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Clinical Observation in Premature Babies with Feeding Intolerance

Beslenme İntoleransı Olan Erken Doğan Bebeklerde Klinik Gözlem

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Abstract

Aim: Feeding intolerance (FI) is a digestive disorder that presents with gastric residue, abdominal distension, and vomiting, especially in preterm infants, and it often causes a prolongation of the transition to full enteral feeding. Nutrition strategies pose a significant clinical challenge for neonatologists. Attempts to treat FI have used methods such as minimal enteral nutrition and a slow increase in sustenance, probiotic use, the prevention or treatment of necrotizing enterocolitis (NEC) and sepsis, and the use of specially formulated foods, but these methods are only partially effective.

Material and Method: Infants born at less than 32 weeks and 1500 g hospitalized in Konya City Hospital between August 2020 and January 2022 were evaluated retrospectively. Babies with and without FI were divided into two groups, and their demographics and clinical conditions were examined. The treatment modalities of the FI group were evaluated.

Results: Of the 86 patients in the study, 36 were included in the FI group and 50 in the healthy control group. Late neonatal sepsis and duration of parenteral nutrition were found to be statistically significantly higher in the group with FI compared to the control group ($p<0.005$). In eight of the patients, hydrolyzed formula was used, and the transition to total enteral nutrition was achieved in a short period.

Conclusion: The diagnosis of FI is based on nonspecific clinical symptoms. When the underlying etiopathogenesis is clarified, treatment approaches may change. According to our study, it has been shown that regardless of the underlying cause of FI, hydrolyzed formulas may be viable as a alternative dietary option for short-term administration.

Keywords: Premature babies, feeding intolerance, nutrition

Öz

Amaç: Beslenme intoleransı, özellikle preterm bebeklerde görülen gastrik rezidü, abdominal distansiyon ve/veya kusma ile kendini gösteren, sıklıkla tam enteral beslenmeye geçişin uzamasına neden olan sindirim bozukluğudur. Beslenme stratejisi, neonataloglar için önemli bir klinik zorluktur. Minimal enteral beslenme ve beslenmenin yavaş arttırılması, probiyotik kullanımı, NEK ve sepsisten korunma/tedavisi, özel formüllü gıdaların kullanılması gibi yöntemlerle beslenme intoleransı tedavi edilmeye çalışılmaktadır, ancak bu yöntemler tam olarak etkili değildir.

Gereç ve Yöntem: Konya Şehir Hastanesinde Ağustos 2020- Ocak 2022 tarihleri arasında yatırılan 32 hf ve/veya 1500 gr altındaki bebekler retrospektif olarak değerlendirildi. Beslenme intoleransı olan ve olmayan bebekler iki gruba ayrılarak demografik ve klinik durumları incelendi. Beslenme intoleransı olan grubun tedavi şekilleri değerlendirildi.

Bulgular: Çalışmaya alınan seksen altı hastanın, 36 tanesi beslenme intoleransı grubuna 50 tanesi sağlıklı kontrol grubuna dahil edildi. Beslenme intoleransı olan grupta geç neonatal sepsis ve parenteral beslenme süresi kontrol grubuna göre istatistiksel olarak anlamlı derecede daha yüksek saptandı($p<0,005$). Hastalardan 8 tanesinde hidrolize formula kullanılarak kısa sürede tam enteral beslenmeye geçiş sağlandı.

Sonuç: Beslenme intoleransı tanısı, spesifik olmayan klinik belirtilere dayanmaktadır. Altta yatan etiyopatogenez netleştiğinde tedavi yaklaşımları değiştirebilir. Çalışmamız ile, beslenme intoleransının altında yatan neden ne olursa olsun hidrolize formulaların alternatif bir beslenme seçeneği olarak kısa süreliğine kullanılabileceği gösterilmiştir.

