Early or Delayed Enteral Feeding for Infants with Abnormal Antenatal Doppler Flow Patterns

Alimentação Entérica Precoce ou Tardia em Recém-Nascidos com Alteração de Fluxos em Ecografia Pré-Natal

Isabel Periquito, Joana Oliveira, Cláudia Fernandes, Marta Ferreira, Rosalina Barroso

Acta Pediatr Port 2018;49:128-33
DOI: 10.21069/APP.2018.7900

Resumo

Introdução: O principal objetivo deste estudo foi determinar o efeito da introdução de alimentação entérica precoce comparado com introdução tardia, na incidência de morbilidade gastrointestinal e tempo até alimentação entérica total, em recém-nascidos com alteração de fluxos em ecografia pré-natal.
Métodos: Análise retrospetiva dos recém-nascidos internados numa unidade de cuidados intensivos neonatais de nível III, em Portugal, entre janeiro de 2004 e dezembro de 2013 com alteração de fluxos em ecografia pré-natal. Foram criados dois grupos baseados no tempo até introdução de primeira alimentação entérica: grupo de alimentação precoce (≤48 horas) e grupo de alimentação tardia (> 48 horas). Os resultados principais foram morbilidade gastrointestinal e mortalidade devido a complicações gastrointestinais.
Resultados: Foram incluídos 46 (47%) de recém-nascidos no grupo de alimentação precoce e 52 (53%) no grupo de alimentação tardia. Não houve diferenças significativas na morbilidade gastrointestinal, incluindo enterocolite necrosante, perfuração ou cirurgia gastrointestinal, íleus séptico ou intolerância alimentar. A alimentação precoce resultou numa diminuição significativa da sepsis tardia (*p*=0,016; *odds ratio* 0,276; intervalo de confiança 95% 0,096-0,789).
Discussão: A introdução precoce de alimentação entérica poderá não ter efeitos significativos na incidência de morbilidade gastrointestinal em recém-nascidos com alteração de fluxos em ecografia pré-natal. Houve uma redução significativa na sepsis tardia, sem condicionar um aumento de risco de morbilidade gastrointestinal.

Palavras-chave: Gastroenteropatias; Nutrição Enteral; Recém-Nascido; Sinais e Sintomas Digestivos; Ultrassonografia Doppler

Abstract

Introduction: The main objective of this study was to determine the effect of early versus late enteral feeding on the incidence of gastrointestinal morbidity and on time to establish full enteral feeding in neonates with abnormal antenatal Doppler flow patterns.
Methods: We retrospectively analysed neonates admitted to a level III neonatal intensive care unit in Portugal between January 2004 and December 2013 with abnormal antenatal Doppler flow patterns. Two groups were created based on the time of first enteral feeding: early feeding group (≤48 hours) and late feeding group (> 48 hours). Primary outcomes were gastrointestinal morbidity and death due to gastrointestinal complications.
Results: Forty-six (47%) infants were included in the early feeding group and 52 (53%) in the late feeding group. There was no statistical difference in gastrointestinal morbidity, including necrotising enterocolitis, gastrointestinal perforation or surgery, septic ileus or feeding intolerance. Early feeding resulted in a significant decrease in late-onset sepsis (p=0.016; odds ratio 0.276; 95% confidence interval 0.096-0.789).
Discussion: Early introduction of enteral feeding may not have a significant effect on the incidence of gastrointestinal morbidity in neonates with abnormal antenatal Doppler flow patterns. There was a significant reduction in late-onset sepsis, without incurring an increased risk of gastrointestinal morbidity.

Keywords: Enteral Nutrition; Gastrointestinal Diseases; Infant, Newborn; Signs and Symptoms, Digestive; Ultrasonography, Doppler

Unidade de Neonatologia, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal
Correspondência
Isabel Periquito
isabelperiquito@gmail.com
Hospital Prof. Doutor Fernando Fonseca, IC19, 2720-276 Amadora, Portugal
Recebido: 31/12/2015 | Aceite: 20/09/2016

