RESEARCH PAPER

Early Aggressive Enteral Feeding in Neonates Weighing 750-1250 Grams: *A Randomized Controlled Trial*

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Background: In preterm neonates, enteral feeding is advanced slowly, considering the risk of necrotizing enterocolitis. Prolonged intravenous alimentation in these neonates, however, may increase the risk of sepsis-related morbidity and mortality, particularly in low resource settings.

Objectives: Objective of this was study to evaluate impact of aggressive enteral feeding on mortality and morbidities among preterm neonates.

Design: Randomized controlled trial.

Participants: Neonates with birthweight 750-1250 g.

Interventions: 131 preterm neonates with birth weight 750-1250 g, admitted to neonatal intensive care unit between April 2012 and June 2014, were randomized to aggressive feeding or conservative feeding regimen.

Outcomes: The primary outcome of the study was all-cause mortality during hospital stay. The secondary outcomes included proportion of sepsis (blood culture proven), necrotizing enterocolitis, feed intolerance, survival without major morbidity at discharge, time to reach full enteral feed (180 mL/kg/d), duration of hospitalization, and average daily weight gain (g/kg).

Results: All-cause mortality was 33.3% in aggressive regimen and 43.1% in conservative regimen, [RR (95%) CI 0.77 (0.49, 1.20)]. Neonates with aggressive feeding regimen reached full enteral feed earlier; median (IQR) 7 (6, 8) days compared to conservative regimen, 10 (9, 14) days; *P* <0.001. There was no difference in culture positive sepsis rate, survival without major morbidities, feed intolerance, necrotizing enterocolitis, duration of hospitalization and average daily weight gain.

Conclusions: In neonates with birth weight 750-1250 g, early aggressive feeding regimen is feasible but not associated with significant reduction in all-cause mortality, culture positive sepsis or survival without major morbidities during hospital stay. Neonates with aggressive regimen have fewer days on IV fluids and reach full feed earlier.

Keywords: *Enteral feeding, Morbidity, Mortality, Necrotizing enterocolitis, Prematurity, Sepsis*.

Clinical Trial Registration: CTRI/2014/06/004663.

Aggressive enteral feeding has been considered a potential risk factor for necrotizing enterocolitis (NEC) in very low birth weight (VLBW) neonates [1-3]. This has often delayed the introduction of enteral feeds in very preterm infants and infants weighing less than 1250 grams. The subsequent grading up of enteral feed volumes has been slow, with parenteral nutrition bridging the nutritional gap till achievement of full enteral feeding. The evidence to support this practice is inadequate and weak. On the contrary, this practice could diminish the functional adaptation of the preterm gastrointestinal tract [4,5]. Prolonged exposure to parenteral nutrition may increase the risk of metabolic complications, bloodstream infections and mortality during neonatal intensive care unit (NICU) stay, and poor subsequent growth and neurodevelopmental outcome, especially in low- and middle-income countries [6-10]. The present study was designed to test the hypothesis whether an early aggressive feeding regimen in preterm infants with birth weight 750-250 g would result in a lower mortality and morbidity compared to conservative feeding regimen.

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METHODS

This randomized controlled open label trial was conducted at a medical school affiliated hospital between April 2012 and June 2014. All inborn neonates with a birthweight of 750-1250 g were screened for eligibility. Neonates with gross congenital malformation of the gastrointestinal tract, severe birth asphyxia (Apgar score <3 at 1 min), and those who could not be fed by enteral route for first four days of life were excluded. The protocol of the study was approved by the institutional ethics committee.

