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Original Research Article

A Randomized Controlled Study Comparing the Efficacy of Early Total Enteral Feeding with Conventional Enteral Feeding in Stable Very-Low-Birth-Weight Infants

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Abstract:

Objective: To assess the impact of early total enteral feeding (ETEF) in comparison to conventional enteral feeding (CEF) on the postnatal age (in days) required for stable very-low-birth-weight (VLBW; 1,000–1,499 g) infants to achieve full enteral feeds.

Methods: In this unblinded randomised controlled study, a total of 180 infants were assigned to either the ETEF group (n = 91) or the CEF group (n = 89). Feeding regimens were commenced as complete enteral feeds in the ETEF group and as minimal enteral nutrition (20 mL/kg) in the CEF group. The remaining daily fluid needs in the CEF group were administered via parenteral route. The primary outcome of the study focused on the postnatal age at which infants achieved full enteral feeds. The secondary outcomes encompassed occurrences of feed intolerance, prevalence of sepsis and necrotising enterocolitis (NEC), and length of hospitalisation.

Results: The baseline variables, encompassing birth weight and gestational age, exhibited comparable characteristics within both cohorts. The neonates in the ETEF group achieved complete enteral nutrition at an earlier stage compared to those in the CEF group (6.5 ± 1.5 vs. 10.1 ± 4.1 days after birth; mean difference –3.6 [–4.5 to –2.7]; $p < 0.001$). The incidence of feed intolerance episodes and clinical sepsis was lower in the ETEF group, with a reduced length of hospitalisation (15.5 vs. 19.6 days) ($p = 0.01$). The occurrence of necrotizing enterocolitis (NEC) exhibited comparable rates within both study cohorts.

Conclusion: The implementation of early total enteral feeding (ETEF) in stable very low birth weight (VLBW) infants leads to accelerated achievement of full feeds and reduces the length of hospitalization, without any heightened susceptibility to feed intolerance or necrotizing enterocolitis (NEC).

Keywords: NEC, CEF.

Introduction

One of the most formidable challenges in the management of preterm infants revolves around the provision of standardized nutritional support [1]. Early and appropriate nutrition is crucial not only for sufficient postnatal growth but also for the mitigation of sepsis and potentially even retinopathy of prematurity [2–4].

The initiation of enteral nutrition for infants with a very low birth weight (VLBW) is frequently postponed for a number of days due to apprehensions regarding feeding intolerance and the development of necrotizing enterocolitis (NEC) [5]. The delay in question hampers the functional adaptation of the gastrointestinal tract, potentially leading to an extended reliance on parenteral nutrition. This prolonged use of parenteral nutrition is associated with increased risks of infection and metabolic complications [6, 7]. The available evidence indicates that the delayed initiation or gradual progression of feedings leads to a prolonged duration in achieving complete feeding establishment [5].

The timely initiation and expeditious progression of enteral nutrition in preterm neonates enhances gastrointestinal maturation, consequently mitigating the susceptibility to necrotizing enterocolitis

(NEC)[2, 8, 9].

Randomised studies have systematically assessed the impacts of various feeding regimens [3, 8–13], and a recent preliminary study has provided evidence in favour of the exclusive enteral feeding approach [10]. Furthermore, there exists compelling evidence suggesting that achieving complete enteral nutrition within a span of seven days in very low birth weight (VLBW) infants is attainable and medically viable, with a recommended intake of 170 mL/kg/day. Importantly, this approach does not result in any discernible rise in apnea episodes, interruptions in feeding, or instances of feeding intolerance, as supported by previous research [9]. However, it is worth noting that there is a scarcity of evidence regarding early total enteral feeding (ETEF) in stable preterm very low birth weight (VLBW) infants weighing between 1,000 and 1,500 grammes, with the exception of an observational study conducted before and after implementation of ETEF, which demonstrated a favourable outcome [14]. Our hypothesis posits that the implementation of early targeted enteral feeding (ETEF) in stable preterm very low birth weight (VLBW) infants will result in the achievement of full enteral feeds at an earlier stage, without any concurrent rise in feed intolerance or necrotizing enterocolitis (NEC), when compared to the conventional enteral feeding (CEF) approach.

