Safety of Initiating Early Enteral Feeding with Slow Volume Advancement in Preterm Infants

Kriangsak Jirapaet MD, MPH*,
Veena Jirapaet RN, PhD**, Suthida Sritipsukho MD***

** Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Faculty of Nursing, Chulalongkorn University, Bangkok, Thailand*
**** Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

Objective: *To determine the safety of enteral feeding within 24 hours of life with slow volume increase on the incidence of necrotizing enterocolitis (NEC) and late-onset sepsis (LOS).*
Design: *Prospective descriptive study.*
Material and Method: *Between January 1998 and December 2001, 117 preterm infants with birth weight ≤ 1,750 g were recruited prospectively, 102 in the human-milk-fed group (HMG) and 15 in the formula-fed group (FG). Feeds were advanced by increments of 10 mL/kg/d, aimed at 150 mL/kg/d in 15 days. Charts of 146 preterm infants admitted during 1996-1997 were reviewed for pre-study incidences of NEC and LOS.*
Results: *NEC developed 3.92% in HMG and 20% in FG (p =.044). LOS developed 2.94% in HMG and 13.33% in FG (p = 0.122). The overall incidence of NEC was almost similar (5.98% vs. 6.16%) while that of LOS was lower (4.27% vs. 12.32%) when compared to the pre-study incidences.*
Conclusion: *The present study provides a practice that seems to reduce LOS risk without increasing NEC risk and confirms the protective effect of human milk against NEC.*

Keywords: *Human milk, Early feeding, Slow volume advancement, Necrotizing enterocolitis, Preterm infant, Late-onset sepsis*

J Med Assoc Thai 2010; 93 (10): 1177-87
Full text. e-Journal: *http://www.mat.or.th/journal*

A standardized feeding regimen in preterm infants for reducing the risk of necrotizing enterocolitis (NEC) while promoting growth has not yet been established. Controversy surrounding the timing of initial enteral feeding and the rate of volume advancement still exists[1,2]. Concern about NEC has precluded preterm infants from early enteral feeding[1,3]. Our anecdotal evidence[4], which is consistent with existing evidence[3,5-11], has shown that withholding enteral feeding and administering parenteral nutrition for prolonged periods to preterm infants has been associated with feeding intolerance, cholestasis, poor growth, osteopenia of prematurity, NEC and infection that may result in death. The risk of sepsis and other complications during total parenteral nutrition (PN) is high and may more than offset any reduction in the risk of NEC[12]. Furthermore, the cost of PN, which is not available at every hospital, is higher when compared to enteral feeding[4,13].

The purpose of the present study was to investigate the safety of enteral feeding initiated within 24 hours of life and advanced feeding volume with an increment of 10 mL/kg/d with avoidance of discontinuation of feeding in preterm infants with birth weight of, or less than, 1,750 g. The primary outcome measure was the incidence of NEC and the secondary outcome measure was the incidence of late-onset sepsis (LOS).

Material and Method

A prospective study of preterm infants cared for at the intermediate care nursery (ICN) and level IIIB neonatal intensive care unit (NICU) of a tertiary university hospital in Bangkok Thailand, between January 1998 and December 2001 was conducted.

Correspondence to:
Jirapaet K, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone & Fax: 0-2418-2560
E-mail: sikjr@mahidol.ac.th

Subjects

All eligible preterm infants with birth weight of, or less than, 1,750 g were enrolled in the present study if they met the inclusion criteria: Apgar score of > 7 at 5 minutes without cardiac compression, no hypotension, no vomiting or bilious-stained gastric aspirate, non-distended and soft abdomen, no major anomalies and congenital abnormalities of gastro-intestinal tract, and clinically stable infant. Gestational age was determined by the last menstrual period and ultrasound. If these two assessment tools were not available or when discrepancies of more than two weeks were present, the Ballard maturation score to assess gestational age was used. Eligible infants were assigned to either receive own mother's milk (human-milk-fed group, HMG) or premature formula (formula-fed group; FG) based on mothers' decision. HMG infants were excluded if they required mixed feeding of HM and formula for longer than 7 days, which was a confounding factor on the present study outcomes.

Charts of preterm infants with a birth weight of, or less than, 1,750 g who were admitted and cared for in the ICN and NICU during 1996 and 1997 and met the same inclusion criteria were reviewed to compare the pre-study incidences of NEC and LOS with the present study outcomes. No major changes in the care of preterm infants occurred in the sick newborn wards during this time except feeding practice. The pre-study feeding routines included initiation of intravenous dextrose solution within the first hours of life and enteral feeding was started on day 3. When there was gastric residual of 20% or more, of individual feeding volume, enteral feeding was discontinued. PN was started when enteral feeding was not tolerated.

