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Original Research

Enteral Nutrition in Newborns with Hypoxic-Ischemic Encephalopathy Undergoing Therapeutic Hypothermia

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Abstract

Objectives: Clinicians are uncertain about the nutrition of patients diagnosed with hypoxic-ischemic encephalopathy due to the risk of necrotizing enterocolitis and feeding intolerance. The nutritional protocols of these patients are still unclear. We aimed to investigate the time of starting nutrition and related conditions in these patients receiving therapeutic hypothermia (TH) treatment.

Methods: This retrospective single-center study evaluated patients hospitalized at our unit and receiving TH between January 2022 and June 2023. Those who started nutrition during TH and after TH were defined as the early enteral nutrition (EEN) and late enteral nutrition (LEN) groups, respectively. Analyses were performed between the two groups.

Results: Our study evaluated 91 patients, of whom 40 were in the EEN group and 51 were in the LEN group. The reaching birth weight time in the LEN group was delayed (10 [5-22] vs. 7.5 [5-25] days, respectively, p<0.001), the transition time to full enteral nutrition was longer (10 [6-20] vs. 7 [5-18] days, respectively, p<0.001), and the hospitalization time was longer (13 [8-43] vs. 9 [7-35] days, respectively, p<0.001) compared with those of the EEN group.

Conclusion: TH is not an obstacle to starting nutrition. Starting nutrition in these patients at an early stage does not increase nutritional complications and shortens their discharge time.

Keywords: Feeding intolerance, hypoxic-ischemic encephalopathy, necrotizing enterocolitis, nutrition

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Hypoxic-ischemic encephalopathy (HIE) is a severe condition that can occur before, during, or after birth, resulting from inadequate oxygen and blood flow to the newborn's brain.[1] According to the World Health Organization, HIE is responsible for approximately 900,000 fatalities annually.[2] In addition to motor and behavioral impairments, cerebral palsy and audiovisual problems are also observed in survivors.[1,3] A multicenter study conducted in our country found that the incidence of HIE was 2.13 per 1000 live births, with HIE patients accounting for 1.55% of all neonatal intensive care unit admissions.[4]

Currently, therapeutic hypothermia (TH) is the only recommended treatment for severe to moderate HIE that occurs in the neonatal period.[5] It improves neurodevelopmental outcomes and significantly reduces the risk of death and severe disability in these patients.[6,7] Neonates exposed to

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asphyxia develop a "diving reflex" a restructuring of blood flow that protects important organs like the heart and brain against hypoxia. This condition accelerates the rate of damage to the organs that are directly affected by hypoxia. Hankins et al.[8] showed that patients who were subjected to asphyxia suffered central nervous system damage along with damage to the liver (80%), kidney (72%), heart (72%), and hematological (54%) damage. HIE continues to be the subject of current research for developing new treatment plans and multiorgan involvement. Enteral nutrition is usually delayed to avoid the risk of necrotizing enterocolitis (NEC) in neonates with HIE who may have undergone intestinal hypoperfusion.[9,10] However, some centers start early minimal enteral nutrition in conjunction with hypothermia treatment.[11,12] Furthermore, clinicians are reticent to administer enteral nutrition to these patients because of the danger of NEC. Delaying enteral nutrition due to the risk of NEC may result in adverse outcomes, including hypoglycemia, sepsis, feeding intolerance, delayed transition to full enteral feeding, and prolonged hospital discharge. The management of newborns and their nutritional protocol during TH is not standardized. We aimed to evaluate the time of starting nutrition and nutrition-related complications in patients receiving TH.

