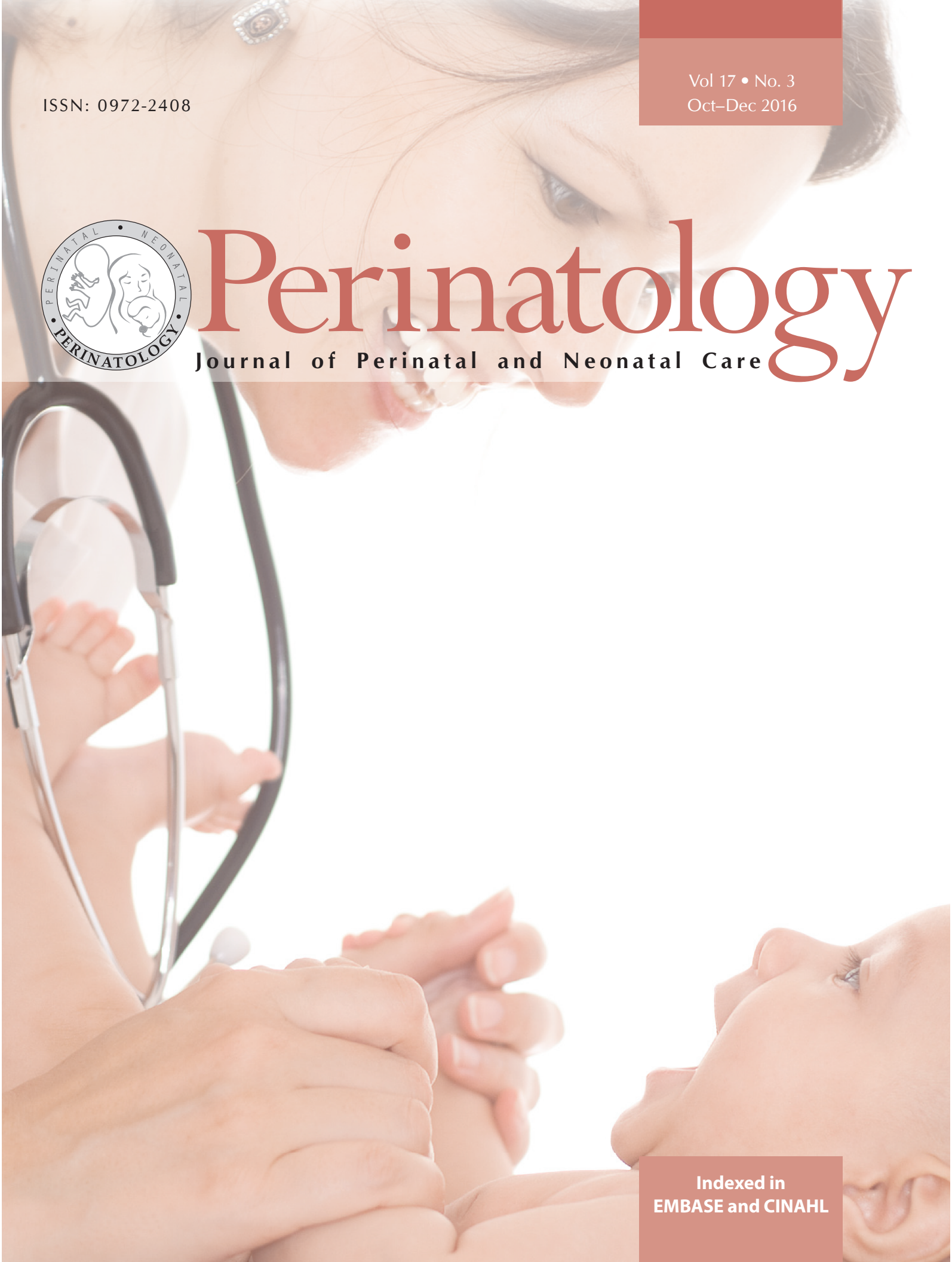
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prematurity (ROP); duration of total parenteral nutrition (TPN) and nursing; and mortality.

Results: A total of 215 neonates were assessed for eligibility, of whom 95 were excluded. Hence, 120 neonates were enrolled in the trial. There was no significant difference in time (in days) to reach full feeds in the 2-h versus 3-h groups (9.53 ± 4.26 vs 9.85 ± 5.48; *P* = .73). There was no significant difference between the 2 groups in any of the secondary outcomes such as time to attain birth weight; time to discharge; anthropometric parameters at discharge; feed intolerance; use of metoclopramide and mosapride; and incidence of NEC, IVH, ROP, and sepsis. The total time spent per day in feeding was significantly lesser in the 3-h feeding schedule groups (*P* = .04).