Introduction

Placental insufficiency leads to a decreased supply of oxygen and nutrients to the fetus, contributing to fetal growth restriction. This may occur in up to 4% to 15% of all pregnancies, and is a major cause of neonatal morbidity and mortality.[1,2] An indirect way to assess placental insufficiency is by antenatal Doppler ultrasound, which can identify increased resistance to umbilical arterial flow and redistribution in the fetal circulation of blood to the heart, brain, lungs and pancreas at the expense of the lower part of the body such as the splanchnic organs.[1,3-6] Deprivation of sufficient blood flow to the gut can lead to an inflammatory cascade due to ischaemia-reperfusion injury, which may result in intestinal disorders ranging from feeding intolerance to necrotising enterocolitis (NEC).[7-10] Although the exact aetiology of NEC is unknown, certain factors seem to increase the risk, such as extremely low birth weight and extreme prematurity.[10-13] Fetal growth restriction and circulation redistribution of the fetal aorta or umbilical artery, in particular absent or reversed end-diastolic flow velocity (AREDFV), have been identified as specific risk factors for NEC in several studies.[4,9,11,14]

Additionally, more than 90% of NEC cases occur after feeding is initiated, which may delay the start of enteral feeding in neonates at highest risk.[4,8,11] However, this may induce villous atrophy and decrease hormone and enzyme production, which is stimulated by enteral milk, further contributing to intestinal dysmotility and dysfunctional adaptation of the immature gastrointestinal tract.[8,15,16] This policy may contribute to prolonged parenteral nutrition, infectious and metabolic complications and prolonged hospitalization.[9,16]

On the other hand, recent data from various trials and reviews including preterm or low birth weight infants and studies including only infants with abnormal antenatal Doppler flow patterns have shown that early introduction of progressive enteral feeds (less than 2-4 days postnatal age) does not have a statistically significant effect on the risk of NEC or mortality in these subgroups.[4,8,11,15]

The aim of this study was to determine the effect of early versus late enteral feeding on the incidence of gastrointestinal morbidity and on time to establish full enteral feeding in neonates with abnormal antenatal Doppler flow patterns.

Methods

We retrospectively analysed all neonates with abnormal antenatal Doppler flow patterns admitted to a level III neonatal intensive care unit in Portugal between January 2004 and December 2013. Inclusion criteria were umbilical artery pulsatility index (UAPI) above the 95th percentile for gestational age, AREDFV in the umbilical artery on at least 50% of waveforms on one occasion during pregnancy or cerebral redistribution pattern defined by UAPI above the 95th percentile, and middle cerebral artery pulsatility index below the 5th percentile for the corresponding gestational age. Only the last measurements before birth were used for the analysis.

Exclusion criteria were twin-twin or fetomaternal transfusion, major congenital/gastrointestinal tract anomalies, rhesus isoimmunisation, Apgar score <3 at five minutes, multiorgan dysfunction, inotropic drug support and red blood cell transfusion associated with NEC in the following seven days.

Other variables analysed included demographic characteristics, duration of parenteral nutrition (lipids and amino acids), enteral prescription regime, type of initial feeding, including human milk (maternal or donor), formula (premature or first infant formula) or both, sepsis, and respiratory and cardiovascular outcomes.

Two groups were created based on the time of first enteral feeding: an early feeding group (EFG) with initiation of enteral feeding ≤48 hours after birth, and a late feeding group (LFG) with first feeding >48 hours after birth.

Primary outcomes were gastrointestinal morbidity, including the diagnosis of modified Bell stage 1, 2 and 3 NEC, gastrointestinal perforation, gastrointestinal surgery, septic ileus, feeding intolerance and death due to gastrointestinal disorders, reviewed by an independent observer. Feeding intolerance was defined by detection of gastric residuals (over 50% of previous feed volume) and abdominal distension.

Secondary outcomes were days to achieve full enteral feeding (defined as adequate intake of enteral nutrition and absence of parenteral nutrition sustained for more than 24 hours), length of stay, late-onset sepsis, patent ductus arteriosus (PDA) requiring treatment, and bronchopulmonary dysplasia (BPD). Sepsis was defined as either clinical (at least two signs or symptoms) or laboratory (at least one): C-reactive protein >2 mg/dL, leukocytes >30 000 cells/µL or <5 000 cells/µL, or platelets <100 000 cells/µL),[17] or culture-positive. PDA was defined on echocardiographic criteria[18] and BPD according to the national consensus.[19]

Data were analysed using IBM® SPSS® software (version 21, IBM SPSS Inc, Chicago, IL). Continuous variables were analysed using the Student's t-test or the Mann-Whitney test. Categorical variables were analysed using a Pearson chi-square test or Fisher's exact test. The primary and secondary outcomes were assessed by

binary logistic regression and linear regression and 95% confidence intervals (CI) were defined. Parameters that were previously identified as significant, as well as selected risk factors such as gender, gestational age, weight, multiple gestation, antenatal steroid exposure and pregnancy complications, were used as independent variables. A p value <0.05 was considered statistically significant.

