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Early versus Late Enteral Feeding in Preterm Intrauterine Growth Restricted Neonates with Antenatal Doppler Abnormalities

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ABSTRACT

Background: Placental insufficiency and decreased placental nutrition transfer from the mother to the fetus are the underlying causes of intra-uterine growth restriction (IUGR), a serious and very frequent issue in the perinatal period. Due to a lack of recent research in the area, the current study aims to compare the outcomes of two different feeding strategies for preterm infants with abnormal Doppler readings: early vs. delayed initiation of enteral feeds. Then we implement the better of the two feedings regimens into our standard clinical practice. **Objective:** The objective of the study was to compare early and late enteral feeding in preterm intrauterine growth restricted neonate to evaluate time to reach full feed, risk of feed Intolerance, weight gain at 10th day of life and length of hospital stays. **Study Design:** The Randomized Control Trial. **Settings:** This study was conducted in the neonatology department Tertiary Care Hospital (Nursery MCH Centre, Pakistan Institute of Medical Sciences, Islamabad Pakistan. **Duration:** 1st June 2022 to 1st December 2022. **Methods:** The sample was collected from the by non-probability consecutive sampling technique. Babies of any sex who meet the requirements during the first 72 hours of life. A total of 80 newborns were recruited out of them n=40 infants were found as early feeding and n=40 was assigned to late feeding. Demographic and baseline information (admission date, age, gender, gestational age, birth weight) of enrolled neonates recorded in the prescribed proforma. Effects of early or late feeding were monitored daily for 10 days. The outcomes in terms of time to reach full feed, weight gain at 10th day of life and feed intolerance were recorded and compared in both groups. All the information entered on the predesigned proforma by the researcher himself to comply with the study protocol attached. **Results:** A total of 80 newborns were recruited out of them n=40 infants were found as early feeding and n=40 was assigned to late feeding. The base line characteristics including birth weight, gestational age, respiratory support etc. were not statistically significant. Also, there is no difference of NEC (0.267) and FI (0.312) in early and late feeding groups. The Cox regression HR: 1.21 (95% CI: 0.829-3.72); p = 0.326). In both groups, the early feeding arm had a shorter median duration by 7 days. Further, the data was compared between early and late feeding group to determined which group is quicker for discontinuation of PN. **Conclusion:** Our study finds that using the feeding initiation and advancement method and AREDF on Doppler with exclusive breast milk results in faster PN cessation and does not increase the incidence of NEC or FI in preterm IUGR infants between 27 and 33 weeks of age.

Keywords: *IUGR, AREDF, PN, Feeding intolerance, Necrotizing enterocolitis.*

INTRODUCTION

Placental insufficiency and decreased placental nutrition transfer from the mother to the fetus are the underlying causes of intra-uterine growth restriction (IUGR), a serious and very frequent issue in the perinatal period. About 23.8 percent of babies have IUGR, with the majority (75% or more) of these cases occurring in Asia.[1] The prevalence of IUGR in Pakistan is around 25%,[2]

which is higher than the threshold at which the WHO would take public health action. Fetal hypoxia has been linked to absent or reversed end diastolic flow velocity (AREDFV), and this has been shown to have negative consequences on fetal development.[3] The survival rate of very preterm infants has increased over the last several decades because to advancements in neonatal treatment. Care in the newborn period is of the utmost importance, and this involves weighing the benefits and hazards of providing appropriate early feeding.[4, 5]

A neonate's growth and development are aided by enteral feeding. When started at a young age, enteral nutrition aids in the maturation of the gut's mucosal epithelium, the immune system, and the microbiome; it also increases digestive tolerance by promoting the appearance of the swallowing response and the development of the sucking reflex.[6-8] Although the gut is anatomically established in preterm infants, its behavior becomes more immature as gestational age decreases. Clinicians have a tough time determining what to give these infants because of their underdeveloped immune systems. Premature infants with intrauterine growth restriction (IUGR) and an increased SD ratio relative to gestational age or an anomaly in umbilical blood flow on prenatal Doppler have an even more serious issue.[3] Concerns about necrotizing enterocolitis (NEC) have sparked an ongoing discussion over when and how much to feed growth-restricted infants with prenatal Doppler abnormalities. There is a higher risk of parenteral nutrition-induced liver failure and infections when feeds are delayed and progressed at a slower pace.[9] Since NEC often develops after a newborn begins receiving enteral feeds, it is now standard practice to postpone the initiation of enteral feeding in babies who are thought to be at the greatest risk.[9] Since authors of published research sometimes fail to provide clarification on fetal growth restriction, there is no evidence to support this technique. The small for gestational age as birth weight below the 10th centile, which may contain some small-normal newborns, for the sake of analyzing other research. Neonates with a history of aberrant prenatal doppler blood flow are considered to have IUGR; this indicates a pathologic decrease in development below their genetic potential. These neonates are often small for their gestational age, although this is not always the case. Few studies showed a total of 115 participants were found in the Cochrane evaluation of early or late initiation of progressive enteral feeding for preterm newborns published in 2008. All the babies were born prematurely and had low birth weights, but none had specified conditions like SGA or IUGR. Breastfeeding began "early" during the first four days after delivery, and "late" between the fifth and tenth. There was no significant variation in NEC rates, but the authors still felt the data were inadequate to guide therapeutic treatment.[10]