Subgroup analysis revealed that among the neonates in the lower birth weight strata (501 to ≤ 1000 g), those fed 2-h reached full feeds earlier compared with those fed 3-h (2-h group: 11.24 ± 2.88 d vs 3-h group: 14.14 ± 4.98 d; *P* = .041).

Conclusions: There was no significant difference in time to reach full feeds in all the neonates, irrespective of whether they were fed 2-h or 3-h. However, neonates < 1000 g reached full feeds earlier when fed more frequently (2-h feeding schedule).

Key Words: Feeding schedule, neonate, full feeds, preterm, very low birth weight, feed intolerance

Introduction

Time to reach full feeds has significant effect on long-term neurodevelopmental outcome in neonates.[1] Physiologic principles favor large-volume and less-frequent feeding schedules.[2,3] However, extremely low-birth-weight (ELBW) and very low-birth-weight (VLBW) neonates across the world are fed more frequently with smaller amount of feeds fearing the risk of hypoglycemia, apnea, feed intolerance, and NEC. There is dearth of scientific data to accept or refute this notion. We hypothesized that when fed less frequently with relatively larger volumes, neonates will reach full feeds earlier. We also postulated that a less frequent feeding schedule would reduce neonate handling and workload on nursing staff, thereby reducing infection rate and length of hospital stay.

Aim

To compare the effect of 3-hourly (3-h) versus 2-hourly (2-h) feeding schedules on time to reach full feeds in neonates weighing ≤ 1500 g

Materials and Methods

This open-labeled, randomized trial with parallel enrollments was conducted at a level 3 NICU in Mumbai. This study was approved by the institute's ethics committee and written informed consent was obtained from the parents/guardians before enrollment.

The study's inclusion criterion was neonates weighing 501 to 1500 g. The exclusion criteria were presence of (i) lethal congenital anomalies/malformations, (ii) gastrointestinal or other congenital malformations having a significant effect on gastrointestinal motility or function (intestinal atresias, meconium plug syndrome, Hirschsprung disease, neuronal intestinal dysplasia, and congenital diaphragmatic hernia), and (iii) other serious conditions potentially lethal or having significant effect on gastrointestinal motility or function directly or indirectly (grade III or grade IV IVH, severe sepsis, acute renal failure, shock with multiorgan involvement, and inborn errors of metabolism).

The neonates were divided into 2 strata based on birth weight: 501 to ≤ 1000 g and 1001 to ≤ 1500 g. The neonates were randomized into 2 groups, 3-h and 2-h feeding schedules, using computer-generated random sequence. The group allocation was concealed by using consecutively numbered and sealed opaque envelopes.

Outcome measures

The primary outcome was time (in days) to reach full feeds. The secondary outcomes were time (in days) to attain birth weight; time (in days) to discharge; weight, length, and head circumference at discharge; feed intolerance, requiring interruption of feeds; incidence of NEC (Bell stage I, II, or III),[4] IVH (Papile stage I, II, III, and IV),[5] screen-positive sepsis (presence of any one of the following: C-reactive protein > 6 mg/L, WBC count < 5000, or IT > 0.2), culture-positive sepsis, hypoglycemia, apnea, jaundice, and retinopathy of prematurity (ROP); duration of total parenteral nutrition and nursing; and mortality.

Feeding protocol

Feeding was started when neonates were hemodynamically stable and no other contraindication for feeding was present. A precise uniform feeding schedule was prescribed for each neonate, indicating the amount and timing of feeds. The initial feeding volume was 20 mL/kg/d, and it was gradually advanced by a volume of 20 mL/kg/d until full feeds were reached. The total feeds recommended for the day were divided into 8 or 12 feeds as per 3-h or 2-h feeding schedule, depending on group allocation. The feeds were administered through an orogastric tube. Expressed breast milk was the milk of choice, and all neonates received expressed breast milk at the introduction of feeds. During feed advancement, preterm formula was used to supplement breast milk when the amount of expressed breast milk was inadequate. The actual feed volume and time of feeding were recorded. Gastric aspirates were measured 6 hourly before a scheduled feed in every neonate. Abdominal girth was measured every 6 hours before a scheduled feed. When significant feed intolerance was present, feeds were withheld and the neonate was investigated for NEC, clinically and radiographically.

