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Feeding Intolerance in Late Preterm Infants: Single Center Experience.

Intolerancia alimentaria en recién nacidos prematuros tardíos: experiencia de un centro

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Abstract

OBJECTIVE: To determine the frequency and clinical features of the late preterm infants with feeding intolerance.

MATERIASL AND METHODS: Medical records of 426 infants with gestational age of $34^{0/7}$- $36^{6/7}$ weeks were retrospectively reviewed for the study. Clinical and demographic features of late preterm infants and episodes of feeding intolerance were recorded.

RESULTS: A total of 54 late preterm infants with feeding intolerance were evaluated and compared with 178 infants without feeding intolerance. Baseline demographics were similar between groups. Mean duration of intolerance period was 2.3 ± 1.2 days. Time to full enteral feeding was significantly longer in late preterm infants with feeding intolerance when compared with infants without feeding intolerance (8 ± 2.3 vs 5.2 ± 1.7 days, respectively, p<0.001). Breastfeeding rates were similar between the groups. Rate of prokinetic use in the feeding intolerance group was 37%. There were no differences between the time to full enteral feeding and the duration of parenteral nutrition between prokinetic users and non-users.

CONCLUSIONS: Although the gestational ages of late preterm infants are close to term and their size is relatively large, they are not like term infants. These infants should be followed closely in terms of feeding problems as well as many morbidities.

KEYWORDS: Premature infant, enteral nutrition, feeding difficulties, morbidity.

Resumen

OBJETIVO: Determinar la frecuencia y características clínicas de los prematuros tardíos con intolerancia alimentaria.

MATERIALES Y MÉTODOS: Para el estudio se revisaron retrospectivamente las historias clínicas de 426 lactantes con una edad gestacional de 340/7 a 366/7 semanas. Se registraron las características clínicas y demográficas de los recién nacidos prematuros tardíos y los episodios de intolerancia alimentaria.

RESULTADOS: Un total de 54 niños prematuros tardíos con intolerancia alimentaria fueron evaluados y comparados con 178 niños sin intolerancia alimentaria. Los datos demográficos iniciales fueron similares entre los grupos. La duración media del período de intolerancia fue de 2,3 ± 1,2 días. El tiempo hasta la alimentación enteral completa fue significativamente mayor en los lactantes prematuros tardíos con intolerancia alimentaria en comparación con los lactantes sin intolerancia alimentaria (8 ± 2,3 frente a 5,2 ± 1,7 días, respectivamente, p<0,001). Las tasas de lactancia fueron similares entre los grupos. La tasa de uso de procinéticos en el grupo de intolerancia alimentaria fue del 37%. No hubo diferencias entre el tiempo hasta la alimentación enteral completa y la duración de la nutrición parenteral entre usuarios y no usuarios de procinéticos.

CONCLUSIONES: Aunque las edades gestacionales de los prematuros tardíos son cercanas al término y su tamaño es relativamente grande, no son como los recién nacidos a término. Estos bebés deben ser seguidos de cerca en términos de problemas de alimentación, así como de muchas morbilidades.

PALABRAS CLAVE: Recién nacido prematuro, nutrición enteral, dificultades de alimentación, morbilidad

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INTRODUCTION

Late preterm (LP) infants are immature in many ways compared with term infants because of the interruption of the normal fetal development in late pregnancy, a critical time for physiologic and metabolic development of the fetus. Although they look as healthy as full-term infants at birth, several studies have found that LP infants are at increased risk for neonatal mortality and morbidities.[1-10]