Subjects and Methods

Subjects and Settings

This unblinded randomized controlled study Special Newborn Care Unit, Neonatal Intensive Care Unit, department of Pediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, in the Department of Pediatrics from January 2021 to October 2022. We included haemodynamically stable intramural preterm VLBW neonates (gestation 28–34 weeks and birth weight 1,000–1,499 g). Infants were excluded if they: (1) required resuscitation beyond initial steps, (2) had major congenital anomalies or a known absence of/reversed end diastolic flow in the um- bilical artery, (3) required respiratory support beyond nasal prongs or hood oxygen (e.g., those who required positive-pressure respi- ratory support [CPAP, high-flow, or PPV]); (4) required vasopres- sor support at the time of randomization, or (5) refused consent.

Randomization and Intervention

The neonates were randomised into an Early Total Enteral Feeding (ETEF) or a Conventional Enteral Feeding (CEF) group within the initial hour of delivery utilising opaque sealed envelopes to guarantee concealment of allocation. The blinding of the investigators or primary care providers was not feasible due to the inherent characteristics of the intervention. The data analysis team, however, was unaware of the information. The determination of gestational age was established through the utilisation of the last menstrual period and an early dating scan, or alternatively, by employing the Expanded New Ballard score in instances where the former methods were not accessible or exhibited a disparity of 2 weeks or greater [15]. Neonates were categorised as small for gestational age if their birth weight fell below the 10th percentile [16]. Following enrolment, the neonates assigned to the Early Total Enteral Feeding (ETEF) group were administered enteral feeding on the initial day at a rate of 80 mL per kilogramme per day. This enteral feeding consisted of either expressed breast milk or hydrolysed formula milk specifically designed for low-birth-weight infants (Dexolac Special Care; Wockhardt Ltd.). The enteral feeding volume was gradually increased by 20 mL per kilogramme each day until reaching a maximum of 150 mL per kilogramme per day, which was then maintained for a continuous period of 24 hours (as shown in Table 1).

Table 1: Enteral feeding protocol (mL/kg) in the study groups

Day of life	Early total enteral feeding	Conventional enteral feeding
D1	80	20
D2	100	40
D3	120	60
D4	140	90
D5	150	120
D6	150	150
D7	150	150

This group did not receive any intravenous fluids unless there was hypoglycaemia (blood glucose<45 mg/dL) or enteral feedings had to be withheld for any other reason. In the clinical experimental framework (CEF) cohort, the process of nourishment was commenced by administering 20 millilitres per kilogramme of expressed breast milk or low birth weight (LBW) formula milk. The remaining nutritional needs were met by intravenous fluids administered through a peripheral line. The enteral nutrition was incrementally increased by 20 mL per kilogramme per day for the following two consecutive days, and subsequently increased by 30 mL per kilogramme per day for the subsequent three days. This was done in conjunction with the administration of intravenous fluids to meet the remaining daily fluid requirement until the enteral feeding reached a rate of 150 mL per kilogramme per day, which was then maintained for a period of 24 hours.

The enteral nutrition volumes were subsequently augmented to 180 millilitres per kilogramme per day in both cohorts, with no neonate being administered parenteral nutrition. If the volume of expressed breast milk was insufficient, the feeds were supplemented with low birth weight (LBW) formula milk, which contains 80 kilocalories per 100 millilitres.

A human milk fortifier with a caloric content of 6.5 kcal per 2 grammes, manufactured by Raptakos, Brett & Co. Ltd., was introduced to the breast milk in order to maintain consistent caloric intake. Additionally, oral calcium and multivitamins were administered to the infant once they reached a feeding volume of 100 mL per kilogramme of enteral feeds.

