Accepted Manuscript online: 2023-04-14 Article published online: 2023-05-19

Comparison of Three Modalities of Feeding in Preterm Infants ≤32 Weeks and ≤1,250 G: A Randomized Controlled Trial

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Am J Perinatol 2024;41(suppl S1):e1792–e1799.

Abstract

Objective Early establishment of enteral feeds is desirable in very preterm infants, but it may be associated with feeding intolerance. Several feeding methods have been studied with no strong evidence to suggest the preferred feeding method to establish early full enteral feeds. We studied three modalities of feeding in preterm infants ≤32 weeks and ≤1,250 g: continuous infusion (CI), intermittent bolus by infusion (IBI), and intermittent bolus by gravity (IBG) for their effect on time to reach full enteral feeds of 180 mL/kg/d.

Study Design We randomized 146 infants, 49 infants in each CI and IBI group and 48 infants in the IBG group. In the CI group, feeds were delivered by an infusion pump continuously over 24 hours. In the IBI group, feeds were given every 2 hours and infused over 15 minutes by an infusion pump. In the IBG group, feeds were delivered by gravity over 10 to 30 minutes. The intervention was continued till infants reached direct breast/cup feeds.

Results The mean (standard deviation) gestation in CI, IBI, and IBG groups were 28.4 (2.2), 28.5(1.9), and 28.6 (1.8) weeks, respectively. The time to reach full feeds in CI, IBI, and IBG were not significantly different (median [interquartile range]: 13 [10–16], 11.5 [9–17], and 13 [9.5–14.2] d, respectively, $p = 0.71$). The proportions of infants who developed feeding intolerance in CI, IBI, and IBG were similar (n [%]: 21 [51.2%], 20 [52.6%], and 22 [64.7%], respectively, $p = 0.45$). There was no difference in necrotizing enterocolitis ≥2 ($p = 0.80$), bronchopulmonary dysplasia ($p = 0.86$), intraventricular hemorrhage ≥2 ($p = 0.35$), patent ductus arteriosus requiring treatment ($p = 0.44$), retinopathy of prematurity requiring treatment ($p = 0.51$), and growth parameters at discharge.

Conclusion In preterm infants, ≤32 weeks of gestation and birth weight ≤1,250 g, there was no difference in time to reach full enteral feeds in the three modalities of feeding. This study is registered with Clinical Trials Registry India (CTRI) and the registration number is CTRI/2017/06/008792.

Keywords
- feeding intolerance
- growth velocity
- very low birth weight infants
- feeding methods

received
November 25, 2022
accepted after revision
April 12, 2023
accepted manuscript online
April 14, 2023
article published online
May 19, 2023

DOI https://doi.org/10.1055/a-2074-1960.
ISSN 0735-1631.

Key Points

- Gavage feeding in preterm infants is either continuous or intermittent bolus feeding.
- Intermittent bolus feeding was evaluated in a controlled time by infusion over 15 minutes.
- The time to reach full feeds was comparable for all three methods.

Adequate nutrition for very preterm infants is essential for optimal growth and neurodevelopmental outcomes. Nutrition can be provided by either the parenteral or enteral route. Provision of enteral nutrition is desirable but fraught with the risk of feeding intolerance.[1,2] Feeding intolerance is frequently encountered, causing feeding disruptions and delays in reaching full feeds. Several feeding methods are practiced to reduce feeding intolerance. The feeding methods used in preterm infants are continuous infusion (CI) or intermittent bolus by gravity (IBG).[3] Bolus feeding stimulates cyclic surges of gastrointestinal tract hormones; it may promote motility, maturation of intestinal lining, and enhance protein anabolism.[4–7] In a busy neonatal intensive care unit (NICU) setting, bolus feeds may be given inadvertently in a much shorter time despite recommendations from the World Health Organization to feed over 10 to 30 minutes.[8] This can be avoided by delivering bolus intermittent feeds by an infusion pump in which the duration can be controlled. The functional limitations of the premature infant's gastrointestinal system, such as delayed gastric emptying or intestinal transit, could hinder its ability to handle bolus feeds.[4–7,9,10] Alternate method of feeding these infants is by CI, which has the potential benefit of enhancing duodenal motor function and improving feeding tolerance.[4,11,12,] At the same time, the CI has shown a significant fat loss in simulation studies, which might impact infant growth parameters.[13–15]

