



Long-term Neurodevelopmental Assessment in Preterm Infants with Early Full Enteral Feeding and Weight Gain Rates

Küçük Prematüre Bebeklerde Erken Tam Enteral Beslenmeye Geçiş ve Kilo Alım Hızları ile Nörogelişimleri Arasındaki İlişkinin İncelenmesi

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ABSTRACT

Objective: This study aims to examine whether there is a relationship between neurodevelopmental outcomes with transition into early full enteral feeding and weight gain rates in preterm infants.

Methods: Evaluated infants' gestational ages were less than 32 weeks, birth weights were between 800 and 1.200 grams, and corrected ages were 24th months. Patients were divided into two groups, of those with transition into full enteral feeding in less than two weeks (group E) and those with transition into full enteral feeding in longer than two weeks (group L). Two additional groups were also compared, of those with weight gain rates above 10 g/day (group 1) and below 10 g/day (group 2), in the first month of life. Differentiations in neurodevelopment scores [mental development index (MDI), psychomotor development index (PDI)] were evaluated.

Results: The total number of assessed infants was 330. Among them, 137 were in group E and 134 were in group L. MDI comparison was 69 and 62, respectively. The PDI comparison was 79 and 73, respectively. Compared with group 1 (n=120), lower MDI and PDI were detected in group 2 (n=110). Accordingly, both factors of late transition into full enteral feeding and low daily weight gain rate were associated with neurodevelopmental impairment. With respect to weight gain, the RR was 2.26 (1.15-4.43), p=0.018. With respect to transition into full enteral feeding, the RR was 3.46 (1.84-6.49), p=0.001.

Conclusion: In the early period of life, feeding difficulties and weight gain rates of preterm infants must be monitored delicately. Nutritional difficulties constitute a negative influence on neurodevelopment.

Keywords: Newborn, preterm infants, early enteral feeding, early weight gain, neurodevelopmental outcomes

ÖZ

Amaç: Bu çalışmada, küçük prematüre bebeklerde erken dönem tam enteral beslenmeye geçiş ve kilo alım hızlarıyla nörogelişim arasında bir ilişki olup olmadığını araştırmak amaçlanmıştır.

Yöntem: Doğum ağırlığı 800-1.200 gram arasında ve gebelik haftası 32 haftadan küçük, düzeltilmiş 24 ayını tamamlamış bebekler çalışmaya alındı. Bu kriterlere uyan bebekler tam enteral beslenmeye geçiş sürelerine göre iki hafta altında olanlar (grup E) ile iki haftadan uzun sürenler (grup L) olarak iki gruba ayrıldı. Kilo alım hızlarına göre de yaşamın ilk ayında ortalama 10 gr/gün üzerinde alanlar (grup 1) ve altında alanlar (grup 2) olarak iki farklı grupta kıyaslandı. Bu gruplar arasındaki farklar ve nörogelişim skorları [mental development indeks (MDI), psikomotor development indeks (PDI)] arasındaki ilişkiler incelendi.

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Bulgular: Çalışmaya alınan 330 bebeğin, 137'si grup E'de, 134'ü grup L'de idi. Bu iki grubun MDI ve PDI'ları kıyaslandığında sırasıyla, ortalama 69'a karşı 62, ve 79'a karşı 73 olduğu görüldü. Grup 1 (n=120) ve grup 2 (n=110) karşılaştırıldığında, grup 2'de daha düşük MDI ve PDI saptandı. Kilo alım hızının az olması ve tam enteral beslenmeye geçişin geç olmasının, nörogelişimsel bozuklukla ilişkili olduğu gösterildi. Kilo alım hızı için RR: 2,26 (1,15-4,43), p=0,018, tam enterale geçiş için 3,46 (1,84-6,49) p=0.001 idi.

Sonuç: Prematüre bebeklerin erken dönemde beslenmeleri ve kilo alım hızları çok dikkatlice takip edilmelidir. Ek morbiditeleri olmayan prematüre bebeklerin bile sadece beslenme sorunları nörogelişimlerini olumsuz etkileyebilmektedir.