Results

Ninety-eight infants were included during the study period. Clinical differences included type of Doppler anomaly, with a larger number of infants with AREDFV and cerebral redistribution pattern in the LFG (p=0.020), a lower gestational age in the LFG (32.1 vs 33.3 weeks, p=0.028) and a larger number of small for gestational age infants in the EFG (67.3% vs 87% in LFG and EFG, respectively, p=0.022). Demographic characteristics, maternal medical conditions and neonatal morbidity are listed in Table 1.

Forty-six (47%) infants were included in the EFG and 52 (53%) in the LFG. The mean time of first enteral feeding was 27 hours and 75.8 hours for EFG and LFG, respectively, being exclusively human milk in 15 (32.6%) infants in the EFG and 22 (42.3%) in the LFG.

Regarding primary outcomes, stage 1 NEC was more common in the LFG (5.8% vs 2.2%), and the only case of stage 3 NEC occurred in the LFG, while gastrointestinal intolerance occurred in 4.3% and 11.5% of the EFG and LFG, respectively.

One infant in the LFG, with a gestational age of 30 weeks, formula-fed, required gastrointestinal surgery due to stage 3 NEC. There was no mortality in either group.

After logistic regression analysis, considering the slight imbalance between the groups, there was no statistical difference in gastrointestinal morbidity including NEC, gastrointestinal perforation or surgery, septic ileus or feeding intolerance (Table 2). Overall gastrointestinal morbidity, defined as at least one gastrointestinal event, occurred in 19% of both groups.

Table 1. Patient characteristics according to feeding group

	Late feeding group n=52, n (%)*	Early feeding group n=46, n (%)*	p
Maternal hypertension (including pre-gestational, gestation-induced and preeclampsia)	18 (34.6)	15 (32.6)	0.834
Diabetes (including types 1 and 2 and gestational)	4 (7.7)	5 (10.9)	0.730
Multiple pregnancy	4 (7.7)	3 (6.5)	1.000
Pre-natal steroids			0.697
Incomplete	4 (7.7)	3 (6.5)	
Complete	34 (65.4)	26 (56.5)	
Type of Doppler anomaly			0.020
Pulsatility index >P95	2 (3.8)	6 (13)	
AREDFV	31 (59.6)	24 (52.2)	
Cerebral redistribution	19 (36.5)	16 (34.8)	
Male	28 (53.8)	25 (54.3)	0.960
Gestational age, mean (SD)	32.1 (2.5)	33.3 (2.9)	0.028
Birth weight, mean (SD)	1336 (382)	1473 (493)	0.129
<1000 g	14 (26.9)	9 (19.6)	
≥ 1000-1499 g	22 (42.3)	18 (39.1)	
≥ 1500 g	16 (30.8)	19 (41.3)	
Small for gestational age	35 (67.3)	40 (87)	0.022
Apgar score at five minutes (median)	9	9	0.571
RDS type 1, requiring surfactant	10 (19.2)	3 (6.5)	0.079
Early onset sepsis	5 (9.6)	7 (15.2)	0.399
First feed			0.297
Human milk	22 (42.3)	15 (32.6)	
Formula	28 (53.8)	31 (67.4)	

AREDFV - absent or reversed end-diastolic flow velocity; P - percentile; RDS - respiratory distress syndrome; SD - standard deviation.
* Unless stated otherwise.

Early feeding resulted in a significant decrease in late-onset sepsis (p=0.016; odds ratio [OR] 0.276; 95% CI 0.096-0.789), reducing the probability of its occurrence by 72.4% (Table 3). Although without statistical significance, early feeding also resulted, on average, in shorter use of lipid-containing solutions and time to achieve full enteral feeding (by four days).

Cardiovascular secondary outcomes (PDA requiring treatment) and respiratory morbidity, such as number of days of invasive ventilation, number of days of continuous positive airway pressure and bronchopulmonary dysplasia, were similar in both groups (Table 3).

Discussion

The results of this study suggest that early introduction of enteral feeding may not have a significant effect on the incidence of gastrointestinal morbidity, such as NEC or feeding intolerance, in infants with abnormal antenatal Doppler flow patterns.