Although there are several feeding methods that have the physiological basis and biological plausibility to improve feed tolerance, only a few have been subjected to experimental validations through randomized controlled trials (RCT).[9,10,16–22] Some trials have compared intermittent bolus feeding with CI feeds, but the results are inconsistent.[17–19,21,22] Cochrane metanalysis comparing bolus versus continuous feeds in very low birth weight infants concluded that the current evidence is inconclusive for determining an optimum feeding strategy because of the small sample size and methodological limitations.[3] In addition, no clinical trials have systematically evaluated intermittent bolus feeding given in a controlled time by infusion. With this background, we compared three modalities of feeding: CI, intermittent bolus by infusion (IBI), and IBG in very preterm infants for their effect on time to reach full enteral feeds, growth parameters, and morbidities.

Materials and Methods

Trials Design, Settings, and Participants

This RCT was done in a neonatal intensive care unit of a tertiary care center in northern India from July 2015 to May 2017. Infants ≤32 weeks and with birth weight ≤1,250 g, in whom orogastric feeds were started within 72 hours of birth, were included. Those born with significant congenital anomalies (gastrointestinal anomalies or lethal malformations) were excluded.

Randomization and Blinding

Infants were randomly assigned to one of the three groups: group A, CI; group B, IBI; and group C, IBG. This was done by an independent investigator using a computer-generated random number table using a variable block size of 3, 6, or 9. The allotment was performed by using sealed, sequentially numbered, opaque envelopes. The nature of the intervention prevented us from blinding.

Intervention

In the CI group, feeds were delivered by an infusion pump continuously over 24 hours. The syringe was loaded with expressed human milk every 6 hours or freshly prepared formula every 2 hours. In IBI group, milk was given every 2 hours and infused over 15 minutes by an infusion pump. In the IBG group, milk was given every 2 hours over 10 to 30 minutes by gravity. The intervention was continued till the infant reached total direct feeds. Total direct feeds were defined as feeding directly from the mother's breast or supplemented with a cup, the volume being ad libitum without the need for an orogastric feed. This was usually attempted at 33 to 34 weeks' postmenstrual age (PMA), depending on the infant's clinical status.

Feeding Protocol

Infants weighing 1,000 to 1,250 g were started on feeds at a volume of 80 mL/kg/d (total enteral nutrition), and the increment was done at a rate of 20 mL/kg/d till infants reached full enteral feeds of 180 mL/kg/d. Infants with absent/reversed end diastolic flow in antenatal doppler, perinatal asphyxia (Apgar's score ≤3 at 5 min), or those who were initially hemodynamically unstable (requiring inotropes) were kept nil per oral for 24 to 48 hours as per clinical status. Incremental feeding regimes, as mentioned below, were subsequently started in these infants. Infants weighing <1,000 g or severe small for gestational age (SGA, <3rd centile) were started on parenteral nutrition and minimal enteral feeds at a volume of 10 to 20 mL/kg/d on day 1. Parenteral nutrition was started at a fluid rate of 80 to 100 mL/kg/d with total calories of 60 to 70 kcal/kg/d, amino acids of 2 to 2.5 g/kg/d, and lipids of 1 to 2 g/kg/d. Fluids/feeds were increased at a rate of 20 mL/kg/d as per clinical discretion. Parenteral nutrition was continued until a 100 mL/kg/d feed volume was achieved. Every attempt was made to give mother's own milk. In case of its nonavailability, preterm formula containing 1.8 g of protein and 79 calories in 100 mL

was used. Expressed human milk was collected and stored as per standard protocol. The milk was fortified with the bovine milk fortifier (FM 85; Nestle, Vevey, Switzerland) once the infant reached a feed volume of 100 mL/kg/d. The fortification was continued till the infant was feeding completely from the mother's breast or till discharge. Feed volume was advanced till the infant reached a volume of 180 mL/kg/d. The intervention was continued till the infants reached total direct feeds as defined earlier. Feeding intolerance was defined as the presence of any of the following: increase in abdomen girth >2 cm in between feeds, presence of abdominal signs such as abdominal wall discoloration, erythema, or tenderness, and presence of hemorrhagic or bilious residuals. Gastric residuals were not checked routinely unless abdominal girth increased by >2 cm in between feeds. Nil per oral hour was calculated.