Feed intolerance was considered in any one of the following cases:

- excessive prefeed gastric aspirates > 50% of the volume of previous feed or 3 mL, whichever was greater;
- gastric aspirate 33% to 50% of the previous feed but > 3 mL and occurs more than 3 times in a 24-hour period;
- presence of bilious gastric aspirate, regardless of volume, after confirming the position of the tube inside the stomach, for 2 consecutive feeds;
- presence of blood in gastric aspirate;
- increase in abdominal girth by 2 cm or more in the previous 6 hours;
- presence of gross blood in stools;
- emesis (vomiting of > 25% of the feed) more than 3 times in a 24-hour period; or
- bile-stained or blood-stained emesis.

In case there was no evidence of NEC, the same feeding schedule was restarted in the neonate. In case the neonate again developed feed intolerance but not NEC, prokinetic medications were sequentially administered. Metoclopramide (0.1 mg/kg/dose, TID) was administered first, followed by mosapride (0.2 mg/kg/dose, BID) if there was no symptomatic improvement in 24 hours and no other contraindications for feeding. If feeding intolerance persisted for > 48 hours despite starting prokinetic medications, the neonate was put on milk infusion with an orogastric tube. Milk was infused for 5 hours continuously with a syringe pump, followed by a break of 1 hour. In case feeding was withheld due to NEC or feed intolerance, following recovery, when feeding was restarted, the originally randomized feeding schedule protocol (2-h or 3-h) was followed. Time taken by a neonate (in days) to tolerate a feeding volume of 150 mL/kg/d for at least 48 hours was recorded as time to reach full feeds.

Weight of the neonates was recorded using an electronic weighing machine, with an accuracy of ± 1 g. Length was measured using an infantometer. Head circumference was measured with a nonstretchable tape.

Hypoglycemia was defined as blood glucose level below 40 mg/dL. Blood sugar level was monitored as per the

protocol. Blood glucose level was monitored from the time of introduction of feeds, as follows: just before the introduction of the first feed, 6 hourly for 48 hours, and then 24 hourly till full feeds were reached.

Apnea was defined as cessation of breathing for > 20 seconds or of lesser duration when accompanied by bradycardia or desaturation. Bilirubin level was estimated through measurements of serum bilirubin levels. Screening for intracranial bleed was performed using ultrasonography on day 7 and day 28 of postnatal age, but earlier when clinically indicated.

Sample size and analysis

Sample size was calculated using the formula for the hypothesis of 2 parallel-sample means. In our unit, with the existing feeding practices, the average time taken by a neonate with birth weight of 500 g to 1500 g to reach full feeds was 15 days (SD ± 4 d, variance 16 d) when fed 2-h. We hypothesized that the neonates fed 3-h will reach full feeds by day 12 of life. For a difference of 3 days, with an error of 0.05 and β error of 0.1 (power = 90%), the estimated sample size was 38 in each group. Anticipating loss to follow-up due to death or transfer to another facility, 50 neonates were to be enrolled in each group. However, we could enroll 60 neonates in each group. Analysis was performed by applying intention-to-treat principle. Categorical variables were compared using the Chi-square test. Continuous measures between groups were compared using the 2-sample *t* test or the Mann–Whitney *U* test as appropriate. Data was analyzed using IBM SPSS version 21 software. A *P* value < .05 was considered significant.

Results

A total of 215 neonates were assessed for eligibility, of whom 95 were excluded, leaving 120 neonates, with parental consent, for this study (Figure). The baseline characteristics were similar in both the groups and are presented in Table 1. There was no significant difference in time (in days) to reach full feeds in the 2-h versus 3-h feeding schedule groups (9.53 ± 4.26 d vs 9.85 ± 5.48 d; *P* = .73). The total time spent per day in feeding was significantly lesser in the 3-h feeding schedule group (*P* = .04). There was no significant difference between the 2 groups in any of the other secondary outcomes such as time to attain birth weight; time to discharge; anthropometric parameters at discharge; feed intolerance; use of metoclopramide and mosapride; and incidence of NEC, IVH, ROP, and sepsis (Table 2).