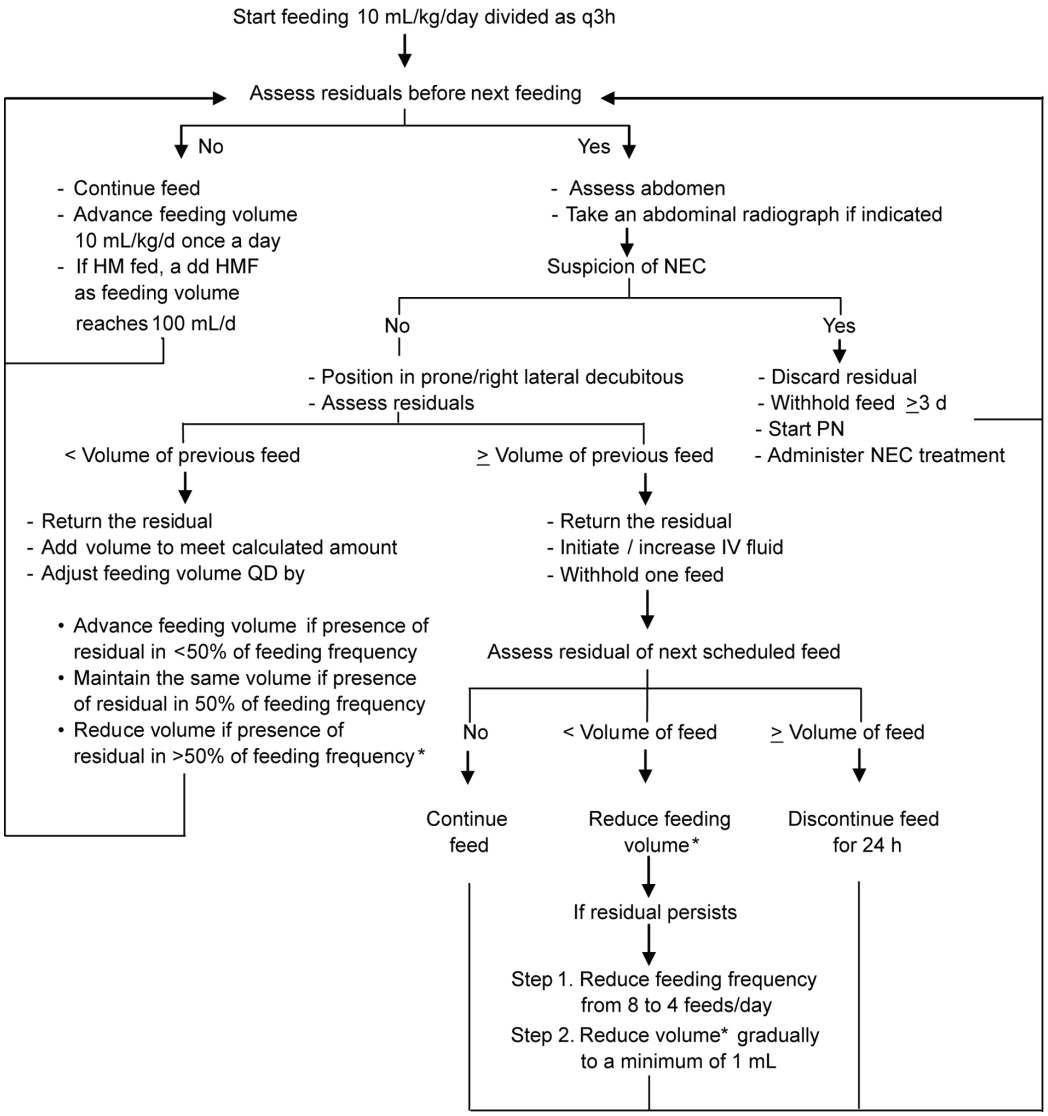
Feeding protocol

In the authors' practices, all mothers have been provided free board and lodging in the sick newborn wards and encouraged to participate in the care of their infants 24 hours a day as a means to prevent NEC and LOS since 1983. The present feeding strategy (Fig. 1) was to initiate very early feeding and avoid discontinuation of enteral feeding unless NEC was diagnosed. Feeding volume adjustment was based on the difference between feeding amount and gastric residual. Placing the infant in the prone or right lateral decubitus position was emphasized during and after feeding when there was gastric residual.

