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REGULAR ARTICLE

# Slow versus rapid enteral feeding advancement in preterm newborn infants 1000–1499 g: a randomized controlled trial

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**Abstract**

Aim: To evaluate whether preterm neonates weighing 1000–1499 g at birth receiving rapid enteral feeding advancement at 30 mL/kg/day attain full feedings (180 mL/kg/day) earlier than those receiving slow enteral feeding advancement at 20 mL/kg/day without increase in the incidence of feeding intolerance or necrotizing enterocolitis.

Methods: A total of 100 stable intramural neonates weighing between 1000 and 1499 g and gestational age less than 34 weeks were randomly allocated to enteral feeding (expressed human milk or formula) advancement of 20 mL/kg/day (n = 50) or 30 mL/kg/day (n = 50).

Results: Neonates in the rapid feeding advancement group achieved full volume feedings before the slow advancement group (median 7 days vs. 9 days) ($p < 0.001$), had significantly fewer days of intravenous fluids (median 2 days vs. 3.4 days) ($p < 0.001$), shorter length of stay in hospital (median 9.5 days vs. 11 days) ($p = 0.003$) and regained birth weight earlier (median 16 days vs. 22 days) ($p < 0.001$). There were no statistical differences in the proportion of infants with apnea, feed interruption or feed intolerance.

Conclusion: Rapid enteral feeding advancements of 30 mL/kg/day are well tolerated by stable preterm neonates weighing 1000–1499 g.

## INTRODUCTION

Enteral feeding routines are not well defined in preterm neonates. Controversy exists regarding how fast to advance enteral feedings (1–4). A relatively more rapid advancement of enteral feedings in preterm infants may improve their growth and nutritional status (4–6), decrease the requirement and hazards of intravenous infusion solutions (5) and potentially shorten the length of hospitalization (5,7). Many of the published studies on feeding advancements are based on retrospective data or small sample size (1,3,8–12). Randomized controlled trials conducted so far (3–6) have not demonstrated any increased risk of necrotizing enterocolitis (NEC) in the rapid feed advancement groups. However, in view of the heterogeneity in study design, sample size, methodology and definitions used in these trials, their results may not be universally applicable. Moreover, most of these trials (3–5) were conducted in developed nations. The only trial from a developing country (6) precluded any firm conclusion on the risk of NEC and rapid enteral feeding, owing to small sample size. A recently published Cochrane meta-analysis (7) concluded that further randomized controlled trials are needed to determine the effect of increase in enteral feed volumes on important clinical outcomes, including the risk of NEC, in preterm infants. We therefore, conducted the present study to address these issues, especially in the context of developing countries.

## METHODS

We included all intramural neonates born between February and September 2008 with birth weight 1000–1499 g and gestational age less than 34 weeks. Gestational age was assessed primarily using the last menstrual period, supported by modified Ballard Score (13). Babies were excluded from enrolment if any of the following was present: (a) Major congenital anomalies. (b) Respiratory distress (respiratory rate >60 per minute at the time of initiation of feeds and enrolment). Infants were enrolled and feeds initiated only after subsidence of respiratory distress. Respiratory distress lasting more than 5 days was however, an absolute exclusion criterion. (c) Requirement of vasopressor support to maintain blood pressure at the time of initiation of feeds. (d) Severe birth asphyxia (Apgar score less than 3 at 1 min). (e) Infants requiring venous or arterial umbilical catheterization at the time of enrolment into the study. (f) Requirement of mechanical ventilation. (g) Infants not fit for enteral nutrition (abdominal distension, vomiting, poor or exaggerated bowel sounds, gastrointestinal bleeding).

### Randomization and allocation concealment

All eligible infants were randomized by computer generated simple randomization sequence to receive slow or fast feeding protocols. Allocation was concealed by opaque sealed envelope technique. The investigators were not blinded to the interventions.

**Slow advancement group**
Feeding was initiated on the first day with 20 mL/kg/day of expressed human milk (EHM) or standard formula of 20 kcal/30 mL (Dexolac; Wockhardt Ltd., Mumbai, India) (when EHM was not available) and advanced by 20 mL/kg/day until maximum enteral feeds of 180 mL/kg/day were attained.

**Rapid advancement group**
Feeding was initiated on the first day with 20 mL/kg/day of EHM or standard formula of 20 kcal/30 mL (Dexolac; Wockhardt Ltd.) (when EHM was not available) and advanced by 30 mL/kg/day until maximum enteral feedings of 170 mL/kg/day were attained. On the last day, the feeds were increased from 170 to 180 mL/kg/day.

