Original Article

Iran J Pediatr
Jun 2012; Vol 22 (No 2), Pp: 171-176

Early versus Late Trophic Feeding in Very Low Birth Weight Preterm Infants

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Received: *Dec 26, 2010*; Final Revision: *Aug 08, 2011*; Accepted: *Sep 26, 2011*

Abstract

Objective: Improved survival of preterm infants, beneficial effects of trophic feeding and limited data on timing management of enteral feeding for very low birth weight preterm infants requires more researches to determine the exact starting time and increased volumes. This study aims to compare early (<48 h) versus late (>72h) trophic feeding with respect to important neonatal outcomes.

Methods: In a cohort study from September 2007 to October 2008, a total of 170 preterm infants (1000-1500 gram, 26-31 weeks) consisting of 125 who received trophic feeding enterally within the first 48 hours of birth (early group) and 45 fed enterally after 72 h0urs (late group), without major congenital birth defects and severe asphyxia entered the study. Bolus feeding was started in both groups at 1-2 cc/kg every 4-6 hours of human milk or preterm infant formula and was advanced 1-2 cc/kg/day if tolerated along with parenteral nutrition. Feeding intolerance, possibility of necrotizing entrocolitis (NEC), episodes of sepsis, body weight, length of NICU stay, and duration of parenteral nutrition were assessed serially.

Findings: There were no statistically significant differences in the clinical and maternal characteristics of infants in the two groups. The time to gain birth weight (13.75±5.21 vs 20.53±6.31 (P<0.001)), duration of parenteral nutrition (9.26±4.572 days vs 14.11±6.415 days (P<0.001)), hospital stay (12.14±8.612 vs 21.11±1.156 (P<0.001)) were significantly shorter in early compared to late feeding group; none of the two groups experienced a high incidence of late onset sepsis (P=0.73). There was 1 case of confirmed NEC in every group.

Conclusion: The benefits of early trophic feeding shown by this study strongly support its use for the preterm infants without adding to complications.

Iranian Journal of Pediatrics, Volume 22 (Number 2), June 2012, Pages: 171-176

Key Words: Trophic Feeding; Preterm Infant; Very Low Birth Weight Infant; Parenteral Nutrition

Introduction

Advanced neonatal cares, improved survival of preterm infants and necessity of providing adequate nutritional regimes has made feeding strategies as one of the major clinical challenges facing NICU staff [1,2]; because of excess prematurity, very low birth weight preterm infants are not often able to be directly breast fed and prolonged parenteral nutrition will predispose them to sepsis and phlebitis[3,4]; on the other hand total enteral feeding by nasogastric

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tube will increase the chance of necrotizing enterocolitis (NEC) [5].

Beneficial effects of human milk in improvement of host defense, digestion and absorption of nutrients, neurodevelopment, gastrointestinal function as well as psychological effects[6], makes it suitable for meeting essential needs of premature infants; whereas enteral feedings in very low birth weight or sick preterm infants are often delayed for several days or weeks after birth because of respiratory compromise or risk of necrotizing enterocolitis[7]; fortunately wisdom of withholding enteral nutrition in preterm infant has been questioned from last 3 decades. Among practiced feeding strategies, trophic feeding which is early initiation of enteral feeding along with parenteral nutrition seems to be the solution [8]; improved feeding tolerance, less need of parenteral nutrition, more mature intestinal motility patterns [4, 9-13], increased growth rate, bone mineralization, stable biochemical measures of nutritional status, improved mineral homeostasis, better calcium and phosphorus retention, higher serum calcium and alkaline phosphates activity, and shorter intestinal transit times have been reported following trophic feeding versus parenteral nutrition [14]. These beneficial effects, in turn, could be associated with a significant economic advantage if they reduce the duration of hospitalization [15].

