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Original Article

Slow versus Rapid Advancement of Enteral Feeding in Preterm Infants Less than 34 Weeks: A Randomized Controlled Trial

Liton Chandra Saha[1]*, Rubina Yaesmin[2], Mahbubul Hoque[1] and MAK Azad Chowdhury[1]

Department of Neonatal Medicine, Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh

[2]FCPS (Paediatrics) part II examinee, Dhaka, Bangladesh

Abstract

Background

Enteral feeding routines are not well defined in preterm neonates. Controversy exists regarding when feedings should be started, whether minimal enteral feedings should be used routinely in small preterm infants and how fast to advance enteral feedings.

Objective

To evaluate the effect of slow vs rapid rates of advancement of enteral feeding volumes on the clinical outcomes in preterm babies less than 34 weeks.

Methodology

A randomized, controlled, single-center trial was conducted in a Neonatal Unit of Dhaka Shishu (Children) Hospital. Infants between 1200 gm and < 2500 gm at birth, gestational age < 34 weeks, and weight appropriate for gestational age were allocated randomly to feedings of expressed human milk and advanced at either 30 mL/kg per day or 20 mL/kg per day. Infant's remained in the study until discharge.

Results

A total of 300 infants were enrolled, 150 infants in the rapid group and 150 in the slow group. Enteral feeding advancements were well tolerated by the intervention group of stable preterm neonates like that of control group both in birth weight <1500 gm and in birth weight (1500 gm - < 2500 gm) study populations (67.27 % vs. 68.42 % and 68.42 % vs. 64.28 %, p value > 0.05). Infants in the intervention group achieved full volume feedings sooner (9.33 days vs. 14.66 days) and (9.12 days vs. 15.5 days), p value < 0.05. Eighteen infants in the intervention group and fifteen in control group were died due to sepsis which was statistically not significant. There was no incidence of NEC in birth weight (1500 gm - < 2500 gm) study populations in both groups. No statistical differences in the proportion of infants with feed interruption or feed intolerance.

Conclusion

Rapid enteral feeding advancements in preterm babies < 34 weeks reduce the time to reach full enteral feeding and the use of PN administration. Rapid-advancement enteral feed also improved short-term outcomes for these high-risk infants.

Keywords: DSH; Enteral feeding; NEC; Prematurity; Rapid; Slow

Introduction

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 Low Birth Weight Infants (LBWIs). These neonates require specialized nutritional support due to their biochemical immaturity, faster growth rates, and increased metabolic demand. The American Academy of Pediatrics (AAP) has suggested that the goal for nutrition of the preterm infant should be to achieve a postnatal growth rate approximating that of the normal fetus of the same gestational age [1,2]. Unfortunately, most preterm infants, especially those weighing less than 1000 g, do not achieve normal fetal growth rates and develop postnatal growth restriction [3]. Moreover optimal enteral feeding methods in preterm infants have not been well defined [4]. Controversy exists regarding when feedings should be started, whether minimal enteral feedings should be used routinely in small preterm infants, and how fast to advance enteral feedings [5-8]. Enteral feedings are frequently advanced slowly in the preterm neonates. This practice may compromise the precarious nutritional status of some of these infants and prolong the use of intravenous fluids. Increments of enteral feeding of 10 to 20 mL/kg per day have been reported as safe in a prospective study [7], but several retrospective studies have suggested that advancing feedings rapidly is associated with an increased risk for NEC [9,10]. In 1 of these studies, feeding increments were as high as 40 to 50mL/kg per day [9]. Conversely, a relatively more rapid advancement of enteral feedings in preterm infants may improve their growth and nutritional status, decrease the need for and hazards of intravenous infusion solutions, and potentially shorten the length of hospitalization. Rayyis et al. [8], reported no difference in the incidence of feeding intolerance or NEC in infants who received 35 mL versus 15 mL feeding advancements. We examined whether infants who were fed initially and advanced at 30 mL/kg per day take fewer days to get to full feedings than those who were fed initially and advanced at 20 mL/kg per day, without increases in their incidence of feeding complications and NEC. Also, we studied whether infants who were fed the higher volume regain birth weight earlier, have fewer days of intravenous fluids, and have a shorter hospital stay than those who were advanced at the slower rate.

