Two-hourly *versus* Three-hourly Feeding in Very Low Birthweight Neonates: *A Randomized Controlled Trial*

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Background: There is no consensus regarding the feeding interval in very low birth weight (VLBW) babies. If 2-hourly feeding schedule is feasible without increasing harm to the neonate, the nursing time consumed in the feeding of VLBW babies can be reduced.

Objective: To study whether 3-hourly feeding is non-inferior to 2-hourly feeding with respect to time to reach full feeds VLBW neonates.

Design: Open labelled, randomized controlled trial.

Subjects: 350 Neonates weighing between 1000 to 1500 grams, in whom feed could be started within 96 hours of life randomized to either 2-hourly or 3-hourly feeding schedule.

Primary outcome: Time to achieve full enteral feed.

Results: The primary outcome of time to achieve full enteral feed was comparable in the two feeding schedule groups (median 5 days IQR 4-6 days in both groups; p value 0.665). Among the secondary outcomes, there were no significant differences in incidence of hypoglycaemia (RR 0.86; 95% CI: 0.29-2.5) feed intolerance (RR 1.08: 95%CI: 0.5-2.3), necrotizing enterocolitis (RR 0.8; 95% CI: 0.22-2.3) in both the groups.

Conclusion: Three hourly feeding does not increase the risk of hypoglycemia, NEC or feed intolerance.

Keywords: *Enteral feeding, Feeding Interval, Feed intolerance, Hypoglycemia, Infant feeding, Necrotizing enterocolitis, Preterm neonates, Very low birth weight.*

Feeding of very low birthweight (VLBW) infants (1000-1500g) is relatively difficult because majority of them are born with inadequate feeding skills, have feed intolerance, and are at an increased risk of necrotizing enterocolitis (NEC). Early initiation of enteral feeding is preferred for preterm VLBW babies with mothers own milk for less NEC and better neurodevelopment outcomes and preventing gastric atrophy and improving gut motility and reaching full feeds early [3-6]. Bolus feeding is preferred for natural surge of gut hormones and helps in reaching full enteral feed early as compared to continuous feeding [7-9].

Regarding, the different feeding intervals, on one hand, less frequent feeding (3-hourly) decreases nursing workload, reduces infant handling and chances of acquiring infections [10]. On the other, it also leads to higher volume per feed, which may decrease feed tolerance. Feeding two-hourly feeds delivers a smaller volume per feed, which is more easily tolerated by the preterm and causes less gastric distension and less gastro-oesophageal reflux [11]. There is no consensus regarding the feeding interval in VLBW babies. Feeding in NICUs requires a major part of the nursing time. The actual workload of nurses in the NICU is tremendous and nurse to patient ratio is often in adequate in low- and middle-income countries (LMICs) [12,13]. Therefore, we conducted the study to determine whether a three three-hourly feeding schedule is non-inferior to a two-hourly feeding schedule with regards to time to achieve full enteral feeds in VLBW neonates.

METHODS

This open-labelled randomized controlled trial was conducted from January, 2018 to March, 2019 in a level III neonatal care unit. Institutional ethics committee approved the study protocol. All inborn neonates weighing between 1000 g and 1500 g, in whom feed could be started within 96 hours of life, were included in the study. The exclusion criteria were major congenital malformations including tracheoesophageal fistula, oesophageal atresia and duodenal atresia that interfered or delayed the feed initiation; severe perinatal asphyxia (APGAR score of <5 at 5 min) or encephalopathy due to any reason; infants with absent or reversed end diastolic flow (AEDF/REDF) in antenatal USG; and infants who were severely sick, on invasive ventilation or in shock. Small for gestational age (SGA) was defined as birthweight less than 10th percentile for that gestation as per the Intergrowth charts [14].

The primary outcome was to compare the time to achieve full enteral feed between the two groups of VLBW infants receiving 2-hourly and 3-hourly feed. The secondary objectives were to compare the incidence of hypoglycemia, feed intolerance and NEC stage 2 or 3 between the two groups. A subgroup analysis of the same outcomes between babies weighing 1000g-1250g and 1250g-1500g was decided a priori.

