The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 7, 2025

EFFECT OF SLOW VERSUS FAST ADVANCEMENT OF ENTERAL FEEDING VOLUME ON THE INCIDENCE OF FEEDING INTOLERANCE AND NECROTIZING ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT NEONATES

Dr. Sauleha Wasif[*1], Dr. Col Muhammad Afzal[2], Dr Nayab Khaliq[3], Dr. Amber Naseer[4], Dr. Rabia Rehman[5], Dr Mariam M. Malik[6]

[*1]*Resident Pediatrics MBBS Quaid-e-Azam international hospital*
[2]*MBBS, FCPS Supervisor Quaid-E-Azam International Hospital*
[3]*MBBS PG Resident Pediatrics Quaid E Azam International Hospital Islamabad*
[4]*MBBS, FCPS Associate Consultant Pediatrics*
[5]*MBBS PG Trainee Pediatrics POF Hospital Wah Cantt*
[6]*MBBS PG Resident Pediatrics PAC Kamra Hospital*

[*1]sauleha057@gmail.com, [2]afzalchpak59@gmail.com, [3]nayab.khaliq@yahoo.com, [4]isbnuml@gmail.com, [5]rehman.rabiwmc@gmail.com, [6]emcube664@gmail.com

DOI: https://doi.org/10.5281/zenodo.16744327

Keywords
Very low birth weight, enteral feeding, feeding intolerance, necrotizing enterocolitis, preterm neonates, fast vs slow feed advancement

Article History
Received on 01 July 2025
Accepted on 16 July 2025
Published on 20 July 2025

Corresponding Author: *
Dr. Sauleha Wasif

Abstract

Objective: *To compare the frequency of feeding intolerance in very low birth weight neonates with slow versus fast advancement of enteral feeding volume and to compare the frequency of necrotizing colitis in very low birth weight neonates with slow versus fast advancement of enteral feeding volume.*

Study design: *Randomized controlled trial.*

Setting: *Department of Pediatrics, Quaid-e-Azam International Hospital.*

Duration of study: *January to June 2025.*

Methodology: *This trial enrolled a total of 180 neonates (<1500g, <35 weeks gestation) were enrolled and randomized into slow (20 mL/kg/day) and fast (30 mL/kg/day) feeding groups. Feeding was administered every two hours until full enteral volume (180 mL/kg/day) was achieved. Feeding intolerance and NEC were assessed using predefined clinical and radiological criteria.*

Results: *Mean age of 6.96 ± 1.90 days, gestational age of 31.99 ± 1.32 weeks, and birth weight of 1294.02 ± 99.65 grams. Gender distribution was balanced (52.8% male, 47.2% female). Feeding intolerance was higher in the fast group (30.0%) than in the slow group (17.8%), approaching statistical significance (p = 0.055), while NEC incidence (13.3% vs. 10.0%, p = 0.486). Stratified analysis revealed significantly higher feeding intolerance in more mature neonates (gestational age >32–35 weeks) with fast feeds (31.1% vs. 12.8%, p = 0.033). Other subgroup differences in feeding intolerance and NEC approaching insignificant difference.*

Conclusion: *Our findings suggest that while fast enteral feeding does not significantly raise NEC risk, it may increase feeding intolerance in select subgroups*

INTRODUCTION

Premature birth is the leading cause of infant death and a nutritional emergency. Premature baby survival rates have grown in recent years,[1-2] and optimal nutrition is the cornerstone of neonatal care to improve neurodevelopmental outcomes on long-term.[3]

Late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) affect 10–15% of very low birth weight (VLBW) infants.[4-6]

Although the pace of feeding advancement varied, studies consistently found that neonates in the fast-feed group achieved full enteral nutrition sooner and had improved recovery timelines, with no marked rise in NEC or feeding intolerance compared to slower-fed counterparts.[7] Early transition to full enteral intake minimizes nosocomial infection and metabolic consequences from extended parenteral nutrition. Feed progression rates that lessen problems and extrauterine development restriction must be proven.[8]