This is being contested more and more, and a recent multi-centric randomized trial found that preterm growth-restricted infants who began receiving enteral feeding at a younger age achieved full enteral feeding sooner, spent less time in the hospital, and were less likely to develop feed intolerance.[2, 11] The randomized control trial on preterm neonates have shown inconsistent findings, with studies demonstrating inadequate information about the influence of early vs late enteral feeding tolerance or NEC outcomes in IUGR infants.[3] Therefore, there is no universally accepted feeding plan for premature neonates with IUGR. Due to a lack of recent research in the area, the current study aims to compare the outcomes of two different feeding strategies for preterm infants with abnormal Doppler readings: early vs. delayed initiation of enteral feeds. Then we implement the better of the two feedings regimens into our standard clinical practice. The objective of the study was to compare early and late enteral feeding in preterm intrauterine growth restricted neonate to evaluate time to reach full feed, risk of feed Intolerance, weight gain at 10th day of life and length of hospital stays.

METHODS

The Randomized Control Trial conducted in the Neonatology department Tertiary Care Hospital (Nursery MCH Centre, Pakistan Institute of Medical Sciences, Islamabad from 1st June 2022 to 1st December 2022.

By using WHO calculator sample size is 80 (40 in each group) for study with level of significance 5%, power of test 90%, test value of population mean 16.8 , Anticipated population mean 24.2 , population standard deviation 9.1.[12]

The sample were collected from the by non-probability consecutive sampling technique. Babies of any sex who meet the requirements during the first 72 hours of life. Preterm infants with development restrictions. The research included infants of both sexes with head ultrasonography Doppler abnormalities and were born at a gestational age of 35 weeks or less and weighed less than the 10th percentile for their gestational age. Major congenital defects, syndromic symptoms, chromosomal abnormalities, suspected inborn metabolic problems, and any infant with confirmed sepsis with shock were excluded from the study.

Permission and approval of the study were taken from the hospital ethical and scientific board. All newborns fulfilling our inclusion criteria were enrolled. A written informed consent was taken from the parent/guardian of the newborn. All the enrolled neonates were randomly

allocated to two treatment groups by computer generated random numbers method. Early groups received nutritional supplementation in the form of expressed breast milk at a rate of 15 ml/kg/day within 24 hours of birth, while late groups received it after 72 hours. Demographic and baseline information (admission date, age, gender, gestational age, birth weight) of enrolled neonates recorded in the prescribed proforma. Early enteral feeding was the initiation of 15 ml/kg/day of expressed breast milk as nutritional support within the first 24 hours of life. However, late enteral feeding was the nutritional support in the form of expressed breast milk 15 ml/kg/day initiated after 72 hours of life. The neonates who were suffering from feeding intolerance had the inability to digest enteral feeding associated with abdominal distension and emesis. Moreover, the full enteral feeds defined as the infant's total nutrition will be from milk as 150 ml/kg/day. Effects of early or late feeding was monitored daily for 10 days. The outcomes in terms of time to reach full feed, weight gain at 10th day of life and feed intolerance were recorded and compared in both groups. All the information entered on the predesigned proforma by the researcher himself to comply the study protocol attached.

Data was entered on computer software SPSS version 22. Quantitative variables like age, gestational age, birth weight, time to reach full feed, weight gain at 10th day of life and feed intolerance was measured. Frequencies and percentages will be calculated for qualitative variable like gender. Outcomes (time to reach full feed, weight gain at 10th day, feed Intolerance and length of hospital stay) were also compared between both groups by applying for Chi square test. Cox and multinomial regression analysis was done for the level of significance. The p-value lower than 0.05 was taken as significant.

RESULTS

A total of 80 newborns were recruited out of them n=40 infants were found as early feeding and n=40 was assigned to late feeding. The base line characteristics including birth weight, gestational age, respiratory support etc. were not statistically significant. However, LOS, weight regain, full feed intake was statistically significant data. In this study there were incidence of feed intolerance reported 9 and 3 neonates in early and late feeding respectively. However, NEC stage II and above were reported 2 and 4 in early and late feeding group respectively. Hence, there is no difference of NEC (0.267) and FI (0.312) in both the groups (Table 1 and 2). Median duration to adequate feedings permitting termination of parenteral nutrition (PN) was shorter in the early feeding group, at 15 days (IQR: 12-17) compared to 24 days (IQR: 18-26). The Cox regression HR: 1.21 (95% CI: 0.829-3.72); p = 0.326). In both groups, the early feeding arm had a shorter median duration by 7 days.