Full enteral feed was defined as 150 mL/Kg/day of enteral feeds, hypoglycaemia was defined as blood glucose concentration <45mg/dL [15]. Feed intolerance was defined as abdominal distension (abdominal girth ≥2 cm), with blood or bile stained aspirates or vomiting or pre-feed gastric residual volume more than 50% of feed volume; the latter checked only once feeds reached 5 mL/kg volume [16]. NEC was defined as per the modified Bells staging.

Parents of the VLBW babies delivered in the hospital Labour room were approached for informed written consent for participation in the study. Those infants who satisfied the eligibility criteria were stratified as per the weight (1000 g – 1250 g and 1251 g – 1500 g, and were randomly allocated to one of the intervention groups using a web based allocation sequence generator. A person not involved in the study generated the randomization. Randomization was done with blocks of variable sizes and the allocations were concealed, by keeping the allocation sequence in serially numbered sealed and opaque envelopes. The nature of intervention prevented blinding of the intervention from the investigators and the treating team. However, the statistician was blinded from the allocation details.

The standard group received enteral feed every 2 hours and the experimental group at 3-hourly intervals. Feeding was started as expressed breast milk as soon as the infant was stable. Preterm formula was used if breast milk was insufficient. The feeding protocol of the unit was uniformly followed for both groups. Feeding was initiated and increased by 30 mL/kg/day in babies weighing 1000-1250 g babies and as complete total enteral feeds (as per the daily standard fluid requirement) in the 1251 to 1500 g weight group babies. In the former group, intravenous fluid was given till enteral feed reached a volume of 120 mL/kg/day. Babies were fed through orogastric tube using the gravity method or with the help of cup/*paladi*, as per gestational maturity. In neonates on oral feeding, the abdominal girth was measured every 12 hours. If the abdominal girth increased by ≥ –2 cm or if baby vomited, gastric residual was checked. Once feed volume was more than 5 mL/kg; if aspirate was milky and <25% of feed volume, feeds were continued and if the aspirate was 25-50%, next feed volume was reduced equal to the aspirate volume. One or two feeds were withheld if the aspirate volume was >50% of the feed volume or (5 mL/kg, whichever is higher) and feeds were restarted with abdominal girth monitoring. If the feed intolerance recurred associated with systemic signs and symptoms or if the aspirate was bile or blood-stained, feeds were withheld for at least 24 hours and restarted when the issue resolved. Dextrose monitoring was done using Gluco-care sense glucometer at 1-hour, 3-hours, 6-hours and then 12-hourly till 72 hours of life or if baby was symptomatic. All blood sugars estimates in the hypoglycemia range were confirmed using laboratory sample. All the hypoglycemia episodes were treated as
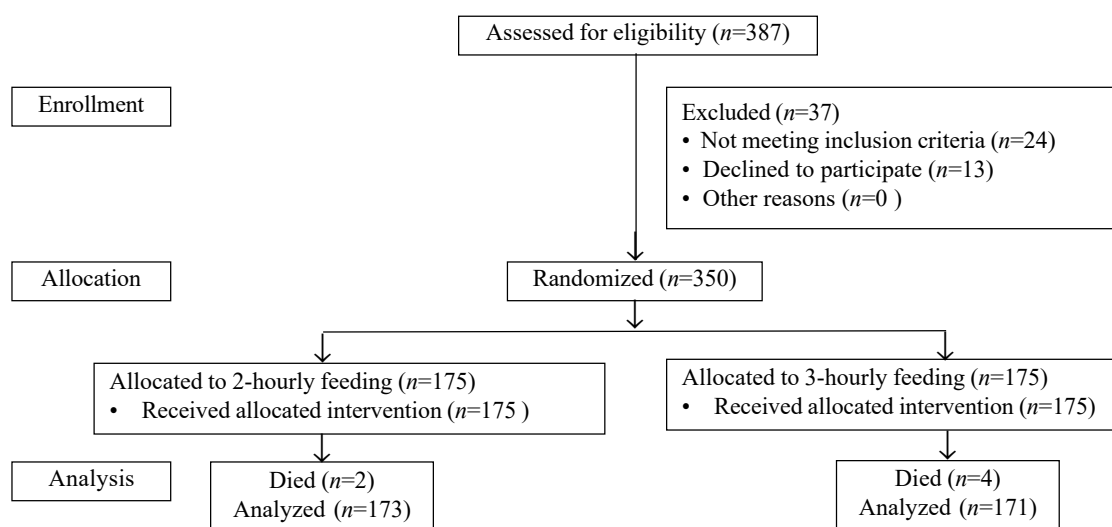
Fig. 1 Study flow chart.

per the standard protocol of the unit.