Although several studies have verified the potential benefits of trophic feeding, there is no general agreement about the optimal timing to start enteral feeds [9,15-16]. A systematic review of Cochrane data base revealed that only time to full enteral feeding, number of days that feedings were withheld and total hospital stay were significantly reduced following trophic feeding [9], but there is still uncertainty about the exact time of starting minimal enteral feeding; another review assessed all studies of parenterally fed low birth weight preterm infants to determine the effects of early enteral feedings initiated shortly after birth compared to delayed enteral feedings [17]; results of two included studies in analyses [3,18] revealed that early feeding had no significant effect on weight gain, necrotizing enterocolitis, mortality, or age at discharge, although important effects cannot be excluded with the small number of patients studied. Bomnell and coworkers in their review wield that early trophic feeding did not provide any evidence to affect feed tolerance or growth rates in VLBW infants [19]. Considering all these results benefits and hazards of early versus delayed initiation of enteral feedings in parenterally fed preterm LBW infants have received very little study, and the effects on major clinical outcome remain uncertain [17,19]. The aim of this study was to compare early (<48 h) versus late (>72h) trophic feeding with respect to important neonatal outcomes: time to regain birth weight, duration of parenteral nutrition, duration of hospital stay and feeding tolerance.

Subjects and Methods

In Alzahra NICU (a referral and training center in east Azerbaijan Province of Islamic Republic of Iran with more than 8000 births a year) trophic feeding is almost being initiated during the first week of life; from a nursing point of view in a prospective cohort study from September 2007 to October 2008, we reviewed the common trend of nutritional practice in our NICU. A total of 170 infants (weighing 1000-1500 grams, 26-31 weeks as determined by a combination of maternal last menstrual period and early antenatal ultrasound) entered the study; 125 infants had received enteral feeding within the first 48 hours after birth "early group" and 45 infants had been enterally fed after 72 h "late group". Infants with major congenital birth defects, severe asphyxia and referred from other hospitals did not meet the inclusion criteria. All infants were daily visited until discharge. Sample size was estimated based on the information derived from pilot study with a type I error of 0.05 and a power of 0.90%. The study was approved by Institutional Review Board of Tabriz University of Medical Sciences Research and Ethics Committee.

Informed written consent was obtained from mothers before enrollment in order to bring their expressed milk and agreement for later following after discharge if needed.

Feeding Protocol: Daily feeding order was maintained at each infant's patient file. Milk advancement and use of parenteral nutrition were consistent for all study infants to provide similar

intakes of fluid and energy. Bolus feeding was the common feeding method. Oral Feeding tube (Radio-opaque feeding tube 2×47mm), was placed by the nurse and was not removed between feeds (changed daily); a syringe positioned above the patient administered feeds, and milk was administered by the law of gravitation. To measure the gastric tube length, we placed the tube tip at the xiphisternum and measured to the ear lobe and then to the mouth for orogastric tubes. Infants in each group received 1-2 cc/kg of human milk or preterm infant formula (Pre-Nan–Nestle Formula, 2 scoops of formula for every 60 ml of boiled water) every 4-6 hours (while there was a lack of breast milk supply) and was advanced 1-2 cc/kg/day if tolerated along with parenteral nutrition. Human Milk Fortifier was added to human milk when the intake reached 100 cc/kg/day (Aptamil FMS FrauenMilchSupplement, 4 scoops for every 100cc of human milk).

Gastric Residual Volume (GRV) an important determinant of feeding tolerance was detected by aspiration of gastric contents from the indwelling orogastric tube before every feeding; whenever the GVR was about 10-30% of the previous feeding volume, the residual was subtracted from the present amount then re-fed and the feeding schedule was resumed as planned. When GVR was more than 30%, without any ominous abdominal signs, two bolus feeds were held; if it was repeatedly more than 30%, feeds were held for 12 hours and infants were followed for other signs of feeding intolerance like: color of aspirated content (bile or blood stained gastric residual), emesis, abdominal distention or tenderness, stool number, hematochezia, number of feeding stops and apnea which were noted in special checklists. Probability of NEC was suspected and confirmed by the presence of feeding intolerance with or without abdominal distention and tenderness, lethargy and temperature instability together with the presence of intramural or portal venous gas in abdominal radiograph [20].

Body weight was measured at the same time each day (by digital baby scale Seca 728 at a 2 gram graduation) for all the infants in both groups until the day of regaining birth weight; duration of hospitalization, parenteral nutrition and other health outcomes (episodes of sepsis and NEC) were assessed serially.

Data Analyses: Data were analyzed using the SPSS for Windows statistical package version 14 and t Student test, χ^2 and Linier regression tests. Statistical significance was set at 0. 05. The data were expressed as mean±SD or n(%).