**Mode of feeding**
All feeds were given as bolus by nasogastric tube at 2-h intervals. Abdominal girth charting was performed before every feed. If the abdominal girth increased by more than 2 cm between the feeds, gastric aspiration was performed (6). If the gastric aspirate was 25–50% of the pre-feed volume, no further increment in feed was made for the next 24 h. Parenteral nutrition was not used as facilities for proper preparation, mixing and delivery of the same are not available in our setting.

**Temporary discontinuation of feeds**
Any of the following conditions was a reason to discontinue feeds temporarily: (a) Feed intolerance (defined as one or more of the following: residual gastric contents of more than 50% of pre-feed volume, vomiting more than three times in any 24-h period, bile or blood stained vomiting, abdominal tenderness, abdominal wall erythema, decreased bowel sounds, abdominal girth increase by more than 2 cm between feeds, gross/occult blood in stools), (b) recurrent apnea (more than three apneas after 1 h of age) (14), (c) neonatal seizure, (d) requirement of mechanical ventilation, (e) requirement of vasopressors. Simultaneously, the patient was investigated for NEC and sepsis (abdominal radiographs, stool for occult blood, sepsis screen, blood culture). Abdominal radiographs were interpreted by a radiologist who was unaware of the group assignment. If investigations for NEC were negative, feeds were resumed at half the volume the patient was receiving at the time of order to receive nil per os, and then advanced according to their initial group assignment (20 or 30 mL/kg/day). Patients with recurrent apnea, neonatal seizure, mechanical ventilation, gastric aspirates or vomiting were also treated similarly. If the patient was diagnosed as NEC, he was treated as per standard management protocol for NEC (15). The study end point was the time when patient regained birth weight or development of stage IIA NEC or greater using Bell's staging criteria (15). The time taken to achieve full enteral feeds (defined as 180 mL/kg/day) was considered as the primary outcome variable.

**Discharge from hospital**
The neonates were discharged from the hospital if they met all of the following criteria: (a) A sustained pattern of weight gain at the rate of 10 g/kg/day for at least 3 days. (b) Maintenance of normal body temperature when fully clothed. (c) Competent cup feeding/breast feeding. (d) Review of hospital course was completed; underlying medical problems had been treated. After discharge from the hospital, the patient had a follow-up visit 1 week and 2 weeks later in the outpatient department during which the weight was recorded. Days taken to regain birth weight were recorded.

**Statistical analysis**
To observe a minimum expected difference of 2 days in the mean time taken to achieve full enteral feeds between the two groups with a standard deviation of 2, a power of 90% and a probability of 5%, it was estimated that the study would require a sample size of 46 subjects. Accounting for attrition, it was decided to recruit a total of 100 subjects. Continuous variables with normal distribution were compared using *t*-test, whereas continuous variables not normally distributed were analysed using Mann–Whitney *U*-test. All proportionate data were analysed with Pearson Chi-square test.

**Ethical approval for the study**
Ethical permission to conduct the study was obtained from the Institutional Ethics Committee. Informed parental consent was obtained before enrolment into the study.

