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REGULAR ARTICLE

Minimal enteral feeding reduces the risk of sepsis in feed-intolerant very low birth weight newborns

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Abstract

Aims: To evaluate the efficacy and safety of minimal enteral feeding (MEF) nutritional practice in feed-intolerant very low birth weight (VLBW) infants.

Methods: A retrospective design using data reported in the clinical charts of VLBW newborns consecutively observed in neonatal intensive care units (NICU) that presents feed intolerance. During the study period, two feeding strategies were adopted: total parenteral nutrition (PN) (group 1) or PN plus MEF (group 2), for at least 24 h. Primary outcome was the time to reach full enteral feeding; secondary outcomes were the occurrence of sepsis, the time to regain birth weight, the length of hospitalization, the occurrence of necrotizing enterocolitis (NEC) Bell stage >II and death.

Results: In total, 102 newborns were evaluated: 51 in group 1, and 51 in group 2. Neonates in group 2 achieved full enteral nutrition earlier (8 days, interquartile range [IQR] 5) compared with subjects receiving total PN (11 days, IQR 5, $p < 0.001$). A reduction of sepsis episodes was observed in group 2 (15.7%) compared with group 1 (33.3%, $p = 0.038$). Additionally, subjects in group 2 regained their birth weight and were discharged earlier. The occurrence of NEC and death were similar in the two groups.

Conclusion: Minimal enteral feeding in very low birth weight infants presenting feed intolerance reduces the time to reach full enteral feeding and the risk of sepsis. This feeding practice does not increase the risk of necrotizing enterocolitis and death.

INTRODUCTION

Providing a safe feeding approach and appropriate nutritional support for very low birth weight (VLBW) infants is a challenging aim in neonatal care (1,2). The concern for precipitating necrotizing enterocolitis (NEC) remains a major limit of enteral nutrition in these subjects (3,4). In the last decades, it has been observed that there is a growing use of parenteral nutrition (PN) to meet many of the nutritional needs of VLBW infants (1). In particular, total PN is commonly considered the primary mean of nourishing premature infants when they show signs of feeding intolerance in order to reduce the risk of developing NEC (3–8). However, the basis for this practice is largely undefined. Clinical manifestations of feeding intolerance may represent a physiological condition related to a late maturity of gut motility typical of many preterm newborns (5,7). Receiving nothing by enteral route (NBE) predisposes a neonate to the consequences of starvation, and a prolonged duration of PN increases the risk of infections (1,9). In addition, enteral fasting may prolong the time to establish full enteral feeding and the length of hospital stay, without advantage on the risk of NEC (10,11). On the other hand, it has been demonstrated that also a small volume of enteral feeding has several advantages when compared with total PN in paediatric patients, including promotion of intestinal motility, maintenance of intestinal barriers, development of beneficial microflora, and reduction of infections (10–18). Thus, we hypothesize that minimal enteral feeding (MEF) instead of NBE may alleviate the side effect of PN in VLBW infants presenting feeding intolerance without increasing the risk for NEC. The aim of this study was to investigate MEF efficacy and safety in VLBW infants presenting feed intolerance.

Abbreviations

CRIB, Critical Respiratory Index for Babies; IQR, interquartile range; IVH, intraventricular haemorrhages; MEF, minimal enteral feeding; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NBE, nothing by enteral route; PN, parenteral nutrition; PDA, patent ductus arteriosus; VLBW, very low birth weight.

METHODS

A retrospective design using data reported in the clinical charts was adopted. The eligible patients were: (a) consecutively observed in neonatal intensive care units (NICU) from September 2001 to September 2003, (b) born with weight <1500 g and (c) presenting at least one episode of feed intolerance, defined by the presence of a gastric residual ≥3 mL/kg associated with abdominal distension (increase of abdominal circumference ≥2 cm) for at least two consecutive feeds. All infants with the following conditions were excluded: (a) Apgar score <3 at 5 min; (b) congenital heart diseases or malformations; (c) critical clinical conditions, as

indicated by a blood pH <6.8, or by the presence of hypoxia with persistent bradicardia; (d) acquired immunodeficiency and (e) incomplete clinical data or deviation for feeding protocol report.