Anahtar Kelimeler: Yenidoğan, prematüre bebek, erken enteral beslenme, erken kilo alımı, nörogelişimsel sonuçlar

INTRODUCTION

One of the ways to reduce preterm morbidity is to initiate early enteral feeding. Inadequate postnatal nutrition, especially in the first four weeks of life, is an independent risk factor for chronic lung disease in preterm infants.¹ Early enteral feeding contributes to the reduction of complications, such as necrotizing enterocolitis (NEC) and late-onset sepsis, through assuring functional cohesion of the gastrointestinal tract and by inhibiting microbial colonization.² The delay of enteral feeding due to intestinal dysmotility prolongs the transition into full enteral feeding. Consequently, as intravenous feeding extends, infectious and metabolic complications increase, and growth and development are also adversely affected.³

Increased energy and macronutrient intake during early postnatal weeks raises the language scores of very low birth weight (VLBW) infants, boosts the developmental quotient scores of those born before 28 weeks, and reduces the incidences of brain damage in magnetic resonance imaging.⁴⁻⁶

In addition to brain damage, undernutrition is known to have further adverse effects such as lower immune response, reduced resistance to infections, inability to accommodate the essential energy for recovering acute or chronic lung diseases, and failure to achieve a proper growth and development rate.⁷

In preterm infants, accelerated weight gain from birth to term age will facilitate a better neurodevelopmental outcome.⁷

This study investigated whether there is a relationship between neurodevelopment and transition into early full enteral feeding and weight gain rates in preterm infants.

METHODS

Infants who were born between January 2013 and December 2017, birth weight was between 800 and 1.200 grams, gestational age of less than 32 weeks were included in the study. By November 2018, their neurodevelopmental examination was completed at the corrected age of 24 months. Medical records were retrospectively accessed from patient files and the hospital electronic database.

Infants who met the criteria above were divided into two groups based on their transitions into full enteral feeding

in less than two weeks (group E) and longer than two weeks (group L). Two additional groups were further compared, based on their average weight gain rates in the first month of life, of those above 10 grams per day (group 1) and below 10 grams per day (group 2).

In our clinic, a strategy close to aggressive nutrition protocols is carried out to switch to enteral nutrition early. Minimal enteral feeding is initiated as soon as possible, preferably with breastmilk (10-20 cc/kg/d) within the first days of life. Parenteral nutrition is gradually reduced and enteral feeding is increased as tolerated. Transition to full enteral feeding is accomplished when 160 cc/kg/d dose is reached.

Moreover, the differences and neurodevelopment scores [mental development index (MDI), psychomotor development index (PDI)] were examined at the corrected age of 24 months. Bayley II (Bayley Scales of Infant and Toddler Development-2nd ed.) developmental test, MDI, and PDI progress were evaluated by a pediatrics division composed of one associate professor of pediatrics and four child development specialists. MDI and PDI scores lower than 70 in either one or both were identified as neurodevelopmental impairment (NDI).⁸

Maternal diabetes, chorioamnionitis, and pre-eclampsia were affirmed in patients' files. Antenatal steroids were administered by a minimum betamethasone application of two doses within 24 h before birth. Small for gestational age (SGA) patients were identified. Infants who required mechanical ventilation for at least 24 h were specified. Intraventricular hemorrhage was diagnosed by cranial trans fontanel ultrasonography, where severities were rated on Papile staging.⁹ Periventricular leukomalacia was diagnosed and staged upon the typical symptoms detected on ultrasonography.¹⁰ NEC was diagnosed and categorized upon modified Bell staging.¹¹ Bronchopulmonary dysplasia (BPD) was classified as either mild, moderate, or severe based on the international diagnostic criteria.¹²

Infants with proven sepsis or meningitis, who had bacterial growth in their blood culture, or who had demonstrated clinical sepsis symptoms were diagnosed with neonatal sepsis. Meningitis was diagnosed if the microorganism was isolated within cerebrospinal fluid samples.

The study was initiated after the confirmation of the Ethics Committee of the University of Health Sciences Turkey, Ankara City Hospital (approval no: E1-20-168, date: 28.05.2020).