Outcome Assessment

The primary outcome was time taken to reach full feeds, i.e., feed volume of 180 mL/kg/d, and tolerated for at least 48 hours. It was calculated from the day feeding was initiated. Secondary outcomes were episodes of feeding intolerance, nil per oral hours, time to regain birth weight, the proportion of infants who developed necrotizing enterocolitis (NEC) stage 2 or beyond,[23] bronchopulmonary dysplasia (BPD; oxygen requirement at 36 wk of PMA),[24] patent ductus arteriosus (PDA) requiring either medical or surgical treatment, retinopathy of prematurity (ROP) requiring treatment, and intraventricular hemorrhage (IVH) ≥2 on cranial ultrasound,[25] culture-proven late-onset sepsis, growth velocity (GV) at the stoppage of intervention and discharge, duration of hospital stay, and all-cause mortality.

Naked weights of infants at approximately the same time of the day were measured using electronic balance scales that were accurate to 5 g (Sunrise Digital Baby Scale). The weighing scale was calibrated every 6 months and maintained in a logbook. Occipitofrontal circumference (OFC) and length were recorded weekly till the time of discharge. OFC was measured using a paper tape placed across the frontal bones above the eyebrows and over the occipital prominence on the back of the head. Infantometer was used to measure length to the nearest of 1 mm. The average of the two independent measurements for OFC and length was taken. Weight GV was noted by the 2-Point Average Weight model from time to regain birth weight till discharge. It was calculated by dividing the total weight difference at 2 points by the number of days and average weight. Length difference from birth to discharge weekly was noted to calculate length increment per week. OFC gain per week was calculated from birth till discharge.

Sample Size Calculation

The sample size was calculated from a previous study done in our institute.[26] The mean duration to reach full feeds in infants ≤1,250 g was 10.6 days with a standard deviation (SD) of 5.7 days. A total of 171 infants with 57 infants in each group were required to detect a difference of 3 days to reach full feeds with a power of 80% and a two-sided significance of 5%.

Statistical Analysis

Data were analyzed using SPSS software version 19. Quantitative data with normal distribution were compared using the Student's *t*-test and one-way analysis of variance test as applicable. Quantitative data with skewed distribution were analyzed using the Mann–Whitney U test. Nonquantitative data were compared using the chi-square or the Fischer's exact test. Time to event was analyzed by using the Kaplan–Meier survival analysis. A two-sided *p*-value of less than 0.05 was considered significant.

Ethics Approval

The trial was approved by the institutional ethics committee and registered with the Clinical Trial Registry of India. Written informed consent was obtained from parents of eligible infants at the time of initiation of feeds.

Results

A total of 185 eligible infants were screened for enrollment. Among these infants, 39 were excluded due to various reasons (►Fig. 1). A total of 146 infants were randomized, 49 infants each in CI and IBI group and 48 infants in IBG group. Of these, 113 infants could reach the primary outcome and were analyzed. The baseline characteristics in the three groups were comparable. The mean (SD) gestation in CI, IBI, and IBG group were 28.4 (2.2), 28.5 (1.9), and 28.6 (1.8) weeks, respectively. The mean (SD) birth weight was 962 (196.3), 974 (184.0), and 961 (171.2) g in CI, IBI, and IBG group, respectively. The proportion of SGA infants and those with antenatal doppler showing absent/reversed end diastolic flow were comparable (►Table 1). Time to reach full feeds in the CI, IBI, and IBG group was similar (median [interquartile range]: 13 [10–16], 11.5 [9–17], and 13 [9.5–14.2] d, respectively, $p = 0.71$; ►Table 2). The proportion of infants who developed feeding intolerance in the CI, IBI, and IBG group were similar. There was no difference in time to regain birth weight and other growth parameters at discharge (►Tables 2 and 3). Other morbidities like the length of hospital stay, late-onset sepsis, NEC ≥2, BPD, IVH ≥2, PDA requiring treatment, ROP requiring treatment, and mortality were similar (►Table 4). In subgroup analysis in infants weighing ≤1,000 g, there was no difference in the feeding, growth-related outcomes, and duration of hospital stay (►Table 5).

