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Comparison of Early versus Late Trophic Feeding in Preterm Very Low Birth Weight Neonates at a Tertiary Care Hospital

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ABSTRACT

Very low birth weight (VLBW) neonates are vulnerable to complications, and nutritional management is an essential determinant of their outcomes. **Objective:** To compare the neonatal outcomes in early trophic feeding (TF) versus late TF in preterm VLBW neonates. **Methods:** This randomized controlled trial was performed at the Department of Paediatrics, Nishtar Hospital, Multan, Pakistan, from June 2025 to December 2025. Sixty preterm VLBW neonates were selected through simple random sampling. Infants were randomized (30 in each group) into early TF (≤48 hours) or late TF (≥72 hours) groups. Feeding was given via orogastric tube using expressed breast milk or preterm formula, along with parenteral nutrition. Outcomes included incidence of necrotizing enterocolitis (NEC), mortality, and hospital stay. Data were analyzed using SPSS 26.0, with p≤0.005 considered statistically significant. **Results:** In a total of 60 neonates, 35 (58.3%) were males, with a mean gestational age of 33.1 ± 2.1 weeks, and a birth weight of 1360.1 ± 67.2 grams, respectively. Overall, NEC occurred in 2 (3.3%), and mortality occurred in 4 (6.7%) neonates. The overall mean hospital stay was 15.4±1.9 days, significantly shorter with early feeding (13.0 ± 1.7 vs 19.3 ± 2.1 days, p<0.001). **Conclusions:** The early TF within 48 hours significantly reduced the hospital stay without increasing NEC or mortality among preterm VLBW infants.

INTRODUCTION

Human milk provides the most suitable nutrition for premature infants, offering well-established benefits in host defense, digestion, neurodevelopment, gastrointestinal maturation, and psychological well-being [1]. Its bioactive components, including immunoglobulins, growth factors, and enzymes, play a vital role in protecting vulnerable preterm neonates against infections and inflammatory conditions. In addition to supporting optimal growth, human milk enhances intestinal barrier function and promotes the development of a healthy microbiome. These effects are particularly crucial in very low birth weight (VLBW) infants, whose physiological immaturity predisposes them to multiple complications [2]. Globally, preterm birth remains a significant public health concern, with an estimated 15 million infants born prematurely each year, accounting for more than one in ten live births [2]. Among these, nearly one million deaths occur annually due to complications associated with prematurity [3]. The burden is especially pronounced in low- and middle-income countries, where healthcare resources are often limited. In Pakistan, the estimated prevalence of preterm births ranges between 15% and 22%, placing it among the

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highest worldwide [4, 5]. This high prevalence results in a substantial number of VLBW neonates requiring specialized neonatal care. These infants are particularly susceptible to complications such as respiratory distress, sepsis, feeding intolerance, and necrotizing enterocolitis (NEC), all of which contribute significantly to neonatal morbidity and mortality [5]. Nutritional management plays a central role in determining outcomes in preterm VLBW neonates, and optimizing feeding strategies remains a key clinical priority [6]. Trophic feeding (TF), also known as minimal enteral nutrition, has gained considerable attention in recent years due to its potential benefits [7]. TF involves the early administration of small volumes of enteral feeds to stimulate gastrointestinal function without imposing a significant metabolic burden [8]. Evidence suggests that TF improves feeding tolerance, reduces dependence on parenteral nutrition, enhances intestinal motility, and accelerates the achievement of full enteral feeding [9]. TF has been associated with shorter intestinal transit time and improvements in biochemical markers of nutritional status compared to parenteral nutrition alone [10, 11].

Despite these advantages, the optimal timing for initiation of trophic feeding remains a subject of ongoing debate, particularly in resource-limited settings where clinical practices may vary. Early initiation of TF has been proposed to reduce the incidence of NEC and shorten hospital stay, whereas delayed initiation is often practiced due to concerns regarding feeding intolerance and potential complications. Given the high burden of preterm VLBW infants in Pakistan, there is a critical need to evaluate feeding strategies that can improve neonatal outcomes in this setting. Therefore, this study was conducted to compare neonatal outcomes in early versus late trophic feeding among preterm VLBW infants, aiming to provide evidence to guide clinical practice in similar high-risk populations.

