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Early Total Enteral Feeding in Stable Very Low Birth Weight Infants: A Before and After Study

by Sushma Nangia,[1] Amit Bishnoi,[2] Ankita Goel,[2] Piali Mandal,[2] Soumya Tiwari,[2] *and* Arvind Saili[1]

[1]Department of Neonatology, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi 110001, India
[2]Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi 110001, India
*Correspondence: Sushma Nangia, Department of Neonatology, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi 110001, India. Tel: 011-23344161-70, Ext 331, Mobile: 91-9810838181, E-mail <drsnangia@gmail.com>.

ABSTRACT

Background: Fear of necrotizing enterocolitis (NEC) has perpetuated delayed initiation and slow advancement of enteral feeding in very low birth weight (VLBW) infants with inherent risks of parenteral alimentation. The objective of this study was to assess effect of early total enteral feeding (ETEF) on day of achievement of full enteral feeds, feed intolerance, NEC and sepsis.

Methods: In total, 208 stable VLBW neonates (28–34 weeks) admitted during 6 month periods of three consecutive years were enrolled. First phase ($n = 73$) constituted the 'before' phase with standard practice of initial intravenous fluid therapy and slow enteral feeding. The second prospective phase ($n = 51$) consisted of implementation of ETEF with infants receiving full enteral feeds as per day's fluid requirement since Day 1 of life. The third phase ($n = 84$) was chosen to assess the sustainability of change in practice.

Results: Day of achievement of full feeds was significantly earlier in Phases 2 and 3 compared with Phase 1 (8.97 and 5.47 vs. 14.44 days, respectively, $p = 0.0001$). Incidence of feed intolerance was comparable between Phases 1 and 2 (22 vs. 14%, $p = 0.28$), with marked reduction in incidence of NEC (14 vs. 4%, $p = 0.028$). There was a significant decrease in sepsis, duration of parenteral fluid and antibiotic therapy as well as hospital stay with comparable mortality.

Conclusion: In stable preterm VLBW infants, ETEF is safe and has the benefit of optimizing nutrition with decrease in sepsis, NEC and hospital stay.

KEYWORDS: early total enteral feeding, necrotizing enterocolitis, sepsis, very low birth weight

INTRODUCTION

Optimal nutrition has been identified as a fundamental factor in reducing mortality and long-term morbidities like extrauterine growth restriction and poor neurodevelopmental outcome in preterm very low birth weight (VLBW) infants (birth weight <1500 g) [1, 4]. According to American Academy of Pediatrics, postnatal growth of preterms should parallel the corresponding intrauterine period [2]. This goal remains elusive to best neonatal centres around the world with almost 90% having growth delay at 36 weeks' corrected age and 40% at 18–22 months of age [3]. In most centres, aggressive early nutritional rehabilitation of preterms is achieved by total parenteral nutrition (TPN) with delayed initiation of enteral feeding. However,

complications like sepsis related to invasive catheters along with gut translocation of bacteria, gut atrophy, thrombosis or bleeding and cholestasis offset the benefits of TPN [5].

Improved understanding of preterm gastrointestinal functions along with increased recognition of beneficial effects of human milk has resulted in trophic feeding along with TPN being put forth as a feasible solution [6–8]. More recently, studies with variable time of initiation of feeds and different feeding regimens have been conducted in preterm infants [9–14]. Ostertag *et al.* [15] found no difference in necrotizing enterocolitis (NEC) between enteral feeding started on Day 1 vs. Day 7 in sick VLBW infants. Recent Cochrane review compared slow vs. fast daily increments of feed volume with no increase in NEC, mortality or feed interruption [16]. Survey of enteral feeding practices among 127 tertiary Neonatal intensive care units (NICU) revealed initiation within 24 h in 35% of preterm neonates when gestational age (GA) was <25 weeks, 43% for GA 25–27 weeks and 71% if GA was 28–31 weeks [17]. However, none of these studies initiated exclusive enteral feeding on the first day of life. Recently, it has been postulated that total enteral feeding may be started safely on the first day in stable low-risk VLBW infants [18]. This physiological approach may be of greater significance in resource-limited settings, where cost and logistics of providing TPN are usually the limiting factors. Hence, this uncontrolled before and after study was undertaken to assess the feasibility, efficacy and sustainability of early total enteral feeding (ETEF) at a tertiary neonatal centre with high patient load.

MATERIALS AND METHODS

This uncontrolled before and after study was conducted at a tertiary care teaching institution. The ethics committee of the institute approved the study protocol.