Discussion

The primary objective of our study was to evaluate the three modalities of feeding, i.e., by CI, IBI over a period of 15 minutes and IBG in very preterm infants ≤32 weeks' gestation or ≤1,250 g birth weight for their impact on time to reach full enteral feeds. We included intermittent feeding by infusion pump as an innovative feeding method with the premise that in a busy intensive care unit, delivering

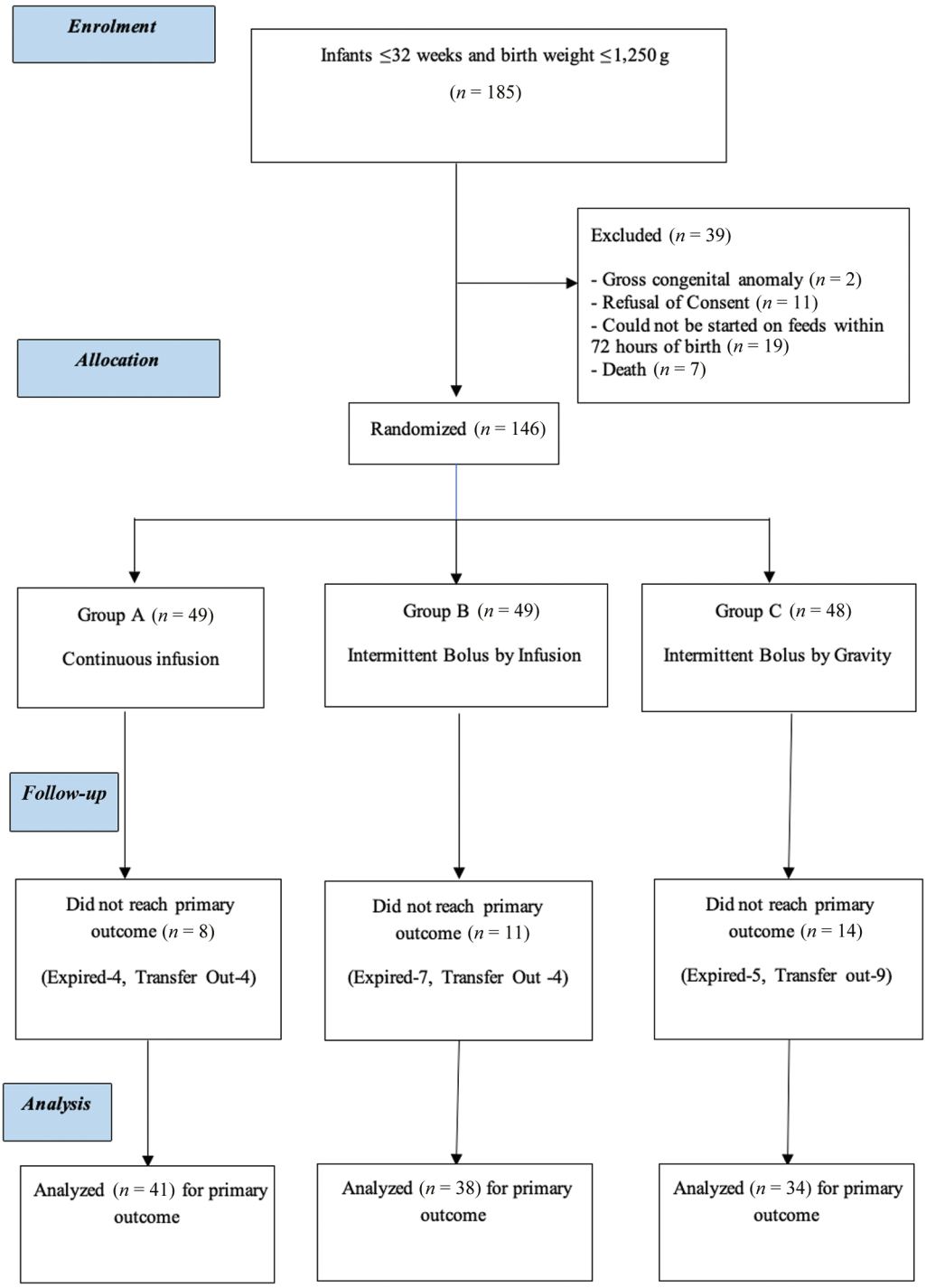

Fig. 1 Flowchart of infant enrollment.