The primary outcome of the study was all-cause mortality during hospital stay. The secondary outcomes included sepsis (blood culture proven), necrotizing

enterocolitis (NEC) stage II or more, feed intolerance (presence of one or more of following: distended/tense/ tender abdomen, increase in abdominal girth by >2 cm in a 2-hour interval, hemorrhagic/bilious aspirate), survival without major morbidity (bronchopulmonary dysplasia/ intraventricular hemorrhage grade III or IV/cystic periventricular leucomalacia/ retinopathy of prematurity requiring treatment) at discharge, time to reach full enteral feed (180 mL/kg/d) and average daily weight gain (g/kg/d) during NICU stay, after achieving birthweight. NEC was defined as per modified Bell's staging [11]; bronchopulmonary dysplasia (BPD) was defined as per National Institute of Health consensus definition 2001 [12]; intraventricular hemorrhage (IVH) was defined as per Papile's classification [13]; and periventricular leucomalacia (PVL) was defined as per de Vries classification [14].

Eligible neonates were enrolled after informed written consent of parents. Neonates were randomly assigned to early aggressive feeding regimen (AR) or conservative feeding regimen (CR) using computer generated block randomization sequence of variable block sizes (4, 6 or 8) stratified for birth weight (750-1000 g and 1001-1250 g). Allocation concealment was ensured by placing the sequence in sealed opaque envelopes. Blinding was not possible due to the nature of the intervention,

Neonates were considered eligible for initiating enteral feeds if they were not on any ionotrope support; and if on mechanical ventilation, had a Mean Airway Pressure <14 mbar and/or Fraction inspired Oxygen <0.7; and the abdomen was soft. In the conservative regimen (CR) group neonates with birthweight 750-1000 g were initiated at a feed volume of 15 mL/kg/day, with subsequent advancement by 15 mL/kg/day. Neonates with birth weight 1001-1250 g were initiated at a volume of 20 mL/kg/day feed, with subsequent daily increments of 20 mL/kg/day. In the aggressive regimen (AR), neonates with birthweight 750-1000 g were initiated with 30 mL/kg/day feeds with subsequent increments of 30 mL/kg/day. In neonates with birthweight 1001-1250 g, feed was initiated at 40 mL/kg/day with subsequent daily increments of 40 mL/kg/day. In both treatment arms, feeds were given as 2-hourly interval bolus feeds, and increments maximized upto 180 mL/kg/day. Mother's own milk was preferred, whenever available. If mother's milk was not available, preterm formula was used. To meet the fluid and nutritional needs not met by enteral feeds, neonates also received parenteral nutrition till the infant tolerated 100-120 mL/kg/day of enteral feeds.

In all enrolled neonates, baseline maternal, antenatal, intrapartum and neonatal details were recorded. Neonates were monitored for feed intolerance and NEC. If abdomen girth increased by >2 cm between feeds or abdomen was tense/tender, gastric aspiration was done to assess type and volume of gastric residues. If abdominal girth had increased by >2 cm and/or residual feed volume was >50% of previous feed volume, feed was withheld for 24 hours or till abdominal signs resolved, whichever was later. If residual feed was 20-50% of feed volume, feeding was continued without an increment for next 24 hrs; if residual volume was <20% of feed volume, increments were made as per assigned group protocol. Enteral feed was also withheld, if neonate was receiving inotropes. In neonates with suspected sepsis, culture data were also recorded.

Sample size was calculated based on our pilot observation, where with conservative feeding, mortality among neonates with birthweight <1250 g was 80%. To detect an expected 30% relative reduction in mortality with the aggressive feeding, 58 neonates were required in each arm for a power of 80% and alpha error of 0.05. We planned to recruit 65 neonates in each arm, expecting 10% attrition of participants.

Statistical analysis: Categorical data were compared using Chi-square test. Continuous data were compared using student t-test or Mann-Whitney U-test. Time to event outcomes were analyzed using Kaplan-Meier curve. A *P* value of <0.05 was considered as significant.

