

Comparison of prolonged low volume milk and routine volume milk on incidence of necrotizing enterocolitis in very low birth weight neonates

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ABSTRACT

Objective: Advancing feedings too rapidly may increase the risk of necrotizing enterocolitis. Few studies have been performed to compare the incidence of NEC from different methods of feeding. Our objective was to compare the results of prolonged low volume milk versus routine volume milk increase on incidence of NEC in VLBW neonates.

Methodology: This study included Premature VLBW neonates admitted to the NICU at Alzahra and Shahid Beheshti Hospitals in Isfahan, between September 2011 and November 2012. On the day that the attending neonatologist chose to begin feedings, study infants were randomly assigned to be fed using minimal (group M) or advancing volumes (group A). Infants of group M who were randomized to minimal volumes were fed 20 mL/kg/d for 7 days in 2-hour cycles consisting of a 20-minutes of gavage of milk or formula followed by about two hours of fasting. After 7 days, feeding volumes for infants were increased by 20 mL/kg/d until a volume of 150 mL/kg/d was achieved and maintained. Infants who were randomized to advancing volumes (group A) were fed with initial 20 mL/kg/d using the same strategy as for infants fed minimal volumes. Then on day two, feeding volumes were increased to 40 mL/kg/d, until a volume of 150 mL/kg/d was achieved. In both groups feeding characteristics, such as milk volumes, gastric residuals, abdominal distension, postnatal ages when full enteral feedings were achieved, NEC and death were recorded daily.

Results: Eighty two neonates completed the study. Only three infant (8.57%) which had been placed in minimal volume group developed suspected NEC, as compared to 12 neonates (25.53%) who were fed advancing volumes. Incidence of milk intolerance and the need for milk cessation was significantly greater in group A than group M. Infants who had been placed in advancing volume group reached full enteral feeding volumes sooner than infants who had been placed in minimal volume group. But average hospital discharge age and average weights at 30 days of life were similar between two groups.

Conclusion: Due to the potential risks of NEC in preterm infants and based on this study feeding strategy (prolonged low milk volume in newborn babies) could be suggested for VLBW neonates. Further studies are needed to confirm these findings.

KEY WORDS: Preterm, VLBW, Feeding, NEC.

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INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the most critical morbidities occurring in preterm infants. In spite of improvements in neonatal intensive care, the incidence of NEC has increased to 7% in very-low-birth-weight (VLBW) infants.^{1,2} Mortality from NEC is 15 to 30% and is especially high in infants with lower birth weight, earlier gestation, and surgical interventions.^{1,3} Infants who have recovered from

NEC are more susceptible to nosocomial infection, malnutrition, growth failure, bronchopulmonary dysplasia, retinopathy of prematurity, and longer hospitalization.^{1,4} Although the cause of necrotizing enterocolitis (NEC) is considered to be multifactorial, 90% of infants develop this disease after being fed, whereas only 10% develop NEC before being fed.⁵ Due to concerns for precipitating NEC and the widespread availability of parenteral nutrition during the 1970s and 1980s, preterm infants were commonly not fed.⁶ This practice was challenged when a series of prospective trials failed to show that the incidence of NEC was higher in infants given small enteral feedings (2–24 mL/kg/d) for the first 7 to 10 days compared with those who were unfed.⁵

Trophic feeding (volumes up to about 24 mL/kg/day) compared with enteral fasting reduces the time taken to establish full feeding and the length of hospital stay without increasing the risk of NEC.^{7,8} Furthermore, evidence exists that mothers who express breast milk for early trophic feeding are more likely to continue to provide breast milk as the continuing principal form of nutrition for their infants.^{8,9} Unfortunately, it seems that some neonatologists interpreted the findings from that studies to show that it is safe to increase feeding volumes after initiating early enteral feedings, and feeding volumes are commonly increased after these minimal feeding volumes are tolerated.⁵ The incidence of NEC was low in some of these previous studies, ranging from 0% to 5%, but none of these studies was designed to compare the incidence of NEC between treatment groups.⁵ A study compared two rates of advancement and found no difference in the incidence of NEC, but with either regimen the incidence of NEC was high.¹⁰