Table 1: Base Line characteristics of early and late feeding infants

Base Line Characteristics		Early feeding	Late Feeding	P value
Birth weight, *n* (%)	≤ 750	6	7	0.811
	751–1000	11	12	
	1001–1200	15	11	
	1201–1400	8	10	
Gestational age (weeks), *n* (%)	27	3	6	0.691
	28	5	8	
	29	9	5	
	30	7	7	
	31	10	8	
	32	6	6	
Maternal status, *n*	Preeclampsia	6	5	0.905
	Advanced age	29	27	
	Oligohydramnios	1	1	
	Preterm labor	2	4	
	Twins	2	3	
Respiratory support, *n* (%)	Nasal IMV	10	10	0.881
	Nasal CPAP	12	15	
	SIMV	15	12	
	No support	3	3	

Table 2: Secondary outcomes of early and late feeding infants

Secondary Outcome		Early feeding	Late Feeding	P value
Gender	Male	6	12	0.090
	Female	34	28	
Age in Hours	12	8	0	<0.001
	24	9	0	
	48	8	0	
	72	9	13	
	96	6	12	
	120	0	15	
Feed Intolerance	No	27	32	0.393
	Yes	8	4	
	NEC	5	4	
Length of stay	48-66	6	10	0.036
	50-57	11	9	
	18-35	6	14	
	15-42	17	7	
Full feed Intake	17-20	31	27	0.045
	23-25	7	11	
	14-19	2	2	
Regain Weight	15-21	8	7	<0.001
	21-26	10	12	
	12--17	10	14	
	17-20	12	7	
Incidence of feed intolerance		9	3	0.312
NEC stage II and above		2	4	0.267

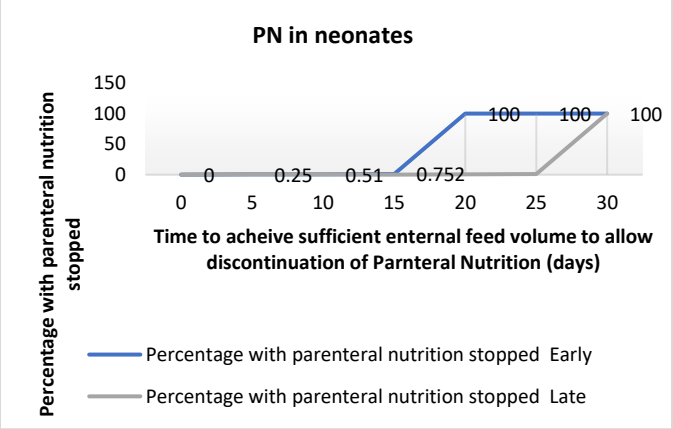
The infants were also divided based on extreme and very preterm babies as per inclusion criteria. In extreme preterm 17 and 19 infants were early and late feeding groups respectively. On the other hand, among very

preterm infants, 23 and 21 infants, respectively, were in the early and late feeding groups. Tables 3 demonstrate that neither the incidence of FI nor the combined outcome of the extremely premature nor the very premature differed statistically from one another. To identify which group is quicker for PN withdrawal, data was also compared between early and late feeding groups (Figure 2). Feed intolerance prevalence.

Table 3: Regression analysis of preterm and feeding groups

Incidence of Food Intolerance		OR	95% CI	P value
Extreme Preterm	**Yes**	1.747	0.442-6.905	0.426
	NEC	0.491	0.092-2.621	0.345
Very Preterm	**Yes**	1.24	0.920-1.780	0.057
	NEC	0.51	0.670-3.67	0.51
Early Feeding	**Yes**	1.75	0.436-7.025	0.43
	NEC	1.352	0.322-5.676	0.68
Late Feeding	**Yes**	1.89	0.860-2.610	0.246
	NEC	1.56	0.540-4.320	0.65

Figure 1: Discontinuation of PN in early and late feeding groups



DISCUSSION

The median time to reach a feed volume adequate to discontinue PN was significantly different between the two groups in this randomized experiment. The HR in both groups show that early feeding achieves feed volume 60-90% quicker than late feeding, enabling PN to be stopped sooner with early feeding. There was no increase in NEC and FI risk associated with the early feeding group's quicker completion of complete meal compared to the late feeding group. Babies that were born very prematurely were able to recover their birth weight much faster as a consequence. There was difference in LOS rates between the early and late feeding groups, despite the fact that the early feeding group weaned off PN quicker. This study include its randomized design, which allowed for the inclusion of very premature infants, the use of stratification since the risk of NEC is greater in extremely premature infants, and the use of prenatal treatment by a fetal-medicine expert to ensure the best possible timing of birth. In situations like ours, the amount of time it takes to increase feed volume to the point when PN can be stopped is a useful outcome metric. Using just breast milk and gradually introducing feed as per the FAP reduced the risk of necrotizing enterocolitis. One weakness of this research is the low sample size of very premature newborns.