RESULTS

***Fig.* 1** depicts the study flow. We enrolled 66 neonates in aggressive feeding, and 65 in the conservative feeding group. ***Table* I** provides a comparison of baseline

TABLE I BASELINE CHARACTERISTICS OF ENROLLED NEONATES

Variables	*Aggressive regimen (n=66)*	*Conservative regimen (n=65)*
Birthweight (g), mean (SD)	1085 (112)	1067 (144)
Gestation (wk), mean (SD)	31.3 (2.8)	30.6 (2.2)
Fetal growth restriction, *n* (%)	41 (62.1)	36 (55.3)
Male gender, *n* (%)	32 (48)	37 (56)
Gestational hypertension, *n* (%)	16 (24.2)	18 (27.6)
#Absent/reversed flow, *n* (%)	13(19.6)	16 (24.6)
Antenatal steroid received, *n* (%)	56 (84.8)	51 (78.4)
Cesarean section, *n* (%)	13 (19.7)	12 (18.5)
Need for resuscitation at birth, *n* (%)	17 (25.8)	11 (16.9)
Respiratory distress at birth, *n* (%)	19 (28.7)	26 (40)
*Age enteral feed initiated (d)	2 (1, 2)	2 (1, 2)

**median (IQR); #End-diastolic flow in umbilical artery.*

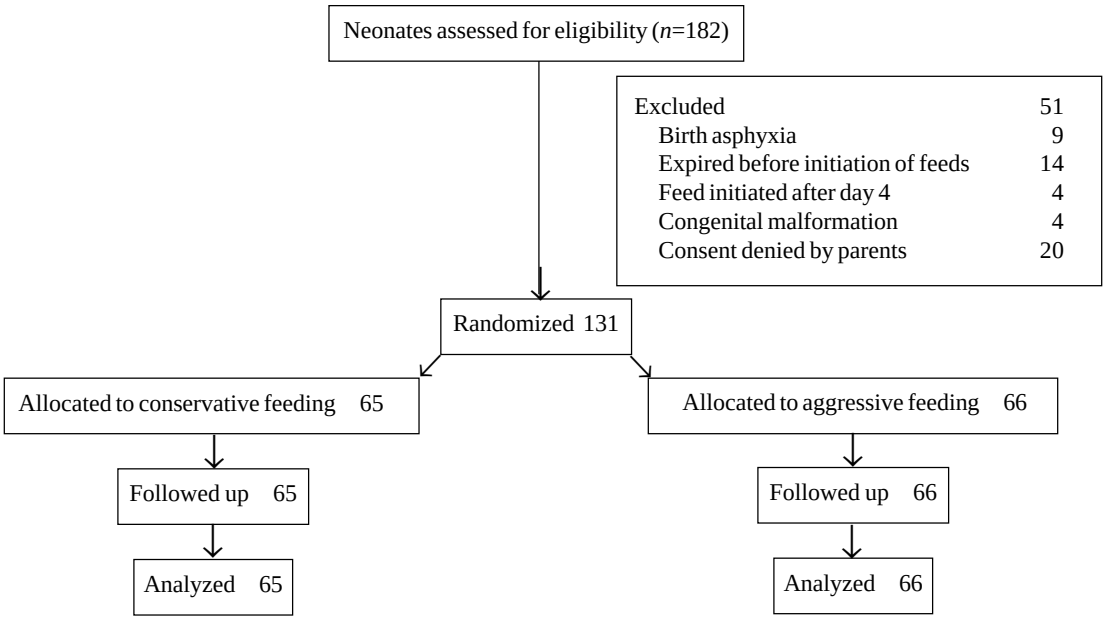

FIG. 1 *Flow of participants in the study.*

characteristics between the study groups. Primary and secondary outcomes of study are depicted in ***Table* II**.

There was a trend towards lower all-cause mortality in the aggressive feeding group, but it was not statistically significant (P=0.25). Frequency of sepsis, NEC and feed intolerance, duration of hospital stay, and weight gain were also comparable between the groups. Neonates in aggressive regimen had fewer days on intravenous fluids and reached full feed earlier (P<0.001).