Feeding protocols during the study period

Enteral feeding was started on the first day of life at 10 mL/kg/day, divided into 12 feeds, using preterm formula in all stable infants. Maternal unfortified milk was administered, whenever available, starting from the 24th hour of life. Aspirate residual from orogastric tube and abdominal circumference were measured before every feed (19). Total amount of gastric residual was calculated daily. The nutritional strategy changed during the 2 years of the study period for the patients presenting feed intolerance: in the first year of the study period when the subjects presented feeding intolerance, they received only total PN and NBE for 24 h, while in the next study year, these patients received PN plus MEF (10 mL/kg/day) for 24 h. This change in feeding protocol was derived from the increased acceptance of MEF in neonatology clinical practice, and it was discussed and approved by all the clinicians giving care to the subjects enrolled in the study. All subjects were evaluated daily. The total amount of enteral nutrition was increased by 20 mL/kg/day in the absence of feed intolerance in the previous 24 h. In the presence of erythematic abdominal wall, absence of bowel sounds or blood in the stools or in aspirates associated with radiological marker of NEC-Bell stage >I (3,4), enteral nutrition was discontinued during both years of the study period. PN was administered through a central vascular access in all subjects to maintain adequate fluid, electrolytes and nutrients intake until full enteral feeding (120 kcal/kg/day) was reached. Total amount of enteral and parenteral fluids were started at 70–100 mL/kg/day and advanced by increments of 20 mL/kg/day until 150–180 mL/kg/day.

Data collection and outcomes

The main demographic and clinical characteristics of the study population, together with the Critical Respiratory Index for Babies (CRIB), were recorded in a specific reporting form. The feed-intolerant patients were grouped on the basis of two time periods, characterized by different nutritional strategies: (a) total PN and NBE and (b) PN plus MEF, for at least 24 h. The efficacy outcome of the two feeding strategies was determined primarily by the time to reach full enteral feeding (at least 120 kcal/kg/day by oral route), secondarily by the incidence of late-onset culture-proven sepsis (positive blood culture obtained after 72 h of life) (20), the time to regain birth weight and the length of hospital stay according to standardized criteria (21). The safety of the two different feeding approaches was assessed by determining the rate of subjects presenting NEC Bell stage >II (3) and the rate of infants' death. The risk factors associated with NEC occurrence including time to start enteral feeding, assumption of breast milk, rate of infants with umbilical catheter, patent ductus arteriosus (PDA), intraventricular haemorrhages (IVH) and feeding intolerance characteristics (total gastric residual as a percentage of total daily feed, maximum gastric residual volume, number of episodes of feeding intolerance) were also collected. Clinical outcomes were systematically reviewed by two independent investigators who were blinded to the study aims and the patients' identity. Any disagreement in opinion between the investigators was subjected to a further review, including a third investigator, and the final decision was based on a consensus of opinion. The study protocol followed the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983, and it was approved by our ethics committee.

Statistical analysis

A statistical analysis was performed by a statistician blind to individual feeding strategy adopted in the two groups of preterm infants. Two population types were used in the analysis of this study. The intention-to-treat (ITT) population included all enrolled patients who followed the feeding study protocol for at least 12 h. The per-protocol (PP) population consisted of the patients in the ITT population who did not violate any major entry condition and the protocol before study completion. The Chi-square test was applied for categorical variables. Continuous variables were expressed as median and interquartile range (IQR) and analyzed with the Mann–Whitney *U*-test. A binary logistic regression analysis was used to predict the presence or absence of NEC in each group based on values of predictor variables: patient's gestational age, birth weight, sex, time to start enteral feeding, rate of infant with umbilical catheter, occurrence of PDA, IVH and intake of breast milk at 14th day of life. The Kaplan–Meier method was used to estimate the probability of hospital discharge at days 40, 50 and 60 in each study group, and the resulting functions were compared with the log-rank test. The statistical analysis was performed with SPSS version 16.0.2 for Windows (SPSS, Inc., Chicago, IL, USA). The study power was calculated on primary outcome with Sample Power software Version 2.0 for Windows (BIOSTAT, Englewood, NJ, USA), and 50 patients in each group were estimated to obtain a power of the study = 80%, type 1 error = 0.05, 2-tailed test. This estimate assumes that the mean difference in the time to reach full enteral feeding is 3 days between the study groups (corresponding to a means of 8 versus 11 days), with a within-group standard deviation of 5 days. The sample size estimate included a dropout as high as 10%.