Enteral feeding was initiated as soon as possible within 24 hours of life when the infant's condition was considered to be stable by the attending neonatologist. Feeds were started at 10 mL/kg/day divided as q3h and advanced by increments of 10 mL/kg/d. The aim was to reach full enteral feed in 15 days (150 mL per kg by birth weight per day). Advancement was initially every day if the infant tolerated the previous 24 hours of feeding. When the infant tolerated feeding well for 4 days and the volume of feeding was behind that which the infant should have received according to age in days of life, feeding was increased every 12 hours until full feeding according to age in days of life was reached. Human milk was either freshly expressed before each feed or kept in the refrigerator. If mother's HM was not available when feeding was initiated or not enough, premature formula (24 kcal/ounce) as used in FG was provided initially until HM was available or enough. Expressed HM was fortified with human milk fortifier to a caloric density of 22 kcal/ounce when feeding volumes reached 100 mL a day and to 24 kcal/ounce when a volume of 150 mL/kg/d was attained.

Method of feeding was intermittent orogastric gavage feedings and administered by gravity infusion in 15 to 20 minutes when body weight was less than 1,650 g. If low oxygen saturation (SpO_2) monitored by pulse oximeter, apnea and/or vomiting developed during or immediately after gavage feeding, the feeding time was increased in an increment of 15 minutes. Spoonfeeding was tried when body weight was 1,650 g, a body weight correlating with a gestational age of 34 weeks at which coordination and integration of sucking, swallowing, and breathing is well developed.[14] When body weight was 1,700 g and the infant could swallow all feed by spoon, breastfeeding was tried with close monitoring for low SpO_2. When low SpO_2 developed, oxygen via cannula was administered. If low SpO_2 was not alleviated, breastfeeding was postponed for a week. Estimates of intake were made by weighing the infant just before and immediately after breastfeeding. The weight difference in grams estimated the milliliters of HM consumed. If the amount sucked was less than the calculated volume, then the infant was spoonfed to meet the calculated volume.

Infants were given dextrose 10% in water 60 mL/kg/d intravenously when enteral feeding could not be started within 4 hours of life or there was hypoglycemia (< 40 mg/dL) that did not ameliorate with enteral feeding. When enteral feeding was successful, the rate of intravenous feeding was reduced to keep the total fluid intake appropriate for advancing postnatal age with a weight loss of 10% of the birth



HM = human milk; HMF = human milk fortifier; NEC = necrotising enterocolitis; PN = total parenteral nutrition; QD = every day

* Reduce feeding volume to the amount passing out the stomach (difference between feeding amount and gastric residual)

Fig. 1 Flow chart illustrating feeding strategy

weight on day 4 to 5 of life. The regain in birth weight was in the second week of life. When infants received full enteral feed according to days of postnatal life for two consecutive days and had normoglycemia, intravenous fluid was discontinued and blood sugar was measured at 1 and 12 hours later. Intravenous fluid was discontinued as soon as possible to reduce the risk of skin damage associated with angiocatheter placement and intravenous fluid leakage and stress from angiocatheter insertions. If the infant could not tolerate feedings within 48 hours after birth or developed NEC, PN was administered.

The infant was evaluated for possible sepsis and/or NEC by obtaining a complete blood count and abdominal radiograph if symptoms and signs of sepsis and feeding intolerance were observed. NEC was defined using Bell's staging criteria. Serum potassium was evaluated once a week or when abdominal distention was detected and maintained at normal range according to the age in weeks of life.

Early-onset sepsis was defined as a systemic illness with clinical signs of sepsis and positive blood culture, developing within the first week of life[15]. LOS was defined as a systemic illness with clinical signs of sepsis and positive blood culture, developing after the first week of life to three months[15].

The infant was weighed at the same time every day using an electronic scale. A weight loss of no more than 10% of birth weight was allowed. Bedside records were reviewed daily for feeding characteristics and outcome. Infants were discharged home when they weighed ≥ 1,700 g, sucked well, had euthermia in a room temperature of 27°C-28°C and had good weight gain (15 g/kg/d or more). All infants were in the present study until hospital discharge.

Statistical analysis

Frequency counts and percentages or means, standard deviations, median and range were calculated as appropriate. Categorical variables were compared using Fisher's Exact test. Continuous variables were compared with t-test or Mann-Whitney U test where appropriated. P-values of 0.05 were considered significant.

Results

Of the 122 preterm infants who were eligible for the present study, five infants were excluded due to mixed feeding beyond day 7 of life from HM inadequacy. As a result, 117 infants completed the present study. No infant was removed from the present study or died. One hundred and two infants received own mother's milk and 15 were formula fed. Only one study infant in HMG required mechanical ventilation. Conditions and treatment found only in infants in HMG were anemia (n = 5), polycythemia from multiple gestation required partial exchange transfusion (n = 8) and blood exchange transfusion (n = 1). Characteristics of mothers and study infants, selected illness or conditions and obstetric complications associated with the study outcomes were similar between the two groups except multiple gestations (Table 1, 2).