Intestinal motor function immaturity causes low motility and delayed gastric emptying in preterm infants, which leads to feeding intolerance. A delay of intestinal maturation generally resulting in prolonged hospital stays. Intestinal dysmotility is usually seen in infants less than 34 weeks of gestation, but may be extended to subsequent weeks.[11,12] Limited data about feeding problems, the need of nutritional support in late preterms have been reported until now.[13,14] Therefore, in this study we aimed to investigate the incidence and clinical characteristics of feeding intolerance in late preterm infants in a tertiary neonatal intensive care unit.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary neonatal intensive care unit (NICU) after approval from the Local Ethics Committee. Medical records of neonates with gestational age $34^{0/7}$ - $36^{6/7}$ weeks and admitted to NICU was considered for inclusion. Exclusion criteria was defined as gastrointestinal anomalies, severe birth asphyxia, congenital heart disease, heart failure, need for invasive respiratory support, history of necrotizing enterocolitis (NEC), sepsis, renal failure, inborn errors of metabolism and chromosomal aberrations.

Parenteral nutrition was started after delivery for all infants. Enteral nutrition (10-20 ml/kg/day) was started on the first day of life as soon as infants' own mothers' breast milk was obtained, and increased as tolerated according to the nutrition protocol of the NICU. Full enteral feeding was defined as 140-150 ml/kg/day. Study infants received own mother's breastmilk, however when human milk was unavailable or insufficient, they received preterm formula. Infants with insufficient sucking or whose clinical condition was not suitable for sucking were fed with an orogastric tube, otherwise they were breastfed.

Presence of gastric residuals (more than 50% of previous feeding volume), abdominal distention and/or vomiting, presence of macroscopic blood in stool, increased abdominal girth and disruption of the patient's feeding were defined as feeding intolerance if any of the sign or symptoms were present.[15] Domperidone (0.75 mg/kg per day) was used as a prokinetic agent in infants with feeding intolerance according to neonatologist's decision.

Demographic and clinical variables of infants with (group 1) or without (group 2) feeding intolerance were recorded and compared with each other. Infants with feeding intolerance (group 1) were further divided into two subgroups based on prokinetic administration (prokinetic users and non-users). The subgroups were compared in terms of clinical outcomes such as time to full enteral feeding and duration of hospitalization.

Statistical Analyses

Patient data were analyzed with the IBM Statistical Package for the Social Sciences *(SPSS)* for Windows 17.0 *(IBM Corp., Armonk, NY)* package program. Categorical variables were analyzed using the chi-squared test. Comparison of mean between two groups was examined using a t-test where the data fit a normal distribution, and the Mann–Whitney U test where the data was non-normal. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

During the study period, 17690 babies were delivered in our hospital and 2844 of them were admitted to the NICU. Of those 426 (15%) were late preterm and 765 (27%) were term infants. Totally 194 of 426 late preterm infants were excluded from the study. 54 of late preterm infants had feeding intolerance **(Figure 1**). The incidence of FI was 23% in late preterm infants.

There were no differences in demographics among infants with or without feeding intolerance. Mean duration of intolerance was 2.1 ± 0.9 days. Time to reach full enteral feeding was 7.8 ± 3.6 days in group 1 and 4.8 ± 1.8 days in group 2. It was significantly longer in infants with feeding intolerance ($p<0.001$) (**Table 1**) Rates of feeding with breast milk were similar in groups. 37% of the infants (n=20) with feeding intolerance were treated with domperidone as a prokinetic agent. There were no differences between the time to reach full enteral feeding and the duration of parenteral nutrition in subgroup analysis between prokinetic users and non-users (**Table 2**).

DISCUSSION

In this study the incidence of feeding intolerance was found as 23% in late preterm infants in a tertiary neonatal center. Feeding intolerance prolongs the time to reach full enteral feeding in late preterm infants. Prokinetic use in infants with feeding intolerance does not shorten this period.