Anahtar Kelimeler: Prematüre infant, beslenme intoleransı, nutrisyon

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INTRODUCTION

The survival rate of preterm infants has increased significantly in recent years due to the development of various medical treatments and life-support technologies. However, quickly and safely achieving total enteral nutrition in preterm infants remains a significant challenge for neonatologists.[1,2] Difficulties with enteral nutrition are due to immature digestion, absorption, and immunological functions. One of these difficulties, feeding intolerance (FI), is a significant problem, especially for babies born at less than 32 weeks of gestational age or fewer than 1,500 g; it occurs in approximately 75% of these cases.[2-4]

FI is a well-known phenomenon in the neonatal intensive care unit (NICU) and is linked to morbidity and mortality in premature infants; however, a universal definition of this concept is lacking. Often, enteral nutrition clinical evidence of intolerance many signs in the literature; the definition is available. The most accepted definition is nutrition decrease, delay, or discontinuation of abdominal gastric residual volume (previously more than 50% of the nutritional amount). It is a digestive disorder with distension and vomiting.[5] Limited gastric acid secretion, restriction in enterokinase, lactase activity, and the deterioration of intestinal flora after birth (cesarean delivery, hospitalization, and antibiotic use) play essential roles, but the etiology is unclear. FI delays the transition to total enteral nutrition and extends the duration of parenteral nutrition in preterm infants, thus increasing the risk of infections, prolonging the length of hospital stays, and increasing economic costs.[6,7] There are some prevention and treatment measures for FI, including the optimization of enteral nutrition, modification of feeding methods, and use of probiotics, but these measures are only partially effective. It is not possible to use a single nutritional protocol or guide for all patients; thus, the feeding strategy for FI is a significant clinical challenge for neonatologists.[6] In this article, we present the characteristics of patients with FI, and we aim to bring to the attention of clinicians our various approaches and experiences regarding nutritional intolerance.

MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 02.03.2023, Decision No: 2023/021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective cohort study was conducted in Konya City Hospital, Turkey, between August 2020 and December 2022. A total of 86 preterm infants born with a gestational age (GA) of<32 weeks and birthweight (BW) of<1500 g were enrolled. Two groups were formed one with FI and one without FI. The exclusion criteria included significant congenital anomalies, death, and lack of family consent.

Clinical characteristics of the study population, such as BW, GA, gender, mode of delivery, administration of antenatal corticosteroids, preeclampsia/eclampsia, infants of diabetic mothers, chorioamnionitis (clinical or histopathological), respiratory distress syndrome (RDS), intraventricular hemorrhage (grade > 3), early- and late-onset sepsis (EOS and LOS, respectively), hemodynamically significant patent ductus arteriosus (PDA), first feeding time, the use of any diets at first feeding, duration of parenteral nutrition, and diet at discharge were recorded. Data on the causes and treatment modalities of FI were collected.

Statistical analyses were conducted using SPSS version 17.0 (SPSS et al.). The results are presented as numbers (n), frequencies (%), means with respective standard deviation (SD), and medians. Nonparametric tests were used to analyze the continuous variables. The chi-square test was used to compare categorical variables. Logistic regression analysis was performed to determine the independent risk factors for FI. Statistical significance was set at $p<0.05$.

RESULTS

Thirty-six neonates with FI and 50 healthy controls were enrolled. The median BW and GA of the patients with FI were 1130 g (840-14,800 g) and 27 weeks (23-30 weeks), respectively. Patients and controls were similar regarding GA, BW, gender, mode of delivery, ratio of antenatal steroids, RDS, intraventricular hemorrhage (IVH), PDA, and EOS (**Table 1**).

Compared with the control group, patients with FI also had a higher incidence of LOS (30% vs. 72.2%), and the duration of parenteral nutrition (nine vs. 14 days) was significantly higher ($p<0.005$). The two groups had similar nutrition, the first feeding time, and nutrition at discharge. In this study, most preterm infants were expressed human breast milk (HBM). The patient group was discharged with amino acid-based formulas (**Table 1**). Logistic regression analysis revealed that LOS (OR: 6.07, 95% CI: 2.35-15.65, $p<0.001$) was independently associated with the development of FI.