Study subjects: Stable preterm infants (GA 28–34 weeks, birth weight 1000–1499 g), not requiring resuscitation beyond initial steps, with normal haemodynamic status (capillary refill time <3 s and mean arterial pressure normal for GA as per Zubrow's chart) and absence of significant respiratory compromise [(no requirement of respiratory support (CPAP or ventilation)] admitted to NICU were included in the study [19, 20]. Exclusion criteria were documented as absence or reversal of end diastolic flow in umbilical arteries and presence of gross congenital malformations.

Study design: The study was divided into three phases. In Phase 1, retrospective data were collected from case files of eligible infants, admitted between January and June 2010, who were treated with standard practice of initial intravenous (IV) therapy (10% dextrose for first 2 days and N/5 saline in 10% dextrose from Day 3 onwards). These neonates also received slow incremental enteral feeding consisting of men on Day 1 (20 ml/kg/day) with successive feed increments of 20 ml/kg/day along with proportionate decrease in the IV fluid volume till the baby reached full feeds (150 ml/kg/day). Between July and December of 2010, 20 stable VLBW neonates were provided ETEF (total fluid requirement for the day provided as enteral feed with no IV fluid) on a pilot basis and strictly monitored for any feeding-related adverse events like feed intolerance or NEC. The response was encouraging, and unit policy to start ETEF was implemented from January 2011 based on literature evidence and pilot experience. During Phase 2, eligible babies were prospectively included from January to June 2011. In this period, there was a change in feeding policy to ETEF, where the day's fluid requirement was provided as enteral feeding with 80 ml/kg on Day 1 of life. Feeding volume of this magnitude (80 ml/kg on Day 1 with daily increments of 20 ml/kg/day to reach 150 ml/kg on Day 5/Day 6 of life) was achieved with biological mother's expressed breast milk predominantly along with remaining deficit fulfilled by preterm formula (80 kcal/100 ml). Bolus feeds were provided every 2 h through orogastric tube with prefeed abdominal girth (AG) charting and abdominal assessment. With this regimen, the neonate did not receive any IV fluid. During the second half of 2011 (July–December), the unit continued with the practice of ETEF. Phase 3 consisted of evaluation of sustenance of ETEF practice from January to June 2012.

Case management: Apart from hemodynamic and vital monitoring, prefeed blood sugar monitoring for all neonates was done by heel-prick method. The frequency of monitoring was every 4 h in the initial

72 h of life and thereafter every 8 h till the end of first week. Sepsis screen and blood culture were sent at admission and in case of any clinical deterioration. Abdominal x-ray and ultrasound were done to look for evidence of NEC in suspected cases. Standard management protocols as per the unit policy were followed for other clinical problems. There was no major change or revision in the unit protocols during the study period.

Outcome measures

The primary objective was to assess the feasibility and sustainability of ETEF by assessing the day of achievement of full enteral feeds, incidence of feed intolerance and incidence of NEC. Secondary objectives included all-cause mortality, incidence of clinical and culture-proven sepsis and durations of antibiotic therapy, IV fluid therapy and hospital stay.

Definitions

1. Full feed achievement: total enteral intake of 150 ml/kg/day sustained for 24 h.
2. Feed intolerance: presence of one or more of the following:
   a. Vomiting more than three times during any 24 h period
   b. Any episode of bile- or blood-stained vomiting
   c. AG increase >2 cm (measured at umbilicus—prefeed)
   d. Abdominal wall erythema or tenderness
   e. Gross or occult blood in stools

Prefeed aspirates were ordered if the AG increased by >2 cm; if the aspirate was milky and <50% of the previous feed volume, then the feed was reintroduced and one feed was omitted, but if milky and >50%, then the feeds were omitted for 24 h. Subsequent feed decisions were based on abdominal assessment and girth measurement. If the aspirates were haemorrhagic or bilious, then the feeds were omitted and neonates evaluated for NEC, sepsis and surgical condition.

3. NEC was suspected in infants with abdominal or systemic symptoms and signs and staged as per modified Bell's classification [21].
4. Clinical sepsis: Clinical signs and symptoms suggestive of sepsis with positive sepsis screen
5. Culture-proven sepsis: Blood culture-proven sepsis in neonate with compatible signs and symptoms

Statistical Analysis

All baseline and outcome data were recorded in a predesigned pro forma, and known variables were compared between Phase 1 (before) and Phase 3 (after).

The data were entered in Excel datasheet, and coded and analysed statistically using software version 11.1 (StataCorp, College station, Texas, USA). Descriptive data were analysed using means and SD. Continuous data with normal distribution were analysed by 't' test and non-normally distributed data by Wilcoxon rank sum test (Mann–Whitney). Categorical data were analysed using χ^2 test or Fisher's exact test. The groups were compared for continuous variables by one-way analysis of variance test. A 'p' value of <0.05 was taken as significant.