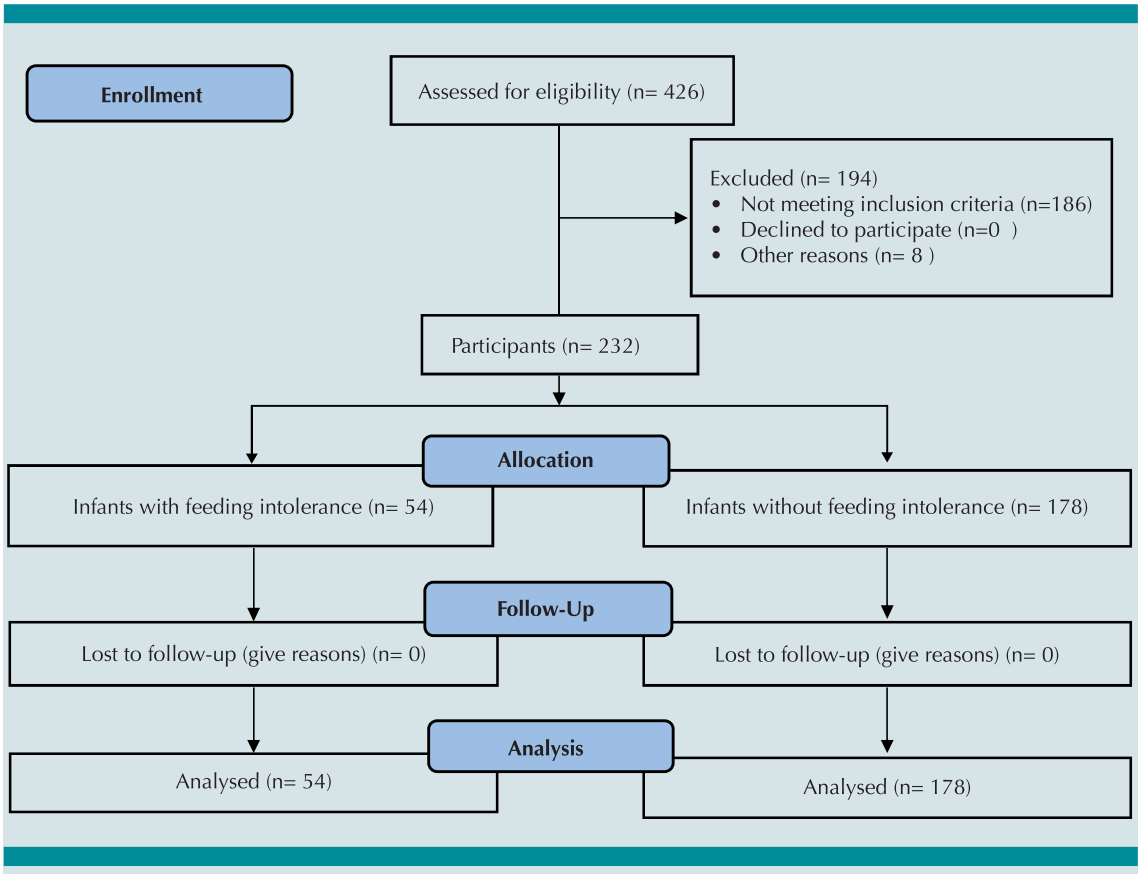

Figure 1. Flow diagram of the study.

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Table 1. Demographic and characteristics of infants with and without feeding intolerance

	Group 1 (n = 54)	Group 2 (n = 178)	p
Gestational age, weeks[a]	35 ± 0.9	35 ± 0.8	0.88
Birthweight, g[a]	2343 ± 635	2299 ± 528	0.61
Male[b]	34 (63)	102 (57)	0.52
Caesarean section[b]	48 (89)	141 (79)	0.16
Apgar score (1 min)[c]	7 (4-8)	7 (2-7)	0.6
Apgar score (5 min)[c]	9 (7-9)	9 (6-9)	0.08
Antenatal steroid use[b]	25 (46)	79 (44)	0.87
SGA[b]	8 (15)	12 (7)	0.06
Feeding with human milk[b]	29 (54)	103 (58)	0.85
Parenteral nutrition, days[b]	6.1 ± 3.2	3.3 ± 1.8	<0.001
Time to full enteral feed, days[a]	7.8 ± 3.6	4.8 ± 1.8	<0.001
Time to access birth weight, days[a]	11.3 ± 3.5	7.7 ± 2.1	0.009
Length of stay in hospital, days[a]	11.2 ± 7.7	7 ± 4.5	<0.001

SGA; small for gestational age.
[a]Mean ± SD, [b]*n* (%), [c]Median (minimum-maximum).