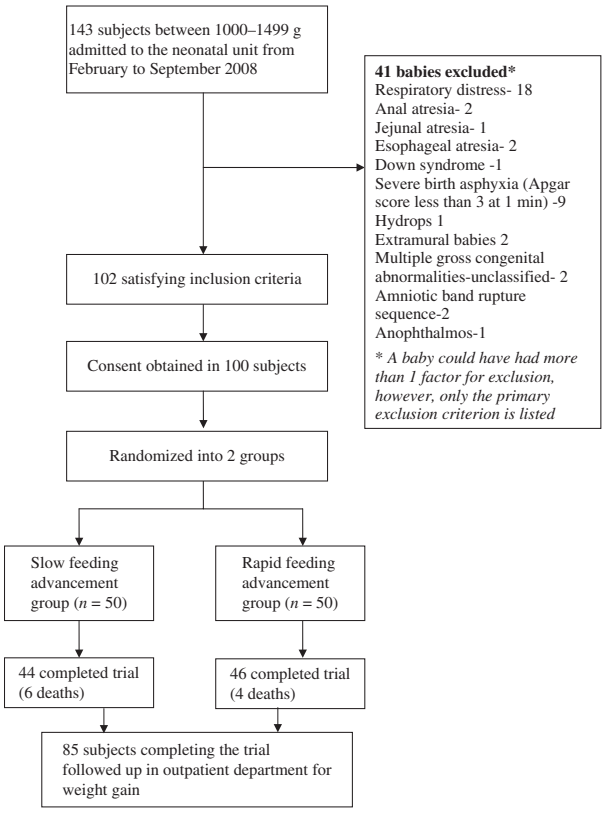


**Figure 1** Flowchart depicting inclusion and follow-up of study subjects.

**Table 1** Demographic variables in the study subjects

| | Slow group (n = 50) | Fast group (n = 50) | p-value |
|---|---|---|---|
| Birth weight (g) (mean ± SD) | 1306.0 ± 129.2 | 1261.4 ± 121.6 | 0.07 |
| Gestational age(weeks) (mean ± SD) | 31.1 ± 1.2 | 30.8 ± 1.1 | 0.2 |
| Gender, n (%) | | | |
| Male | 28 (56) | 26 (52) | 0.69 |
| Female | 22 (44) | 24 (48) | |
| Age at which feedings began (h) (Median, range) | 6.0 (2.0–87.0) | 4.0 (2.0–92.0) | 0.2 |
| Mode of delivery, n (%) | | | |
| Vaginal delivery | 32 (64) | 38 (76) | 0.19 |
| Caesarean Section | 18 (36) | 12 (24) | |
| Intrauterine growth (%) | | | |
| AGA | 40 (80) | 36 (72) | 0.35 |
| SGA | 10 (20) | 14 (28) | |
| Apgar at 1 min (mean ± SD) | 7.4 ± 2.1 | 7.6 ± 1.3 | 0.39 |
| Apgar at 5 min (mean ± SD) | 8.5 ± 1.1 | 8.5 ± 0.9 | 0.51 |
| Apgar at 10 min (mean ± SD) | 8.8 ± 0.7 | 8.9 ± 0.6 | 0.67 |
| No. infants fed with (%) | | | |
| Exclusive human milk | 9 (18) | 6 (12) | 0.62 |
| Human milk + formula | 36 (72) | 37 (74) | |
| Formula only | 5 (10) | 7 (14) | |

## RESULTS

A total of 143 neonates with birth weight between 1000 and 1499 g were admitted to the neonatal unit between February and September 2008. Figure 1 depicts the inclusion and follow-up of study subjects. 100 neonates were enrolled; 50 each were randomized into slow and rapid feeding volume advancement groups respectively. Both groups were similar with respect to baseline demographic parameters (Table 1). Eighty-five babies came for follow-up after discharge (42 in the slow group and 43 in the rapid group).

Six babies in the slow group and 4 in the rapid group died before full volume feeds could be achieved. Neonates in the rapid feeding advancement group achieved full volume feedings earlier. They had significantly fewer days of intravenous fluids ($p < 0.001$), lesser duration of hospital stay ($p = 0.003$) and shorter time to regain birth weight ($p < 0.001$). There were no statistical differences between the two groups in the number of infants with apnea, feed interruption or feed intolerance (Table 2). The incidence of NEC was similar in both groups.

Four babies in the rapid group developed nosocomial sepsis (*Klebsiella* 3, *Escherichia coli* 1), while five in the slow group (*Klebsiella* 3, *E. coli* 1, Coagulase negative *Staphylococcus aureus* 1) developed nosocomial septicaemia. The causes of death in the slow feeding advancement group were *Klebsiella* sepsis (two cases), intraventricular haemorrhage (two cases), pulmonary haemorrhage (one case) and NEC (one case). The causes of death in the rapid feeding advancement group were *Klebsiella* sepsis (one case), NEC (two cases) and intraventricular haemorrhage (one case). There were no significant differences in the demographic characteristics of babies not completing the trial (deaths) versus those who completed the trial (Table S1). Recurrent apnea and increased gastric residuals (>50%) were the most common reasons for feed interruption (Table S2).

## DISCUSSION

Preterm babies require optimal nutritional support because of physiological immaturity, increased nutritional demands and faster growth rates. A major concern related to enteral nutrition of these infants is the development of NEC, as a result of which enteral feedings are often advanced slowly. This practice may be associated with delaying the establishment of full enteral nutrition, which may have implications on the overall costs of neonatal care (16). It may also be associated with infectious and metabolic risks that may have adverse consequences for survival, growth and development (17). Randomized controlled trials as well as the recently published Cochrane meta-analysis (7) do not support the view that rapid enteral feeding advancement leads to NEC. Rayyis et al. (4) did not detect an increase in the

