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Original Article

Mesenteric tissue oxygenation status on the development of necrotizing enterocolitis

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ABSTRACT

Background. Necrotizing enterocolitis (NEC) is an important cause of morbidity and mortality in preterm infants. There is limited data about the role of mesenteric oxygenation status during the first enteral feeding. Therefore, the aim of this study was to determine the mesenteric tissue oxygen saturation values before, during and after the first enteral feeding and to evaluate the effect of these values on the development of NEC in preterm infants.

Methods. A total of 105 preterm babies with ≤ 32 gestational weeks were included in this prospective study. The continuous monitoring of the mesenteric tissue oxygenation status was performed before, during and 3 hours after the first feeding by near-infrared spectroscopy (NIRS).

Results. The mean gestational week and birth weight of the study group were 28.8±2.1 weeks, and 1215±387 g, respectively. The first enteral feeding was started at 2.4±1.4 days with breast milk in 85% of infants. A total of 12 infants (11.4%) developed NEC (66% stage II, 34% stage III). The mean mesenteric tissue oxygen saturation levels of the infants that developed NEC were significantly lower both before and one hour after feeding (56.1±3.4 vs. 34±8.8, and 47.4±3.3 vs 37.8±10.9, respectively) compared with infants that did not develop NEC.

Conclusions. Lower mesenteric tissue oxygenation values measured before, and one hour after enteral feeding was associated with NEC development. We suggest that lower mesenteric tissue oxygenation during continuous monitoring of first enteral feeding may be used to predict NEC development during follow-up.

Key words: enteral feeding, near-infrared spectroscopy, necrotizing enterocolitis, NICU, premature.

Necrotizing enterocolitis (NEC) is the most frequent and lethal gastrointestinal tract emergency in preterm newborns.[1] Though more than 50 years have passed since its definition, its pathophysiology has not been elucidated completely.[1] Prematurity, bacterial colonization, formula feeding, and intestinal ischemia were reported as the main risk factors that contribute to the complex pathogenesis.[2] The most accepted NEC hypothesis includes enteral feeding in the presence of intestinal hypoxia-ischemia-reperfusion, and abnormal intestinal colonization with pathogens that provoke an inappropriate inflammatory response in intestinal epithelial cells of premature infants.[3,4]

Therefore, it seems reasonable to establish the intestinal oxygenation status before and during the first enteral feeding attempts in premature infants and determine the high-risk infants for the development of NEC.

Near-infrared spectroscopy (NIRS) has been increasingly used to provide continuous monitoring of tissue oxygen saturation (StO_2) in neonates, especially for cerebral, renal and mesenteric oxygenation.[5] Limited number of studies investigated the effect of intestinal oxygenation status during enteral feeding as a

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biomarker of mesenteric perfusion on feeding intolerance and intestinal complications in preterm infants.[6-9] In addition, lower mesenteric tissue oxygenation and increased fractional tissue oxygen extraction (FTOE) was found in preterm infants during the early course of NEC.[10] Also, low mesenteric/cerebral oxygen saturation values and high mesenteric/cerebral FTOE levels were reported to be associated with bowel perforation or death in premature infants with NEC.[11]

However, to our best of knowledge, no study evaluated the possible association between mesenteric tissue oxygenation during the first enteral feeding and subsequent development of NEC in preterm infants. The aim of this prospective study was to determine the continuous mesenteric tissue oxygenation during the first enteral feeding and also to explore the possible association between these values and subsequent NEC development during the follow-up period.

Material and Methods

Study population

This prospective observational study was performed at two tertiary Neonatal Intensive Care Units. Preterm infants ≤32 gestational weeks, and hospitalized in these two centers between December 2015 and December 2017 were included. Infants with gastrointestinal/major congenital and/or genetic anomalies, hemodynamically significant patent ductus arteriosus (diameter ≥2.0 mm or left atrium to aortic root ratio ≥1.4 or retrograde flow in descending aorta), severe intraventricular hemorrhage (grade III, IV) and hemodynamically unstable patients, need of volume or inotrope treatment, babies who have anemia (hemoglobin <12 g/dl) and need red blood cell transfusion, infants died within the first 3 days of life were all excluded.