All neonates underwent blood glucose monitoring in accordance with the unit's protocol. Thermal support is administered to all neonates in our clinical setting via an open warmer. All feedings were administered every 2 hours via gavage or spoon feedings. The abdominal region was evaluated prior to each feeding by assessing the abdominal circumference, in addition to conducting an examination of the abdomen to identify any signs of erythema or tenderness.

Feeding was discontinued temporarily if the neonate had feed intolerance (defined as the presence of 1 or more of the following):

(a) vomiting >3 times during any 24-h period;
(b) any episode of bile/blood-stained vomiting;
(c) abdominal girth increase of >2 cm between feeds with gastric aspirate >25% of the previous feeding volume (milk) or any amount of haemorrhagic or bilious fluid;
(d) abdominal wall erythema/tenderness;
(e) gross or occult blood in stools; or
(f) NEC (diagnosed by modified Bell's criteria [17]), shock [18], or recurrent apnoea (>3 episodes in 1 h).

The cessation of enteral nutrition initiated an investigation for necrotizing enterocolitis (NEC) and sepsis, which was conducted through clinical, radiological, and laboratory assessments.

The identified medical condition was managed and enteral nutrition was resumed at 50% of the prior enteral feed rate, gradually increasing over time.

Outcome Variables and Their Measurements

All neonates were provided with standard care in accordance with the unit protocol, which included kangaroo mother care for thermal support in addition to care under a radiant warmer and administration of caffeine, among other interventions. The principal objective of this investigation was to ascertain the precise day on which full feeding was achieved, as defined by the administration of 150 mL/kg of sustenance and its maintenance for a continuous duration of 24 hours.

The secondary outcome variables included episodes of feed intolerance, the occurrence of clinical/probable sepsis (as defined by a positive sepsis screen in the presence of clinical suspicion of sepsis), the occurrence of necrotizing enterocolitis (NEC), the length of hospital stay, the age at which birth weight was regained postnatally, and the weight at one month of postnatal age.

Data regarding the feeding process (including the time of initiation, method, type of feeding, and tolerance), daily weight measurements, the age at which birth weight was regained, additional neonatal health issues (such as apnea, respiratory distress, seizures, intraventricular haemorrhage, patent ductus arteriosus [PDA], and retinopathy of prematurity), as well as the need for medical interventions (such as oxygen therapy, antibiotic administration, umbilical catheterization, continuous positive airway pressure [CPAP], and mechanical ventilation) were meticulously documented using a pre-established template. The blood glucose levels were assessed at 2, 6, 12, 24, 48, and 72 hours.

When the clinical team had suspicions of sepsis based on perinatal risk factors or clinical signs (as adapted from the Integrated Management of Childhood Illness [IMNCI] algorithm) [19], a sepsis screening was conducted [20, 21]. The new-born was diagnosed with clinical/probable sepsis (clinical and laboratory findings indicative of a bacterial infection without a confirmed culture) or culture-positive sepsis (presence of the aforementioned symptoms along with a positive blood culture).

The patient was diagnosed with intraventricular haemorrhage [22] and retinopathy of prematurity [23], and appropriate management was provided in accordance with established clinical protocols. Echocardiography was performed to evaluate the presence of a suspected ductus and subsequently treated if deemed to have hemodynamic significance [24]. All discharged babies were followed up for assessment of growth, evaluation of mile stones, and provision of vaccination.

Results

The cohort under investigation during the designated research duration, a total of 421 preterm infants, with gestational ages ranging from 28 to 34 weeks and weights ranging from 1,000 to 1,499 grammes, were delivered. Out of these infants, 241 were excluded from the study based on the predetermined exclusion criteria.

Additionally, 8 infants unfortunately passed away before the completion of the study. The baseline variables exhibited comparable characteristics within both groups.