Preterm babies are more likely to develop brain and heart-related health issues later in life, especially if they experience poor growth or inadequate nutrition during the newborn period. Numerous studies have found that early and increased nutrition supplementation affects preterm baby growth and clinical outcomes. Neurodevelopment, BPD avoidance, and ROP reduction are these effects.[9] A growth-related study found that extremely low birth weight infants with higher weight quartiles had better neurodevelopmental outcomes at 18 months. However, breast milk is recommended for preterm newborns.[10]

Compared to the fast/control group, the slow feeding group demonstrated significantly reduced rates of feeding intolerance (15.7% vs. 24.1%) and NEC (7.9% vs. 16%), highlighting potential benefits of gradual feed progression.[11] Stable preterm infants generally tolerate accelerated feeding schedules and reach full enteral nutrition sooner, without a significant increase in NEC risk. However, existing reviews show inconsistent outcomes, reflecting considerable variability in primary measures and underscoring the lack of definitive clinical evidence to establish optimal feeding protocols.

The rationale of this study is that limited local data is available regarding this topic and Pakistan is still considered to be a developing nation, its health care system is not particularly well developed; prematurity is one of those conditions that are still on the rise in our country. Based on the existing evidence, prospective preventative measure for necrotizing enterocolitis (NEC) in premature neonates should be promoted. Appropriately structured randomized controlled trials are required to determine NEC as a significant complication in premature neonates. Its prevention can significantly reduce morbidity and mortality of these neonates. The purpose of this study is to determine the incidence of feeding intolerance and NEC in very low birth weight neonates with slow versus fast advancement of enteral feeding.

METHODOLOGY

With ethical approval, the study was conducted as a randomized controlled trial over six months from January'25 to June'25 in the Pediatrics Department at Quaid-e-Azam International Hospital, Islamabad. A total of 180 neonates were enrolled using WHO sample size calculation, assuming the expected incidence of feeding intolerance to be 15.8% in the slow feeding group and 7.8% in the fast feeding group, with a 5% level of significance and 80% power. Eligible participants included all neonates with a birth weight less than 1500 grams and gestational age under 35 weeks, who started formula feeding within 12 to 48 hours of birth and had no obvious abnormalities or chromosomal anomalies. Neonates were excluded if they had severe asphyxia (Apgar score <3, umbilical pH <7.15, BE <–15 mmol/L), were partially or fully breastfed, had congenital malformations (e.g., cleft palate, intestinal atresia, cyanotic heart disease, omphalocele or gastroschisis), had delayed initiation of feeding beyond five days due to complications, were unfit for enteral nutrition, or required respiratory support.

After obtaining informed consent from the parents, neonates were randomly allocated into two groups. Group S (Slow Feeding Regimen) received enteral feed advancement of 20 mL/kg/day, while Group F (Fast Feeding Regimen) received 30 mL/kg/day, until the target volume of 180 mL/kg/day was achieved. Feeding was provided by trained staff as bolus intragastric or oral feeds every two hours. Depending on birth weight and gestational age, limited amounts of breast milk were introduced with incremental

increases. Full enteral feeding was defined as oral intake of 180 mL/kg/day. Infants were followed until hospital discharge.

Feeding intolerance was characterized by abdominal distension and gastric residuals exceeding 50% of the previous feed, particularly when feed volumes ranged between 20–75 mL/kg/day. Mild abdominal distension and retention of 2–3 mL, amounting to 50%–100% of feed volume, were considered feeding tolerance. Feedings were discontinued and NEC assessment was initiated if gastric retention was bloody, bilious, or associated with abdominal distension exceeding 1.5 cm increase in circumference per day. NEC was diagnosed after two weeks of zinc supplementation based on clinical evaluation, stool occult blood, abdominal ultrasound, and X-ray findings, confirmed by an unbiased neonatologist.

