Original Article

Slow versus Fast Enteral Feed Advancements in Very Low Birth Weight Infants: A Randomized Controlled Trial

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Objective: *To evaluate the tolerance of rapid advancement of enteral feeds in VLBW babies.* ***Setting****: Tertiary teaching hospital.* ***Design:*** *Randomized controlled trial.* ***Methods:*** *All stable neonates with birth weight <1250 grams were included in the study. The primary outcome variable was the time taken to achieve full enteral feeds (defined as 180 ml/kg/day). The secondary outcome variables were incidence of Necrotizing enterocolitis (NNEC) and incidence of apnea. At 48 hours, the infants were randomized into the slow advancement group (enteral feeds advanced by increments of 15 ml/kg/day) or fast advancement group (enteral feeds advanced by increments of 30 ml/kg/day). The monitoring during feeding included daily weight record, two hourly abdominal girth charting, gastric aspirates, apnea, time taken to reach full enteral feedings and for NNEC.* ***Results:*** *There were 53 infants who were enrolled for the study (27 in the fast advancement group and 26 in the slow advancement group). In the fast advancement group, 20 (74%) completed the trial; whereas 14 (53.8%) in the slow advancement group completed the study. The two groups were comparable for birth weights, gestational age, sex, intrauterine growth status, Apgar and CRIB scores. The infants in the fast group reached full enteral intake of 180ml/kg/day significantly earlier (10 ± 1.8 days) than in the slow group (14.8 ± 1.5 days). The two groups were comparable for episodes of feed intolerance, apnea, NNEC. Infants in the fast group regained birth weight significantly earlier (median 18 days) than in the slow advancement group (median 23 days).* ***Conclusions:*** *Stable VLBW neonates can tolerate rapid advancements of enteral feeding without increased risk of adverse effects.*

Key words: *Enteral feeding, Low birth weight, NNEC.*

THE technological advances that have occurred in the field of neonatal intensive care in the past decades have resulted in an increased survival of an increasing number of premature and very low birth weight infants. These infants require specialized nutritional support because of a high degree of biochemical immaturity, faster growth rates and increased demands resulting from increased risk of respiratory problems, apnea and sepsis. The nutritional needs in such situations are generally met by the provision of parenteral nutrition. Enteral nutrition has generally been delayed because of fears of poor gut tolerance and risk of necrotizing enterocolitis. This traditional view of withholding feeds in VLBW infants has recently been challenged. Provision of trophic feeds has been found to result in faster maturation of the gut, making it much more

receptive for subsequent enteral feeds. In addition recent trials have suggested that faster feed increments are well tolerated in stable very low birth weight (VLBW <1500 g) babies and do not necessarily lead to increased incidence of NNEC. This study was designed to test the hypothesis that rapid advancement of enteral feeds in VLBW babies is tolerated well.

Material and Methods

The study was conducted in a tertiary level teaching hospital. All infants with birth weight <1250 g were included in the study. Neonates were excluded if there were any gross congenital abnormality, if the infant at 48 to 72 hrs of life required pressor support, had abdominal distention, recurrent apnea or respiratory distress requiring supplemental oxygen by hood.

Outcome variables

The primary outcome variable was the time taken to achieve full enteral feeds (defined as 180 ml/kg/day). The secondary outcome variables were incidence of Necrotizing enterocolitis (stages II or more of Bell's criteria) and incidence of apnea.

Sample size estimate

To observe a difference of five days in the time taken to achieve full enteral feeds between the two groups with a standard deviation of 3, a power of 80% and a probability of 5%, it was estimated that the study would require a total sample size of 20 subjects.

Randomization and feeding protocol

All infants included in the study were given gastrointestinal priming on day one and two with expressed human milk at the rate of 5 ml/kg/day 4 hourly. At 48 hours the infants were randomized into the slow or fast feeding protocols by opening opaque sealed envelopes containing the computer generated randomization sequence to which the investigators were blinded.

Slow advancement group

Infants in this group were started on enteral feeds at the rate of 15 ml/kg/day on the first day. Thereafter, enteral feeds were advanced by increments of 15 ml/kg/day till maximum enteral feeds of 180 ml/kg/day were attained.

Rapid advancement group

Infants in this group were started on enteral feeds at the rate of 15 ml/kg/day on the first day. Thereafter, enteral feeds were advanced by increments of 30 ml/kg/day till maximum enteral feeds of 180 ml/kg/day were attained.

Both groups received expressed human milk by intermittent nasogastric bolus feeds at 2 hourly intervals. Abdominal girth measurement were done prefeed. When an abdominal girth increment of >2 cm between feeds was observed then gastric aspiration was done.

(*a*) If gastric aspirate was 30-50% of pre feed volume and / or ³3 ml/kg (which ever was greater) then no further increase in feeds was made over the next 24 hours.

(*b*) If gastric aspriates were >50% of prefeed volume, then feeding was discontinued temporarily for 24 hours. During this period the infant was investigated for sepsis and Necrotizing enterocolitis (blood counts, abdominal skiagrams, stool for blood and reducing substances). If investigations turned out to be negative, then feeds were restarted at half the volume the infant was receiving at the time of discontinuation of feeds. If the infant was diagnosed to have necrotizing enterocolitis then the management was as per the standard management protocol for Necrotizing enterocolitis.