Methods

Patients and Study Design

This retrospective, single-center cohort study was conducted after receiving Harran University Clinical Research Ethics Committee Approval (HRÜ/23.18.04). Our study was conducted in accordance with the principles set forth in the Declaration of Helsinki. The patients' files and electronic medical records were evaluated retrospectively. The inclusion criteria were as follows: neonates admitted to our neonatal intensive care unit with a diagnosis of moderate and severe HIE and treated with TH between January 2022 and June 2023. The exclusion criteria included patients with gastrointestinal anomalies that impeded nutrition, those who died before full enteral nutrition could be started, and patients with incomplete file data. Demographic information (birth weight, gestational age, gender, mode of delivery and APGAR scores), blood gas parameters, and clinical data (seizure history, presence of an umbilical catheter, invasive ventilation duration and need for inotropic support, amplitude-integrated electroencephalogram (aEEG) and cranial magnetic resonance imaging (MRI) findings) were obtained. In addition, the patients' nutrition starting time and nutrition-related conditions (transition time to full enteral nutrition, reaching birth weight time, discharge weight, nutritional content, feeding intolerance and NEC) were recorded. The patients were divided into two groups: those who started nutrition during TH were referred to as the early enteral nutrition (EEN) group, and those who started nutrition following hypothermia treatment were referred to as the late enteral nutrition (LEN) group. To investigate the nutrition-related factors, a series of analyses were conducted and compared between the groups.

Therapeutic Hypothermia Protocol

Therapeutic hypothermia was performed with the Arctic Sun® (Medivance Corp, Louisville, Co.) in our unit. The patient's core temperatures were monitored with a rectal temperature probe and maintained between 33.5°C–34.5°C for 72 hours. The vital signs, rectal temperature, daily weight, and nutritional status of the patients were recorded. Hypothermia treatment indications in our unit were as follows:[13-15] 1) The neonates with postnatal age ≤6 hours and gestational age ≥ 36 weeks; 2) metabolic or mixed acidosis with a pH value <7.00 or base excess (BE) < −16 mmol/L in a sample blood gas taken from umbilical cord or within the first hour after birth; 3) 10th min APGAR score <5 or ongoing resuscitation initiated at birth and continued for at least 10 min; 4) Severe or moderate encephalopathy on clinical examination according to Sarnat and Sarnat staging system; 5) Existence of abnormal trace irregularity on an aEEG if used; 6) When two additional findings (low Apgar score and encephalopathy findings) are positive in neonates with pH value <7.00–7.15 and BE −10–(−16).

Nutrition Protocol

Two different neonatal specialists were working in our unit during the study period. Nutritional protocols of patients were different accordingly. The patients in EEN group started on minimal enteral nutrition (10 ml/kg/day) during TH, with increments of 30-50 ml/kg/day introduced following TH. The patients in the LEN group didn't start nutrition during TH; however, enteral nutrition was started at 30-50 ml/kg/day after TH, with subsequent increments of 30-50 ml/kg/day.

During follow-up, any deterioration in the patients' nutritional plan due to vomiting, gastric residue, or abdominal distension (reduction in nutritional volume by at least half or the omission of two consecutive feedings) was considered feeding intolerance.[16,17] NEC was defined according to the modified Bell staging system, which is based on clinical findings such as bilious vomiting, abdominal distention, occult or gross blood in stool (no fissures), and radiographic findings such as pneumatosis intestinalis, portal vein gas and pneumoperitoneum.[18]

Statistical Analysis

Statistical analyses were carried out using IBM SPSS Version 23 (Chicago, USA). The Shapiro-Wilk test was employed to determine if the continuous variables had a normal distribution. The normally distributed variables were evaluated using the independent Student's t-test. The Mann-Whitney U test was used to assess variables that did not follow a normal distribution. The correlation between categorical variables was determined using the chi-square and Fisher's exact tests. A p-value <0.05 indicated statistical significance.

Results

TH was performed on a total of 99 patients during the study period. Of these, 8 were not included in the study because they died before full enteral nutrition could be started. Thus, a total of 91 patients were evaluated in our study. The mean birth weight of the patients was 3194.95±448.458 g, and 29 of them (31.9%) were female. The number of patients born via cesarean section was 62 (68.1%), and the median gestational age was 38 (35-42) weeks. Moderate HIE was observed in 76 (83.5%) patients, and a total of 2 patients developed exitus. A total of 40 patients started enteral nutrition during TH treatment and were referred to as the EEN group, and 51 patients started enteral nutrition after TH and were referred to as the LEN group. When the two groups were compared in terms of demographic data (birth weight, gestational age, gender and mode of delivery) no statistically significant differences were found. The 1st, 5th, and 10th min APGAR scores were not statistically different between the groups. There was no statistical difference between the two groups in terms of blood gas parameters, such as pH, the partial pressures of carbon dioxide, bicarbonate, and BE values. The lactate levels were significantly higher in the LEN group than the EEN group (12.216±4.334 vs. 10.028±3.162, p=0.009, respectively). No statistically significant difference was observed between the EEN and LEN groups for HIE degree, mortality, clinical seizures, abnormal aEEG and MRI findings (Table 1).