In another study by Berseth CL, et al, published in 2003 in two groups of VLBW newborns prolonged minimal milk volume group (M) and a group of feeding increasing 20 mL/kg/day (group A) were studied. Infants who were randomized to minimal volumes were fed 20 mL/kg/d for 10 days in 4-hour cycles consisting of a 2-hour infusion of milk or formula followed by two hours of fasting. Finally, after reviewing and comparing the two groups, incidence of NEC was lower in group M.⁵

Small enteral feedings accelerate maturation of gastrointestinal function.^{5,11-14} However, it is not known whether larger feeding volumes accelerate maturation of gastrointestinal function even more. In an effort to assess both risk and benefits of using larger feeding volumes, Berseth CL, et al also

assessed whether larger feeding volumes would accelerate maturation of gastrointestinal function even more than minimal feeding volumes do. It showed that the development of GI function does not differ between the two groups.⁵ Necrotizing enterocolitis (NEC) is a common acute abdominal condition and is also among the most common and devastating diseases seen in the neonatal period.¹⁵⁻¹⁹ Since length of hospital stay or the financial cost of necrotizing enterocolitis short bowel syndrome is substantial.^{20,21} The total annual estimated cost of caring for affected infants in the United States is between \$500 million and \$1 billion.¹⁶ Furthermore, since few studies have been performed to compare the incidence of NEC from different methods of feeding⁵ this study was conducted with the aim of comparing the results of Prolonged low volume milk versus routine volume milk increase on incidence of NEC in VLBW neonates.

METHODOLOGY

Infants admitted to the newborn intensive care unit (NICU) at Alzahra and Shahid Beheshti Hospitals in Isfahan, between September 2011 and November 2012 were included in this study. Inclusion criteria was infants born at birth weight equal and lower than 1500 gr. Infants who had congenital anomalies and who developed NEC or intestinal perforation before feedings were excluded. Infants entered the study on the day that the attending neonatologist decided to initiate enteral feedings. Study infants were randomly assigned to be fed using minimal (group M) or advancing volumes (group A), as described below. Infants were initially fed unfortified expressed breast milk or formula. Infants of group M who were randomized to minimal volumes were fed 20 mL/kg/d for 7 days in 2-hour cycles consisting of a 20-minutes of gavage of milk or formula followed by near two hours of fasting. These infants were given parenteral nutritional support throughout these seven days. After those seven days, feeding volumes for infants were increased by 20 mL/kg/d until a volume of 150 mL/kg/d was achieved and maintained. Infants who were randomized to advancing volumes (group A) were fed with initial 20 mL/kg/d using the same strategy as for infants fed minimal volumes. Then on day two, feeding volumes were increased to 40 mL/kg/d; on study day three, volumes were increased to 60 mL/kg/d, and so forth, until a volume of 150 mL/kg/d was achieved. Parenteral nutrition was gradually tapered as enteral feeding volumes were increased.

Table-I: Modified Bell Staging Criteria for Necrotizing Enterocolitis.^{22,23}

Stage	Classification	Clinical Signs	Radiologic Signs
I	Suspected NEC	Abdominal distention Bloody stools Emesis/gastric residuals Apnea / Lethargy	Ileus/dilation
II	Proven NEC	As in stage I, Plus; Abdominal tenderness \pm Metabolic acidosis Thrombocytopenia	Pneumatosis intestinalis &/ or portal venous gas
III	Advanced NEC	As in stage II, plus; Hypotension Significant acidosis Thrombocytopenia / disseminated intravascular coagulation Neutropenia	As in stage II, with pneumo- peritoneum

Modified form Waish MC, Kliegman RM; Necrotizing enterocolitis: treatment based on staging criteria, *Pediatr Clin North Am* 33:179,1986.

Feeding volume was then maintained at 150 mL/kg/d. Human Milk Fortifier was added to 25 mL of expressed breast milk on the day that feeding volumes reached 120-150 mL/kg/d.