The data analyzed include continuous variables, i.e. age, gestational age, and birth weight, were summarized as mean values with standard deviations. Categorical variables, such as gender, occurrence of NEC, and incidence of feeding intolerance, were expressed as frequencies and percentages. Group comparisons for categorical outcomes were conducted using the chi-square test, with a significance threshold set at $p < 0.05$. To account for potential confounding factors, stratification was performed for variables like age, gestational age, and birth weight, and the chi-square test was reapplied post-stratification to assess statistical significance.

RESULTS:

Table 1: Descriptive Statistics and Frequency Distribution

Of 180 neonates were analyzed, with the majority (58.3%) aged between 1 and 7 days at the time of inclusion. The mean age was 6.96 ± 1.90 days. Regarding gestational age, the cohort was almost equally distributed, with 48.9% of neonates born between 27 and 32 weeks and 51.1% between >32 and 35 weeks, yielding a mean gestational age of 31.99 ± 1.32 weeks. In terms of birth weight, 52.2% of the neonates weighed approximately less than 1300 grams (Group 1), while the remaining 47.8% were in Group 2 (≥1300 g), with a mean birth weight of 1294.02 ± 99.65 grams. The sample showed a nearly equal gender distribution, with 52.8% males and 47.2% females.

Table 2: Comparison of Feeding Intolerance and Necrotizing Enterocolitis (NEC) Between Groups

This table compares the incidence of feeding intolerance and NEC between neonates who received slow versus fast advancement of enteral feeding volumes. Feeding intolerance was observed in 17.8% of the slow advancement group compared to 30.0% in the fast advancement group. Although this difference was notable, but not significant($p = 0.055$). Regarding NEC, the slow group showed a slightly lower incidence (10.0%) than the fast group (13.3%); ($p = 0.486$). These findings suggest a trend toward higher feeding complications with faster feeding advancement, though not definitively significant across the full sample.

Table 3: Effect Modifiers on Feeding Intolerance and NEC by Group

It explores how key clinical factors—age, gestational age, and birth weight—modify the relationship between feeding advancement speed and the outcomes of feeding intolerance and NEC.

In the age group of 1–7 days, feeding intolerance was more frequent in the fast group (34.7%) compared to the slow group (21.4%), though the p-value (0.129) was not significant. A similar trend was seen in neonates aged >7–14 days, with higher feeding intolerance in the fast group (24.4% vs. 11.8%, $p = 0.162$). When stratified by gestational age, a statistically significant difference was found among infants born >32–35 weeks: feeding intolerance occurred more frequently in the fast group (31.1%) than the slow group (12.8%), with a p-value of 0.033, suggesting that more mature preterm neonates might be more vulnerable to rapid feeding increases. For birth weight subgroups, feeding intolerance remained more frequent in the fast group in both <1300 g (31.5% vs. 20.0%, $p = 0.213$) and ≥1300 g (27.8% vs. 16.0%, $p = 0.185$) groups.

For NEC, differences between groups across all effect modifier categories (age, gestational age, and birth weight) were minimal and statistically non-significant. For instance, in the 1–7 day group, NEC occurred in 10.2% of fast-fed neonates and 8.9% of slow-fed neonates ($p = 0.824$). Similarly, among infants weighing <1300 g, NEC was observed in 13.0% (fast) vs. 7.5% (slow) ($p = 0.396$). None of the subgroup comparisons showed statistically significant p-values,

indicating no strong effect modification for NEC based on these factors.

TABLE 1: DESCRIPTIVE STATISTICS AND FREQUENCY DISTRIBUTION

Variable	Categories / Mean ± SD	n	Percent (%)
Age (days)	1–7 days	105	58.3
	>7–14 days	75	41.7
	Mean ± SD	6.96 ± 1.90	
Gestational Age (weeks)	27–32 weeks	88	48.9
	>32–35 weeks	92	51.1
	Mean ± SD	31.99 ± 1.32	
Birth Weight (g)	Group 1 (≈<1300 g)	94	52.2
	Group 2 (≈≥1300 g)	86	47.8
	Mean ± SD	1294.02 ± 99.65	
Gender	Male	95	52.8
	Female	85	47.2