We observed that nutrition was started in the patients on median 4th (1-8) day and switched to full enteral nutrition time on median 8th (5-20) day. The reaching birth weight time was median 9 (5-25) days, and the total hospitalization time was median 12 (7-43) days. The transition time to full enteral nutrition was delayed (10 [6-20] vs. 7 [5-18] days, respectively, p<0.001); the reaching birth weight time was longer (respectively, 10 [5-22] vs. 7.5 [5-25] days, respectively, p<0.001) and the hospitalization time was longer (13 [8-43] vs. 9 [7-35] days, respectively, p<0.001) in the LEN group compared with the EEN group. One patient developed NEC and six patients developed feeding intolerance. There was no statistical difference between

Table 1. Distribution of patients' demographic and clinical data and blood gas parameters

	All patients (n=91)	The early enteral nutrition group (n=40)	The late enteral nutrition group (n=51)	p
Birth weight, g*	3194.95±448.458	3261.13±414.527	3143.04±470.876	0.214
Gender (female) n (%)	29 (31.9)	12 (30)	17 (33.3)	0.822
Mode of Delivery (Caesarean) n (%)	62 (68.1)	30 (75)	32 (62.7)	0.260
Gestational weeks, week**	38 (35-42)	39 (35-42)	38 (35-41)	0.066
1st min APGAR score**	5 (1-8)	5 (1-8)	4 (1-7)	0.837
5th min APGAR score**	6 (1-9)	7 (3-9)	6 (1-8)	0.339
10th min APGAR score**	7 (1-9)	7 (5-9)	7 (1-9)	0.265
PH*	6.911±0.134	6.937±0.129	6.892±0.135	0.114
The partial pressure of carbon dioxide* mmHg	70.38±23.34	71.358±23.516	69.614±23.406	0.726
Bicarbonate* mmol/L	13.277±3.342	13.953±2.811	12.757±3.646	0.088
Base excess* mmol/L	-17.898±4.447	-17.083±4.145	-18.537±4.609	0.122
Lactate*	11.254±3.995	10.028±3.162	12.216±4.334	0.009
Seizures in 72 h n (%)	13 (14.3)	3 (7.5)	10 (19.6)	0.135
Abnormal aEEG trace n (%)	22 (24.2)	6 (15)	16 (31.4)	0.087
Abnormal cranial MRI n (%)	16 (17.5)	5 (12.5)	11 (21.6)	0.284
Modarete of HIE n (%)	76 (83.5)	36 (90)	40 (78.4)	0.165
Mortalty rate n (%)	2 (2.2)	0	2 (3.9)	0.502

*Values are given as mean±standard deviation. ** Values are given as median (minimum - maximum). Results showing the statistical comparison between the early and late enteral nutrition groups. aEEG: Amplitude-integrated electroencephalogram; HIE: Hypoxic-ischemic encephalopathy; Min: Minute; MRI: Magnetic resonance imaging.