RESULTS

Two hundred and forty-two clinical charts were reviewed. One hundred and twelve presented at least one episode of feed intolerance and were considered eligible for the study: 10 patients were excluded (8 cardiac or intestinal malformations, 2 incomplete clinical data), and 102 were analyzed. Fifty-one subjects out of 102 were classified in group 1 (total PN and NBE), and 51 in group 2 (PN plus MEF). Five subjects (2 in group 1 and 3 in group 2) showed deviation from the feeding protocol and were included in the ITT

Table 1 Main demographic characteristics of the study population

	Group 1 (Total PN)	Group 2 (PN + MEF)
Male, n (%)	26 (51.0)	21 (41.2)
Birth weight, g (IQR)	1100 (865–1280)	1095 (885–1290)
Small for gestational age, n (%)	8 (15.7)	9 (17.6)
Gestational age, weeks (IQR)	29 (28–31)	29 (27–30)
CRIB score	1 (0–2)	1 (0–2)
Age at the first episode of feeding intolerance, days (IQR)	6 (3–11)	7 (3–10)

Data expressed as median (IQR) when not specified. The study groups were comparable for variable reported in this table.
PN = parenteral nutrition; MEF = minimal enteral feeding; IQR = interquartile range; CRIB = Critical Respiratory Index for Babies.

Table 2 Risk factors associated with the NEC development

	Group 1 (Total PN)	Group 2 (PN + MEF)
Time to start enteral nutrition, h	11 (8–12)	8 (7–9)
Umbilical catheter, n (%)	38 (74.5)	38 (74.5)
Patent ductus arteriosus, n (%)	7 (13.7)	8 (15.7)
Intraventricular haemorrhage stages III–IV, n (%)	7 (13.7)	7 (13.7)
BM/total enteral feeding at day 14 of life	0.4 (0.2–0.5)	0.5 (0.3–0.6)
BM/total enteral feeding at discharge	0.3 (0.2–0.4)	0.3 (0.2–0.4)

Data expressed as median (IQR) when not specified. The study groups were comparable for variable reported in this table.
NEC = necrotizing enterocolitis; PN = parenteral nutrition; MEF = minimal enteral feeding; BM = breast milk; IQR = interquartile range.

analysis. The study groups were comparable for birth weight, gestational age, sex and CRIB score (Table 1), and for variables that may influence NEC development (Table 2).

The amount of gastric residual was comparable in the two groups: the median total gastric residual, as a percentage of total daily feed volume, was 32% in group 1, and 34% in group 2; the maximum median residual was 5.0 mL/kg (IQR 4.0 mL/kg) and 4.5 mL/kg (IQR 3.0 mL/kg) in group 1 and 2, respectively. The rate of patients that presents at least two episodes of feeding intolerance was similar between the two groups (Table 3).

The neonates in group 2 showed a shorter duration of central vascular access and reached full enteral nutrition earlier (Table 3). A significant difference between the two groups was observed in the incidence of culture-proven late-onset sepsis (Table 3). The pathogens identified were: *Staphylococcus aureus* (20%), *Candida albicans* (29%), *Klebsiella pneumoniae* (38%), *Serratia marcescens* (12%) and *Proteus mirabilis* (10%). One patient in group 1 (septic shock) and 2 patients in group 2 (disseminated intravascular coagulation) died because of sepsis complications. A significant difference was observed between the two groups in the time to regain birth weight (Table 3). Finally, the Kaplan–Meier functions showed a significant difference in the time to reach hospital discharge at days 40, 50 and 60 of life (Fig. 1).