Data Recording

(*a*) The baseline clinical features of the infants enrolled for the trial included birth weight, gestational age, Apgar scores at 1 and 5 min, CRIB (Clinical Risk Index for Babies) score, need for mechanical ventilation, duration of mechanical ventilation, umbilical venous/arterial catheterization.

(*b*) The monitoring during feeding included daily weight record, two hourly abdominal girth charting, gastric aspirates as indicated, apnea, time taken to reach full enteral feedings, clinical features of Necrotizing enterocolitis and laboratory investigations as indicated (blood counts, and cultures, abdominal *X*-rays and stool examination).

Statistical analysis

All continuous data was analyzed by the use of t-test or appropriate non-parametric tests. All proportionate data was analyzed with Chi-square or Fisher exact test. The institutional ethics committee approved the study protocol.

Results

There were 53 infants who were enrolled for the study - 27 in the fast advancement group and 26 in the slow advancement group. Out of the infants randomized to the fast advancement group, 20 (74%) completed the trial; whereas 14 (53.8%) allocated to the slow advancement group completed the study.

Loss to Follow up

Table I compares the salient baseline characteristics of the neonates completing and not completing the trial. The neonates not completing the trial had significantly lower birth weights. This group of neonates also had lower mean gestational age and a higher mean CRIB score (Clinical Risk Index for Babies) than those completing the trial, though the differences were not statistically significant. The neonates who were lost to follow-up had all died. The causes of death in the fast group were sepsis (3), NNEC (2), Respiratory distress syndrome (1) and prematurity (1). The causes of death in the slow group were sepsis (10), inborn error of metabolism (1) and pulmonary hemorrhage (1).

Baseline Characteristics

The two groups were comparable for birth weights, gestational age, sex, intrauterine growth status, Apgar and CRIB scores (*Table II*). The groups were also comparable for the number needing mechanical ventilation or umbilical catherization prior to enrollment in the study.

Outcome variables (Table III)

It was observed that the infants in the fast group reached full enteral intake of 180 ml/kg/day significantly earlier then in the slow group. There was an average difference of about 5 days between the groups ($P < 0.001$).

The two groups were comparable for the number in whom feeds were to be interrupted or its duration, episodes of increased gastric residues and abdominal girth or apnea. There were only two cases of NNEC (neonatal Necrotizing enterocolitis) during the entire study and both infants belonged to the fast advancement group. The diagnosis of NNEC was made at day six and eight of life in both infants respectively. Both of them also had associated septicemia and died prior to completion of the trial.

Infants in the fast group regained birth weight significantly earlier than in the slow advancement group.

TABLE I–*Comparison of Baseline Variables in Infants Completing the Trial and Lost to Follow up.*

Parameter	Completed Trial (n = 34)	Loss to follow up (n = 19)
Birth weight (grams) *	1091.0 ± 130.7	981.6 ± 152.3
(Mean ± SD)		
Gestational age (weeks)	33.4 ± 2.2	31.9 ± 2.1
(Mean ± SD)		
1 minute Apgar score	7.6 ± 1.8	7.9 ± 1.5
(Mean ± SD)	(n = 31)	(n = 17)
5 minute Apgar score	8.3 ± 1.1	8.3 ± 0.8
(Mean ± SD)	(n = 33)	(n = 18)
CRIB score	1.3 ± 0.8	3.0 ± 1.9

*P< 0.001

TABLE 2–*Comparison of Baseline Variables Between Slow and Fast Advancement Group.*

Parameter		Fast group (n = 27)	Slow group (n = 26)
Birth weight (g) (Mean ± SD)		1058.1 ± 147.4	1045.2 ± 149.6
Gestation age (wks) (Mean ± SD)		33.1 ± 2.3	32.6 ± 2.1
Sex	Male	12 (44.4%)	11 (42.3%)
	Female	15 (55.5%)	15 (57.6%)
Intra uterine growth status	SGA**	25 (92.5%)	26 (100%)
	AGA	2 (7.4%)	—
Apgar score -1 min		7.8 ± 1.5	7.6 ± 1.9
(Mean ± SD)		(n = 24)	(n = 24)
Apgar score -5 min		8.3 ± 1.1	8.3 ± 0.9
(Mean ± SD)		(n = 26)	(n = 25)
CRIB score*		1.8 ± 1.5	2 .0 ± 1.4
Mean ± SD			

Note: None of the parameters are significantly different.
*CRIB - Clinical Risk Index for Babies.
**SGA - Small for Gestational Age, AGA - Appropriate for Gestational Age.