TABLE 2: COMPARISON OF FREQUENCY OF FEEDING INTOLERANCE AND NECROTIZING COLITIS IN VERY LOW BIRTH WEIGHT NEONATES WITH SLOW VERSUS FAST ADVANCEMENT OF ENTERAL FEEDING VOLUME

Outcome	Group	Yes (%)	No (%)	Total	P value
Feeding Intolerance	Slow feeding	16 (17.8%)	74 (82.2%)	90	0.055
	Fast feeding	27 (30.0%)	63 (70.0%)	90	
NEC	Slow feeding	9 (10.0%)	81 (90.0%)	90	0.486
	Fast feeding	12 (13.3%)	78 (86.7%)	90	

TABLE 3: COMPARISON OF FREQUENCY OF FEEDING INTOLERANCE AND NECROTIZING COLITIS IN VERY LOW BIRTH WEIGHT NEONATES WITH SLOW VERSUS FAST ADVANCEMENT OF ENTERAL FEEDING VOLUME ACCORDING TO POTENTIAL EFFECT MODIFIERS

Effect Modifier	Outcome	Group	Yes (n,%)	No (n,%)	Chi-Square p-value
Age: 1-7 days	Feeding Intolerance	Slow feeding	12 (21.4%)	44 (78.6%)	.129
		Fast feeding	17 (34.7%)	32 (65.3%)	
Age: >7-14 days		Slow feeding	4 (11.8%)	30 (88.2%)	.162
		Fast feeding	10 (24.4%)	31 (75.6%)	
Gestational Age: 27-32 weeks		Slow feeding	10 (23.3%)	33 (76.7%)	.548
		Fast feeding	13 (28.9%)	32 (71.1%)	
Gestational Age: >32-35 weeks		Slow feeding	6 (12.8%)	41 (87.2%)	.033
		Fast feeding	14 (31.1%)	31 (68.9%)	
Birth Weight: upto 1300gram		Slow feeding	8 (20.0%)	32 (80.0%)	.213
		Fast feeding	17 (31.5%)	37 (68.5%)	
Birth Weight:>1300-1500gram		Slow feeding	8 (16.0%)	42 (84.0%)	.185
		Fast feeding	10 (27.8%)	26 (72.2%)	
Age: 1-7 days	NEC	Slow feeding	5 (8.9%)	51 (91.1%)	.824
		Fast feeding	5 (10.2%)	44 (89.8%)	

Age: >7-14 days		Slow feeding	4 (11.8%)	30 (88.2%)	.518
		Fast feeding	7 (17.1%)	34 (82.9%)	
Gestational Age: 27-32 weeks		Slow feeding	6 (14.0%)	37 (86.0%)	.451
		Fast feeding	9 (20.0%)	36 (80.0%)	
Gestational Age: >32-35 weeks		Slow feeding	3 (6.4%)	44 (93.6%)	.956
		Fast feeding	3 (6.7%)	42 (93.3%)	
Birth Weight: upto 1300gram		Slow feeding	3 (7.5%)	37 (92.5%)	.396
		Fast feeding	7 (13.0%)	47 (87.0%)	
Birth Weight:>1300-1500gram		Slow feeding	6 (12.0%)	44 (88.0%)	.796
		Fast feeding	5 (13.9%)	31 (86.1%)	

DISCUSSION:

Our study focused on comparing slow and fast enteral feeding progression in VLBW neonates to determine their impact on feeding intolerance and NEC. While a trend toward higher feeding intolerance was observed in the fast advancement group (30.0%) compared to the slow group (17.8%), the difference approached but did not reach statistical significance ($p = 0.055$). Similarly, NEC was more frequent in the fast group (13.3% vs. 10.0%, $p = 0.486$), though without significant difference. These findings reflect an ongoing global debate regarding optimal feed progression strategies for preterm neonates. [12]