Subgroup analysis revealed that among the neonates in the lower birth weight strata (501 to ≤ 1000 g), those fed 2-h reached full feeds earlier compared with those fed 3-h (11.24 ± 2.88 d vs 14.14 ± 4.98 d; *P* = .041) (Table 3).

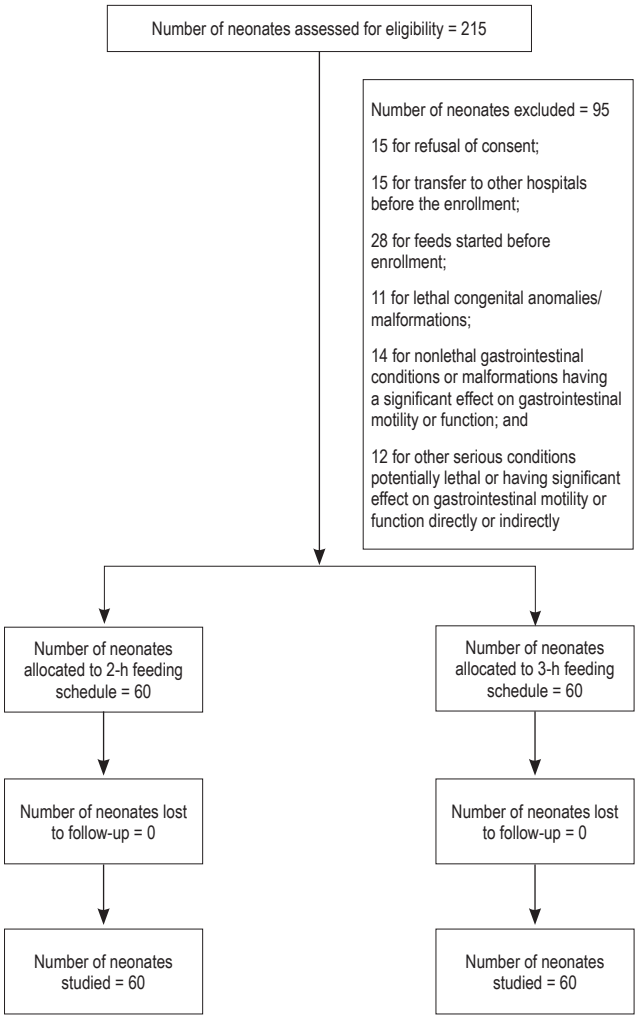


Figure. Study Enrollment and Allocation

Table 1. The Demographic and Other Baseline Characteristics of the 2 Feeding Schedule Groups

Characteristics	2-h Feeding Schedule Group (n = 60)	3-h Feeding Schedule Group (n = 60)
Hypertensive Disorder in Pregnancy[a]	18 (30%)	15 (25%)
Abnormal Doppler (Absent or Reversal of Flow)[a]	12 (20%)	10 (16.7%)
Gestational Diabetes[a]	3 (5%)	5 (8.3%)
Antenatal Steroids[a]	45 (75%)	41 (66.7%)
Gestational Age,[b] wk	30.10 ± 2.84	30.50 ± 2.68
Birth Weight,[b] g	1176.00 ± 249.46	1139.00 ± 225.47
Length at Birth,[b] cm	37.86 ± 3.55	38.25 ± 3.82
Head Circumference at Birth,[b] cm	27.15 ± 2.3	27.63 ± 2.56
Sex[a]		
Male	29 (48.3%)	34 (56.7%)
Female	31 (51.7%)	26 (43.3%)
SGA[a]	12 (20%)	14 (23.3%)
RDS[a]	45 (75%)	36 (60%)
PDA[a]	19 (31.70%)	15 (25%)
C + EOS[a]	1 (1.7%)	1 (1.7%)
SC + EOS[a]	24 (40%)	15 (25%)
Volume of First Feed,[c] mL	3 (2, 3)	5 (3, 5)
Expressed Breast Milk at First Feed[a]	60 (100%)	60 (100%)
Day of Life at Introduction of First Feed[b]	3.08 ± 1.45	3.08 ± 1.50
No. of Neonates Requiring Ventilatory Support[a]	10 (15%)	8 (13.30%)
No. of Neonates Requiring CPAP Support[a]	38 (63.40%)	34 (56.70%)

[a]Values are expressed as mean ± SD; [b]Values are expressed as number (percentage); [c]Values are expressed as mL (median, IQR) (25th and 75th percentile).
C + EOS, culture-positive early-onset sepsis (within 72 h of birth); CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SC + EOS, screen-positive early-onset sepsis; SGA, small for gestational age.