Discussion

The present study was designed to address the issue of tolerance of rapid advancement in the developing country setting. This study gains importance because of the limited number of clinical trials that are available till date. There have been three randomized controlled trials(1-3), two case control studies (4,5) and one systematic review(6) on the subject of feed volume advancements till date. All these studies have come from a single nation, the USA. The similarities between the earlier mentioned studies and the present trial

TABLE III– *Comparison of Outcome Variables Between Slow and Fast Advancement Groups.*

Parameter	Fast group (n = 27)	Slow group (n = 26)
Days to full enteral feeds ** (Mean ± SD)	10 ± 1.8 (n = 20)	14.8 ± 1.5 (n = 14)
Number in whom feeding was interrupted (%)	14 (51.8%)	17 (65.3%)
Number with increased gastric residues	3 (11 %)	1 (3.8%)
Number with increased abdominal girth(> 2cm)	4 (14.8%)	1 (3.8%)
Number who developed apneic episodes (%)	12 (44.4%)	15 (57.7%)
Total number of apneic episodes* (Median, Range)	9 (2-70) (n = 20)	9 (1-99) (n = 14)
Maximum percentage of weight loss* (Mean ± SD)	11.9 ± 4	12.5 ± 4.1
Days to regain birth weight* (Median, Range)	18 (11 -30)	23 (16-38)

**P< 0.001, * Calculated from amongst the infants completing the trial.

are that they have all enrolled neonates of similar birth weights and gestation, ages at enrollment, feeding route and frequency. The outcome variable that was common to all the studies was necrotizing enterocolitis. The present study design is however, distinct in that the earlier studies, did not include gastrointestinal priming and used exclusively or predominantly preterm formula.

There is abundant literature on the benefits of trophic feeding in preterm enteral nutrition(7-12). Most of these studies have reported improved subsequent tolerance to enteral feeding in VLBW infants. In most of these studies trophic feeding was provided during the first 7-10 days of life before standard increments in enteral feeding volumes were initiated (these volume increments ranged from 15-20 ml/kg/day). The trophic feeding volumes used in these trials ranged between 10-15 ml/kg/day. In the present trial however, trophic feeding was initiated from the first day of life and provided volumes of 5 ml/kg/day for the first 2-3 days of life. Since the study objective was not to evaluate the benefit of trophic feeding, gastrointestianl priming was carried out in both the fast and slow advancement groups. The enteral feeding volume increments that have been used in the five earlier trials(1-5) have been variable. The volume increments in the slow advancement groups have ranged from 10 ml/kg/day to 23 ml/kg/day, with a median value of 20 ml/kg/day. The volume increments in the rapid advancement groups have ranged from 15 ml/kg/day to 45 ml/kg/day, with a median value of 30 ml/kg/day. The incremental schedules of 15 ml/kg/day in the slow group and 30 ml/kg/day in the fast group that were adopted for the present study were based on the median value derived from the above-mentioned trials.

The median age at initiating feeding in the earlier published trials(1-4) ranged from 3-7 days. The age of enrolment was 3 day for the present study, which is similar to the earlier

Key Messages

- Stable VLBW neonates can tolerate rapid advancements of enteral feeding (upto 30 ml/kg/d) without increased risk of adverse effects.
- Rapid feed advancement results in faster regain of birth weight and thus could shorten duration of hospital stay and consequently reduce costs for the care of these infants.

trials and thus makes all these studies comparable. The other similarities that were there in the present study and the earlier trials was that most of the earlier trials used the intermittent nasogastric feeding regimen as in the present study. The present study exclusively used human milk for the feeding of infants enrolled into the trial. The only other trial where mixed human milk and preterm formula feeding was used was that by Caple, *et al.*(2).

The average birth weight of the babies enrolled in the present trial was approximately 1050 grams and the average gestation was approximately 33 weeks. These are similar to the birth weights and gestation in the infants enrolled in the earlier trials. However, an important point of difference of the babies enrolled in the present trial was that most of them were infants had experienced intrauterine growth retardation in contrast to earlier published trials wherein most of the babies were appropriately grown preterm infants.

The time taken to achieve full enteral feeds (180 ml/kg/day) was the primary outcome variable for the present study. The fast enteral feed group reached full enteral feeds significantly earlier (mean 10 days), than in the slow advancement group (mean 14.8 days). The results of the present study are similar to that of Rayyi, *et al.*(3) who used a similar feeding protocol to the one employed in the present study. It was observed in their study that the fast groups attained full enteral feeds of 180 ml/kg/day by the 11th day and the slow group by the 15th day. These differences were statistically significant.

The observations of the present study are comparable to the observations made by Kennedy, *et al.*(6) in their systematic review wherein there was a significant relation in the days to full enteral feeds and the days to regain birth weight in infants randomized to the fast advancement protocol. The small sample size of the present trial precludes any firm conclusion on the risk of NEC and rapid enteral feeding. One has also to be cautious in recommending universal rapid advancement in all very low birth weight babies. It is possible that infants <1000 g, those who are moderately sick and those with hemodynamic instability may not be appropriate candidates for rapid enteral feeding protocols. In the context of the developing nations, the use of early and rapid enteral feeding protocols using exclusive human milk especially in babies between 1000-1500 g would decrease hospital morbidity and lead to better weight gains during hospital stay. Whether this would translate to shortened duration of stay and consequently reduced hospital costs for the care of these infants would remain to be seen in future trials.

Contributors. AS collected and analysed the data, and wrote the draft manuscript. SR designed and monitored the study, analysed the data and critically reviewed the final manuscript. SR will be the gurantor for the study.
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