Statistical Analysis

Baseline demographics and neonatal outcomes were compared among two groups: infants with early and late feeding, using the chi-square test for categorical variables and the Student's t-test for continuous variables. To further examine the effect of full enteral feeding and weight gain, multiple logistic regression models were applied to compare the primary and secondary outcomes between the groups. The odds ratio (95% confidence interval) of outcomes was determined based on the final multiple logistic regression models derived by the backward variable selection procedure with an inclusion criterion of 0.05. The gestational age and birth weight were used as covariates to correct the data according to these variables. Data management and all statistical analyzes were performed using Statistical Package for the Social Sciences for Windows® version 22 (IBM, USA). A two-sided significant level of 0.05 was used.

RESULTS

Out of 380 patients, 50 were disqualified due to inappropriate data, surgery requiring morbidity, grade 3-4 intraventricular hemorrhage, or detection of congenital anomaly. A total of 330 patients were involved in the study. The average birth weight was 1017±73 grams. Patients were born between 24th-32nd weeks of gestational age, where the average was 28±1.9 weeks.

As patients were grouped upon NDI conclusions, they displayed similarities in terms of birth weight, gestational week, mode of delivery, administration of antenatal or postnatal steroids, and sepsis (Table 1).

As patients were grouped according to nutritional conditions, group E displayed higher MDI and PDI scores than group L, the difference was statistically significant. As daily weight gain rates were compared, group 1 displayed statistically higher MDI and PDI scores than group 2 (Table 2).

Taking gestational week and weight at birth into account, nominal regression analyses point out that group L has demonstrated an NDI increase that is 3.46 times [95% confidence interval (CI): 1.84-6.49] higher than group E, whereas group 2 has demonstrated an NDI increase that is 2.26 times (%95 CI: 1.15-4.43) higher than group 1. Delays in full enteral feeding and low rates of daily weight gain were independent risk factors for worsened NDIs.

DISCUSSION

This study validates that a delay in full enteral feeding and a slow weight gain rate during NICU stay increase the probability for NDI diagnoses during the corrected age of 24 months examinations, independent of all other morbidities.

Preterm infants are prone to NDI risk.¹³ Previous studies demonstrate the particular consequence of weight gain rate in the early neonatal period on neurodevelopment through the preceding time.^{5,6,14,15} The study by Franz et al.¹⁶, reveals that on multiple regression analyses, taking perinatal risk factors and socioeconomic circumstances

	MDI >70 and PDI >70 n=218	MDI/PDI <70 n=112	p
Birth weight (grams)	1023±119	1009±110	0.254
Gestational age (weeks)	28.3±1.9	28.1±1.8	0.253
Male gender (n, %)	125 (57)	62 (56)	0.730
Singleton (n, %)	188 (86)	94 (85)	0.573
SGA	30 (13)	20 (18)	0.325
Chronic lung disease, moderate severe (n, %)	71 (32)	45 (40)	0.170
Intraventricular hemorrhage (grade 1-2), in any USG	101 (46)	58 (52)	0.347
Antenatal steroid (n, %)	163 (74)	88 (78)	0.443
Received postnatal steroid (n, %)	66	41	0.244
Sepsis (n, %)	81	39	0.676
Breastmilk at discharge			
Exclusive	120	63	0.329
Mixed	50	30	
Formula only	48	17	

MDI: Mental development index, PDI: Psychomotor development index, USG: Ultrasonography, SGA: Small for gestational age

into account, slower weight gain rate during the NICU stay is correlated with impaired neurological examination findings and decreased cognitive capacity scores at a median age of 5.4. Another study by Ehrenkranz et al.⁷, proves that increased weight gain rate of VLBW infants during NICU stays is correlated with decreased cerebral palsy (CP) incidences, lesser MDI <70 and PDI <70 scores, reduced number of anomalies in neurological examinations and lower NDI frequencies, during the 18th-24th month evaluations. Likewise, in our study, there were 2.26 times more NDI diagnoses within the group of lesser daily weight gain rates.