intermittent feeding by gravity within the recommended duration may be a challenge. No randomized controlled studies have systematically evaluated these three methods to assess feed tolerance in preterm infants. Although multiple trials have been conducted on continuous feeding versus intermittent bolus feeding by gravity, the results are conflicting and inconclusive.

In our study, there was no difference in the time (days) to reach full feeds in the three groups. Both bolus and continuous feeding strategies have some physiological advantages, but these did not translate into a clinically significant outcome of earlier achievement of full enteral feeds. Akintorin et al[17] randomized a similar cohort of preterm infants with birth weight 700 to 1,250 g in two groups: continuous versus intermittent bolus feeding by gravity. There was no difference in the days to reach 100 kcal/kg/d for at least 48 hours. A similar intervention done by Silvestre et al[18] did not find a difference in days to reach full feeds in the two groups. Our results are consistent with the findings of these two RCTs, which included similar cohorts and comparable

Table 1 Baseline characteristics

Baseline characteristics	Group A CI ($n = 49$)	Group B IBI ($n = 49$)	Group C IBG ($n = 48$)	*p*-Value
Gestation (wk)[a]	28.4 (2.2)	28.5 (1.9)	28.6 (1.8)	0.91
Birth weight (g)[a]	962 (196.3)	974 (184.0)	961 (171.2)	0.92
Male	25 (51.0%)	27 (55.1%)	23 (47.9%)	0.77
SGA	9 (18.4%)	13 (26.5%)	11 (22.9%)	0.62
Vaginal delivery	13 (26.5%)	10 (20.4%)	11 (22.9%)	0.82
Complete ANS	40 (81.61%)	33 (67.3%)	39 (81.2%)	0.13
Gestational hypertension	19 (38.8%)	10 (20.4%)	18 (37.5%)	0.09
A/REDF	9 (18.4%)	10 (20.4%)	11 (22.9%)	0.85
Multiple gestation	19 (38.8%)	21 (42.9%)	19 (39.5%)	0.68
PPV at birth	10 (20.4%)	7 (14.3%)	8 (16.7%)	0.40

Abbreviations: A/REDF, absent/reversed end diastolic flow; ANS, antenatal steroids; CI, continuous infusion; IBG, intermittent bolus by gravity; IBI, intermittent bolus by infusion; PPV, positive pressure ventilation; SGA, small for gestational age.
Note: All values are expressed as *n* (%) unless specified otherwise.
[a]Mean (standard deviation).

Table 2 Outcomes in infants who reached primary outcome

Outcomes	Group A CI ($n = 41$)	Group B IBI ($n = 38$)	Group C IBG ($n = 34$)	*p*-Value
Full feeds (d)[a]	13 (10–16)	11.5 (9–17)	13 (9.5–14.2)	0.71
100 mL/kg/d (d)[a]	7 (5–11)	6 (4–12)	9 (5–10.2)	0.76
Duration of PN[a]	8 (6–13)	10 (7–14)	9 (6–12)	0.81
TBW (d)[a]	9 (6–12)	11 (6.5–13)	10 (7–12)	0.38
DOI day[a]	37 (28–55)	43 (27.5–57.5)	35 (25–57)	0.70
Feeding intolerance, *n* (%)	21 (51.2%)	20 (52.6%)	22 (64.7%)	0.45
NPO hours[a]	60 (22–102)	56 (10–102)	48 (18–120)	0.69
EHM (%)	63.3	62.1	66.1	0.53

Abbreviations: CI, continuous infusion; DOI, duration of Intervention; EHM, expressed human milk percent of total milk consumed during neonatal intensive care unit stay; IBG, intermittent bolus by gravity; IBI, intermittent bolus by infusion; NPO, nil per oral; PN, parenteral nutrition; TBW, time to regain birth weight.
[a]Median (interquartile range).