The infants were weighed daily by the nurse using a standardized and well calibrated digital weighing machine ± 5g (Seca). A neonate was considered to have completed the study once the infant reached full enteral feeds. (≥150 mL/kg/day) and maintained it for 48 hours without any feed intolerance [17].

Taking the mean time difference to achieve full enteral feed as 1.1 days [18], the minimum required sample size, with 90% power of study and 5% level of significance was 350 (175 patients per group).

Statistical analysis: Categorical outcome variables were analyzed by Chi-square test with continuity correction or Fisher exact test, Estimates of strength of association were deduced by calculating relative risks with their respective 95% confidence intervals. An intention-to-treat analysis was done.

RESULTS

The flow of subjects in the study is shown in **Fig. 1**. The baseline demographic and clinical characteristics were comparable between the two groups (**Table I**). Six babies died (2 in 2-hourly and 4 in 3-hourly group). Time to achieve full enteral feed was comparable in the two groups of neonates [median (IQR), 5 days (4-6) in both groups; *P*=0.665]. We performed sensitivity analysis using worst case scenario, assigning maximum (15) days to reach full feeds by dead babies in 3-hourly group and minimum (2) days to 2-hourly group. The hazard ratio (95% CI) was 1.022 (0.829-1.262) with *P*= 0.88 (**Fig. 2**).

Range of time for attaining full enteral feeds was 3-15 days. 11 neonates were outliers and reached full enteral feeds between 10-15 days of life. None of these outliers had hypoglycaemia. One baby was 29 weeks gestation and had no other morbidities. Rest of the babies were of 32-34 weeks gestation, all 10 had feed intolerance and 9

Table I Baseline Characteristics of the Very Low Birthweight Infants in the Study

	2-hourly feeding (n=175)	3-hourly feeding (n=175)
Preterm	169 (96.6)	171 (97.1)
Gestation (wk)*	32.3 (2.3)	32.5 (2.3)
Male	104 (59.4)	104 (59.4)
AGA*a*	110 (62.9)	101 (57.7)
Birthweight 1000-1250 g	62 (35.4)	64 (36.6)
Birthweight 1251-1500 g	113 (64.6)	111 (63.4)
Birthweight (kg)*	1.32 (0.14)	1.31 (0.15)

*Values in no. (%) except *mean (SD); ᵃAGA: Appropriate for gestational age.*
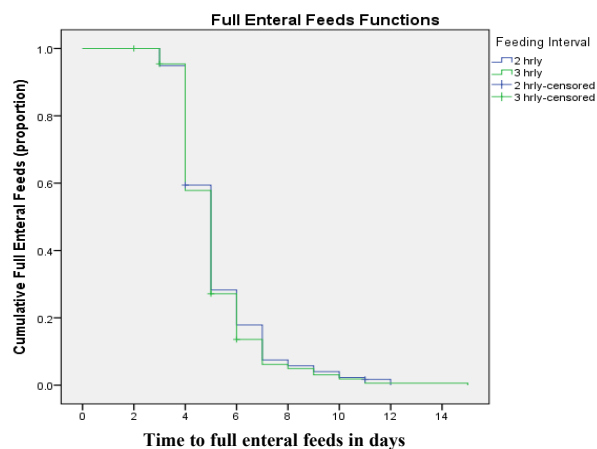
Fig. 2 *Kaplan Meier graph for time to reaching full enteral feed volume by infants in the 2-hourly and 3-hourly feeding groups.*

had NEC and one had ileal atresia. Among the secondary outcomes, there were no significant differences in incidence of hypoglycaemia, feed intolerance and NEC in both the groups (**Table II**). Hypoglycemia, feed intolerance and NEC occurred at mean (SD) 38.8 (34.31) and 49.43 (31.53) hours of life, 29.8 (30.47) and 28.8 (28.11) hours of life and 5.8 (3.7) and 7.7 (0.96) days of life in the two-hourly and three-hourly feeding groups, respectively.