DISCUSSION

In the present study, aggressive enteral feeding was not associated with a significant reduction in mortality or other morbidities. Neonates in aggressive feeding regimen had a reduced duration of intravenous alimentation and reached full enteral feeds earlier. Incidence of NEC and feed intolerance was comparable in two regimens.

Findings of our study are consistent with most previous observations, where neonates in rapid advancement group achieved full feeds earlier and had significantly fewer days of intravenous fluids, regained birthweight earlier and had shorter length of stay in hospital, with a comparable mortality and morbidity [15-22]. In a recent randomized controlled trial, Sanghvi,

TABLE II COMPARISON OF PRIMARY AND SECONDARY OUTCOMES IN TWO FEEDING GROUPS

Outcome variables	*Aggressive regimen (n=66)*	*Conservative regimen (n=65)*	*RR (95% CI)*	*P value*
Mortality, *n* (%)	22 (33.3)	28 (43.1)	0.77 (0.49-1.20)	0.25
Sepsis, *n* (%)	17 (25.8)	24 (36.9)	0.69 (0.41-1.17)	0.17
Feed intolerance, *n* (%)	12 (18.2)	17 (26.2)	0.69 (0.36-1.33)	0.27
NEC stage II/III, *n* (%)	1 (1.5)	2 (3)	0.49 (0.04-5.29)	0.55
IVH grade III,IV/cystic PVL, *n* (%)	3 (4.5)	4 (6.1)	0.73 (0.17-3.17)	0.68
Survival without major morbidities, *n* (%)	43 (65.2)	34 (52.3)	1.2 (0.93-1.66)	0.14
Time to reach full feed (d), median (IQR)	7 (6, 8)	10 (9, 14)	-	<0.01
Duration of hospital stay (d), median (IQR)	24.9 (21.6, 28.2)	26.6 (22.8, 30.3)	-	0.68
Average daily weight gain (g/kg), mean (SD)	12.2 (5.4)	11.7 (4.4)	-	0.66

NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leucomalacia.

WHAT IS ALREADY KNOWN?

- Early aggressive feeding in VLBW neonates is considered to increase the risk of feed intolerance and necrotizing enterocolitis.

WHAT THIS STUDY ADDS?

- Aggressive enteral feeding in neonates with birthweight 750-1250 g does not seem to affect mortality or risk of feed intolerance.

et al. [23] assessed feasibility of exclusive enteral feeding without any parenteral nutrition in neonates with birthweight 1200-1500 g. They observed that exclusive enteral feeding in this population was feasible with shorter duration of hospital stay.

The strength of our study was enrolment of relatively smaller neonates, who are more at risk of NEC and other morbidities. Abnormal umbilical artery doppler and need for ventilatory requirement were not excluded from the study, making our findings more generalizable to sick and growth-restricted neonates. Limitations of our study were inability to mask intervention from caregivers and investigator, and inadequate power for primary outcome.

Findings of our study reaffirm the feasibility of early aggressive feeding regimen in neonates, 750-1250 g birth weight. No significant difference in mortality in our study could be due to fact that we calculated sample size for hypothesized 30% relative reduction with aggressive feeding with an estimated 80% mortality with conventional feeding. However, mortality during study period with conventional feeding regimen was 43%. A 10% absolute reduction in mortality did not reach statistical significance, perhaps due to inadequate power of study. On post-hoc calculation, power of our study to detect this difference was 32.5%. To detect this observed different with 80% power, 367 neonates in each group would be required. Similarly, due to small sample size, we could not substantiate difference in culture-positive sepsis or survival without major morbidities.

We conclude that early aggressive feeding regimen in neonates with birth weight 750-1250 g does not seem to be associated with significant reduction in all-cause mortality, culture positive sepsis or survival without major morbidities during NICU stay. Aggressive feeding regimen seems to be well tolerated in this population with reduction in duration of intravenous fluids with early achievement of full enteral feeding.

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