Six patients in the FI group had necrotizing enterocolitis (NEC), and 20 had LOS. Intestinal maturation was accepted as the cause of FI symptoms in 10 patients (**Table 2**). Antibiotics and probiotics were used alone or in combination to treat these patients. Eight patients benefited only from amino acid-based formulas (**Table 3**).

Table 1: Demographic and clinical characteristics

	FI group (n = 36)	Control group (n = 50)	P value
GA*, weeks	27 (23-30)	28 (23-30)	0.325
Birth weight* (g)	1130 (837-1480)	1225 (680-1490)	0.020
Gender (n/%)			
Female	17 (47.3%)	23 (46%)	0.482
Male	19 (52.7%)	27 (54%)	
Delivery type (n/%)			
VD	4 (11.1%)	10 (20%)	0.271
C/S	32 (88.9%)	40 (80%)	
Antenatal steroids (n/%)			
No	11 (30.5%)	13 (26%)	0.566
Single dose	1 (2.8%)	4 (8%)	
Full dose	24 (66.7%)	33 (66%)	
Maternal disease (n/%)			
No	28 (77.8%)	46 (92%)	0.150
Preeclampsia	7 (9.4%)	3 (6%)	
Gestational diabetes	1 (2.8%)	1 (2%)	
PPROM (n/%)			
No	33 (91.7%)	49 (98%)	0.169
Yes	3 (8.3%)	1 (2%)	
RDS (n/%)			
No	12 (33.3%)	24 (48%)	0.174
Yes	24 (66.7%)	26 (52%)	
IVH (n/%)			
No	34 (94.4%)	50 (100%)	0.092
Yes	2 (5.6%)	0 (0%)	
PDA (n/%)			
No	17 (47.2%)	33 (66%)	0.082
Yes	19 (52.8%)	17 (34%)	
EOS (n/%)			
No	35 (97.2%)	45 (90%)	0.195
Yes	1 (2.8%)	5 (10%)	
LOS (n/%)			
No	10 (27.8%)	35 (70%)	<0.005
Yes	26 (72.2%)	15 (30%)	
First feeding time (h)	2.47 ± 1.10	1.98 ± 0.87	0.139
Use of any diets at first feeding			
Fortified HBM	23 (63.9%)	37 (74%)	0.314
Formula for PM	13 (36.1%)	13 (26%)	
Duration of parenteral nutrition (days)	14 (7-42)	9 (5-18)	<0.005
Diet at discharge			
Fortified HBM	16 (44.4%)	40 (80%)	0.005
Formula for PM	11 (30.6%)	10 (20%)	
Hydrolyzed formulas	9 (25.0%)	0 (0%)	

VD: vaginal delivery; C/S: Cesarean section; PPROM: preterm premature rupture of membranes RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage (grade>3), PDA: hemodynamically significant patent ductus arteriosus; EOS: early-onset sepsis; LOS: late-onset sepsis; ROP: retinopathy of prematurity (severe ROP defined as ROP requiring treatment); HBM: human breast milk; PM: premature infant.

Table 2: Causes of FI (n/%)

Disease	n (%)
NEC	6 (16.6%)
LOS	20 (72.2%)
Diğer	10 (11.2%)

NEC: necrotizing enterocolitis; LOS: late onset sepsis.