Table 2. Demographic and characteristics of infants in prokinetic users and non-users

	prokinetic users (n = 20)	prokinetic non-users (n = 34)	p
Gestational age, weeks[a]	35 ± 0.85	35 ± 0.92	0.82
Birthweight, g[a]	2325 ± 693	2353 ± 609	0.87
Male[b]	13 (65)	21 (62)	0.81
Caesarean section[b]	19 (95)	29 (85)	0.39
Apgar score (1 min)[c]	7 (4-7)	7 (4-8)	0.31
Apgar score (5 min)[c]	9 (7-9)	9 (7-9)	0.12
Antenatal steroid use[b]	12 (60)	13 (38)	0.16
SGA[b]	4 (20)	4 (12)	0.45
Feeding with human milk[b]	10 (50)	21 (62)	0.63
Day of feeding intolerance[a]	2 .15 ± 0.7	2.1 ± 0.9	0.82
Parenteral nutrition, days[b]	6.4 ± 2.6	5.9 ± 3.5	0.63
Time to full enteral feed, days[a]	8.1 ± 2.9	7.7 ± 4	0.65
Time to access birth weight, days[a]	11.1 ± 3.3	11.4 ± 3.8	0.62
Length of stay in hospital, days[a]	13.5 ± 10.1	9.8 ± 5.6	0.08

SGA; small for gestational age.
[a]Mean ± SD, [b]*n* (%), [c]Median (minimum-maximum).

Late preterm infants constitute a significant proportion of preterm births, and despite their gestational ages being near term and their relatively larger size, they differ substantially from term infants and face heightened risks of morbidity and mortality.[16] Given these vulnerabilities, close observation immediately after birth is imperative. Late preterm infants are particularly prone to feeding intolerance in the early postnatal period due to physiological immaturity, including factors such as gastrointestinal tract immaturity, gastrointestinal dysmotility, and a high incidence of gastroesophageal reflux. Therefore, making it crucial to monitor their feeding cues and responses closely.[16,17]

Maturation of mechanical functions of the gastrointestinal tract (suck-swallow coordination, gastroesophageal sphincter tone and intestinal motility etc.) are important factors in the success of premature infants' feeding. These functions are not fully developed until approximately 34 weeks of gestational age. Intestinal dysmotility is usually seen in infants less than 34 weeks gestation, but may be extended to subsequent weeks.[11,12,18] Immaturity of intestinal function, delayed motility and gastric emptying leads to feeding intolerance in some LP infants. Also feeding problems are important reasons for delay in discharge.[8,12]

Jackson et al. reported factors associated with the rate of achieve to full enteral feeding in late preterm infants.[13] They explained that the factors influencing achieving of full enteral feeding include gestational age, birthweight and cardiac, gastrointestinal and neurological medical conditions. In our study, we excluded infants with such problems in order to rule out cardiac, gastrointestinal and neurological medical conditions that may change the transition process of late preterm infants to full enteral feeding. In addition, patients with severe respiratory distress were also excluded from our study, since severe respiratory distress and the need for an invasive mechanical ventilator may affect the time of transition to full enteral feeding in infants. *Gianni et al.* reported that late preterm infants are at high risk of requiring nutritional support during hospital stay.[14] In their study, rate of infants requiring parenteral nutrition was 4.4% and 33.8% of the infants required intravenous fluids.