The NEC (Bell stage >II) incidence observed was similar in the two groups (Table 3). One patient in group 1 died because severe NEC (stage IV) developed after 13 days of life. In group 2, one newborn experienced severe NEC (stage III) at day 18, but a prompt surgical therapy (resection of terminal ileum and ileocaecal valve) resulted in symptom resolution. The number of deaths was not significantly different between the two groups (Table 3). The results according to the PP analysis were similar to those of the ITT analysis.

Table 3 Study outcomes

	Group 1 (Total PN)	Group 2 (PN + MEF)	p
Patients with NEC, n (%)	1 (2.0)	1 (2.0)	0.999
Central vascular access duration, days	12 (10–15)	7 (5–9)	<0.001
Time to reach full enteral feeding, days	11 (10–15)	8 (5–10)	<0.001
Patients with ≥2 episodes of feeding intolerance, n (%)	14 (27.5)	15 (29.4)	0.826
Patients with late onset sepsis, n (%)	17 (33.3)	8 (15.7)	0.038
Time to regained birth weight, days	12 (10–14)	9 (8–9.5)	<0.001
Death, n (%)	2 (3.9)	3 (5.9)	0.647

Data expressed as median (IQR) when not specified.
NBE = nothing by enteral route; MEF = minimal enteral feeding; NEC = necrotizing enterocolitis; IQR = interquartile range.

DISCUSSION

The results suggest that MEF could be an efficacious and safe strategy in VLBW infants presenting feed intolerance. This nutritional approach could be able to reduce the time to reach full enteral feeding and the incidence of sepsis without increasing the risk of NEC and death in this setting. Bloodstream infections are the most common severe complication of PN (20). Numerous strategies have been attempted to prevent the risk of PN-related sepsis with different successes (21–23). Our data suggest that continuing enteral nutrition in feed-intolerant patients results in a more rapid advancement of feeding, which in turn determines a reduced time to reach full enteral nutrition and the duration of PN (11). It has also been demonstrated that total PN directly impairs the immune response to bacterial infections (24,25). We speculate that a small volume of enteral feeding may reverse this effect (24,25).

Cochrane meta-analysis on preventive strategy for NEC (11), including 9 prospective, randomized clinical trials, showed no convincing evidence for the beneficial effects of MEF compared with NBE in parenterally fed VLBW neonates. However, this meta-analysis was not designed to verify the MEF effect on NEC occurrence (11). Several studies included in this meta-analysis showed a number of methodological limitations. The method of randomization was usually not stated, it was unclear whether the investigators could anticipate treatment group before randomization, and most studies did not include all patients in the outcome assessments. In some trials, the results concerning outcomes such as days to reach full enteral feeding and to regain birth weight may be biased by the exclusion from the analysis of infants who developed complications (11). No benefit of