The findings are partially consistent with the Cochrane review by Oddie et al.,[13] which included 10 trials with 3,933 infants and concluded that slower feeding advancement did not significantly reduce the incidence of NEC (RR: 0.91, 95% CI: 0.74–1.13) or feeding intolerance but resulted in delayed achievement of full enteral nutrition and prolonged hospitalization. Similarly, Yang et al[14] reported in their systematic review of 29 randomized controlled trials that fast feed advancement reduced the time to full feeds and hospital stay without increasing NEC risk (RR: 0.95, 95% CI: 0.74–1.22) or mortality. These meta-analyses support the notion that rapid feeding protocols may be safe and clinically advantageous in terms of resource use and infant recovery, although our study did not observe statistically significant clinical benefits. Notably, our stratified analysis found a significant increase in feeding intolerance among more mature preterm neonates (gestational age >32–35 weeks) receiving fast advancement (31.1% vs. 12.8%, $p = 0.033$), suggesting a possible paradoxical vulnerability in this subgroup. While this contrasts with the general assumption that higher gestational age confers better tolerance, similar age-specific sensitivities have not been widely reported and warrant further exploration.

Other regional and international studies echo the safety of early or rapid advancement of feeds. Patole et al[15] found that early total enteral feeding (ETEF) led to quicker achievement of full feeds and shorter hospital stays in stable VLBW infants, with no increase in NEC incidence (6% in ETEF vs. 8% in controls, $p > 0.05$). Likewise, De Silva and Wickramasinghe[16] observed in a Sri Lankan cohort that rapid feed advancement significantly shortened the time to full feeds (9.6 ± 2.1 vs. 13.2 ± 3.4 days, $p < 0.01$) without affecting NEC rates (3.3% vs. 6.6%). Interestingly, some studies have emphasized the benefits of early structured protocols over the pace of feed advancement itself. For instance, Saini and Jain[17] demonstrated that implementing a systematic feeding protocol incorporating early trophic feeding and human milk resulted in improved tolerance and lower NEC rates, highlighting the importance of standardization and supportive care.

Debata et al[18] further support the use of human milk and minimal enteral nutrition to promote gut maturation and reduce complications in preterm neonates, while cautioning that unnecessarily slow feeding may prolong dependence on parenteral nutrition, thereby increasing infection risk. Similarly, Dutta et al[19] recommended starting trophic feeds within 24 hours of life and advancing by 15–20 mL/kg/day, reinforcing the idea that neither overly rapid nor overly cautious feeding is ideal but rather individualized, evidence-based progression.

Contrary to the findings of our study where feeding intolerance was numerically higher in the fast group, Muneer et al[20] found no such increase in their

randomized trial of 140 preterm infants, in which the rapid group had a significantly shorter time to full feeds (9.4 ± 1.8 vs. 14.2 ± 3.1 days; $p < 0.001$) without any significant differences in NEC or mortality. Similarly, Perez et al[21] stressed the need for early human milk-based feeding strategies globally, noting that delayed feeding may inadvertently increase risks of infection and hospital-related complications.

Taken together, these findings suggest that while faster feeding protocols are generally safe and efficient in most clinical settings, the risk-benefit balance may vary depending on gestational maturity, birth weight, and institutional capabilities. The trend toward higher feeding intolerance in the fast group observed in our study—particularly among neonates of relatively higher gestational age—raises an important question about whether such infants are more sensitive to feed volume fluctuations or subject to other unmeasured confounders such as subtle gastrointestinal immaturity or subclinical infections.

The strengths of our study include its randomized controlled design, stratified analysis of confounding variables, and adherence to well-defined feeding protocols. However, limitations must be acknowledged. The single-center setting may limit generalizability, and the modest sample size may have reduced power to detect smaller differences, particularly in NEC outcomes. Moreover, the exclusion of breastfed infants limits applicability in settings with high exclusive breastfeeding rates.

CONCLUSION:

Our findings support existing evidence that fast enteral feed advancement does not significantly increase NEC but may be associated with increased feeding intolerance in certain subgroups. Given the complex interplay of nutritional, developmental, and systemic factors in preterm neonates, further multicenter randomized trials with larger sample sizes and standardized feeding protocols are necessary to refine optimal feeding strategies, especially in low-resource settings like Pakistan.

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