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Feeding intolerance associates with late onset sepsis in very low birth weight infants

Çok Düşük Doğum Ağırlıklı Bebeklerde Beslenme İntoleransının Geç Neonatal Sepsis ile İlişkisi

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ÖZ

Amaç: Çok düşük doğum ağırlıklı (ÇDDA) bebeklerdeki beslenme intoleransının geç neonatal sepsis (GNS) ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya doğum ağırlığı ≤1500 gram veya gestasyon haftası ≤32 hafta olan infantlar dahil edildi. Kültür ile kanıtlanmış GNS tanısıyla izlenen bebeklerin demografik ve klinik özellikleri, doğum ağırlığı ve gestasyon haftası benzer olan kontrol grubu ile karşılaştırıldı.

Bulgular: Toplam 408 infant (GNS olan n=136, GNS olmayan n=272) değerlendirildi. Çalışmaya dahil edilen hastaların ortalama (±SD) gestasyon haftası ve doğum ağırlığı 27.8 hafta (±1.6) ve 1016.92 gram (±200.39) idi. GNS olan bebeklerde sadece anne sütü ile beslenme oranı daha düşük, beslenme intoleransı daha fazlaydı (sırasıyla p=0.028, p<0.001). GNS olan bebeklerde doğum ağırlığına ulaşma süresi, tam enteral beslenmeye geçiş zamanı, hiç beslenmediği gün sayısı, total parenteral nutrisyon ihtiyacı olan gün sayısı GNS olmayan grup ile karşılaştırıldığında anlamlı olarak daha yüksekti (sırasıyla p=0.048, p<0.001, p<0.001, p<0.001). Günlük kilo alımının, 1.ve 4. haftadaki kilo alımının GNS olan grupta anlamlı olarak daha düşük olduğu bulundu (sırasıyla p=0.000, p=0.045 ve p=0.046). Lojistik regresyon analizinde respiratuar distres sendromu (OR=1.76, 95% CI 1.12-2.76;p=0.013), beslenme intoleransı (OR=3.84 95% CI 2.36-6.24; p<0.001) ve sadece anne sütü ile beslenmenin (OR=0.60, 95% CI 0.39-0.94;p=0.025) GNS gelişimi ile bağımsız olarak ilişkili olduğu gösterildi.

Sonuç: Beslenme intoleransı bağırsağın immunolojik ve bariyer fonksiyonlarını bozarak sepsis gelişimini kolaylaştırır.

Anahtar kelimeler: beslenme intoleransı,sepsis,prematüre

ABSTRACT

Aim: To determine the association between feeding intolerance and late onset sepsis (LOS) in very low birth weight (VLBW) infants.

Materials and Methods: In this retrospective study inborn infants with a gestational age less than 32 weeks or birth weight less then 1500 grams were enrolled. Demographic and neonatal characteristics of infants who had culture proven LOS were compared with the control infants, matched for birth weight and gestational age.

Results: A total of 408 infants (LOS n=136, non LOS n=272) were analyzed. The mean (SD) gestational age and birth weight of the whole cohort were 27.8 weeks (±1.6) and 1016.92 grams (±200.39). Exclusively breast feeding was lower and feeding intolerance was more frequent in LOS group (p=0.028, p<0.001; respectively). Time to regain birth weight, time to reach full enteral feeding, nothing per oral day, duration of the requirement of total parenteral nutrition were longer in LOS group compared to non LOS group (p=0.048, p<0.001, p<0.001, p<0.001; respectively). Weight gain per day, weight gain at first and fourth week of life were significantly lower in infants with LOS (p=0.000, p=0.045 and p=0.046; respectively). Logistic regression analysis revealed that respiratory distress syndrome (OR=1.76, 95% CI 1.12-2.76;p=0.013), feeding intolerance (OR=3.84 95% CI 2.36-6.24; p<0.001) and exclusively breast feeding (OR=0.60, 95% CI 0.39-0.94;p=0.025) were independently associated with the development of LOS.

Conclusion: Feeding intolerance impairs the immunologic and barrier functions of the gut and facilitates the onset of sepsis.

Keywords: feeding intolerance,sepsis,prematurity

INTRODUCTION

Late onset sepsis (LOS) is an important cause of morbidity and mortality for very low birth weight (VLBW) infants admitted to neonatal intensive care unit. There are numerous predisposing risk factors for sepsis have been described; immaturity, long term requirement of mechanical ventilation, intravascular catheterization, the duration of hospitalization, occurence of feeding intolerance, long term usage of parenteral nutrition, lack of breast milk, concomitant neonatal morbidities such as respiratory and cardiovascular diseases (1).To maintain the adequate

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nutrition; parenteral nutrition is essential if critically ill neonates are unable to be fed enterally. In experimental models, it has been shown that certain elemental diets and parenteral nutrition are associated with loss of intestinal barrier functions and lead to bacterial translocation. And animals with protein malnutrition were found to be more susceptible to sepsis than normal nourished animals (2).