DISCUSSION

In this +open labelled, randomized controlled trial, there was no significant difference in the time taken to achieve full enteral feed between very low birthweight infant receiving 2-hourly or 3-hourly feeds.

Two babies were given two feeds at two-hourly intervals rather than three-hourly. For one baby found to have ileal atresia after enrolment and reached full feeds on day 15 of life. An important risk of bias though was the lack of blinding, which was impossible because of the nature of the interventions. The standardized feeding protocol and the use of pre-defined outcome measures may have reduced the risk of this bias. In this study, the advancement of enteral feeds was fast (at the rate of 30 mL/kg/day) which is the current norm to achieve early

Table II Secondary Outcome Measures in Neonates in the Two-hourly *vs*. Three-hourly Feeding Groups

Outcome	Feeding schedule		RR (95% CI)
	2-hourly (n=175)	3-hourly (n=175)	
Hypoglycemia	6 (3.4)	7 (4.0)	0.86 (0.29-2.49)
Feed intolerance	13 (7.4)	12 (6.9)	1.08 (0.5-2.3)
NEC	4 (2.3)	5 (2.9)	0.8 (0.22-2.29)

#Values in no. (%); NEC: Necrotizing enterocolitis.

Appropriate for gestational age

WHAT IS ALREADY KNOWN?

• Intermittent two-hourly bolus feeding is recommended for very low birthweight neonates.

WHAT THIS STUDY ADDS?

• It is feasible and safe to administer three-hourly feeding schedule for very low birthweight babies weighing 1000-1500 gram.

FEF [20]. Formula was used in 14.9% babies and there was no difference in its use in both the groups. The study was adequately powered to detect the difference of 1 day in the duration to achieve full feeding, which was the primary outcome. Time to reach full enteral feeds was kept as a primary outcome as it was a very important outcome for neonate. Once intravenous cannula and fluids are removed, the exposure of baby to risk of sepsis goes down indirectly [17]. NEC and mortality though are hard outcomes, but rare and sample size would have gone very high because of lower event rate. There were three protocol deviations

However, our results are similar to previous studies [18,20], even though, Ibrahim, et al. [18] had a slower advancement of feeding. The total nursing time spent on feeding per day has also been shown to be significantly less in three hourly groups [20,21].

DeMauro, et al. [22] did a retrospective cohort study in infants weighing 500-1500 grams and found that achieving full enteral feed was better in neonates receiving 2-hourly feeds. However, this was a retrospective study with a different population, and they used continuous feeding in cases of severe feed intolerance and excluding these from further analyses [22]. Others [23,24] have also reported similar results.

Though this study showed that there was no difference in time to reach full feeds and incidence of adverse events like feed intolerance, NEC and hypoglycemia, a non-inferiority trial can be planned to show that three-hourly feeding is noninferior to two-hourly feeding.

Razak [25] carried out systematic review and meta-analysis in 2019, including seven RCTs and three observational studies comprising 952 babies and found no significant differences in the outcomes: time to reach full enteral feeding, necrotizing enterocolitis, feed intolerance, and hypoglycemia. Dutta, et al. [17] systematically reviewed the literature and gave suggestion to administer three-hourly feed for babies weighing >1250 g and found insufficient evidence to choose between two-hourly versus three-hourly feed for babies weighing ≤1250 g. Further subgroup analysis of our study will give more information about the neonates in two different weight groups of 1000 to 1250 and 1251 to 1500 grams.

Three-hourly feeding in very low birthweight babies does not without increase the time to achieve full enteral feeds or increase the incidence of feed intolerance, hypoglycemia and NEC.

REFERENCES

1. Saifon C, Joshua PV, Ann-Beth M, et al. Global, regional, and national estimates of levels of preterm birth in 2014: A systematic review and modelling analysis. Lancet Global Health. 2019;7:e37-46.

2. UN Inter-Agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality: Report 2017. New York: United Nations Children's Fund, 2017.

3. Morgan J, Young L, Mc Guire W. Delayed introduction of progressive enteral feeds to prevent NEC in very low birthweight infants. Cochrane Database Syst Rev. 2014;12: CD001970.