Early introduction of enteral feeding in infants with fetal growth restriction, particularly those at high risk, has been considered a risk factor for increased incidence of NEC. However, there is growing evidence that enteral feeding may not be as significant in the pathogenesis of NEC as previously considered. Several studies have shown no difference in the incidence of NEC, particularly for Bell stages 2 and 3.[4,8,9,20] Two Cochrane reviews published in 2013, which included preterm or low birth weight infants with and without abnormal antenatal Doppler flow patterns, that analysed early trophic feeding versus enteral fasting and delayed introduction of progressive enteral feeds, concluded that the incidence of NEC, gastrointestinal tolerance and growth rates were unchanged, although further controlled trials were warranted.[11,15]

Early initiation of enteral feeding has also been associated with significant reductions in parenteral nutrition, time to achieve full enteral feeding and high-dependency care.[4,11] In this study, although without statistical significance, infants in the EFG reached full enteral feeds

Table 2. Primary outcomes

	Late feeding group n=52; n (%)*	Early feeding group n=46; n (%)*	p
Necrotising enterocolitis	4 (7.7)	3 (6.5)	0.43
Stage 1	3 (5.8)	1 (2.2)	
Stage 2	0 (0)	2 (4.3)	
Stage 3	1 (1.9)	0 (0)	
Gastrointestinal perforation	1 (1.9)	0 (0)	0.52
Gastrointestinal surgery	1 (1.9)	0 (0)	0.52
Septic ileus	4 (7.7)	4 (8.7)	0.60
Feeding intolerance	6 (11.5)	2 (4.3)	0.37
Overall gastrointestinal morbidity (at least one of the above)	10 (19.2)	9 (19.6)	0.36

* Unless stated otherwise.
Adjusted for hypertension, diabetes, prenatal steroids, type of Doppler anomaly, multiple gestation, gestational age, gender, birth weight, small for gestational age, Apgar score, type of first feed, sepsis, ventilation support, respiratory distress syndrome type 1, patent ductus arteriosus requiring treatment.

Table 3. Secondary outcomes

	Late feeding group n=52; n (%)*	Early feeding group n=46; n (%)*	p	aOR	95% CI
Duration of lipid-containing parenteral nutrition, mean (SD)	8.8 (7.3)	6.6 (7.8)	0.792	NS	NS
Days to reach full enteral nutrition, mean (SD)	15.1 (11.6)	11.2 (9.4)	0.441	NS	NS
Cholestasis	3 (5.8)	1 (2.2)	0.62	NS	NS
Length of hospital stay, mean (SD)	37.4 (20)	30.1 (21.4)	0.782	NS	NS
Late-onset sepsis	22 (42.3)	7 (15.2)	0.016	0.276	0.096-0.789
Invasive ventilation support (days), mean (SD)	7.4 (3.8)	13 (15.6)	0.918	NS	NS
Continuous positive airway pressure	13 (28.3)	24 (46.2)	0.405	NS	NS
PDA requiring treatment	3 (5.8)	4 (8.7)	0.174	NS	NS
Bronchopulmonary dysplasia	6 (11.5)	4 (8.7)	0.06	NS	NS

aOR - adjusted odds ratio; CI - confidence interval; NS - not significant; PDA - patent ductus arteriosus; SD - standard deviation.
* Unless stated otherwise.
Adjusted for hypertension, diabetes, prenatal steroids, type of Doppler anomaly, multiple gestation, gestational age, gender, birth weight, small for gestational age, Apgar score, type of first feed, sepsis, ventilation support, respiratory distress syndrome type 1, patent ductus arteriosus requiring treatment.

on average four days earlier than the LFG, and required fewer days of lipid-containing parenteral nutrition.

Prolonged parenteral nutrition is associated with an increase incidence of intravenous device complications such as line blockage, sepsis and pulmonary embolism.[21] Decreasing the number of days of parenteral nutrition also reduces the number of catheter days, with less skin insult and less opportunity for pathogenic invasion.[20] This study showed a statistical reduction in late-onset sepsis, reducing its occurrence by 72.4%, without incurring an increased risk of gastrointestinal morbidity. Although other studies have also shown that early enteral feeding is associated with a reduced risk of healthcare-associated infection, a recent randomised study showed no difference in the incidence of late-onset sepsis.[4,20]

The use of parenteral nutrition as an alternative source of nutrients has other known side effects, such as administration errors, cholestasis, osteopaenia of prematurity and metabolic complications.[9,21,22]

In conclusion, the results of this study suggest that early introduction of enteral feeding (less than 48 hours of post-natal age) in infants with abnormal antenatal Doppler flow patterns does not appear to lead to a significant increase in gastrointestinal morbidity, such as NEC or feeding intolerance. Furthermore, early introduction of enteral feeding appears to be a significant independent protective factor for late-onset sepsis. The small number of infants included and the study's retrospective nature may limit the conclusions to be drawn from this study. It was not possible to specify the clinical criteria leading to early or late feeding. The authors assume that this decision may have been related to the more conservative approach 10 years ago, type of Doppler anomaly, lower gestational age or the absence of human milk. Infants with perinatal complications that could further compromise gut perfusion were excluded, which means that the results may not be applicable to all neonates with abnormal antenatal Doppler flow patterns.