Table 1: Demographic and clinical characteristics of study infants

Characteristics		Early group (n=125)	Late group (n=45)	*P* Value
Infant Sex (%)	Female	75 (60)	40	0.02
	Male	18 (40)	60	
Gravidity (%)	G1	71 (56.8)	28 (62.2)	0.3
	G2	21 (16.8)	6 (13.3)	
	G3 and more	33 (26.4)	11 (24.5)	
Delivery Method (%)	NVD*	40 (32.0)	16 (35.6)	0.4
	Cs**	85 (68.0)	29 (64.4)	
Resuscitation after birth (%)		91	100	0.3
Cause of preterm labor (%)	Preeclampsia	38 (30.6)	8 (17.8)	0.2
	Multiple pregnancy	13 (10.5)	11 (24.4)	
	Preterm rupture of membrane	6 (4.8)	1 (2.2)	
	Placental abruption	6 (4.8)	3 (6.8)	
	Others	62 (49.3)	22 (48.8)	
Surfactant administration (%)		24 (19.20)	10 (22.20)	0.7
Birth weight (g) [mean (SD)]		1335.4 (903.2)	1233.6 (154.5)	0.4
Gestational age (wk) [mean (SD)]		29.1 (0.9)	29.4 (1.3)	0.4
First minute Apgar [mean (SD)]		6.7 (1.6)	6.4 (4.2)	0.4
Fifth minute Apgar [mean (SD)]		9.0 (5.7)	8.2 (1.4)	0.4

SD: standard deviation

Table 2: Main outcomes of early versus late trophic feeding in very low birth weight preterm infants

Outcomes	Early group* (n=125)	Late group* (n=45)	*P* Value	CI‡ 95%
Time to gain birth weight (days)	13.75 (5.21)	20.53 (6.31)	*P*<0.001	-8.71 - -4.85
Stay days (days)	12.14 (8.61)	21.11 (1.15)	*P*<0.001	-12.63 - -2.76
Duration of Parenteral Nutrition (days)	9.26 (4.57)	14.11 (6.41)	*P*<0.001	-6.92 - -4.85

* Data are presented as mean (Standard Deviation) / ‡ CI: confidence Interval

Findings

All infants were born in Alzahra Hospital without congenital birth defect; intra uterine growth retardation was observed in 8.8% of early and 4.4% in late group. Fluid and energy intake and medication were equal in the two groups; 36 and 63.2% of infants in early group had received enteral feeds in the first 24h and 24-48h of life respectively, whereas 40.0% of infants in late group had been enterally fed in the fourth day, and 60% enjoyed enteral feeding after the fifth postnatal day.

There were no statistically significant differences in the clinical and maternal characteristics of the 170 infants among groups (Table 1). The time to gain birth weight was significantly shorter in early versus late feeding group. Infants with early enteral feeding were discharged sooner than infants who received trophic feeding later. Intravenous catheters were in place for parenteral nutrition more days in infants who were in late group; however this group did not experience a higher incidence of late onset sepsis (5.2% vs. 4.4%, *P*=0.7) (Table 2).

Signs of feeding intolerance did not show statistical differences in the two study groups whereas infants in late feeding group delayed the time required attaining complete enteral feeding (160 ml/kg/day by tube-feeding) (Table 3).

Discussion

Recently enteral feeding has been encouraged in ill preterm neonates. Infants exposed to trophic feeding had significantly greater energy intake, greater weight gain and head growth, improved milk tolerance, less requirement for parenteral nutrition, less sepsis, fewer days of supplemental oxygen and were discharged from hospital earlier [8,9,21-22]. Our findings are contributed to this knowledge; but for such an essential issue in the care of VLBW preterm infants, there is quite inadequate data about the start time of enteral feedings which has been compounded by its effect on important neonatal outcomes, particularly necrotizing enterocolitis [8,9,23,4]. Our study differed from those reported previously in start time of trophic feeding, birth weight and gestational age, besides we report the outcomes from nursing view.