Nasal continuous positive airway pressure (NCPAP) (6 cmH_2O) was applied to all babies after birth. They were transferred to the neonatal intensive care unit (NICU) with nasal CPAP. In nasal CPAP failure, firstly non-synchronized nasal intermittent positive pressure ventilation was applied. However, babies whose respiratory support was insufficient were intubated and received ventilation support in volume-guaranteed mode. Target oxygen saturation was targeted between 90-94%. Intratracheal surfactant were administered to infants who needed FiO_2 more than 0.30 for target saturation.

Uludag University Faculty of Medicine Clinical Research Ethics Committee approved the study (2012-26/11) and the signed approved parental consent was obtained from all families.

Study design

All of the infants were started total parenteral nutrition during the admission and enteral feeding was started with breast milk as soon as possible and if not available with preterm formula at amounts of 10-20 ml/kg given at 3-hour intervals as a bolus. With the decision of enteral feeding, mesenteric, renal, and cerebral StO_2 were measured by NIRS for a 4 hours period starting from 1 hour before the first feeding, and continued during 3 hours of enteral feeding. The systemic oxygen saturation (SaO_2) of the infants were monitored simultaneously using a pulse oximetry device (Nellcor, Covidien-Medtronic, Minneapolis, US). The patients were followed up for the development of NEC. During follow-up, modified Bell criteria were used for the diagnosis, and staging of infants with NEC.[12] Demographical, prenatal and natal characteristics, and neonatal morbidities were all recorded. The infants with stage I NEC were excluded.

Near-infrared spectroscopy

INVOS 5100 near-infrared spectroscopy (Covidien, Mansfield, US) was used. NIRS data were recorded at 6-second intervals. Cerebral and renal sensors were placed on the anterior frontal region and on the left lumbar region, respectively. For mesenteric StO_2 measurement, sensors were placed on the infraumbilical region at the center of the abdominal wall.

Mean cerebral, renal, and mesenteric NIRS data obtained 1 hour before, during and 1, 2, and 3 hours after first enteral feeding were calculated. To minimize erroneous measurements stemming from movements, and malposition of the sensors, mean values of all measurements performed within +/- 15 minutes were taken into consideration. FTOE of the patients were calculated using the following formula: FTOE=SaO_2-StO_2 /SaO_2.

Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v23 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean ± standard deviation or median (minimum-maximum), as appropriate. All differences associated with a chance probability of 0.05 or less were considered statistically significant. Receiver-operating characteristics (ROC) analysis was performed by MedCalc version 18.2.1 statistical program. Values of $p<0.05$ were considered significant.

Results

During a period of two years, a total of 147 babies born at a gestational age of ≤ 32 weeks were hospitalized in the NICU. When the infants with exclusion criteria and without parental consent were excluded, 105 preterm babies were included in the study (Fig. 1).

The mean gestational age, and birth weights of the study group were 28.8±2.1 weeks, and 1215±387 g, respectively. The mean first enteral feeding time was 2.4 ± 1.4 days and 85% of the patients were breastfed. A total of 12 infants (11,4%) developed NEC; 8 (7,6%) had stage 2 and 4 (3.8 %) had stage 3. Although there were no significant differences in infants with and without NEC in terms of demographical features, the time of first enteral feeding was statistically significantly later in babies with NEC ($p<0.001$) (Table I).

No significant differences were detected between infants with and without NEC in terms of mean cerebral and renal StO_2. The mean mesenteric StO_2 were significantly lower before feeding (56.1±3.4 vs. 34±8.8) and one hour after feeding (47.4±3.3 vs 37.8±10.9) in cases that subsequently developed NEC compared with those who did not develop NEC (Table II). In the NEC group, mesenteric tissue oxygen saturations at the 2nd and 3rd hours after the first enteral feeding were found to be lower, but this difference was not significant (Table II). Similarly, FTOE levels before and 1 hour after feeding were significantly higher in cases that developed NEC (Fig. 2). The ROC analysis showed a cut-off of 42, 43, 47, 45 % for before the first feeding, the first hour after first feeding, the second hour after first feeding and, the third hour after the first feeding respectively for prediction of NEC (Table III).