Our study evaluates infants between 800-1.200 grams. This is due to two reasons, since infants over 1.200 g exhibit relatively lesser feeding difficulties, but infants under 800 g outstand with separate morbidities. Stable born preterm infants at a gestational age of 32 weeks and more or heavier than 1.500 g usually initiate enteral feeding right from birth, very much like term infants.¹⁷ Nevertheless, extremely preterm or VLBW infants devour prolonging gastric passage time, they are subject to insufficient intestinal motility and have higher probability of developing NEC.¹⁷

Our study concedes the early full enteral feeding as all nutritional intake is enteric with no parenteral support and it is initiated within the first two weeks of life. Studies demonstrate that transition into full enteral feeding in small preterm infants will shorten the hospital stay and decrease the incidence of clinical or culture-proven sepsis because the duration of parenteral feeding duration reduces.^{3,18,19} Feeding intolerance and delay of transition into full enteral feeding are associated with poor mental activities, as the corrected 24th month examinations suggest.^{20,21} In line with the general literature, our study has also confirmed that patients delayed for full enteral feeding have displayed 3.46 times more NDI incidences, as the corrected 24th month examinations suggest.

Since our study has a retrospective design, we were not able to use Bayley 3 scaling, which is a rather novel

technique. if both Bayley 2 and 3 scales were projected on the same group of infants, the Bayley 2 scale would suggest lower scores.²²⁻²⁴ Therefore, the neurodevelopmental scores of our patients may have been measured lower. Notwithstanding, as Bayley 2 scores appear lower, this may avert a curtailment on the diagnosis of actual neurodevelopmental delays.²⁵

A recent study investigating long-term outcomes of preterm infants fed an exclusive human milk-based diet during hospitalization reported an absence of severe cognitive developmental delay using a Bayley 3 cutoff score of 70 measured at 18-22 months corrected gestational age.²⁶ In our study, there was no significant difference between the infants with or without NDI in terms of exclusive breastfeeding at discharge. Nevertheless, the exclusive breastfeeding ratio at discharge among patients without NDI was higher.

Study Limitations

The limitation of this study is that relatively handpicked groups of patients were evaluated. Operated SGA, BPD, NEC, and CP patients were excluded. Additionally, evaluated preterm infants had reasonable family and environmental factors, so they appeared on the corrected 24th month examinations. However, these restrictions enabled a particular emphasis on the assessment of nutritional problems.

Another limitation of the study is that our study does not contain information about oral feeding characteristics. Since the feeding of the infants was evaluated within the first month of life, the main aspect was the target to reach full enteral feeding and its effects on neurodevelopment. In a retrospective study, which was designed to reveal the factors associated with the full oral feeding time, it was observed that infants with a full enteral feeding transition time shorter than <14 days were able to achieve full oral feeding better.²⁷

The strength of this study was that there were an abundant number of patients and all were followed up by the same

	Group 1 n=120	Group 2 n=110	p
MDI	79 (±18)	67 (±16)	0.00
PDI	82 (±19)	73 (±16)	0.00
	Group E n=137	Group L n=134	p
MDI	69 (±11)	62 (±11)	0.00
PDI	79 (±18)	73 (±17)	0.008

NDI: Neurodevelopmental impairment, MDI: Mental development index, PDI: Psychomotor development index, USG: Ultrasonography, SGA: Small for gestational age

medical institution. As a result, there were no differences among patient follow-ups and assessment strategies.

CONCLUSION

In conclusion, preterm infants bear multiple morbidities at once. Nevertheless, enteral feeding should not be ignored either. Since preterm infants are born small, objectives must be set anyhow, both for the initiation and for the full transition into enteral feeding. Thus, appropriate means may be embraced to accomplish the predefined objectives.

Ethics

Ethics Committee Approval: The study was initiated after the confirmation of the Ethics Committee of the University of Health Sciences Turkey, Ankara (approval no: E1-20-168, date: 28.05.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.E.C., Design: F.E.C., Data Collection or Processing: E.O., M.B., G.K.Ş., B.C., Z.Ü., F.E.C., Analysis or Interpretation: E.O., G.K.Ş., H.G.K.K., F.E.C., Literature Search: E.O., Writing: E.O.

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