Primary Outcome Variable: The infants of the ETEF group attained full feeding earlier than those of the CEF group (6.5 ± 1.5 vs. 10.1 ± 4.1 days; mean difference –3.6 [–4.5 to –2.7]; p < 0.001) (Table 2).

Table 2:

Variable	Early total enteral feeding (n = 89)	Conventional enteral feeding (n = 91)	Mean difference (95% CI)/RR (95% CI)	p value
Infants with feed intolerance	14 (15.9)	26 (30.2)	0.5 (0.3 to 0.9)	0.002
Clinical sepsis	24 (26)	54 (60.6)	–	<0.001
Culture-positive sepsis	3 (3.3)	7 (7.8)		0.19
Duration of antibiotics treatment, days	12.86±7.70	12.9±8.1	–0.1 (–4.1 to 4.0)	0.97
Necrotising enterocolitis (any stage)	1 (1.1)	5 (5.8)	–	0.12
Apnoea	2 (2.3)	12 (14.0)	–	0.005
Intraventricular haemorrhage	5 (5.7)	5 (5.8)	–	1.00
Patent ductus arteriosus	0	7 (8.1)	–	0.01
Shock	6 (6.5)	5 (5.6)	–	0.27
Duration of intravenous fluids,1 days	0.0	5	–2.2 (–3.9 to –0.38)	0.02
Days to regaining birth weight	13.2±0.7	14.0±0.7	–0.8 (–2.7 to 1.1)	0.40
Weight at discharge, g	1,375.0±104.1	1,378.2±93.5	–3.1 (–33.1 to 26.8)	0.83
Hospital stay, days	14	18	–4.1 (–6.9 to –1.2)	0.01
Weight at 1 month, g	1,588.1±150.6	1,480.5±147.0	107.7 (60.9 to 154.4)	<0.001

Secondary Outcome Variables

The ETEF group exhibited a statistically significant decrease in episodes of feed intolerance (14 vs. 26; p = 0.002) and clinical sepsis (24 vs. 54; p = 0.003) compared to the control group. Additionally, the ETEF group had a shorter duration of hospital stay (15.5 vs. 19.6 days; p = 0.01) as shown in Table 3.

The rate of weight gain was 6.3 grammes per kilogramme per day in the experimental treatment with enteral tube feeding (ETEF) group, and 5.06 grammes per kilogramme per day in the control enteral feeding (CEF) group. The duration required for infants to regain their birth weight and the weight at the time of discharge was comparable between the two cohorts. The neonates in the experimental treatment group exhibited a greater body mass at one month postnatal. There were no instances of hypoglycemia or hyperglycemia observed in the infants.

The prevalence of clinically significant patent ductus arteriosus (PDA) and apnea was found to be elevated in the group receiving continuous enteral feeding (CEF).

Table 3 presents the factual enteral intake during the initial 10-day period, while Table 4 illustrates the quantities of expressed breast milk and preterm formula administered within the first 8 days in both study cohorts.

Table 3: Actual enteral feeding (mL/kg) received by the studygroups

Day of life	Early total enteral feeding	conventional enteral feeding
D1	7	18.8
D2	8	33.6
D3	103.3	44.0
D4	119.7	63.0
D5	134.0	84.0
D6	148.7	100.4
D7	155.4	115.6
D8	158.6	124.6
D9	165.3	133.5
D10	169.3	138.6

Table 4: Volume of expressed breast milk and formula milk received by the study groups