Table 3 Growth characteristics

At discharge	Group A CI ($n = 40$)	Group B IBI ($n = 37$)	Group C IBG ($n = 33$)	*p*-Value
Weight growth velocity (g/kg/d)	13.6 (3.3)	13.2 (3.6)	14.1 (2.9)	0.57
Length increment (cm/wk)	0.73 (0.17)	0.75 (0.17)	0.77 (0.17)	0.70
OFC gain (cm/wk)	0.66 (0.12)	0.61 (0.14)	0.62 (0.14)	0.34

Abbreviations: CI, continuous infusion; IBG, intermittent bolus by gravity; IBI, intermittent bolus by infusion; OFC, occipitofrontal circumference.
Note: Variables expressed as mean (standard deviation).

interventions. Similar findings were observed by Rövekamp-Abels et al,[21,22] who enrolled infants with higher birth weight (<1,750 g) in comparison to our study.

Two randomized trials have shown conflicting results and favor either continuous or intermittent feeding methods. Dsilna et al[10] randomized preterm infants 24 to 29 weeks' gestation and birth weight <1,200 g in three groups: continuous nasogastric, intermittent nasogastric, and intermittent orogastric feeds. Infants who received continuous feeds reached full feeds earlier as compared with both intermittent groups taken together. Further, the authors reported that infants with birth weight <850 g randomized to the continuous feeding group had greater benefits in terms of reaching full feeds than the whole cohort. On the other hand, another

Table 4 Other secondary outcomes

Outcome	Group A CI ($n = 49$)	Group B IBI ($n = 49$)	Group C IBG ($n = 48$)	*p*-Value
Length of hospital stay[a]	44 (29.5–62.5)	50 (32.5–70)	43 (26–64.7)	0.58
Late-onset sepsis	25 (51%)	23 (46.9%)	20 (41.7%)	0.65
NEC $\geq$ stage 2	1 (2%)	2 (4.1%)	2 (4.2%)	0.80
BPD	8 (16.3%)	10 (20.4%)	8 (17.4%)	0.86
IVH $\geq$ grade 2	0 (0%)	1 (2.0%)	2 (4.2%)	0.35
PDA requiring treatment	1 (2.0%)	1 (2.0%)	1 (2.2%)	0.44
ROP requiring treatment	3 (6.1%)	4 (8.2%)	1 (2.2%)	0.51
Mortality	4 (8.2%)	7 (14.3%)	5 (10.4%)	0.77

Abbreviations: BPD, bronchopulmonary dysplasia; CI, continuous infusion; IBG, intermittent bolus by gravity; IBI, intermittent bolus by infusion; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.
Note: Variables expressed as *n* (%) unless specified otherwise.
[a]Median (interquartile range).

Table 5 Outcomes related to feeds in infants $\leq$1,000 g

Outcomes	Group A CI ($n = 19$)	Group B IBI ($n = 20$)	Group C IBG ($n = 18$)	*p*-Value
Full feeds (d)[a]	15 (15–20)	14.5 (9.2–18.5)	14 (11.7–18)	0.24
100 mL/kg/d (d)[a]	10 (6–13)	8.5(5–12)	10 (6–12.5)	0.44
Duration of PN[a]	11 (8–15)	10 (7–14)	11 (6–15.7)	0.57
TBW (d)[a]	10 (6–12)	13 (9–18)	11.5 (7–14)	0.25
Feeding intolerance, *n* (%)	12 (63.2%)	13 (65.0%)	15 (83.3%)	0.33
NPO hours[a]	96 (49–150)	46 (11–102)	72 (30–147)	0.15
NEC $\geq$ 2, *n* (%)	0 (0%)	2 (10%)	1 (5.6%)	0.37
DOI day[a]	51 (39–86)	56 (50–76)	55 (38.2–64.7)	0.80
Length of hospital stay[a]	72 (50–103)	68 (59–84)	60 (46–86)	0.60

Abbreviations: CI, continuous infusion; DOI, duration of intervention; IBG, intermittent bolus by gravity; IBI, intermittent bolus by infusion; NEC, necrotizing enterocolitis; NPO, nil per oral; PN, parenteral nutrition; TBW, time to regain birth weight.
[a]Median (interquartile range).