RESULTS

A total of 208 infants were included in the study during the 6 month periods of consecutive years 2010–2012. Phase-wise distribution was 73, 51 and 84 in Phases 1, 2 and 3, respectively (Fig. 1). Demographic and baseline characteristics of study subjects during the three phases were comparable (Table 1).

Primary outcome

With ETEF, there was a statistically significant decrease in days required to achieve full feeds along with an earlier regain of birth weight ($p = 0.0001$) (Table 2). Moreover, ETEF was not associated with any increase in feed intolerance or NEC.

Secondary outcome

ETEF was associated with a marked decrease in incidence of both clinical and culture-proven sepsis (92 and 44% in Phase 1 to 23 and 3.5% in Phase 3; $p = 0.0001$). This was accompanied by a significant reduction in duration of antibiotic therapy and IV fluid administration ($p = 0.0005$). Days to regain

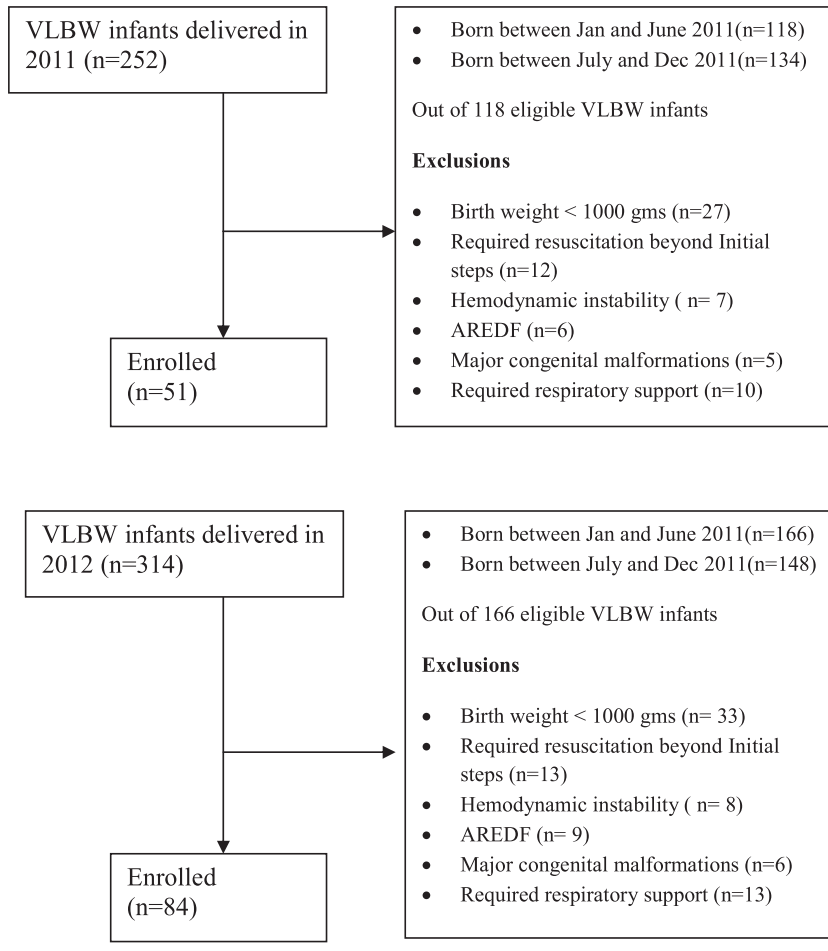

Fig. 1. Trial flow of study.

Table 1. Baseline characteristics of study subjects

Parameter	Phase 1 ($N = 73$)	Phase 2 ($N = 51$)	Phase 3 ($N = 84$)	p value
Gestation (weeks)*	31.5±1.1	32.5 ± 0.78	32.2 ± 2.3	0.30
Birth weight (grams)*	1243±192	1341 ± 182	1252 ± 220	0.078
Male sex#	41 (56%)	21 (42%)	46 (55%)	0.50
Registration status in antenatal clinic—booked#	59 (77%)	43 (84%)	73 (87%)	0.15
APGAR score§	7 (6–8)	7 (7–7)	8 (7–8)	0.38
Small for gestational age#	27 (37%)	18 (35%)	33 (40%)	0.50
Antenatal steroids course#	48 (66%)	42 (72%)	66 (82%)	0.79

Note: *Mean (95% confidence interval), #Number (%), §Median (interquartile range).