Day	ETEF feed, mL/kg	CEF feed, mL/kg	95% CI	p value
Expressed breast milk				
D1	14.45±9.98	15.03±5.33	–1.76 to 2.92	0.6263
D2	28.13±13.51	24.94±12.3	–6.98 to 0.60	0.0992
D3	52.38±19.8	40.05±23.28	–18.63 to –5.96	0.0002
D4	84.25±27.44	60.57±34.46	–32.85 to –14.50	<0.0001
D5	118.02±34.37	81.37±43.85	–48.25 to –25.04	<0.0001
D6	143.41±27.41	97.01±52.25	–58.71 to –34.08	<0.0001
D7	152.65±22.28	113.56±57.7	–52.01 to –26.16	<0.0001
D8	156.9±28.11	121±61.6	–50.03 to –21.76	<0.0001
Formula milk D1	57.26±20.03	3.93±4.29	–57.56 to –49.09	<0.0001
D2	56.37±54.80	8.92±7.96	–58.90 to –35.99	<0.0001
D3	49.83±23.66	4.88±6.68	–50.03 to –39.86	<0.0001
D4	38.16±19.48	2.87±6.17	–39.52 to –31.05	<0.0001
D5	17.32±18.06	2.75±6.41	17.40 to –9.19	<0.0001
D6	3.52±12.7	3.04±9.09	–3.72 to 2.76	0.7706
D7	1.51±7.85	1.49±5.39	–1.99 to 1.95	0.9841
D8	0.55±4.71	1.95±8.07	–0.54 to 3.34	0.1581

Discussion

Our research findings indicate that the early initiation of total enteral feeding in preterm very low birth weight (VLBW) infants weighing between 1,000 and 1,499 grammes leads to a quicker attainment of full feeds, without any associated rise in the risk of necrotizing enterocolitis (NEC). Our research endeavours to explore the efficacy of total enteral nutrition on day 1 (80 mL/kg) in facilitating the timely attainment of full feeds, along with potential ancillary benefits. The timely initiation and expeditious attainment of complete enteral nutrition are of paramount importance in the medical context.

The incidence of enteral feed intolerance episodes was reduced in the ETEF (Early Total Enteral Feeding) group, suggesting that feed volume alone may not be the sole determining factor for the development of feed intolerance. Additional variables, such as notable patent ductus arteriosus (PDA), clinical sepsis, and apnea, which exhibited a higher incidence within the CEF cohort, could potentially offer a plausible rationale. These concurrent medical conditions have the potential to hinder the flow of blood to the mesentery, which can consequently have negative effects on the process of feeding [27]. The cohort that underwent exclusive enteral feeding exhibited a reduced incidence of apnoea, thereby suggesting that the augmented feeding regimen did not result in an exacerbation of apnoea. Frequently, apnoea is commonly perceived as an indication of gastro-oesophageal reflux, yet scientific investigations have unequivocally demonstrated that the causal relationship is reversed. Specifically, it has been observed that infants experiencing apnoea subsequently develop gastro-oesophageal reflux. There were no instances of hypoglycemia or hyperglycemia complications observed in either cohort.

While the occurrence of culture-positive sepsis and the length of intravenous antibiotic treatment were comparable between the two cohorts, the likelihood of clinical sepsis and the percentage of newborns receiving antibiotics were twice as elevated in the CEF group. This observation potentially suggests an excessive diagnosis of clinical sepsis in neonates experiencing feed intolerance. The frequent interruptions in feeding necessitate the utilisation of parenteral access. Furthermore, the immunosuppressive effects of parenteral nutrition and the long-term implications of sepsis on hospitalisation duration and subsequent clinical outcome have been extensively documented in the medical literature [25]. The occurrence of necrotizing enterocolitis (NEC) was comparable between the two cohorts, yet significantly lower than the average prevalence reported in existing scholarly literature. This observation suggests that factors beyond feeding play a crucial role in the development of NEC.