Discussion

To the best of our knowledge, this is the first study that evaluated the possible role

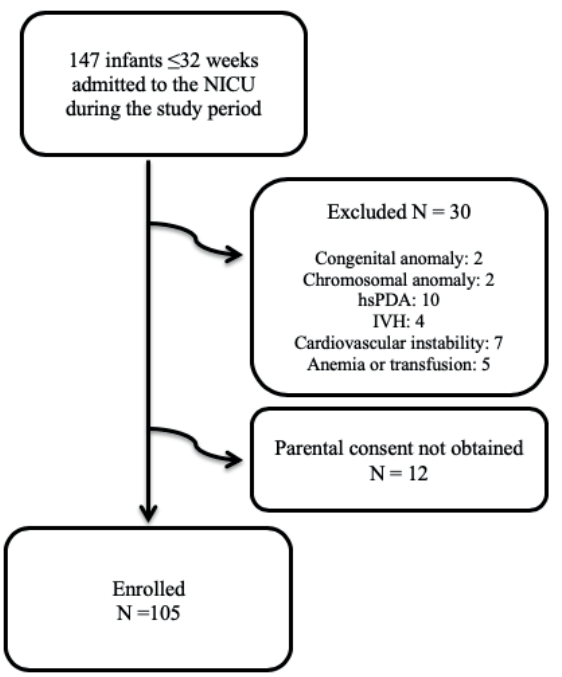

Fig. 1. Flow chart of the study enrollment (NICU: Neonatal intensive care unit, hsPDA: Hemodynamically Significant Patent Ductus Arteriosus, IVH: Intraventricular hemorrhage).

Table I. Demographics and characteristics of all infants enrolled in the study.

	NEC group n=12	Non-NEC group n=93
Maternal features		
Preeclampsia, n (%)	7 (58.3)	35 (37.6)
Premature rupture of membranes, n (%)	1 (8.3)	7 (7.5)
Antenatal steroid, n (%)	9 (75)	66 (70.9)
Caesarian section, n (%)	10 (83.3)	77 (82.7)
Neonatal features		
Birth weight (g), mean±std	1068±335	1237±358
Gestational age, mean±std	28.1±1.3	28.9±2.2
Small gestational age (<10 percentile), n (%)	4 (33.3)	20 (21.5)
Male gender, n (%)	7 (58.3)	46 (49.4)
Apgar score-1, mean±std	5.7±2.0	4.8±2.1
Apgar score-5, mean±std	7.0±1.7	6.8±1.7
Respiratory distress syndrome, n (%)	9 (75)	60 (64)
Mechanical ventilation, n (%)	8 (66.6)	50 (53.7)
Human milk feeding, n (%)	10 (83.3)	80 (86)
First day of enteral feeding, mean±std*	4.0±2.6	2.2±0.9
Development of NEC, day	12.3±5.3	-
Probiotic supplementation, n (%)	4 (33.3)	20 (21.5)
CRIB-II Score, mean±std	7.5±2.6	5.7±3.3

*p=0.0001

Table II. Cerebral, renal, and mesenteric tissue oxygen saturation (StO_2) values of infants before and after first feeding.