***Corresponding author:** Liton Chandra Saha, Department of Neonatal Medicine, Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh, Tel: +880 1711463273; E-mail: sahaliton11@gmail.com, sahaliton11@yahoo.com

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Materials and Methods

This Randomized Controlled Trial (RCT) was conducted from July 2017 to June 2018 Special Care Baby Unit (SCABU) and NICU in Dhaka Shishu (Children) Hospital, Bangladesh after the approval from the Institutional Review Board of the hospital. A total of 300 infants were enrolled, 150 infants in the intervention group and 150 in the control group. Preterm neonates with birth weight 1200 gm to < 2500 gm, gestational age < 34 weeks, postnatal age < 72 hours and hemodynamically stable babies were included in the study. Preterm neonates with major congenital abnormalities, severe perinatal asphyxia (Apgar score < 3 at 5 min), Infants with ventilator support and SAG (Small for Gestational Age) were excluded from the study. Both male and female were included in this study. Sample was selected by fulfilling the inclusion and exclution criteria and after obtaining consent from the parents for enrolment in the study. Sample subjects were assigned to either slow enteral feeding or rapid enteral feeding group through simple randomization and allocation was concealed by sealed envelop, which were equal in number for each group. Data was collected by using a structured questionnaire containing all the variables. A detailed history was taken from mother/caregiver and from the record and then entered in the structured questionnaire. Feeding was initiated as soon as the baby was stable. Expressed human milk was used. In the intervention group, feeding was initiated with 30 ml/kg per day and advanced by 30 ml/kg per day until 170 ml/kg per day was reached. Feeding in the control group was initiated with 20 ml/kg per day and advanced by 20 ml/kg per day until 170 ml/kg per day was reached. Before starting enteral feeds, a test feed was given, when feed was tolerated, then feeding was continued. However, when there was evidence of feeding intolerance e.g. the infant had > 30-50% gastric residue of the previous feed or gastric residual 3 ml/kg body weight, apnea, bilious vomiting, abdominal distention, gatrointestinal bleeding, paralytic ileus or NEC, then subsequent feeding was not being given. During that period the infant was investigated for sepsis and NEC (complete blood count, CRP, blood culture, abdominal X-ray, serum electrolytes, occult blood test). During the whole study period feeding was checked usually before giving every 3rd feeding whether the previous feed was tolerated or not. Bolus feeding was given through nasogastric tube every 2 hours for 20 minutes by the action of gravity; when the infants become more accustomed to enteral feeding with improvement of coordinated sucking, swallowing and breathing, gradually feeds was given by spoon or cup and finally successful breast feeding. A total daily fluid intake of 170 ml/kg was maintained by concomitant reduction in parenteral nutrition. When enteral intake was exceed 150 ml/kg/day, parenteral nutrition was discontinued. The maximum enteral feeds of 170 ml/kg/day was achieved. During hospital stay, both the groups was monitored for daily weight gain, nosocomial infection, feeding intolerance, necrotizing enterocolitis, physiologiacal parameters (heartrate, respiratory rate, temperature and oxygen saturation) and duration of hospital stay by a single observer at the same time every day. The criteria for hospital discharge was uniform among the study infants: Satisfactory weight gain (i.e. weight gain 15-20 gm/day) while receiving full oral feeding, maintenance of thermal stability and resolution of acute medical conditions, mother was confident to take care her baby. A statistical analysis was carried out by using the Statistical Package for Social Sciences version 19.0 for Windows. The results were reported as mean (± S.D) for slow enteral feeding and rapid enteral feeding. Student's independent't' test was used for comparison between continuous variables. Pearson chi-square test and Fisher's exact test were used for comparison between categorical variables. Fisher's exact test was used if frequencies for categorical variables were < 5. Pearson chi-square test was used for all other categorical variables. Statistical significance was set at 0.05 level of probability (i.e. p value < 0.05 was considered as significant). The aim and objective of the study along with its procedure, methods, risks and benefits were explained to the respondent's parents in easily understandable local language and informed consent were taken from the guardian. No financial burden were given to the parents and no extra investigation were done except the routine one.

Sample size has been calculated with the formula:

$$n = \frac{p_1(1-p_1)+p_2(1-p_2)}{(p_1-p_2)^2} \times (Z_\alpha + Z_\beta)^2$$
$$= \frac{0.54(1-0.54)+0.74(1-0.74)}{(0.54-0.74)^2} \times (1.96+0.85)^2$$

[Here, P_1=Outcomein control 54 % (0.54)
P_2 = Outcome in case 74 % (0.74)
Z_α = 1.96
Z_β = 0.85 (at 80 % power)]
N = 87 (in each group)