Table 2. Outcome parameters

Parameter	Phase 1 ($N = 73$)	Phase 2 ($N = 51$)	Phase 3 ($N = 84$)	p value
Day of full feed achievement* (days)	14.44± 6.2	8.97± 4.9	5.47± 1.8	0.0001
Day of regaining birth weight* (days)	16.4±7.6	14.1±6.5	12.3±5.8	0.0006
Incidence of feed intolerance#	16 (22%)	7 (14%)	12 (14%)	0.28
Incidence of NEC#	10 (14.2%)	2 (4%)	0	0.028
Incidence of clinical sepsis#	67 (92%)	24 (47%)	19 (23%)	0.0001
Incidence of culture-proven sepsis#	32 (44%)	6 (12%)	3 (3.5%)	0.0001
Duration of antibiotic therapy* (days)	11.2±6.8	4.3±6.1	2.1±4.2	0.0001
Duration of IV therapy*(days)	12.1±5.7	6.47±3.2	1.5±0.4	0.0005
Duration of hospital stay*(days)	28.04±6.76	19.47±5.22	15.5±4.04	0.0005
Mortality#	3 (4%)	1 (2%)	1 (1.2%)	0.18

Note: *Mean ± SD, #Number (%).

birth weight and duration of hospital stay were significantly lower post-intervention. No episodes of hypoglycaemia were recorded in any of the three phases. All-cause mortality remained comparable between the three study periods (Table 2).

DISCUSSION

This study strongly suggests the nutritional and growth benefits of total enteral feeding introduced from Day 1 of life in stable preterm VLBW infants without significant gastrointestinal or infectious complications. The results of this study when taken together with other recent works suggest the potential benefits of total enteral feeding outweighing the unproven risks of NEC in stable VLBW infants.

Feeding intolerance and increased length of time to reach full enteral feedings are significantly associated with a poorer mental outcome in preterm neonates at 24 months corrected age [22]. In a Cochrane meta-analysis of nine studies assessing the role of trophic feeding on number of days to reach full feeds, the weighted mean difference was lower by 2.55 days in the trophic feeding group [23]. The results of our study also show faster achievement of full feeds and faster regaining of birth weight. Despite introduction of full feeds, the incidence of NEC decreased significantly along with significantly shorter duration of hospital stay decreasing parental concern and economic burden in a resource-limited setting. These results are congruous with pilot study by Sanghvi *et al.* [24], which initiated full enteral feeding on Day 1 of life. In Sanghvi's study, the group started on full enteral feeds on Day 1 regained birth weight earlier (5.52 vs. 12.7 days) with a shorter duration of hospital stay and no increased risk of NEC. However, this study included babies between 1200 and 1500 g with a much smaller sample size. Nonetheless, it suggests ETEF as being a resourceful and relatively safe practice, especially in a resource-poor set-up.

In the present study, ETEF was also associated with a significant reduction in both clinical and culture-proven sepsis, thereby limiting the need for prolonged IV antibiotics and cannulations. The observational study of Hartel *et al.* [25] found that VLBW infants born in centres with slow advancement of feeds had a significantly higher rate of sepsis compared with centres with rapid feed advancement, which was particularly evident for late-onset sepsis (14.0 vs. 20.4%; $p = 0.002$). Furthermore, higher usage of central venous lines (48.6 vs. 31.1%, $p < 0.001$) and antibiotics (92.4 vs. 77.7%, $p < 0.001$) was seen in centres with slow advancement. Flidel-Rimon *et al.* [26] also concluded that early enteral feeding was associated with a reduced risk of nosocomial sepsis. The possible mechanisms involved include prevention of gastrointestinal atrophy, prevention of alteration in gut flora and associated overgrowth of enteropathogenic species, promotion of mucosal immunity by gut-associated

lymphoid tissue; and decreased use of TPN and IV catheters, thereby preserving the skin integrity [26].

Being a before and after study, the current study suffers from the limitations of a non-experimental study with the first phase being a retrospective chart review-based data, potentially overestimating the effectiveness of ETEF. Although efforts were made to ensure consistency in the measurements over similar time with no major environmental or policy change (except for the feeding regimen) to prevent any threats to internal validity of the study, sustained improvement in patient care processes over the years may have contributed in some ways to the better results in the last two phases. In view of the encouraging results of this study, we are tempted to recommend early initiation of total enteral feeding in stable VLBW infants. However, it would be worth exploring the same in a well-designed randomized controlled trial with adequate numbers to substantiate the findings.

CONCLUSION

In stable preterm VLBW infants (1000–1499 g), total enteral feeding initiated on Day 1 of life appears safe without an increased risk of NEC and with benefits of optimizing nutrition, avoidance of parenteral fluid therapy and inadvertent antibiotic usage along with a significantly shorter duration of hospital stay.

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