WHAT THIS ARTICLE TELLS US THAT IS NEW

- Early introduction of enteral feeding (≤48 hours) in neonates with abnormal antenatal Doppler flow patterns does not appear to increase the risk of gastrointestinal morbidity, including necrotising enterocolitis, gastrointestinal surgery, septic ileus or feeding intolerance.
- Early introduction of enteral feeding in these infants appears to have a protective effect by reducing the incidence of late-onset sepsis.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the preparation of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Pierre-Fabre/SPP Award for best pediatric communications presented in international congresses abroad in 2014.

Referências

1. Gagnon R. Placental insufficiency and its consequences. Eur J Obstet Gynecol Reprod Biol 2003;110:99-107.
2. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002;19:140-6.
3. Hecher K, Campbell S, Doyle P, Harrington K, Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation: Arterial, intracardiac, and venous blood flow velocity studies. Circulation 1995;91:129-38.
4. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, et al. Early or delayed enteral feeding for preterm growth-restricted infants: A randomized trial. Pediatrics 2012;129:e1260-8.
5. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001;18:571-7.
6. McMillen IC, Adams MB, Ross JT, Coulter CL, Simonetta G, Owens JA, et al. Fetal growth restriction: Adaptations and consequences. Reproduction 2001;195-204.
7. Baschat AA. Fetal responses to placental insufficiency: An update. BJOG 2004;111:1031-41.
8. Karagianni P, Briana DD, Mitsiakos G, Elias A, Theodoridis T, Chatziioannidis E, et al. Early versus delayed minimal enteral feeding and risk for necrotizing enterocolitis in preterm growth restricted infants with abnormal antenatal Doppler results. Am J Perinatol 2010;27:367-73.
9. Dorling J, Kempley S, Leaf A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. Arch Dis Child Fetal Neonatal Ed 2005;90:F359-63.
10. Yee WH, Soraisham AS, Shah VS, Aziz K, Yoon W, Lee SK. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics 2012;129:e298-304.
11. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis

in very low birth weight infants. Cochrane Database Syst Rev 2014;12:CD001970.
12. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 2000;182:198-206.
13. Manogura AC, Turan O, Kush ML, Berg C, Bhide A, Turan S, et al. Predictors of necrotizing enterocolitis in preterm growth--restricted neonates. Am J Obstet Gynecol 2008;198:638.e1-5.
14. Malcolm G, Ellwood D, Devonald K, Beilby R, Henderson-Smart D. Absent or reversed end diastolic flow velocity in the umbilical artery and necrotising enterocolitis. Arch Dis Child 1991;66:805-7.
15. Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane database Syst Rev 2013;3:CD000504.
16. Ramani M, Ambalavanan N. Feeding practices and necrotizing enterocolitis. Clin Perinatol 2013;40:1-10.
17. Direção Geral da Saúde. Protocolo para a vigilância epidemiológica das infeções nosocomiais nas unidades de cuidados intensivos neonatais. Lisboa: DGS; 2007.
18. Direção Geral da Saúde. Tratamento médico e cirúrgico do canal arterial no pré-termo. Norma n.º 021/2012. Lisboa: DGS; 2012.
19. Proença E, Vasconcello G, Rocha G, Carreira ML, Mateus, Santos ID, et al. Displasia boncopulmonar [accessed 30 November 2015]. Available at: http://www.spp.pt/UserFiles/file/Protocolos/Displasia_Boncopulmonar_RN_2009.pdf
20. Flidel-Rimon O, Friedman S, Lev E, Juster-Reicher A, Amitay M, Shinwell ES. Early enteral feeding and nosocomial sepsis in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004;89:F289-92.
21. Meadows N. Monitoring and complications of parenteral nutrition. Nutrition 1998;14:806-8.
22. Calkins KL, Venick RS, Devaskar SU. Complications associated with parenteral nutrition in the neonate. Clin Perinatol 2014;41:331-45.