Comparing obstetrical complications affecting antimicromial uses in the infants between groups (Table 1), there were no statistical differences in the number of mothers who had rupture of membranes > 18 h (p = 0.52), chorioamnionitis (p = 0.32) and urinary tract infection (p = 0.42). Regarding factors associated with reduced NEC risk, there was no difference in the

Table 1. Selected maternal demographic data, illness and obstetric complications

	HMG* (n = 102)	FG Group* (n = 15)	p-value
Maternal age: teenage/advanced	5 (4.9)/10 (9.8)	1 (6.6)/4 (26.6)	1.00
Number of pregnancies:			0.56
Para I	64 (62.7)	11 (73.3)	
Multipara	38 (37.2)	4 (26.6)	
Obstetrical complications			
IUGR	5 (4.9)	1 (6.6)	0.567
Pregnancy induced HT	19 (18.6)	3 (20)	1.00
Rupture of membranes > 18 h	26 (25.5)	2 (13.3)	0.52
Chorioamnionitis	7 (6.8)	2 (13.3)	0.32
Intrapartum/postpartum fever > 38°C (100.4°F)	1 (0.9)/1(0.9)	0	
Placenta previa with antepartum hemorrhage	2 (1.9)	0	
Receipt of antenatal antibiotic	8 (7.8)	1 (6.6)	1.00
Receipt of antenatal steroid	23 (22.5)	2 (13.3)	0.52
Number of doses 1	9 (8.8)	0	
2	3 (2.9)	1 (6.6)	
3	3 (2.9)	0	
4	8 (7.8)	1 (6.6)	
Delivery by: vagina/cesarean section	68 (66.6)/34 (33.3)	8 (53.3)/7 (46.6)	0.38
Multiple gestation	11/98 (11.2)	1/13 (7.6)	0.00
Urinary tract infection	3 (2.9)	1 (6.6)	0.42

* Values represent in number (%)

HT = hypertension; IUGR = intrauterine growth retardation

Table 2. Characteristic and medical illness of infants in the human-milk-fed group and the formula-fed group by birth weight

Birth weight group, g	≤ 1,000 HMG/FG	1,001-1,250 HMG/FG	1,251-1,500 HMG/FG	1,501-1,750 HMG/FG	Total HMG/FG	p-value
Number of infants	4/1	9/1	34/5	55/8	102/15	
Gestational age, wk (mean ± SD)*	27.2 ± 2.0/29	31.4 ± 2.3/33	32.6 ± 1.8/32 ± 1.3	33.2 ± 1.6/33 ± 2	32.7 ± 2.2/32.2 ± 2.0	0.42
IUGR, n (%)	0/0	1/0	2/0	2/1	5 (4.9)/1 (6.6)	0.57
Sex: male:female, n	3:1/1:0	1:8/1:0	13:21/4:1	29:26/4:4	46:56/10:5	0.17
Birth weight, g (mean ± SD)*	875 ± 136/870	1,214 ± 45/1,230	1,370 ± 77/1,334 ± 65	1,634 ± 65/1,620 ± 70	1,483 ± 206/1,449 ± 229	0.59
Apgar score 5 min, median (range)					10 (6-10)/9 (7-10)	0.28
PDA, n (%)	2/1	6/0	10/2	7/1	25 (24.5)/4 (26.6)	1.0
Receipt of indomethacin, n (%)	0/0	2/0	1/1	4/0	7 (6.8)/1 (6.6)	1.0
Respiratory distress, n (%)	3/1	7/0	16/5	24/2	50 (49)/8 (53.3)	0.79
Receipt of oxygen	1/1	6/0	11/3	9/0	27 (26.5)/4 (26.6)	1.00
$FiO_2 \leq 0.4$, n	0/1	2/0	5/3	7/0	14 (51.9)/4 (100)	0.28
$FiO_2 > 0.4$, n	1/0	4/0	6/0	2/0	13 (48.1)/0	
Receipt of nasal CPAP, n (%)	0/0	2/0	1/1	1/0	4 (3.9)/1 (6.6)	0.50
Receipt of no intravenous fluid, n (%)	0/0	0/0	2/0	9/1	11 (10.8)/1 (6.6)	1.00
Receipt of parenteral nutrition, n (%)	3/1	5/0	5/1	4/1	17 (16.7)/3 (20)	0.72
Umbilical catheterization, n (%)	2/1	4/0	5/2	5/1	16 (15.7)/4 (26.6)	0.18
Necrotizing enterocolitis, n	2/1	0/0	1/1	1/1	4 (3.9)/3 (20)	0.04
Sepsis: early:late onset, n (%)	1:0/1:1	0:0/0:0	3:0/0:1	0:0/2:0	4 (3.9):0/3(2.9):2 (13.3)	-/0.12