Feeding tolerance can be challenging for VLBW infants because of the comorbidities due to prematurity. Prolonged time to reach full enteral feeding, duration of hospitalization and time to regain birth weight is often the result of feeding intolerance. Formula fed infants were showed to have increased risk for LOS than breast fed infants (3). Infants who have received breast milk were showed to achieve full enteral feeding earlier and had parenteral nutrition shorter than formula fed infants. In several studies it has been shown that parenteral nutrition is associated with an increased risk of LOS (4). So clinicians should aim to cessase the use of parenteral nutrition as soon as possible via achievement of full enteral feeding preferably with breast milk in order to limit exposure to parenteral nutrition. In our study we aimed to determine the importance of feeding intolerance as a predisposing risk factor for LOS.

MATERIALS AND METHODS

Patients and Methods

We selected inborn babies with a gestational age less than 32 weeks or birth weight less then 1500 grams admitted at the Neonatal Intensive Care Unit of Zekai Tahir Burak Women's Health, Health Application and Research Center from January 2013 to June 2016 in this retrospective study. During the study period, neonatal characteristics of 136 premature infants who had culture proven LOS were reviewed. The infants with LOS were matched for gestational age and birth weight with infants without LOS, who served as control subjects. We excluded patients with major congenital anomalies and anomalies that may interrupt enteral nutrition. We recorded clinical data, collected from the medical records, including birth weight, gestational age, gender, type of delivery, Apgar score, CRIB score used for neonatal mortality score, occurence of respiratory distress syndrome (RDS), presence of haemodynamically significant patent ductus arteriosus (PDA), severe intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD). Full enteral feeding was defined as enteral feeding with 150 ml/kg/day feed volume sustained for 72 hours. To assess the feeding tolerance we registered the time from birth to full enteral feeding achievement, time to regain birth weight, nothing peroral day, duration of parenteral nutrition. Body weight measurements weekly up to 4 weeks were recorded. Weight gain per day(body weight minus birth weight, divided by birth weight and chronological age, g/kg/day)and weight gain per week (g/kg/week)during the first 4 weeks were calculated. Feeding intolerance was defined as; gastric residuals or bilious emesis, gastric residuals in ≥ 50% of previous feed volume, grossly bloody stools, abdominal tenderness or discoloration, emesis more than 3 times/day and clinical or radiological evidence of necrotising enterocolitis (NEC). Type of enteral feeding was defined as exclusive breast milk when available or preterm formula or breast milk and preterm formula. The rate of mortality, duration of hospitalization and weight at discharge were recorded. LOS was defined as presence of clinical signs of sepsis developed after 3 days of life with (1) the isolation of the organism in blood culture and/or elevated C-reactive protein, leukocyte count of >25.000/mm3 or <5.000/mm3 and immature to total neutrophil ratio of > 0.2. The pathogenes isolated in culture were recorded.

Statistical analysis

Statistical analyses were conducted using the SPSS version 17.0 (SPSS Inc., Chicago,IL,USA). The results are presented as numbers (n), frequencies (%), medians with interquartil range (IQR) and mean ± standart deviation. The chi-square test was used to compare categorical variables and t-test to compare continuous variables. Independent risk factors were analyzed via multivariable regression analysis. P values <0.05 were considered significant

RESULTS

In this study,premature infants with a gestational age less than 32 weeks or birth weight less then 1500 grams were enrolled. Neonatal characteristics of 136 premature infants who had culture proven LOS were compared with 272 premature infants without LOS. The mean (SD) gestational age and birth weight of the whole cohort were 27.8±1.62 weeks and 1016±200g. Patients with LOS and without LOS had similar median gestational age and birth weight (respectively 28 and 28 weeks,p=0.93 and 960 g and 1050 g, p=0.14).Neonatal characteristics of the study population are described in Table 1.