RCT by Dollberg et al[9] showed results in favor of intermittent bolus feeds over continuous feeds. They enrolled infants <1,250 g and observed that infants in the intermittent bolus group reached full feeds 8 days earlier than continuous feeds. However, this was a small pilot study in which only 28 infants were randomized. Cochrane meta-analysis[3] included these studies and found no difference in time to achieve full enteral feeds. On the contrary, in a recent metanalysis, Wang et al included one additional study[21,22] and reported that the time to reach full feeds was longer in continuously fed infants than in intermittent bolus fed infants.[27] The discrepancy in findings of these two metanalysis calls for well-designed randomized controlled studies to guide an optimum feeding strategy in very preterm infants.

Tolerance to achieve full feeds and successful weaning from parenteral fluids are important determinants of clinical outcomes in preterm infants. In our study, there was no difference in the proportion of infants who developed feeding intolerance or duration of nil per oral hours in the three groups. Various authors have defined feeding intolerance differently but have not observed differences in continuous or bolus feeding methods.[16,17,19,20] In contrast, Rövekamp-Abels et al[21,22] observed less gastric residual volume and feed interruptions in the bolus feeding method. We also did not find significant differences in other secondary outcomes like days to reach feed volume of 100 mL/kg/d, duration of parenteral nutrition, time to regain birth weight, length of hospital stays, and proportions of infants who developed NEC.

Growth in preterm infants is an important clinical outcome and has been evaluated in most studies that have compared various feeding strategies. In our study, there was no difference in weight GV (g/kg/d), length increment (cm/wk), and OFC gain (cm/wk) in the three groups. Three other studies have reported similar results.[16,18,20] On the contrary, Schanler et al[19] observed that infants fed by the continuous feeding method gained weight slower than infants fed by the intermittent bolus feeding method. Preclinical studies have shown that there is a greater loss of fat in the CI method, postulating poor weight gain.[13–15]

Cochrane systematic review[3] on continuous and intermittent feeding methods in preterm infants observed a trend toward early discharge for infants less than 1,000 g birth weight with results favoring the continuous feeding method. With this background, we performed a subgroup analysis to evaluate the impact of three feeding strategies in infants <1,000 g birth weight. Contrary to the meta-analysis, we did not find a difference in the duration of hospital stay in the three groups.

The strength of our study is that we compared a novel method of intermittent feeding by infusion given over a stipulated period with other conventional feeding methods. In addition, we had an evidence-based aggressive feeding strategy derived from our unit's experience[28] and contemporary publications.[29,30] Feeding protocol and feeding intolerance were well-defined to maintain uniformity in the study. However, our study had certain limitations. Intervention could not be blinded, and the study sample size could not be completed. The calculated sample size was 171 infants, but we could randomize only 146 infants because this study was time-bound, being part of a postgraduate dissertation. In addition, due to the high transfer out and mortality rates, only 113 infants could reach the primary outcome. We also found that the growth parameters of enrolled infants were below recommended norms.[31] This could be due to fortification commencement after infants reached 100 mL/kg/d of feeds, slow increments of feeding at 15 to 20 mL/kg/d, and a significant proportion of severe SGA infants. A more aggressive fortification and a larger incremental regime would probably have resulted in better growth.

Conclusion

In preterm infants ≤ 32 weeks of gestation and birth weight ≤ 1,250 g, there was no difference in time to reach full enteral feeds in the three feeding methods: continuous feeding or intermittent feeding by infusion pump or intermittent feeding by gravity. Other feeding-related outcomes, growth parameters, and clinical morbidities were also similar.

Trial Identification Number

This study is registered with Clinical Trials Registry India (CTRI) and the registration number is CTRI/2017/06/008792.

Authors' Contributions

V.K. and A.T. conceptualized and designed the study, supervised the data analyses, drafted the initial manuscript, reviewed, and revised the manuscript. N.K. and P.G. conceptualized the study and reviewed and revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

The authors are very grateful to the NICU nurses who were involved in the care of the infants and the families who participated in the study.

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