METHODS

This randomized controlled trial (NCT07229885) was conducted in the Department of Pediatrics, Nishtar Hospital, Multan, from June 2025 to December 2025, after approval from the Institutional Ethical Review Board (Ref. No. 8987/NMU; dated 12th May 2025). A sample size of 60 was calculated using the Open EPI online sample size calculator, taking the duration of hospitalization among late versus early TF as 12.1 ± 8.6 days vs 21.1 ± 1.2 days, respectively, with 95% significance level and 80 power of the study [10]. A total of 60 preterm VLBW neonates, aged 1–28 days of either gender, were included using a simple random sampling technique. Exclusion criteria included transfer from other hospitals after initiation of antibiotics, congenital anomalies, hypoxic-ischemic encephalopathy, central nervous system impairment, neonatal sepsis, and multiple gestations. Written informed consent was obtained from parents or guardians before enrollment. VLBW was defined as live-born < 37 completed weeks of gestation with a birth weight ≤1500 g, measured using a calibrated digital scale [6]. At enrolment, gender, age, gestational age at delivery, and mode of delivery were documented. Participants were randomized into two groups using a computer-generated randomization sequence with a 1:1 allocation ratio. Allocation concealment was ensured using sequentially numbered, sealed, opaque envelopes prepared by an independent researcher not involved in patient recruitment. Each envelope contained the group assignment and was opened only after enrollment of the participant, thereby preventing selection bias. The early TF group received trophic feeding initiated within 48 hours following birth, whereas the late TF group received trophic feeding initiated after 72 hours. Feeding was administered through radio-opaque orogastric tubes (2×47 mm) placed by trained nurses and changed daily. Expressed breast milk was used when available; otherwise, preterm formula milk (Pre-NAN, Nestlé), prepared as two scoops in 60 ml of boiled water, was provided. Feeds were administered using a syringe at 1–2 ml/kg every 4–6 hours and advanced by 1–2 ml/kg/day as tolerated. Parenteral nutrition was provided to all infants. Feeding tolerance was assessed clinically before each feed. Tolerance was defined by the absence of significant gastric residuals (less than 50% of the previous feed volume), absence of abdominal distension (increase in abdominal girth >2 cm from baseline), no visible bowel loops, and no episodes of bilious or blood-stained vomiting. Additional indicators of intolerance included apnea, bradycardia, or signs suggestive of necrotizing enterocolitis, such as abdominal tenderness or discoloration. In cases of feeding intolerance, feeds were withheld or reduced at the discretion of the attending neonatologist. Neonates were observed for the development of NEC during their NICU stay. NEC was labelled as clinical features of vomiting, abdominal distension, thrombocytopenia <100,000/µL, blood in stools, along with radiological findings such as intramural bowel gas, portal venous gas, or pneumoperitoneum on abdominal X-ray. Each neonate was followed until discharge or death, and the hospital stay in days was documented.

Data were analyzed in IBM-SPSS Statistics, version 26.0. Quantitative data were expressed as mean ± standard deviation (SD), or median and interquartile range (IQR), as per the Shapiro-Wilk test. Categorical data were shown as frequencies and percentages. The hospital stay was compared using the independent samples t-test or Mann-Whitney U test (as appropriate). Potential effect modifiers

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like gender, gestational age, birth weight, type of milk, and mode of delivery were controlled through stratification, followed by post-stratification analyses using an independent sample t-test or Mann-Whitney U test, taking p<0.005 as significant. The CONSORT Diagram was shown. In a total of 60 neonates, 35 (58.3%) were males. The mean gestational age and birth weight were 33.1 ± 2.1 weeks and 1360.1 ± 67.2 grams, respectively. The residential status of 38 (63.3%) neonates was rural, and 22 (36.7%) urban (Figure 1).

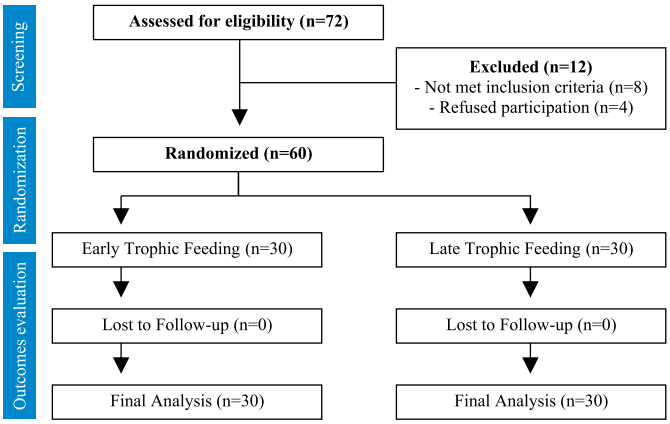

Figure 1: CONSORT Diagram

RESULTS

Among early TF neonates, 17 (56.7%) were male, and 13 (43.3%) were female, whereas in the late TF group, 18 (60.0%) were male and 12 (40.0%) were female (p=0.793). Gestational age ≤32 weeks was documented in 8 (26.7%) neonates in the early, and 12 (40.0%) in the late TF group, with >32 weeks in 22 (73.3%) and 18 (60.0%) neonates, respectively (p=0.273). Vaginal delivery was observed in 21 (70.0%) neonates in each group, and cesarean section in 9 (30.0%) neonates in each group. Birth weight ≤1300 g was recorded in 9 (30.0%) neonates in both groups, while >1300 g was noted in 21 (70.0%) neonates in each group. Human milk feeding was received by 19 (63.3%) neonates in the early group and 23 (76.7%) in the late TF group, whereas preterm formula was given to 11 (36.7%) and 7 (23.3%) neonates, respectively (p=0.260) (Table 1).