4. Nangia S, Vadivel V, Thukral A, Saili A. Early total enteral feeding versus conventional enteral feeding in stable very low birthweight infants: A randomised control trial. Neonatology. 2019;115:256-62.

5. Gibertoni T, Corvaglia L, Vandini S, et al. Positive effect of human milk feeding during NICU hospitalization on 24-month neurodevelopment of VLBW infant: An Italian Cohort Study. PLoS One. 2015;10: e0116552:1-13.

6. McClure R.J. Trophic feeding of the preterm infant. Acta Paediatr. 2001;90:19-21.

7. Rayyan M, Rommel N, Allegaert K. The fate of fat: Preexposure fat losses during nasogastric tube feeding in preterm newborns. Nutrients. 2015;7:6213-23.

8. Rogers SP, Hicks PD, Hamzo M, Veit LE, Abrams SA. Continuous feedings of fortified human milk lead to nutrient losses of fat, calcium and phosphorous. Nutrients.

2010;2:230-40.

9. Premji S, Chessel L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. Cochrane Database Syst Rev. 2002; 4:CD001819.

10. Jeannette AR, Douglas S, Thelma P, Jeffrey H, Michael K, Eileen TL. Nurses staffing and NICU infection rates. AMA Pediatr. 2013;167:444-50.

11. Lane AJ, Coombs RC, Evans DH, Levin RJ. Effect of feed interval and feed type on splanchnic haemodynamic. Arch Dis Child Fetal Neonatal Ed. 1998;79:F49-53.

12. Sherenian M, Profit J, Schmidt B, *et al.* Nurse-to patient ratios and neonatal outcomes: A brief systematic review. Neonatology. 2013; 104:179-83.

13. Neogi SB, Malhotra S, Zodpey S, Mohan P. Assessment of special care newborn units in India. J Health Popul Nutr. 2011;29:500-9.

14. Villar J. Ismail L.C, Victoria CG. International standards for newborn weight, length, head circumference by gestational age and sex: The newborn cross-sectional study of the INTERGROWTH-21st project. Lancet. 2014;384:857-68.

15. Adamkin DH. Neonatal hypoglycemia. Semin Fetal Neonatal Med. 2017;22:36-41.

16. Härtel C, Haase B, Browning-Carmo K, et al. Does the enteral feeding advancement affect short-term outcomes in very low birthweight infants? J. Pediatr Gastroenterol Nutr. 2009;48:464-70.

17. Dutta S, Singh B, Chessell L, et al. Guidelines for feeding very low birthweight infants. Nutrients. 2015;7:423-42.

18. Ibrahim NR, Van Rostenberghe H, Ho JJ. Short versus long feeding interval for bolus feedings in very preterm infants. Cochrane Database Sys Rev. 2016; CD012322.

19. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birthweight infants. Cochrane Database Sys Rev. 2015:CD001241.

20. Dhingra A, Agrawal SK, Kumar P, Narang A. A randomised controlled trail of two feeding schedules in neonates weighing less than or equal to 1750g. J Matern Fetal Neonatal Med. 2009;22:198-203.

21. McCallie KR, Lee HC, Mayer O, Cohen RS, Hintz SR, Rhine WD. Improved outcomes with a standardized feeding protocol for very low birthweight infants. J Perinatol. 2011;31:S61-7.

22. DeMauro SB, Abbasi S, Lorch S. The impact of feeding interval on feeding outcomes in VLBW infants. J Perinatol. 2011;31:481-6.

23. Rudiger M, Herrmann S, Schmalisch G, Wauer RR, Hammer H, Tschirch E. Comparison of 2-hourly versus 3-hourly enteral feeding in extremely low birthweight infants, commencing after birth. Acta Paediatr. 2008;97:764-9.

24. Chu E, Freck S, Zhang L, Bhakta KY, Mikhael M. Three-hourly feeding intervals are associated with faster advancement in very preterm infants. Early Hum Dev. 2019;131:1-5.

25. Razak A. Two-hourly versus three-hourly feeding in very low-birth-weight infants: A systematic review and meta-analysis. Am J Perinatol. 2020;37:898-906.