (16) reported impaired neurodevelopment in moderate NH, and Mc Kinlay et al (17) showed impaired executive and visual-motor functions in the presence of moderate asymptomatic hypoglycemia. Therefore, the presence of symptomatic or asymptomatic NH is a real risk for a neurodevelopmental negative prognosis.

There exists scarce data about NH and its association with cerebral vascular resistance. Aleksic et al reported increased PI and RI indices reflect the increased vascular resistance (5). Higher MCA PI values in our study group reflected increased MCA vascular resistance and impaired cerebral perfusion. It is suggested that increased PI reflects increase in cerebral vascular resistance, and CBF is increased as an autoregulatory response mechanism. Lower FTOE showed decreased cerebral tissue oxygen consumption and compromised cerebral perfusion even though autoregulatory mechanisms exist.

There were no significant differences in terms of Hb levels in both groups. Higher rcSO2 values in the study group may be a result of increased CBF and higher PI values of MCA may reflect the increased vascular resistance. We suggest that an increased cerebral vascular resistance lead to impaired cerebral perfusion, and tissue oxygen extraction was decreased. Beside this, increase in CBF was a compensatory autoregulatory response mechanism for impaired cerebral perfusion. Early feeding and parenteral dextrose supply after detection of NH prevented further hypoglycemia in our study population. This is one of the important limitations of this study, because the exact cerebral NIRS values at hypoglycemia can only be detected and evaluated at very early stages of life because hypoglycemia was corrected in all infants after interventions.

CONCLUSIONS

To the best of our knowledge, this is one of the pioneer studies that evaluate cerebral tissue perfusion in infants with NH, in the early hours of life. Hypoglycemia is a real neurodevelopmental threat. With this study, we conclude that even if clinically significant symptoms of neonatal hypoglycemia had not developed, long term neurological outcomes should be followed in infants with NH due to impaired cerebral perfusion.

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