Recently feeding difficulties in LP infants have been evaluated in several studies *Wang et al*. reported poor feeding in 75.9% of LP infants.[12] *Kalyoncu et al*. concluded that, LP infants have feeding problems 14 times more likely than term infants.[19] In a study by *Celik et al*. 34% of LP infants had feeding difficulty.[20] *Lubow et al*. reported a significant increase in rates of feeding problems in LP infants when compared with term infants (36% vs 5%, $p< 0.001$).[21] In a review published by *Teune et al.,* feeding problems have been reported in 34% of LP infants.[22] However, these studies have focused on feeding difficulty described by inability to suck from breast or bottle. In our study, we evaluated feeding intolerance rather than feeding difficulty in LP infants. According to our knowledge this is the first study to evaluate feeding intolerance in LP infants. In our study, 23% of LP infants had feeding intolerance. We have left out the reasons that could affect nutrition beyond late prematurity such as major congenital anomalies, asphyxia, sepsis and severe respiratory distress when calculating the incidence of feeding intolerance. Our lower rate of feeding intolerance might be due to the fact that these patients are excluded.

Domperidone, a peripheral dopamine D2-receptor antagonist, is frequently used as a prokinetic agent in the treatment of intestinal motility disorders because of its effects on motility and gastric emptying. There is limited number of studies about domperidone use in newborns. *Gounaris et al*. showed that significant promotion of gastric emptying in very low birthweight preterm infants with domperidone administration.[23] In our study, no significant difference was detected between

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the domperidone users and non-users in terms of time to reach full enteral feeding or duration of hospitalization. This might be due to small sample size of our study. In addition, the slowing of intestinal motility and gastric emptying might not be the only cause of nutritional intolerance in late premature babies.

Our study was notably constrained by its retrospective design, which inherently introduces limitations associated with data collection and potential biases. Moreover, the sample size of patients with nutritional intolerance was relatively small, impeding our ability to draw robust conclusions and potentially limiting the generalizability of our findings. Furthermore, it's essential to acknowledge the scarcity of clinical experience with domperidone in neonates, highlighting the need for caution and further investigation when considering its use in this population. Additionally, the incomplete understanding of domperidone's pharmacokinetics in neonates underscores the importance of conducting dedicated studies to elucidate its metabolism, distribution, and elimination pathways in this vulnerable patient group.

In summary, addressing feeding intolerance in late preterm infants necessitates a comprehensive approach that targets the various factors contributing to feeding difficulties. Healthcare providers should prioritize close monitoring of these infants, especially during the critical early postnatal period, to swiftly identify signs of intolerance and intervene as necessary. An individualized and vigilant approach to feeding management is paramount to ensuring the optimal growth and well-being of late preterm babies. Breast milk is considered the best enteral nutrition option for late premature babies, as it is for all babies. Therefore, facilitating breastfeeding and providing lactation support, including consultation services, can significantly enhance feeding success in this vulnerable population. Furthermore, careful titration of feeding volumes, with strategies such as initiating smaller, more frequent feeds and employing slow feeding techniques, can help mitigate intolerance episodes and foster successful feeding progression. Proactive management of feeding intolerance, characterized by early identification and timely intervention, is crucial to prevent prolonged intolerance periods and facilitate the timely transition to full enteral feeding. By adopting a multifaceted approach that integrates these strategies, healthcare providers can effectively address feeding intolerance in late preterm infants and promote their overall health and development. The increasing prevalence of late preterm neonates underscores the critical need to deepen our understanding of and approach to this unique subgroup of preterm infants. Ongoing research is essential to unravel the complex mechanisms underlying feeding intolerance in this population and to devise targeted interventions that effectively address these challenges.

CONCLUSION

While late preterm infants may share similarities with term infants in terms of gestational age and size, it's crucial to recognize that they possess unique vulnerabilities and medical needs. Despite their proximity to full term, late preterm infants are not equivalent to term infants, and it's imperative to address and manage their specific conditions appropriately. Moreover, this vulnerable population requires close monitoring for feeding intolerance, as they may be at increased risk due to their physiological immaturity and other underlying factors. Therefore, healthcare providers should maintain heightened vigilance and provide tailored care to optimize outcomes for late preterm infants.

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