Results

This Randomized Control Trial (RCT) was conducted in Dhaka Shishu Hospital during July 2017 to June 2018; patients who fulfill the inclusion criteria were enrolled in this study. A total of 520 of preterm < 34 wks LBW babies were admitted in the SCABU and NICU during the study period. 335 satisfying the inclusion criteria. After getting consent a total of 300 infants were enrolled, 150 infants in the intervention group and 150 in the control group. Both were divided into two study population groups like birth weight < 1500 gm and birth weight (1500 gm - < 2500 gm) respectively. There were no significant differences regarding the demographic characteristics between the two groups. No significant difference was found in feeding outcome between case and control group of the study population (in birth weight < 1500 gm) and in study population (in birth weight 1500 gm - < 2500 gm) respectively. Enteral feeding advancements were well tolerated by the intervention group of stable preterm neonates like that of control group both in birth weight < 1500 gm and in birth weight (1500 gm - < 2500 gm) study populations (67.27 % vs. 68.42 % and 68.42 % vs. 64.28 %, p value > 0.05). Infants in the intervention group achieved full volume feedings sooner (9.33 days vs. 14.66 days) and (9.12 days vs. 15.5 days), p value < 0.05. Regained birth weight earlier and had fewer days of intravenous fluids in comparison to slow feeding group. Eighteen infants in the intervention group and fifteen in control group were died due to sepsis which was statistically not significant. There was no incidence of NEC in birth weight (1500 gm - < 2500 gm) study populations in both groups. No statistical differences in the proportion of infants with feed interruption or feed intolerance (Tables 1-6).

Discussion

Defining the best method for feeding preterm infants remains a challenging goal. These infants often have feeding difficulties primarily because of immaturity of their gastrointestinal system. However, it is presumed that slow enteral feeding may be well-tolerated than rapid enteral feeding. This randomized controlled trial was carried out to

evaluate the tolerance of rapid advancement of enteral feed in preterm low birth weight babies. Besides this, benefits and risks between these two groups were also determined.

Parameters	Slow Group (n = 150)	Rapid Group (n = 150)	p value
Gestational age (Wks)	31.65 (± 1.85)	30.75 (± 1.11)	0.28
Weight on admission (gm)	1633.70 (± 322.25)	1700.58 (± 230.44)	0.07
Enrolment age (hours)	38.56 (± 1.74)	39.17 (± 1.55)	0.30
Sex			
• Male	92	87	0.53
• Female	58	63	

Table 1: Demographic characteristics of the study population.

Characteristics	Slow n = 55	Rapid n = 38	Total	p value*
Feeding tolerance	37 (67.27 %)	26 (68.42 %)	63	0.82
Feeding intolerance	18 (32.73 %)	12 (31.58 %)	40	1.0
Abdominal distention	12 (21.81 %)	09 (23.68 %)	21	0.65
Vomiting	27 (49 %)	16 (42.10 %)	43	0.87
Increase gastric residual/ Gastric aspirates > 50 %	12 (21.81 %)	08 (21.05 %)	20	0.79
Feeding interruption	15 (27.27 %)	10 (26.31 %)	25	1.0
Necrotizing Enterocolitis (NEC)	3 (5.45 %)	2 (5.26 %)	5	0.27
*$\chi 2$ test				

Table 2: Feeding outcome of the study population (in birth weight < 1500gm).

Baseline characteristics	Slow n = 95	Rapid n = 112	Total	p value*
Feeding tolerance	65 (68.42 %)	72 (64.28 %)	137	0.34
Feeding intolerance	30 (31.58 %)	40 (35.71 %)	70	0.47
Abdominal distention	36 (37.89 %)	44 (39.28 %)	80	0.95
Vomiting	30 (31.57 %)	32 (28.57 %)	62	0.87
Increase gastric residual/ Gastric aspirates > 50 %	12 (12.63 %)	14 (12.5 %)	26	0.44
Feeding interruption	27 (28.42 %)	36 (32.14 %)	63	0.85
Necrotizing Entero Colitis (NEC)	00	00	00	--
*$\chi 2$ test				

Table 3: Feeding outcome of the study population (in birth weight 1500 gm to < 2500 gm).

	Slow group (n = 55)		Rapid group (n = 38)		p value*
	Mean	± SD	Mean	± SD	
Duration of IV fluid (days)	9.33	0.30	6.66	0.50	<0.001
Time taken for full enteral feed (days)	14.66	0.58	9.33	0.50	<0.001
Duration of Hospital Stay (days)	17.38	0.75	13.14	2.11	0.003
Days to regain birth weight	12.72	0.76	7.86	1.06	0.001
*Independent 't' test					

Table 4: Clinical outcome of the study population (in birth weight < 1500 gm).

	Mean	± SD	Mean	± SD	
Duration of IV fluid (days)	10.00	0.84	5.75	0.98	<0.001
Time taken for full enteral feed (days)	14.50	1.29	9.12	0.79	<0.001
Duration of hospital stay (days)	16.50	2.48	12.13	1.50	<0.001
Days to regain birth weight	11.88	2.21	7.93	1.48	<0.001
*Independent 't' test					

Table 5: Clinical outcome of the study population (in birth weight < 1500 gm).