Table 1: Comparison of Baseline Characteristics among Study Groups (n=60)

Characteristics		Early TF (n=30), n (%)	Late TF (n=30), n (%)	p-value
Gender	Male	17 (56.7%)	18 (60.0%)	0.793
	Female	13 (43.3%)	12 (40.0%)	
Residence	Urban	10 (33.3%)	12 (40.0%)	0.592
	Rural	20 (66.7%)	18 (60.0%)	
Gestational Age (Weeks)	≤32	8 (26.7%)	12 (40.0%)	0.273
	>32	22 (73.3%)	18 (60.0%)	
Milk Type	Human Milk	19 (63.3%)	23 (76.7%)	0.260
	Preterm Infant Formula Milk	11 (36.7%)	7 (23.3%)	

TF: trophic feeding; Chi-square test applied

NEC was documented among 2 (3.3%) neonates. Mortality was documented among 4 (6.7%) neonates. The overall mean duration of hospital stay was 15.4 ± 1.9 days. NEC was observed among 1 (3.3%) neonate in both study groups. Mortality was documented among 2 (6.7%) neonates in each study group. The mean duration of hospitalization was significantly shorter among the early TF group in comparison to the late TF group (13.0 ± 1.7 days vs. 19.3 ± 2.1 days, p<0.001). Among males, the mean hospital stay was 12.8 ± 1.8 days with early feeding and 19.2 ± 2.3 days with late feeding (p<0.001), while in females, it was 13.2 ± 1.5 days and 19.5 ± 1.6 days, respectively (p<0.001). Urban neonates had a mean hospital stay of 12.6 ± 1.9 days in the early group compared with 19.3 ± 2.4 days in the late group (p<0.001), and rural neonates had 13.0 ± 1.6 versus 19.2 ± 1.5 days, respectively (p<0.001). For gestational age ≤32 weeks, the mean stay was 12.1±1.3 days in the early TF group and 19.6 ± 2.0 days in the late TF group (p<0.001), while for >32 weeks it was 13.3 ± 1.8 and 19.1 ± 2.1 days, respectively (p<0.001). Vaginally delivered neonates had a mean stay of 12.6 ± 1.7 days in the early group and 19.4 ± 2.1 days in the late group (p<0.001), whereas cesarean section neonates had 14.0 ± 1.3 days and 19.0 ± 1.9 days, respectively (p<0.001). Birth weight ≤1300 g was associated with 13.2 ± 1.2 days in the early group and 19.3 ± 1.7 days in the late group (p<0.001), while neonates >1300 g stayed 12.9 ± 1.9 and 19.3 ± 2.2 days, respectively (p<0.001). Neonates receiving human milk had a mean stay of 13.2 ± 1.5 days in the early group and 19.0 ± 1.9 days in the late group (p<0.001), while those on preterm formula stayed 12.7 ± 2.1 and 20.1 ± 2.4 days, respectively (p<0.001). Subgroup analysis with respect to duration of hospitalization among study groups is shown (Table 2).

Table 2: Comparison of Hospital Stay with Respect to Study Variables among Study Groups (n=60)

Characteristics		Early TF (n=30)	Late TF (n=30)	p-value
Gender	Male	12.8 ± 1.8	19.2 ± 2.3	<0.001
	Female	13.2 ± 1.5	19.5 ± 1.6	<0.001
Residence	Urban	12.6 ± 1.9	19.3 ± 2.4	<0.001
	Rural	13.0 ± 1.6	19.2 ± 1.5	<0.001
Gestational Age (Weeks)	≤32	12.1 ± 1.3	19.6 ± 2.0	<0.001
	>32	13.3 ± 1.8	19.1 ± 2.1	<0.001
Mode of Delivery	Vaginal Delivery	12.6 ± 1.7	19.4 ± 2.1	<0.001
	Cesarean Section	14.0 ± 1.3	19.0 ± 1.9	<0.001
Birth Weight (grams)	≤1300	13.2 ± 1.2	19.3 ± 1.7	<0.001
	>1300-1500	12.9 ± 1.9	19.3 ± 2.2	<0.001
Milk Type	Human Milk	13.2 ± 1.5	19.0 ± 1.9	<0.001
	Preterm Infant Formula Milk	12.7 ± 2.1	20.1 ± 2.4	<0.001