	NEC group n=12	Non-NEC group n=93
Before first feeding (%)		
• Cerebral StO_2, mean±std	69±7.3	70±13.2
• Renal StO_2, mean±std	64.6±17.2	66.2±20
• Mesenteric StO_2, mean±std*	34.8±10.9	56.1±3.4
1st hour after feeding (%)		
• Cerebral StO_2, mean±std	64.5±8.3	69.7±13
• Renal StO_2, mean±std	66.1±16.4	68±19.2
• Mesenteric StO_2, mean±std*	37.8±10.9	47.4±3.3
2nd hour after feeding (%)		
• Cerebral StO_2, mean±std	69±7.8	68.1±15.8
• Renal StO_2, mean±std	72±18.8	70±18.7
• Mesenteric StO_2, mean±std	40±23	52±24
3rd hour after feeding (%)		
• Cerebral StO_2, mean±std	67±8.1	67.8±17.4
• Renal StO_2, mean±std	71±17.5	65.4±20.5
• Mesenteric StO_2, mean±std	41.7±23	49.5±25

NEC: necrotizing enterocolitis, StO_2: tissue oxygen saturation
*p=0.0001

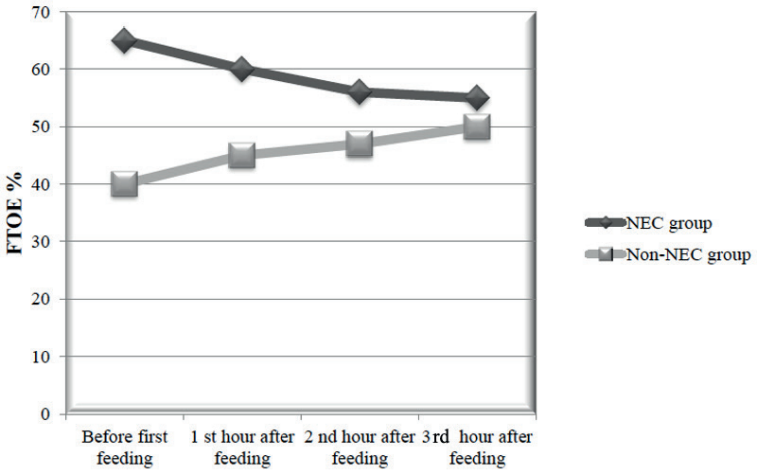

Fig. 2. Fractional tissue oxygen extraction (FTOE) values of infants with necrotizing enterocolitis (NEC) and non-NEC infants before and after first feeding.

Table III. Criterion values and coordinates of the ROC curve.

Variable Mesenteric StO_2, (%)	Cut off	Sensitivity	Specificity	AUC	95% Cl	P
Before first feeding	42	83	100	0.987	0.890 to 1.000	<0.001
1st hour after feeding	43	83	92	0.924	0.797 to 0.983	<0.001
2nd hour after feeding	47	75	93	0.813	0.661 to 0.918	<0.001
3rd hour after feeding	45	83	87	0.833	0.684 to 0.931	0.005

ROC: receiver operating characteristic, StO_2: tissue oxygen saturation, AUC: area under the ROC curve

of mesenteric tissue oxygenation during the introduction of first enteral feeding and subsequent development of NEC in preterm infants. This study suggested that lower mesenteric StO_2 and higher FTOE values before, and during the first hour of the enteral feeding were associated with the development of NEC during the follow-up period.

The incidence of NEC in very-low birth weight (VLBW) babies was reported up to 13% according to the large multicenter studies and neonatal networks.[13] The incidence of severe NEC (11.4%) in our study was similar to the literature. Despite major recent developments in the care of preterm infants, a highly sensitive and specific test for the early diagnosis of NEC is still lacking.

As prematurity, ischemia, feeding and abnormal colonization were reported as the main risk factors, a non-invasive diagnostic approach for these risk factors may provide early and accurate NEC diagnosis in preterm infants. NIRS has been increasingly used in the last years for the assessment of cerebral perfusion in both term and preterm infants. In addition, the non-invasive measurement of StO_2 and FTOE may be also calculated by the SaO_2 measurements.[11]

As the ischemic necrosis of intestinal mucosa is a stable sign in the histopathological examination of advanced stage NEC, detection of the decrease in the abdominal StO_2 related to mesenteric perfusion alterations before the development of NEC may offer a very reasonable diagnostic approach. Indeed, animal studies also yielded that lower NIRS measurements might be used for the early diagnosis of NEC.[14]