Table 3: Treatment of FI (n)

Treatment administered	15
Antibiotics	15
Probiotics	6
Antibiotics and probiotics	7
Hydrolyzed formulas	8

DISCUSSION

In this study, we found that the first feeding time and usage of human breast milk (HBM) were similar between the two groups, but that the duration of total parenteral nutrition was more prolonged in patients with FI. FI in preterm infants can be a sign of various problems, ranging from minor, self-limiting illnesses to severe, life-threatening ones.[4,5] Cetinkaya et al. showed that FI was an independent risk factor for LOS development in premature very low BW (VLBW) infants.[8] LOS is a significant complication of prematurity and the leading cause of morbidity and mortality. Early enteral feeding should start as soon as possible to enhance gastrointestinal maturation by stimulating hormone secretion and motility. Delaying the introduction of enteral feeding causes prolonged parenteral nutrition; therefore, parenteral nutrition is associated with complications such as bloodstream infections.[8,9] In our study, we found that the presence of late sepsis increased the risk of FI six times.

It is well known that HBM is the best choice for infants and is associated with a lower incidence of FI, NEC, and LOS.[10,11] Our study found that breastfeeding with HBM exclusively was similar in the two groups. We thought that the development of FI with breastfeeding was due to an intrinsic factor, such as lactose intolerance or differences in genetics and microbiome.

Many studies have found pathologic high-risk factors associated with FI (e.g., low GA, low BW, RDS, enteral feeding delay, premature infant formula feeding, and hemodynamically significant patent ductus arteriosus (hsPDA).[12] In our study, there were no statistical differences in comorbidities and clinical characteristics between the two groups.

One of the underlying causes of FI is NEC pathophysiology. This condition can damage the intestinal lining and lead to the malabsorption of nutrients and a host of other problems. Diagnosing FI and NEC can be challenging, as their symptoms can be similar to those of other conditions; however, doctors can use a combination of blood tests, stool tests, and imaging studies to help make a diagnosis. Once a diagnosis is made, treatment can begin. Treatment for FI often involves avoiding deleterious food or ingredients. In some cases, supplements or alternative foods may be recommended to help replace missing nutrients. The treatment of NEC may involve antibiotics to control infection, surgery to remove damaged tissue, or other interventions, depending on the severity of the condition. NEC is a leading cause of mortality and morbidity in preterm infants and deficient BW infants.[13] Antibiotics and probiotics were used alone or in combination to treat these patients (probiotics and amino acid-based formula [AAF]). Six patients in the FI group had NEC.

HM is associated with less FI and is recommended by the World Health Organization as the first-choice milk for preterm infants. However, when HBM cannot be used in patients with FI, the alternative formulas include preterm formula (PF), partially hydrolyzed formula, extensively hydrolyzed formula, AAF, and others. PF is used frequently in preterm infants.[3,6,14]

In our study, eight babies with resistant FI were fed with AAF and switched to full enteral feeding as early as possible. Hydrolyzed protein formula (HPF) has also been shown to accelerate early feeding advancement in VLBW infants, and Tormo et al. showed that HPF induced higher motilin levels than intact protein formula. Additionally, protein hydrolysis may accelerate gastrointestinal transit via reduced β-casomorphin activity.[15] Mengyuan et al. reported that HFs might improve gastrointestinal tolerance in preterm infants, including reducing the risk of FI and shortening the time required to transition to full enteral feeding. Given the paucity of data on the topic, whether AAF can benefit FI LBW neonates via the exact mechanisms as HFs is still being determined.[16] A study by Raimondi et al. presented, in infants with severe FI, inadequate BW, short-term AAF feeding as a rescue strategy was concluded to be safe and effective. The long-term nutritional adequacy of AAF and HPF in extremely preterm neonates still requires further study.[17]

CONCLUSION

The current definition of FI is based on nonspecific clinical signs. It does not guide clinicians on how to differentiate developmental FI from pathological FI. The clear presentation of an underlying etiopathogenesis may also change treatment approaches. Based on our study, regardless of the underlying cause of FI, AAFs and HFs may be viable alternative nutritional options to be applied for a short time. However, in premature infants with FI, randomized controlled studies are needed to confirm the methodology related to treatment approaches in a robust and large number of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 02.03.2023, Decision No: 2023/021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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