**Table 2** Outcome variables in the study subjects

| | Slow group | Fast group | p-value |
|---|---|---|---|
| Time taken for full enteral feeds (days)* (Median, interquartile range) | 9.0 (9.0–11.0) | 7.0 (7.0–9.5) | <0.001† |
| Duration of intravenous. fluids (days) (Median, interquartile range) | 3.4 (3.0–6.2) | 2.0 (2.0–4.1) | <0.001† |
| Duration of hospital stay (days) (Median, interquartile range) | 11.0 (10.0–15.0) | 9.5 (8.4–13.8) | 0.00† |
| Discharge weight (g) (Mean ± SD) | 1224.7 ± 121.4 | 1195.8 ± 112.7 | 0.22 |
| Days to regain birth weight (Median, interquartile range)‡ | 22.0 (14.0–28.0) | 16.0 (12.0–23.0) | <0.001† |
| NEC cases, n (%)§ | 1 (2) | 2 (4) | 1 |
| No. infants with feed interruption, n (%) | 12 (24) | 8 (16) | 0.34 |
| No. Infants with apnea, n (%) | 14 (28) | 9 (18) | 0.24 |
| No. infants with gastric aspirates >50%, n (%) | 5 (10) | 4 (8) | 0.73 |
| Mortality (%) | 6 (12) | 4 (8) | 0.51 |
| Maximum weight loss (percentage of birth weight) (Mean ± SD) | 9.2 ± 0.5% | 8.1 ± 0.3% | 0.04† |
| Day by which maximum weight loss occurred (Median, Interquartile range) | 8.2 (7.0–11.5) | 7.0 (6.5–10.3) | 0.05† |

*Calculated from neonates who survived and completed the trial.
†p-value significant.
‡Calculated from infants who came for follow-up.
§All these babies died.

incidence of NEC even with feeding advancements of 35 mL/kg/day. Similarly, in trials by Caple et al. (5) and Salhotra et al. (6), feeding advancements of 30 mL/kg/day were not associated with increased incidence of NEC.

We showed in the present study that the rapid enteral feeding advancement group achieved full enteral feeding earlier than the slow feeding advancement group, had fewer days of intravenous fluids and shorter duration of hospital stay. Babies less than 1000 g were excluded as they are often sick, have a higher mortality and may not be appropriate candidates for rapid feeding protocols (6). The incidence of NEC in the study was only 3%. The incidence of NEC in preterm infants weighing 1000–1499 g described in the literature is 5–12% (16). Factors other than rate of feed advancement, such as infection, hypoxia, ischaemia, formula milk (18) and prematurity per se have been considered important in the pathogenesis of NEC (4). Therefore, certain authors argue that the risk of NEC should not be considered in isolation of other potential clinical outcomes while formulating feeding policies and practice for preterm infants (19). Our results did not show any difference between the two groups in the proportion of babies with NEC. However, the study was not powered to detect clinical or statistical differences in the proportion of infants with NEC, as this was not the primary outcome variable.

The strengths of our study are its large sample size and a good follow-up of the discharged patients. The post-hoc power of the study was 95%. Our study adds important information on policy and practice regarding management of these infants. To decrease the effect of potential bias, we defined feeding intolerance by strict criteria. Allocation concealment was ensured, criteria for temporary discontinuation of feedings were set and the radiological diagnosis of NEC was made by a radiologist who was not aware of the group assignment. Our study also had some limitations. The investigators were not masked to the allocated interventions. Masking caregivers and investigators to the nature of these interventions is unlikely to be possible (7). Secondly, a majority of the babies were on mixed human milk and formula feeds. At discharge, however, a majority had made a successful transition to exclusive human milk feedings. Thirdly, the median difference in the time to regain birth weight must be interpreted with caution given the non-blinded design and absence of data regarding feeding practice post-discharge. Fourthly, as we did not routinely use parenteral nutrition for the enrolled subjects, time to regain birth weight could be affected by a catabolic state because of a deficit in early protein intake in this age group. Finally, one must be cautious while extrapolating our results to all preterm neonates. Infants who are sick, asphyxiated or haemodynamically unstable may not tolerate rapid enteral feeding. Although the study shows short-term tolerability of rapid feeding protocols in a cohort, results should be interpreted with care given the lack of long-term data to assess the impact of rapid versus slow feed advancement.

We used intermittent nasogastric feeding in the present study. Universal recommendations regarding the best tube feeding method for premature infants less than 1500 g are not available (20). While some studies have shown that continuous gavage feedings are more beneficial in promoting gastrointestinal tolerance and growth (21), others have shown that these infants achieve similar growth patterns whether they are fed continuous or intermittent feedings (22).

To conclude, our results support rapid enteral feeding protocols (increments of 30 mL/kg/day) for enteral nutrition of stable preterm neonates weighing 1000–1499 g.

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None.

**COMPETING INTERESTS**

None stated.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1** Comparison of demographic characteristics of neonates who completed the trial versus those who did not complete the trial (deaths)

**Table S2** Reasons for discontinuation of feedings in both the groups

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