After these experimental data, abdominal StO_2 were found to be significantly lower in infants that developed NEC in a two-centered clinical

study and abdominal StO_2<56% were stated as an independent risk factor for the development of NEC in preterm infants.[15] The authors also reported significantly more variations both during and after feeding in the first two weeks of life. Our results were in accordance with this study as the mean mesenteric saturation levels were always lower than 56% in infants before, during and after first enteral feeding in premature infants. Therefore, we may speculate that lower mesenteric oxygen saturation, especially lower than 42% may predict subsequent NEC development during the hospitalization period.

A strong association between mesenteric FTOE and intestinal fatty acid binding protein levels were reported during the first 16 hours after NEC onset that suggested the simultaneous occurrence of decreased splanchnic perfusion and intestinal damage.[10] The authors suggested that mesenteric FTOE might offer valuable information about the degree of intestinal injury. NIRS monitoring was reported to be useful in preterm infants with definite NEC to differentiate the infants who would develop complicated NEC.[11] The lower mesenteric and cerebral oxygenation values and increased FTOE were also found to be associated with adverse outcomes including bowel perforation and death.[11] Similarly, increased mesenteric FTOE during the first enteral feeding was detected in our study. Therefore, we suggest that increased mesenteric FTOE levels may help neonatologists to identify the high-risk infants for NEC development. However, we could not find any differences in both cerebral and renal oxygenation levels in association with first enteral feedings to predict subsequent NEC development.

There are conflicting data about the correlation between mesenteric tissue oxygenation and feeding intolerance during the first introduction of enteral feeding in preterm infants. In a clinical study, lower abdominal saturations and mesenteric-cerebral oxygenation ratio were detected in infants that developed feeding intolerance.[7] Similarly, lower mesenteric oxygenation and increased FTOE were reported in response to both initial and full enteral feedings in infants with absent/reversed antenatal end diastolic flow (AREDF).[12] As both feeding intolerance and AREDF are important risk factors for NEC, these results should be interpreted in this manner. In contrast, abdominal StO_2 recorded during the first postnatal days was found to not provide helpful information about nutritional tolerance in the follow-up period.[6] This difference may be explained by the cerebral autoregulation mechanisms that keep tissue oxygenation stable.

Although the superior mesenteric artery flow rates after feeding show an increase in healthy preterm infants, this finding was not detected by Doppler US in infants who later developed feeding intolerance or NEC.[16] Contrary to Doppler US, NIRS provides continuous data about mesenteric oxygenation without the need of trained personnel. In our study, persistently lower mesenteric oxygenation levels were detected in infants that subsequently developed NEC. Therefore, we may suggest using NIRS alone or in combination with Doppler US for the prediction of NEC earlier in high-risk preterm infants.

In conclusion, NIRS may provide valuable data about the intestinal oxygenation status during the first enteral feeding in preterm infants. Lower mesenteric StO_2 and increased FTOE levels in preterm infants with normal cerebral and renal StO_2 during the introduction of first enteral feeding may predict subsequent NEC development. NIRS findings may be used to determine, characteristics of enteral feeding in high-risk infants for NEC development. However, prospective studies including a larger number of infants with prolonged NIRS monitorization periods are required to elucidate the exact role of intestinal tissue oxygenation during the early enteral feeding on subsequent NEC development in preterm infants.

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Author contribution

The contributions of all authors must be described in the following manner: The authors confirm contribution to the paper as follows: study conception and design: HO, MÇ, NK; data collection: BAD, MÇ; analysis and interpretation of results: HO, MÇ, NK; draft manuscript preparation: BAD, HO. All authors reviewed the results and approved the final version of the manuscript

Ethical approval

Uludag University Faculty of Medicine Clinical Research Ethics Committee approved the study (2012-26/11) and the signed approved parental consent was obtained from all families.

Conflict of interest

Authors state no conflict of interest.

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