In both groups feeding characteristics, such as milk volumes, the presence of milk in the stomach two hours after completion of a feeding (i.e., gastric residuals), abdominal distension, postnatal ages when full enteral feedings were achieved, NEC and death were recorded daily. Furthermore discharge home age, 30 days weight and the association of PDA, IVH and cholestatic jaundice were also determined.

Decisions regarding feeding intolerance and NEC were made uniformly in both groups. In short, the presence of (lavage) and volume of milk remaining

Table-II: Characteristics of Study Infants [Mean (SD)].

Characteristic	Advancing group	Minimal group	P *
Gestational age (wk)	30.86 \pm (2.34)	30.22 \pm (2.13)	0.2
Birth weight (g)	1228.09 \pm (177.25)	1170 \pm (239.93)	0.2
Age feeds begun (Day)	4.04 \pm (2.67)	3.79 \pm (1.71)	0.6

* two way ANOVA test

in the stomach two hours after the completion of feeding was considered "feeding intolerance" and diagnosis of NEC was made according to the following Table-I.

RESULTS

In our study, 82 neonates were decussate randomized and completed the study, and the results were analyzed by intention to treat. Demographic characteristics were similar between the two groups (Table-II). Primary adverse outcomes were clearly different between the two methods of feeding.

Only three infant (8.57%) which had been placed in minimal volume group developed suspected NEC, as compared to 12 infants (25.53%) who were fed advancing volumes (P: 0.02).

Infants who had been placed in advancing volume group reached full enteral feeding volumes clearly sooner than infants who had been placed in minimal volume group (average full enteral feeding time in A group was 13.4 \pm (5.69) days and in M group was 18.44 \pm (3.94) days. (P < 0.001; Table-III), but they required approximately equal hospital stay time so average hospital discharge age was similar between two groups. Average hospital stay time in group A was 28.04 days and in group M was 28.29 days. (P: 0.94, Table-III). Average weights at 30 days

Table-III: Primary and Secondary Outcomes in our Study.

Outcome	Group Advanc (A)	Group Minimal (M)	P Value
n	47	35	-
NEC (%)	12 (25.53%)	3 (8.57%)	0.02 *
Milk intolerance (Lavage) (%)	24 (51.1%)	9(26.5%)	0.01 *
Frequent milk intolerance	8 (17.0%)	2 (5.9%)	0.13 *
Abdominal distension	13 (27.65%)	3 (8.57%)	0.02 *
Age full enteral feeds (d; median and range)	13.4 (8-36)	18.44 (13-26)	< 0.001 ~
Age at discharge (d; median and range)	28.04 (11-80)	28.29 (15-56)	0.47 ~
Body Weight at 30 days (gr)	1607.11	1522.06	0.15 ~
IVH (%)	5 (11.1%)	6 (17.6%)	0.4 *
PDA (%)	7 (15.6%)	6 (17.6%)	0.8 *
Death (%)	2 (4.3%)	0	0.33 #
direct hyperbilirubinemia	1	0	0.57 #

* Chi-square # Fisher s Exact test ~ two way ANOVA test

of life in group A was 1607.11gr and in group M was 1522.06 gr then average weights at 30 days of life were similar between the two groups (P:0.31; Table-III).

The incidence of neonatal sepsis and cholestatic jaundice were similar between the two groups (P: 0.57; Table-III). Only one neonate was suffering from direct hyperbilirubinemia (average Bill Total: 7.3, average Bill Direct: 3.87 in hospital stay course) in the group A and finally at the subsequent examination he was diagnosed with neonatal hepatitis. The incidence of PDA and IVH in group A was 7 (15.6%) And 5 (11.1%) respectively and in group M was 6 (17.6%) and 6 (17.6%). (P: 0.8 and P: 0.4, respectively).

Incidence of milk intolerance and the need to milk cessation was significantly greater in group A than group M (incidence of milk intolerance in group A was 24 times (51.1%) and in group M 9 times (26.5%) (P: 0.01). In addition, incidence of frequent milk intolerance (Relavage: more than 2 times) was 8 times (17.0%) and in group M was 2 times (5.9%) but statistically difference was not significant. (P: 0.13).