Weight in admission			Study group		Total	p value*
			Slow	Rapid		
< 1500 gm	Outcome	Discharged with Breast feeding	48	34	82	1
		Died	7	4	11	
	Total		55	38	93	
1500 - < 2200 gm	Outcome	Discharged with Breast feeding	87	98	185	0.68
		Died	8	14	20	
	Total		95	112	207	
Grand Total			n = 150	n = 150	300	
*$\chi 2$ test						

Table 6: Comparison of mortality of the study population (as per group).

Both slow and rapid enteral feeding groups were comparable in gestational age, weight on admission, age on admission and sex. There was no significant difference of these demographic characteristics of the study population between the two groups. Enteral feeding advancements were well tolerated by the intervention group of stable preterm neonates like that of control group both in birth weight < 1500 gm and in birth weight (1500 gm - < 2500 gm) study populations (67.27 % vs. 68.42 % and 68.42 % vs. 64.28 %, p value > 0.05). This finding is also consistent with previous studies done by Caple J. et al., and Krishnamurthy S [11,12].

Rapid enteral feeding group needed shorter duration of Intravenous fluid than slow enteral feeding group both in birth weight < 1500 gm and in birth weight (1500 gm - < 2500 gm) study populations (6.66 days vs. 9.33 days and 5.75 days vs. 10.00 days, p value > 0.05). This is consistence with some previous studies done by Caple J. et al., and Krishnamurthy S [11,12].

Infants in the intervention group achieved full volume feedings sooner (9.33 days vs. 14.66 days) and (9.12 days vs. 15.5 days), p value < 0.05. This is also consistence with some previous studies done by Caple J. et al., and Krishnamurthy S [11,12].

Rapid enteral feeding took significantly fewer days to regain weight than slow enteral feeding both in birth weight < 1500 gm and in birth weight (1500 gm - < 2500 gm) study populations (7.86 days vs. 12.72 days and 7.93 days vs. 11.88 days, p value > 0.05). This finding is well supported by Cochrane review conducted by Opiyo N. et al. Oxford University, Oxford, UK, 2009 [13].

In rapid enteral feeding group regained weight is earlier because calorie intake was high in comparison to slow feeding group. As it is not possible for us to provide TPN (Total Parenteral Nutrition) in preterm low birth weight babies because it is expensive and its administration procedure is not well established in our hospital setup.

Rapid enteral feeding took significantly shorter duration of hospital stay than slow enteral feeding. This is consistence with some previous studies done by Krishnamurthy S, 2010 and Karagol BS et al., [12,14]. But there was no significant difference between the two groups in few other studies which were conducted by Caple J et al., and Rayyis and Salhotra A [9,11,15]. In their studies, both the groups were kept in the hospital until they reached to the higher limit of the weight of their respective age group but the long-term clinical importance of these effects are unclear. Feeding was interrupted in both slow and rapid enteral feeding groups. There was no statistically significant difference between the two groups. This is also similar with few other related studies done by Caple J. et al., and Krishnamurthy S [11,12].

Frequency of feeding complication e.g. abdominal distention, feeding intolerance and increase gastric residual were more in rapid enteral feeding than slow enteral feeding, but there was no significance difference between these two groups; p value for mentioned variables were > 0.05. It also confirmed with all the mentioned previous studies. In case of vomiting the frequency was more in slow enteral feeding than rapid one, but again this is not statistically significant; p value > 0.05.

Regarding Necrotizing Enterocolitis (NEC), there was no significant difference for both the groups in this study. Meticulous observation, proper sepsis screening and prophylactic antibiotic was given when necessary. Moreover, only breast milk was provided and no formula milk was added in this study. In all the previous mentioned studies, few incidents of NEC were present and it was similar for both the groups but not statistically significant [9,11-16].

In this study, mortality was almost equal (10.00 % vs. 12.00 %; p value was > 0.05) for both in slow feeding and rapid feeding due to only sepsis which was statistically not significant. In all the previous mentioned studies, little mortality was found due to both NEC and sepsis; these incidents of NEC and sepsis were similar for both the groups but not statistically significant where the study was done by Caple J. et al., and Krishnamurthy et al. [11,12].

Conclusion

In this study, Rapid enteral feeding advancements in less than 34 wks infants reduce the time to reach full enteral feeding and the use of PN administration. This feeding practice does not increase the risk of sepsis, NEC, or death. The data suggest that rapid advancement of enteral feeding protocol is safe and can be adapted in neonatal intensive care units. But future trials are needed to determine the long-term clinical importance of the effect of this intervention on long-term outcomes, especially for ELBW infants.

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