Table 2. Distribution of patients' nutritional status and related conditions

	All patients (n=91)	The early enteral nutrition group (n=40)	The late enteral nutrition group (n=51)	p
First nutrition time **day	4 (1-8)	3 (1-3)	4 (4-8)	**<0.001**
Transition time to full enteral nutrition **day	8 (5-20)	7 (5-18)	10 (6-20)	**<0.001**
The reaching birth weight time** day	9 (5-25)	7.5 (5-25)	10(5-22)	**<0.001**
Hospitalization time** day	12 (7-43)	9 (7-35)	13 (8-43)	**<0.001**
Discharge weight*, g	3315.82±462.854	3334.38±413.491	3301.27±501.767	0.737
Invasive mechanical ventilation time** day	1 (0-33)	0.5 (0-10)	1 (0-33)	**0.034**
Umbilical catheter n (%)	66 (72.5)	24 (60)	42 (82.4)	**0.032**
Inotropic support n (%)	17 (18.7)	4 (10)	13 (25.5)	0.102
Nutrition with Formula n (%)	53 (58.2)	21(52.5)	32 (2.7)	0.442
Necrotizing enterocolitis n (%)	1 (1.1)	0	1 (2)	1.00
Feeding intolerance n (%)	6 (6.6)	1 (2.5)	5 (9.8)	0.224
Sepsis n (%)	4 (4.4)	0	4 (7.8)	0.070

*Values are given as mean±standard deviation. ** Values are given as median (minimum - maximum). Results showing the statistical comparisons between the early and late enteral nutrition groups.

the two groups. The time of invasive ventilation was longer (1 [0-33] vs. 0.5 [0-10] days, respectively, p=0.034) and the number of patients with an umbilical catheter was higher (42 [82.4%] vs. 24 [60%], respectively, p=0.031) in the LEN group compared with EEN group (Table 2).

Discussion

Delaying of starting enteral nutrition during TH in the units is due to the fear of NEC and feeding intolerance. There is no evidence to support this fear, but it is rather a custom. Reports indicate that enteral nutrition during TH is safe and may reduce the risk of sepsis, as well as lower the incidence of NEC, hypoglycemia, and feeding intolerance.[19] We found that starting nutrition early during TH did not increase nutrition-related complications, and the transition time to full enteral nutrition, reaching their birth weight, and hospitalization time were shorter. Similar observations were made in a study conducted in China, where patients who received early minimal enteral nutrition during TH experienced a lower rate of abdominal distension, shorter hospitalization times, and no increase in the incidence of NEC.[20] Gale et al.[21] reported that NEC was rare in newborns receiving enteral nutrition during TH. They concluded that enteral nutrition during TH is safe and associated with more favorable outcomes compared to delayed nutrition. Alburai et al.[22] demonstrated that minimal enteral nutrition during TH is safe and leads to shorter time to full enteral nutrition and higher breastfeeding rates at discharge. Our patients had low sociocultural levels and the rate of breastfeeding was low. The rate of formula feeding was higher in the LEN group than in the EEN group, although it was not statistically significant.

Enteral nutrition is also associated with shorter parenteral nutrition time and central venous line duration, which are considered as risk factors for late-onset sepsis.[23] A study conducted using the national neonatal research database, examined the data of 6030 TH-administered newborns showing that the administration of parenteral nutrition during TH was associated with a higher rate of late-onset sepsis.[24] The umbilical catheter rate was higher and the invasive ventilation period was longer in the LEN group. Sepsis developed in four patients in the LEN group, and all of them had an umbilical catheter. A study observed that more caution should be exercised when starting to feed babies with high lactate levels and impaired renal function, as these values may be related to the time taken to transition to full enteral nutrition. It has been shown that feeding clinically stable newborns with HIE as soon as possible is associated with better clinical outcomes.[25] In our study, the lactate levels were significantly higher in the LEN group. The need for inotropic support was higher in the LEN group, although not statistically significant.

Conclusion

Our study's limitations are that it is a single-center, retrospective analysis, and low number of cases. However, it holds value given its focus on HIE, a topic still under active investigation in neonatal research. Based on our findings, early initiation of enteral nutrition in patients undergoing TH appears to be safe. It does not increase nutrition-related complications and may contribute to a shorter hospitalization period. Future multicenter, prospective studies with adequate sample sizes are necessary to determine the optimal type, timing, frequency, and volume of enteral nutrition. Additionally, only 15 patients in our study group had severe asphyxia, and we were unable to analyze them separately. We believe that further research is needed on this topic, and that distinct nutritional protocols may be established for moderate and severe asphyxia cases.

Disclosures

Ethics Committee Approval: The study was approved by the Harran University Clinical Research Ethics Committee (date: 02.10.20, no: HRÜ/23.18.04).

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