Birth weights of those infants who developed NEC in group A ranged from 740 to 1480 gr (Average birth weights: 1145.45gr) and Gestational ages ranged from 28 to 35 weeks (Average Gestational ages: 30.72 week). The time from the initiation to feedings to the time of diagnosis of NEC ranged from 6 to 29 days. Two infants who died in this subgroup had a birth weight of 740, 1200 grams and Gestational ages 32, 28 weeks. Both these babies died within 6 days of birth. In group

M, two neonate developed suspected NEC. They had a birth weight of 900, 1010 grams (Average birth weights: 955 gr) and Gestational ages 30, 28 weeks (Average Gestational ages: 29 week). No infants died in group M. Characteristics of infants who developed NEC are shown in Table-IV.

DISCUSSION

Results of our study show there is a higher risk for NEC between VLBW neonates who were fed advancing feeding volumes (routine method) compared with those whose feeding volumes remained low during the first 7 days of feeding. In some previous studies,¹¹⁻¹³ Dunn et al study showed that the use of early hypocaloric small amounts of milk can be harmless.¹¹ Our study showed that using small amounts of milk result in fewer complications than large quantities of milk. However, Rayyis et al study reported that the NEC incidence in different ways of increase in the volume of milk was relatively uniform.¹⁰ The effects of time prolonging of low volume milk on incidence of NEC has been investigated in some studies.⁵ Berseth CL et al showed that neonates whose milk remained constant 20 cc/kg/day for 10 days had NEC incidence about 10 times less than who were assigned to advancing feeding volumes (P value).⁵ In our study NEC incidence was fewer in group M(minimal) than group A (advance) too (P value). In Berseth CL study average hospital discharge age was 64 and 76 days in advance and minimal group respectively (P value < 0,001)⁵ but in our study, average hospital discharge age was similar between two groups.

Kennedy et al concluded that although more rapid rates of advancing feedings in premature low-birth-weight infants can shorten time of regain birth weight and achieve full feedings but it is unclear whether this strategy should be adopted as routine practice because of limited information regarding safety (broad confidence intervals for the incidence of necrotizing enterocolitis) and the effect on length of hospital stay (broad confidence intervals)²⁴ On the other hand Morgan J et al in their study concluded that slow advancement of enteral feed volumes did not reduce the risk of NEC in VLBW infants.

Furthermore increasing the volume of enteral feeds at slow rather than faster rates results in several days delay in regaining birth weight and establishing full enteral feeds but the long term clinical importance of these effects was unclear. Finally they suggested that further randomised controlled trials are needed to determine how the

Table-IV: Characteristics of neonates with NEC.

Case	Group	GA (Weeks)	BW (Grams)	Age feeds Begun (Day)	Age of NEC (Day)	Age at discharge (Day)	BW at 30 days
1	M	30	900	3	22	42	1030
2	M	28	1010	3	15	52	1030
3	M	32	850	2	5	31	1250
4	A	29 (5d)	1060	6	11	45	1130
5	A	34	1180	2	11	22	1600
6	A	32	740	2	6	Death	Death
7	A	28 (5d)	970	3	29	38	1350
8	A	35	1480	2	13	27	2050
9	A	30	1050	4	10	31	1250
10	A	30	1380	5	17	23	1600
11	A	28 (4d)	1210	3	15	70	1280
12	A	28 (5d)	1200	2	6	Death	Death
13	A	26 (6d)	980	4	10	35	1200
14	A	32	1200	9	18	53	1600
15	A	30	1130	4	24	34	1260

rate of daily increment in enteral feed volumes affects clinical outcomes in VLBW infants.²⁵ Based on our study although with longer period of low milk, full enteral feeding time increases, but complications such as NEC and feeding intolerance were reduced therefore it can be suggested as an initiative to improve infant feeding management.

CONCLUSION

Due to the potential risks of NEC in preterm infants and based on the findings of this study which showed that prolonged low milk volume in newborn babies could reduce the incidence of NEC and considering that the average duration of hospitalization and birth weight at 30 days and in both groups showed no significant difference this feeding strategy could be suggested for VLBW neonates. Further studies need to be conducted to confirm our findings.

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