Table 2. Primary and Secondary Outcomes of the 2 Feeding Schedule Groups

	2-h Feeding Schedule Group (n = 60)	3-h Feeding Schedule Group (n = 60)	*P* Value, 2-Tailed
Primary Outcome			
Time to Reach Full Feeds,[a] d	9.53 ± 4.26	9.85 ± 5.48	.73
Secondary Outcomes			
Time To Regain Birth Weight,[a] d	11.11 ± 5.25	10.51 ± 5.90	.56
Time To Discharge,[a] d	43.74 ± 20.23	46 ± 21.47	.56
Anthropometric Measurements at Discharge			
Weight,[a] g	1963.33 ± 317.69	1991.01 ± 82.46	.67
Length,[a] cm	43.14 ± 2.98	43.14 ± 2.98	.67
Head Circumference,[a] cm	30.65 ± 1.86	31.02 ± 2.09	.49
Feed Intolerance[b]	24 (40%)	28 (46.7%)	.43
Use of Metoclopramide[b]	18 (30%)	22 (36.7%)	.42
Use of Mosapride[b]	8 (13.3%)	8 (13.3%)	.30
Milk Infusion[b]	5 (8.3%)	8 (13.3%)	.30
Feed Intolerance on Milk Infusion[b]	0 (0%)	4 (6.7%)	.15
NEC[b]	2 (3.3%)	5 (8.3%)	.30
NEC stage 1[b]	1 (1.7%)	2 (3.3%)	.63
NEC stage 2[b]	1 (1.7%)	2 (3.3%)	.63
NEC stage 3[b]	0 (0%)	1 (1.7%)	.63
IVH[b]	3 (5%)	2 (3.3%)	.55
IVH grade I[b]	3 (5%)	2 (3.3%)	.65
IVH grade II[b]	0 (0%)	0 (0%)	—
IVH grade III[b]	0 (0%)	0 (0%)	—
IVH grade IV[b]	0 (0%)	0 (0%)	—
C + LOS[b]	5 (8.3%)	8 (13.3%)	.93
SC + LOS[b]	5 (8.3%)	8 (13.3%)	.68
Hypoglycemia[b]	1 (1.7%)	1 (1.7%)	1
Apnea[b]	0 (0%)	1 (1.7%)	.60
ROP[b]	12 (20%)	10 (16.70%)	.81

Contd.

Table 2. *Contd.*

Jaundice[b]	45 (75%)	42(70%)	.68
Duration of TPN, d	6.88	7.02	.88
Total Nursing Time Spent on Feeding per d, min	50	74	.04
Mortality, n	0	0	0

[a]Values are expressed as mean ± SD; [b]Values are expressed as number (percentage).
C + LOS, culture-positive late-onset sepsis (after 72 h of birth); SC + LOS, screen-positive late-onset sepsis (after 72 h of birth); IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.

Table 3. Subgroup Analysis of Neonates Between the 2 Feeding Schedule Groups

Birth Weight of 501 to 1001 g				
	2-h Feeding Schedule Group (n = 42)	3-h Feeding Schedule Group (n = 42)	MD (95% CI)	*P* Value, 2-Tailed
Time to Reach Full Feeds[a]	11.24 ± 2.88	14.14 ± 4.98	- 2.92 (- 0.12, - 5.72)	.041; S
Feed Intolerance[b]	9 (50%)	13 (72.2%)	0.30	—
Hypoglycemia[b]	1 (5.6%)	1 (5.6%)	1	—
Apnea[b]	0 (0%)	1 (5.6%)	1	—
Birth Weight of 1001 to 1500 g				
	2-h Feeding Schedule Group (n = 18)	3-h Feeding Schedule Group (n = 18)	MD (95% CI)	*P* Value, 2-Tailed
Time to Reach Full Feeds[a]	8.86 ± 4.55	7.80 ± 4.47	1.06 (3.03, - 0.91,)	.29; NS
Feed Intolerance[b]	16 (38%)	15 (35.7%)	1	—
Hypoglycemia[b]	0 (0%)	0 (0%)	1	—
Apnea[b]	0 (0%)	0 (0%)	1	—

[a]Values are expressed as mean ± SD; [b]Values are expressed as number (percentage).
MD, mean difference; NS, not significant; S, significant.