Redistribution of blood supply to the important organs, caused by chronic fetal hypoxia due to extrinsic aetiologies, increases the risk for NEC.[13] While there was some evidence of a link between AREDF and NEC in earlier research[14], no causal link could be shown in more recent ones. Recently, a meta-analysis was conducted on three studies including 613 IUGR newborns with AREDF on UA Doppler to determine the efficacy of delaying the initiation of progressive enteral meals for the prevention of NEC in extremely low birthweight babies. There was no impact of delayed introduction of enteral meals on NEC, as estimated by the effects estimate of 0.87 (95% CI 0.54-1.41)[15, 16] The research also shows that preterm may tolerate the termination of PN at enteral feed quantities lower than what is generally considered safe, leading to a reduced risk of sepsis. Early removal of IV fluids in premature infants has the potential to reduce hospital stays, alleviate NICU congestion, and decrease LOS-related morbidity and death; however, no research has been conducted on this topic in underdeveloped countries.

Premature birth is still a major risk factor for NEC, and this condition has both immediate and long-term effects.[17] In an attempt to decrease NEC, NICUs throughout the globe have delayed enteral feeds out of concern that the gut could be hypoxic, particularly in newborns with abnormal Dopplers. The unintended consequence of worsening the nutritional status of already-vulnerable neonates.[18, 19] There have been a number of studies done to see whether there is a correlation between starting enteral feedings early and getting to full feedings sooner without increasing the risk of necrotizing enterocolitis (NEC).[20] We found no correlation between the rate of feed intolerance and NEC in the early feeding group and the rate at which they reached full enteral feeds. The length of mechanical ventilation, the time it took to reach the birth weight, and the number of days the infant was on PN all increased when feeding was delayed.[21]

The fact that our investigation lacked the statistical power to demonstrate statistical significance for these outcomes. Adherence to a protocolized feeding schedule is a more crucial component in lowering NEC.[22] McClure and Newell evaluated 100 newborns and found one case of

NEC in the trophic group and two instances in the control group, which contradicts the findings of Van Ellburg *et al* analyzed 42 infants and found no cases of NEC in the unfed group.[23] Seventeen of the neonates in the trophic group had NEC during the experiment by Schanler *et al*., whereas only ten of the newborns in the control group did. NEC rates in 692 babies were 10.5% for MEF and 9.4% for control infants, which is consistent with the findings of the meta-analysis by Tyson and Kennedy.[24] This is consistent with the findings of the current investigation as well. Recent research looked at three studies totaling 613 IUGR newborns with AREDF on UA Doppler to see whether delaying the start of progressive enteral meals for NEC prevention in extremely low birthweight babies is effective.[11] There was no impact of delayed introduction of enteral feeds on NEC, as estimated by the effects estimate of 0.87 (95% CI0.54-1.41).[25] The researchers behind experiment have looked at whether or not SGA/ IUGR neonates delivered with abnormal Dopplers benefit more from being fed early or later.[26] We found that delaying enteral feedings in premature neonates with abnormal dopplers increases the risk of necrotizing enterocolitis (NEC), which in turn increases the risk of the other complications.

CONCLUSION

Our study finds that using the feeding initiation and advancement method and AREDF on Doppler with exclusive breast milk results in faster PN cessation and does not increase the incidence of NEC or FI in preterm IUGR infants between 27 and 33 weeks of age. The rapid development of enteral feeding has prompted the necessity for comparative studies. In conclusion, preterm growth-restricted neonates with abnormal prenatal Doppler who begin receiving enteral feeds early achieve complete enteral feeds more quickly, but this practice has no discernible impact on the prevalence of necrotizing enterocolitis or feeding intolerance. The major focus should be on determining an individualized feeding approach for these fragile newborns.

LIMITATIONS

The primary limitation of this study is that all information were retrospectively obtained from a single site and depended on reliable, comprehensive and accessible preterm data.

SUGGESTIONS / RECOMMENDATIONS

To further clarify the function of feeding protocols, however, large multicenter randomized controlled trials are necessary due to the comparatively small sample size.

CONFLICT OF INTEREST / DISCLOSURE

None declared.

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