Tablo 1. Demographic and clinical characteristics of study groups

	LOS group (n=136)	non LOS group (n=272)	p value
Birth weight (g)*	960 (830-1180)	1050 (882-1180)	NS
Gestational age (week)*	28(27-29)	28 (27-29)	NS
Gender, male (%)	63 (46.3)	131 (48.2)	NS
Type of delivery, C/S (n,%)	123 (90.4)	223 (81.9)	0.025
Multiple pregnancy (n,%)	34 (25)	52 (19.1)	NS
APGAR score at 5 min.*	7 (6-8)	8 (7-8)	0.02
CRIB score*	3,5 (2-5)	2 (1-4)	0.02
Premature rupture of membranes (n,%)	33 (24.2)	49 (18)	NS
Chorioamnionitis (n,%)	16 (11.7)	27 (9.9)	NS
RDS (n,%)	101 (74.2)	176 (64)	NS
PDA (n,%)	77 (56,6)	113 (41,5)	0.004
IVH (n,%)	102 (75)	188 (69)	NS
BPD (n,%)	64 (47)	92 (33)	0.001

* Data are median (interquartile range).

C/S, cesarean section; RDS, respiratory distress syndrome; PDA patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NS, not significant

There was no statistically significant difference in terms of the frequency of RDS and IVH between the groups (respectively p=0.051 and p=0.217) but PDA and BPD were more frequent in infants with LOS (respectively p=0.004 and p=0.001).

Exclusive breast feeding was lower and feeding intolerance was more frequent in LOS group (respectively p=0.028 ve p<0.001). Time to regain birth weight, time to reach full enteral feeding, nothing per oral day, duration of total parenteral nutrition were longer in LOS group than non LOS group (respectively p=0.048, p<0.001, p<0.001, p<0.001). Weight gain per day was lower in LOS group (p=0.01). Weight gain at first and fourth week of life were significantly lower in infants with LOS (respectively p=0.045 and p=0.046).The characteristics of feeding tolerance are described in Table 2.

Table 2. The characteristics of feeding tolerance

	LOS group (n=136)	Non LOS group (n=272)	p value
Feeding intolerance (n,%)	108 (79.4)	133 (48.8)	<0.001
Time to regain birth weight (days)*	13 (10-16)	12 (9-15)	0.048
Time to reach full enteral feeding (days)*	20 (16-29)	14 (11-17)	<0.001
Nothing per oral day*	3 (1-6)	0 (0-2)	<0.001
Time of the requirement of total parenteral nutrition (days)*	17 (12-24)	11 (9-14)	<0.001
Weight gain per day (g/kg/day)*	16.1 (13.3-19.8)	17.55 (14.8-21.5)	0.012
Weight gain at first week (g/kg/day)*	-9.83(-13.82-(-3.01))	-7.25 (-12.23-(-2.42))	0.045
Weight gain at second week (g/kg/day)*	1.72(-1.32-4.80)	2.19 (-1.25-5.49)	NS
Weight gain at third week (g/kg/day)*	6.39(2.65-8.39)	6.80 (4.11-9.42)	NS
Weight gain at fourth week (g/kg/day)*	8.31(6.20-11.59)	9.60 (6.68-12.50)	0.046

*Data are median (interquartile range).
NS; not significant.

Breast milk was used when available and formula was used when breast milk was not available or enough for the premature infants. Feeding intolerance was more common and exclusively feeding with breast milk was lower in patients with LOS (respectively p<0.001 and p=0.028).

In logistic regression analysis; RDS (OR=1.76; 95% CI 1.12-2.76; p=0.013) and feeding intolerance (OR=3.84; 95% CI 2.36-6.24;p<0.001) were identified as independent risk factors for LOS development. Feeding with exclusive breast milk (OR=0.60; 95% CI 0.39-0.94;p=0.025) was identified as an independent factor inversely associated with LOS development.

The median duration of hospitalization was 70 days (IQR 49-90) in LOS group and 58 days (IQR 47-79) in non LOS group, there was statistically significant difference between the groups (p=0.017). And the mortality rate was higher in LOS group (p=0.016).

Most of the LOS were caused by gram positive pathogenes. Staphylococcus epidermidis were the most frequent LOS pathogenes (%41.2 of all infections), followed by Klebsiella pneumoniae (%20.6) and Staphlococcus capitis (%9.6). Isolated microorganisms in blood culture are shown in Table 3.

Table 3. Microorganisms isolated in blood culture

	n (%)
Staphylococcus epidermidis	56 (41.2)
Klebsiella pneumoniae	28 (20.6)
Staphlococcus capitis	13 (9.6)
Klebsiella oxytoca	10 (7.4)
Enterococcus faecalis	10 (7.4)
Staphylococcus hominis	5 (3.7)
Staphylococcus aureus	5 (3.7)
Pseudomonas aeruginosa	3 (2.2)
Enterobacter aerogenes	3 (2.2)
Stenotrophomonas maltophilia	1 (0.7)
Acinetobacter baumannii	1 (0.7)
Escherichia coli	1 (0.7)

DISCUSSION

In this study we found that time to reach full enteral feeding, time to regain birth weight, nothing per oral day, duration of total parenteral nutrition are longer in patients with LOS. Exclusive breast feeding was found to be lower and feeding intolerance was more frequent in LOS group. LOS is an important complication of prematurity and the leading cause of morbidity and mortality. Prematurity, parenteral nutrition, requirement of prolonged ventilation, intravascular access and feeding intolerance promotes the LOS unfortunately.