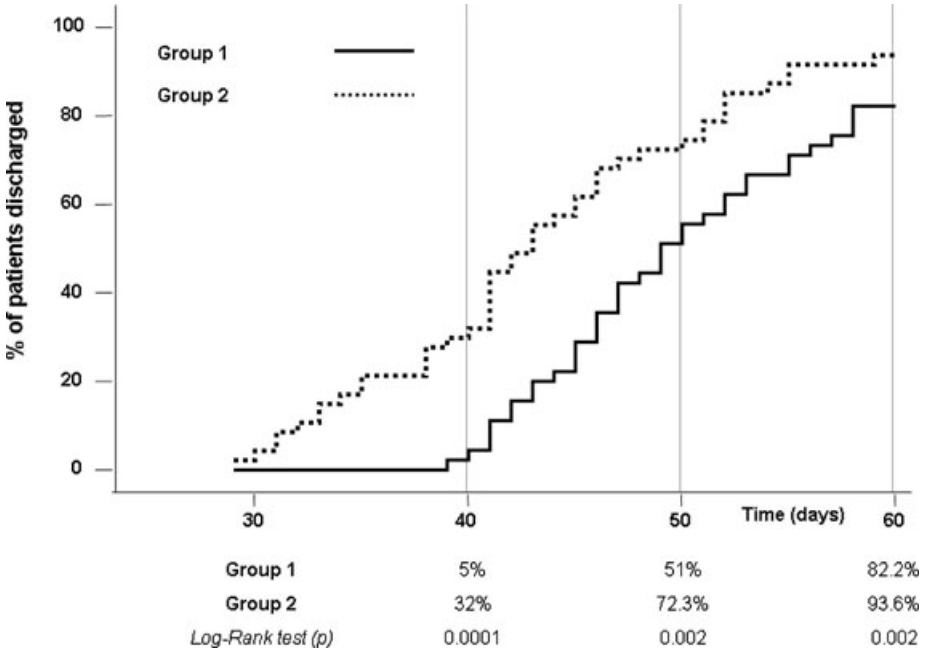

Figure 1 Kaplan–Meyer analysis shows a significant difference between VLBW feeding-intolerant infants administered with total parenteral nutrition (PN, group 1) and with PN plus minimal enteral feeding (MEF, group 2) at days 40, 50 and 60 of life in percentage of patients discharged from neonatal intensive care unit.

MEF was reported from the largest study of Becerra et al. (11). However, in this trial, the infants appear to be less 'ill' than in some other trials, and this study has been published only as an abstract (11). The Cochrane meta-analysis also showed that very delayed feedings results in a reduced incidence of NEC compared with MEF, but this benefit might be offset by an increased mortality or a long-term morbidity as a result of greater malnutrition or the hazards of prolonged use of vascular lines and parenteral nutrients (11). Finally, in most of these studies, the nutritional strategy for feeding-intolerant subjects was not clearly presented. Nevertheless, none of the previous prospective studies aimed to demonstrate the utility of MEF in feeding-intolerant VLBW. Additional to the previous evidences, our data suggest a role of MEF in this particular setting. We showed a similar incidence of NEC in feed-intolerant newborn receiving total PN or MEF. We speculate that continuing enteral nutrition in feed-intolerant infants may contribute to the growth of a balanced intestinal microflora and promote maturation of intestinal functions, thereby decreasing the incidence of PN-induced mucosal atrophy and bacterial overgrowth and translocation, which in turn could be protective for NEC (4,18,26–29).

We also report that MEF promotes regain of birth weight and minimizes the duration of hospital stay when adopted in preterms presenting feeding intolerance. Thus, the MEF administration in feed-intolerant VLBW infants results also in cost saving through the reduction of hospital stay. In our country, the cost of hospitalization is estimated as about 750 euro/day for a VLBW infant. The difference in the duration of hospitalization between the two groups was 10 days, resulting in a saving of about 7500 euro per patient when MEF strategy was adopted in infants presenting signs of feed intolerance.

The major limitations of the study are derived from the retrospective design. However, it would be quite difficult to blind the caregivers to neonate feeding in order to assess the efficacy of different nutritional strategies in a prospective study (11). The differences observed between the two groups could be influenced, at least in part, by the improvement of the NICU clinical practice during the study period. In addition, the interpretation of the results should take into account that the NEC incidence was not used for the power calculation of the study.

CONCLUSION

Clinical evidences derived by our results suggest that suspension of enteral feeding on the basis of detection of the first sign of feeding intolerance would represent a cumulative risk for sepsis and not a protective strategy versus NEC. Therefore, when making decision about suspending enteral nutrition in feed-intolerant preterm babies, it should be remembered that diet plays an important role in the intestinal development and systemic defence (30). Our data, supporting the feasibility and efficacy of MEF administration in feed-intolerant VLBW patients, open the way for future trials.

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