Definition of early feedings may vary among different practitioners and neonatal units. Early minimal enteral feeding is a common trend in Alzahra NICU and infants are being visited by four minimal enteral feeding is a common trend in Alzahra NICU and infants are being visited by four neonatologists and attending physicians but timing preferences differ; we defined early feedings as initiation of enteral nutrition during the first 48 hours after birth, although many

Table 3: Feeding tolerance in study groups

Signs of feeding intolerance	Early group (n=125)	late group (n=45)	*P* Value
Vomiting (%)	10(8)	2(4.4)	0.73
Gastric Residual Volume >30% (%)	33(26.4)	15(33.3)	0.44
Bile or blood stained residuals (%)	2(1.6)	0 (0)	0.99
Melena (%)	0	0	-
Diarrhea (%)	0	0	-
No stool more than 24h (%)	2 (1.6)	2(4.4)	0.28
Bowel distention (%)	16 (12.8)	9 (20)	0.32
Apnea (%)	9 (7.2)	3 (6.7)	0.99
Days of feeding stop [mean (SD)]	0.54 (0.02)	0.91 (2.02)	0.23
Days to complete enteral feeding [mean (SD)]	10.31 (4.25)	13.20 (7.11)	0.01

clinicians might consider it during the first 4 days [17,19,24]. Trophic feeding after the first 72h of life was assumed late while it may vary in different studies [3,17,24].

Fortunately we meet good outcomes in early feeding group. Increased costs is relevant to prolonged inpatient stay [25-27]. Economic burden of NICU stay on family, government and insurance system is an important issue in preterm birth [27-29]; two systematic reviews on the matter revealed that trophic feeding resulted in significant reduction in stay days[9,17]. In our study infants in early group were associated with a decrease in length of hospital stay; this reduction was by 42% in early group which is a valuable finding.

Parenteral nutrition can be accompanied with sepsis and some other metabolic and fluid and electrolyte mismanagement for preterm infants. Efforts are done to shorten the duration of TPN by emphasizing the factors can be avoided or monitored[25]. Minimal Enteral Nutrition (MEN) by breast milk is followed by lower rate of sepsis [8,23]; a mean reduction of over 4 days in parenteral nutrition, as found in this study, corresponds with results of Archana et al [23] that significantly reduce the associated morbidity and provide considerable economic savings and bring peace to stressed parents and family [27,28]. Although in our study duration of parenteral nutrition and intravenous catheter was shorter in early group, differences in occurrence of sepsis were not significant because of inadequate power of our study for detecting sepsis prevalence.

Feeding intolerance and increased length of time to reach full enteral feedings is significantly associated with a poorer mental outcome in preterm neonates at 24 months corrected age [29]. Nine studies included in the meta-analysis by Tyson et al [9] examined the role of trophic feeding on the number of days to reach full enteral feeding; the weighted mean difference (WMD) was lower by 2.55 days in the trophic feeding group. We also found a reduction in need for parenteral nutrition and time to take full enteral milk which support the findings of previous studies that trophic feeding improves later milk tolerance [3,9,17]; although infants in both groups had some minor gastrointestinal complications but it was not significant.

In previous studies [17,19], the effect of early trophic feeding on the number of days to regain birth weight was not significantly different while there was a comparable reduction in the overall time to attain birth weight in early group infants in our study which coincidence with results of Mc Clure et al [8], this may arise from different time zones of enteral feeding start, different age and weight in group of studied infants.

A meta-analysis of nine studies with 650 participants [9] showed no significant difference in the incidence of necrotizing enterocolitis among infants given trophic feedings or no feedings, this result was backed by another systematic review[19] but available data still couldn't exclude important beneficial or harmful effects; the present study did not have the power to note the differences about occurrence of necrotizing enterocolitis. There was 1 case of confirmed NEC in every group while considering the sample size in each group, NEC was higher in late group.

Limitations of the research: Although our study manifested beneficial effect of early starting of trophic feeding, more randomized controlled trials (RCTs) considering enteral feeding initiation in different time zones after birth are recommended. We could not compare the result considering the efficacy of mother milk and formula; later studies are better to investigate this matter about infants who did not meet our inclusion criteria and follow their later developmental and health status.

Conclusion

Results support the benefits of early trophic feeding for the preterm infant, reduced number of days of parenteral nutrition, successful tolerance of nutritive enteral feeds and reduced hospital stay and better weight gain during the first days of life. It seems that better education of mothers for expressing their milk and handing to NICU to use in trophic feeding is important. Further large scale clinical trials are needed to determine the best initiation time considering some important outcomes like NEC and sepsis.

Acknowledgment

This study was granted by Research Deputy of Tabriz University of Medical Sciences; we thank

the nursing staff of the Alzahra Neonatal Intensive Care Unit, the staff of the Lactation Program and all the neonatologists, attending physicians and parents of neonates.

Conflict of Interest: None

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