Limitations

Our study lacked blinding of nurses and attending clinicians due to the nature of the intervention. The percentage of neonates in each group who received preterm formula in addition to expressed breast milk was not analyzed. This was difficult, as the neonates in each group received widely varied percentage of formula milk in addition to expressed breast milk. Variations in availability of milk within each group (preterm formula vs expressed breast milk) could limit the generalizability of our study.

Conclusion

We conclude that a 3-h feeding schedule is as effective as a 2-h feeding schedule in achieving full enteral feeding in neonates weighing ≤ 1500 g.

Discussion

Our study results confirm that both (2-h and 3-h) feeding schedules are equally effective in reaching full enteral feeding, without any increase in feeding intolerance. Our study also suggests that the effect of the 3-h feeding schedule is similar to that of the 2-h feeding schedule on various other secondary outcomes including hypoglycemia and apnea, except that feeding time was significantly less in the 3-h feeding schedule group. However, our study was not adequately equipped to analyze these secondary outcomes.

This was a randomized trial with robust methodology and appropriate sample size for the primary outcome. In our study population, 30% neonates (n = 36, total enrollment = 120) had a birth weight of ≤ 1000 g, compared with 23% (n = 22, total enrollment = 94) in the study by Dhingra et al.[6] There were no drop-outs in our study.

In our study, time to reach full feeds (in days) in both the feeding regimens was similar (9.85 ± 5.48 d vs 9.53 ± 4.26 d, *P* = .73). This finding is similar to the finding by Dhingra et al[6] (2-h vs 3-h groups: 8.1 [3.9] vs 8.9 [5.9], *P* = .49). Time to reach full feeds was lesser in their study, but neonates in their study were relatively heavier (mean weight of 1210 g in 3-h group and 1249 g in 2-h group) than those in our study (mean weight

of 1176 g in 3-h group and 1139 g in 2-h group). Our findings were also in conformity with the findings by Rüdiger et al[7]; median (range) time until complete enteral feeding (26 [7–69] vs 20 [12–58]) was not significantly different.

There was no statistically significant difference in other secondary outcomes (Table 2). Incidence of hypoglycemia in our study was low; one in each group. This may be because the neonates randomized in our study were relatively stable and were followed up for incidence of hypoglycemia only till they reached full feeds or 28 days of postnatal age (whichever was later). The incidence of apnea was also low; 1 in 3-h group and 0 in 2-h group. In our unit, we have a standard policy that all neonates ≤ 34 weeks receive prophylactic caffeine citrate from day 1 of birth.

In our study, we found that time spent per neonate per day for feeding is significantly less in the 3-h groups compared with the 2-h groups. Dhingra, et al[6] also reported similar kind of findings.

Neonates who are fed only 8 times a day (3-h) are less likely to be handled or disturbed compared with those who are fed 12 times (2-h) a day. Lam et al[8] observed that when the number of patient contacts decreases from 2.8 to 1.8 per patient per hour, the healthcare infection rate decreased significantly from 11.3 to 6.2 per 1000 patient days. However, the screen-positive or culture-positive sepsis rate was not different in our study between the 2 groups.

After a post hoc subgroup analysis, we observed that the time taken to reach full feeds in neonates weighing ≤ 1000 g, fed 2-h was significantly less by a mean of 2.9 days (mean difference [95% CI]: - 2.92 [- 0.12, - 5.72]; P = .04). Our findings were in accordance with the findings by DeMauro et al.[9] They observed that the neonates fed 2-h reached full feeds 2.7 days sooner than the neonates fed 3-h (95% CI: 1.5, 3.9). We also did a subgroup analysis for various important outcomes, namely, incidence of feed intolerance, hypoglycemia, and apnea. There was no statistically significant difference in the weight between the 2 weight strata (Table 3). It is important to note that our study was not equipped adequately for these outcomes of this subgroup analysis.

It may be preferable to feed neonates weighing ≤ 1500 g 3-h for practical convenience. However, 2-h feeding schedules may be better in neonates weighing ≤ 1000 g, but adequately powered studies are needed to recommend the same.

Key Messages

What is already known: There is wide variation in the feeding schedule in ELBW and VLBW neonates.

What this study adds: In VLBW neonates, a 3-h feeding schedule is as effective as a 2-h feeding schedule for time to reach full feeds.

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All authors were involved in the management of patients, designing of the study, drafting the article, and analysis and interpretation of data. The authors thank the parents of the neonates who were part of this study.

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