Enteral nutrition has a great impact for the growth and development of the gastrointestinal tract. Early enteral feeding should be started as soon as possible to enhance the gastrointestinal maturation by stimulating the hormone secretion and motility (5).Delaying the introduction of enteral feeding causes prolonged parenteral nutrition therefore parenteral nutrition associated complications like bloodstream infections and prolonged hospital stay will ocur. But among the clinicians, the fear of NEC, sometimes induce them to withold feedings. These fears lead them to delay introduction of early enteral feeding, insufficient and slow advencement in nutrition. As it is well known that breast milk is the best choice for babies, it has been reported to decrease the incidence of LOS, NEC and readmission for hospital (6). In our study we found that exclusive feeding with breast milk was lower in patients with LOS similar to literature.

Feeding intolerance has a clinical and prognostic importance in the survival of the premature infants. If it occurs at any time of the neonatal period, generally leads the interruption of the enteral feeding, prolongs the time to reach full enteral feeding and hospitalization. The most frequent signs of feeding intolerance include presence of gastric residuals, abdominal distension and apnea/bradycardia (7). The warning signs should be kept in mind as it is important to realize and manage this condition. Gane et al., analyzed risk factors for NEC and found that sepsis, formula feed, perinatal asphyxia, treatment with caffeine and umbilical catheterization are associated risk factors. Antenatal steroids and breastfeeding were found to have beneficial effect on NEC. Multivariate analysis revealed that sepsis was the most important risk factor in that study (8). Hassani et al., identified risk factors for LOS in a multicenter study and concluded that exposure to parenteral feeding more than 10 consecutive days was associated with LOS. Also breast milk was found to have protective effect for LOS development (4). Similar to the previous studies we found that RDS and feeding intolerance were identified as independent risk factors for LOS development and exclusively breastfeeding was found to be protective for LOS. Breast milk contains bioactive factors which influence the immunity and protects the mucosa and increases the maturity of gastrointestinal bacterial colonization. It also contains anti-infective enzymes and cytokines, which are not present in formula feeds (8) .The use of breast milk in premature infants has been showed to decrease LOS, NEC and rehospitalizations after discharge. Also breast milk improves feeding tolerance and shortens the duration of parenteral nutrition (9). Due to its protective properties, all the mothers should be encouraged to express breast milk even if she could not breast feed their babies because of the immaturity

Inflammatory processes result in damage in lung tissue and will enhance BPD, also inflammation induces prostoglandins and lead the risk of patency of ductus arteriosus (PDA) and increases pulmonary blood flow. Escalante et al. showed that PDA, NEC, ROP and periventricular leukomalacia were more frequent in patients with LOS (10), in our study we found that BPD and PDA were more frequent in patients with LOS, but no statistically difference was found in the rate of RDS and IVH.

Postnatal growth restriction is very important that can affect long term growth and neurodevelopment and can be hindered by multiple factors associated with prematurity. Ehrenkranz et al., evaluated postnatal growth rates in VLBW infants in a large prospective study and showed that infants who experience neonatal morbidities such as chronic lung disease, LOS and NEC, regained birth weight later and gained body weight more slowly than infants without neonatal morbidities (11) Infants undernutrition might be more prone to develop BPD and LOS (12). Undernutrition affects the delicate brain of these tiny infants and the association between poor postnatal nutrition and impaired neurodevelopmental outcomes have been shown in premature infants (6). Current guidelines recommend that these babies should be fed to achieve the appropriate postnatal growth rate and weight compatible with normal fetuses at the similar postconceptional age (9). Early enteral and appropriate parenteral nutrition seems to be preferred feeding method in these babies to improve the postnatal growth restriction and contribute the neurodevelopment. As it is pointed out that sepsis is the one of the leading factor for neurodevelopment, we should avoid babies from infections.

In conclusion feeding intolerance has been found as an independent risk factor for LOS development in premature VLBW infants. Reduction the duration of parenteral nutrition and improving the achievement of full enteral feeding via breast milk should be aimed in these babies in order to protect them from infections. Also it should be kept in mind that neurodevelopmental outcomes could be improved with the help of preventive strategies against infections.

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