The length of hospitalisation was reduced by 4 days in the ETEF group, which aligns with findings from a previous study involving very low birth weight (VLBW) infants weighing between 1,200 and 1,500 grammes [11]. However, this reduction in hospital stay was slightly higher than what was observed in an Indian study that included infants with lower weight at discharge [9]. Premature hospital discharge significantly impacts the overall incurred hospital expenses. In this study, the duration required to restore birth weight exhibited similar results among both cohorts, indicating that this outcome is likely influenced by the quantities of fluids administered/ingested rather than the actual

assimilation of essential nutrients. Clinical stability, characterised by a favourable trajectory in weight acquisition and attainment of a minimum weight of 1,300 g, alongside the mother's assurance in providing adequate care for the infant, constituted crucial factors in determining the appropriateness of discharge. Notably, these criteria were comparable across both study cohorts. Previous studies comparing the gradual and accelerated progression of feeding have documented reduced time periods for achieving birth weight restoration with the expedited advancement of feeds [2, 7–9]. None of these clinical studys, however, initiated Early Therapeutic Enteral Feeding (ETEF) on day 1, except a study conducted by Sanghvi et al. [10], which demonstrated comparable discharge weights in the two groups, as observed in the current study.

The neonates in the experimental treatment with enhanced therapeutic feeding (ETEF) group exhibited a statistically significant increase in weight at the one-month follow-up assessment. The rate of weight gain was 6.3 grammes per kilogramme per day in the experimental treatment with enteral tube feeding (ETEF) group, and 5.06 grammes per kilogramme per day in the control enteral feeding (CEF) group. Although this increase in body mass cannot be ascribed to the nutritional procedures during the neonatal period, the expedited release of infants in the Early Term Exclusive Feeding (ETEF) cohort, despite having similar discharge weights, may have conferred a favourable outcome for the infants in this cohort compared to those in the Conventional Exclusive Feeding (CEF) cohort. No prior investigations have documented this particular outcome. While it was anticipated that a significant number of infants would receive intravenous fluids as per the study design, it is worth noting that the average duration of fluid administration was also longer in the CEF group. The mean difference in duration was found to be 2.2 days, with a 95% confidence interval ranging from -0.38 to -3.9. The previous study has also reported a similar observation regarding the extended duration of intravenous fluid therapy in the cohort with gradual advancement of feeding [2].

The primary advantage of our research lies in its rigorous methodology and the diligent monitoring of all infants included in the study over a specified period of time. The enteral nutrition protocol for the commencement, progression, and discontinuation of feeds was explicitly established prior to the commencement of the research to mitigate potential bias. Furthermore, meticulous documentation was conducted to record the precise quantities of enteral feeds administered to the neonates, along with the proportions of expressed breast milk and preterm formula received by them. Allocation concealment was appropriately implemented, although blinding was unfeasible given the inherent characteristics of the intervention. Our research has certain constraints. This study was conducted at a single medical centre. The study was unable to account for and ensure consistent calorie intake between the two groups due to variations in the proportion of expressed breast milk and formula. However, it is important to note that at the time of discharge, all infants were exclusively receiving breast milk. Unstable sick neonates were excluded from the study, as well as those who necessitated positive-pressure respiratory support such as CPAP, high-flow, or PPV. Additionally, extremely low birth weight (ELBW) infants were also excluded, as they may not be suitable candidates for the feeding protocols under investigation. The external generalizability of our findings is restricted to stable preterm very low birth weight (VLBW) populations exclusively. Furthermore, our research findings indicate that there are only transient benefits in the short-term. It is imperative to assess the post-discharge trajectory of growth and neurodevelopmental outcome in order to gain valuable medical insights.

Conclusions

According to our research findings, it is indicated that stable very low birth weight (VLBW) infants can be effectively nourished through exclusive enteral feeds initiated immediately after birth, obviating the necessity for intravenous fluid administration. Esophageal atresia with tracheoesophageal fistula (ETEF) leads to prompt achievement of complete enteral nutrition and decreases the occurrence of sepsis and the length of hospitalisation without elevating the likelihood of necrotizing enterocolitis (NEC).

Statement of Ethics: This study was approved by the ethics committee of the institute. Informed written parental consent was obtained.

Disclosure Statement: The authors have no conflicts of interest to disclose.

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