TF: trophic feeding; Independent sample t-test applied

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DISCUSSION

The present study demonstrated that early TF significantly reduced the duration of hospital stay among preterm VLBW infants compared with late TF. This finding carries important clinical and health system implications as prolonged hospitalization is a recognized burden in neonatal care in low- and middle-income countries [12]. Sallakh-Niknezhad and colleagues found a stay of 12.14 ± 8.61 days in the early TF group versus 21.11 ± 1.16 days in the late TF [10]. Biswas and colleagues also documented a longer stay in the late feeding group, although the differences in their cohort did not reach the same level of statistical contrast [12]. Variability in sample selection and local NICU practices may account for the smaller observed difference. The present study also showed that the beneficial effect of early TF on hospital stay persisted across subgroups of gender, gestational age, residence, birth weight, mode of delivery, and type of milk. These findings align with Maqbool *et al.* who reported hospital stay of 12.1 ± 8.6 days in the early group compared with 21.1 ± 9.1 days in the late group among neonates below 34 weeks of gestation [11]. The similarity of results across different trials suggests that early feeding is beneficial irrespective of small variations in gestational maturity, providing reassurance that the practice is safe in very preterm infants as well. Comparable outcomes have been described previously, evaluating full enteral feeding in preterm infants between 28 and 34 weeks and observed improved stability of weight gain and fewer complications when compared with partial feeding [13]. Mortality was relatively low in both study groups (6.7% with each approach). These findings align with Kennedy *et al.* who found no effect of early feeding on mortality in randomized clinical trials [14]. Biswas *et al.* also reported similar mortality in both groups, with 16.7% deaths in the early group and 16.9% deaths in the late group [12]. These concordant findings imply that while early feeding reduces hospitalization, it does not confer a measurable survival advantage. This may be explained by the multifactorial etiology of mortality in VLBW infants, which often involves severe comorbidities beyond feeding tolerance, such as sepsis, respiratory distress, or congenital malformations [15, 16]. NEC was diagnosed in only 1 infant in each study group in the present trial. This low frequency echoes the findings of Biswas et al. who reported NEC in 6.7% of early-fed and 7.7% of late-fed neonates [12], and Javied *et al.* who found NEC in 5.6% of infants receiving early TF [17]. Sallakh-Niknezhad and colleagues also documented a single NEC case in each group [10]. In this study, neonates receiving human milk in the early group had a mean hospital stay of 13.2 ± 1.5 days compared with 19.0 ± 1.9 days in the late group, while those on preterm formula stayed 12.7 ± 2.1 and 20.1 ± 2.4 days, respectively. Although both human milk and formula recipients benefited from early initiation, the absolute values indicate a slightly greater advantage in formula-fed neonates. This pattern may reflect the relatively slower adaptation of gut function in formula-fed neonates who start feeds late, rather than an inherent superiority of formula [18]. Human milk is consistently shown to reduce the risk of infection, enhance nutrient absorption, and improve long-term neurodevelopment [19]. These benefits were highlighted in earlier reports, including the review by Nangia *et al.* which showed reduced incidence of NEC and sepsis when early enteral feeding included human milk [20]. The present findings therefore reinforce the primacy of human milk as the feed of choice, while also demonstrating that early initiation is beneficial regardless of milk type [21].

The lack of observed mortality benefit despite a significant reduction in hospital stay likely reflects the multifactorial nature of mortality in preterm VLBW infants. In this study, mortality was low and comparable between groups, limiting the ability to detect a statistically significant difference. Early trophic feeding is primarily known to improve gastrointestinal function, feeding tolerance, and clinical stabilization, which may translate into shorter hospitalization rather than a direct survival advantage. Relatively modest sample size and a single-center study design may limit the generalizability of these findings. The use of biomarkers of gut maturity and immune function could provide mechanistic insights to explain observed differences. The study also noted only short-term outcomes, so more studies are required to see the long-term outcomes of various feeding strategies among preterm VLBW infants.

CONCLUSIONS

The early TF, within 48 hours, significantly reduced the hospital stay without increasing NEC or mortality among preterm VLBW infants. The findings support early initiation of minimal enteral nutrition.

Authors' Contribution

Conceptualization: S
Methodology: NA, S, GN, AH, AUR, NR
Formal analysis: NA, AH
Writing and Drafting: NA, S, GN, AUR, NR
Review and Editing: NA, S, GN, SH, AUR, NR

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflicts of Interest

All the authors declare no conflict of interest.

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