Mean ± SD values reports when n > 1
IUGR = intrauterine growth retardation; PDA = patent ductus arteriosus; CPAP = continuous positive airway pressure

Table 3. Feeding tolerance characteristic in the human-milk-fed group and the formula-fed group (mean ± SD)

Birth weight group, g	≤ 1,000 HMG/FG	1,001-1,250 HMG/FG	1,251-1,500 HMG/FG	1,501-1,750 HMG/FG	Total HMG/FG	p-value
Age at first successful enteral feeding*, h (mean ± SD)	17.0 ± 4.7/27	42.7 ± 21.5/19	19.4 ± 14.3/20.4 ± 11.6	12.0 ± 9.5/12.4 ± 11.6	19.6 ± 15.0/16.5 ± 11.3	0.42
Age at full volume reached, d (mean ± SD)	18.0 ± 4.1/16	15.2 ± 3.1/13	15.3 ± 7.8/25 ± 17.1	12.8 ± 4.5/14.6 ± 7.6	14.3 ± 5.6/17.6 ± 11.1	0.23
Plasma glucose level**, mg/dL (mean ± SD)						
at 1 h	78.0 ± 12.1/70	70.2 ± 10.8/73	63.0 ± 17.2/73.4 ± 20.8	64.0 ± 13.6/95.3 ± 14.0	64.7 ± 14.1/79.6 ± 27.3	0.12
at 12 h	81.0 ± 13.5/80	73.6 ± 21.6/58	70.9 ± 21.1/82.0 ± 13.9	64.5 ± 12.2/61.7 ± 4.7	68.1 ± 15.8/73.3 ± 14.5	0.31

Mean ± SD values reports when n > 1
* First success feeding defined as no gastric residual after feeding of 10 mL/kg/day divided as q3h
** Plasma glucose level after IV fluid discontinuation

number of pregnancy induced hypertension (p = 1) and receipt of antenatal steroid of more than one dose (p = 0.52). In connection with factors increasing risk of NEC and LOS (Tables 2), there were no statistical differences between groups in the number of IUGR (p = 0.56), Apgar scores at 5 minutes (p = 0.28), PDA (p = 1), receipt of indomethacin (p = 1), umbilical catheterization (p = 0.18), and receipt of intravenous fluid (p = 1) and PN (p = 0.72).

Enteral feedings could be successfully given within 4 hours of life in 11 infants in the HMG (10.7%) and one in the FG (6.6%) without intravenous dextrose and parenteral nutrition (Table 2). For those receiving only 10% dextrose solution intravenously, all except one in 91 infants of HMG and all 14 of infants in FG, could tolerate feeds and their intravenous glucose could be successfully withheld as planned. All plasma glucose levels were normoglycemic at 1 hour and 12 hours after the discontinuation of intravenous dextrose in both groups (Table 3). Only one infant in the HMG who had been on dextrose solution for hypoglycemia still had marginal plasma glucose level when the amount of HM was full feed according to age in day of life for two consecutive days. As a result, intravenous dextrose infusion had to be continued.

NEC was observed in seven studied infants (5.98%) of which five were under 1,500 g, six (86%) had PDA of which four (57%) received indomethacin and one had umbilical venous catheter placement (Table 4). All infants had suspected NEC. The incidence of NEC was significantly lower in HMG 3.92% (4 in 102 infants) and 20% (3 in 15 infants) in FG. (p = 0.044). The incidences were 9.2% (5 in 54) in infants under 1,500 g, 4.08% (2 in 49 infants) in infants weighing 1,001 to 1,500 g, and 50% (2 in 4 infants) in those weighing 751 to 1,000 g. Although infants in HMG had polycythemia, exchange transfusion and blood transfusion that risked NEC, the incidence of NEC was lower than infants in FG..

The overall incidence of LOS was 4.27% (5 in 117 infants). The LOS incidences did not differ between HMG and FG (2.94% vs. 13.33%; p = 0.12). In infants less than 1,500 g, the incidence of LOS was 2.12% (1 in 47) in HMG and 28.57% (2 in 7) in FG.

Chart review for the pre-study NEC and LOS incidences, 154 infants met the study inclusion criteria. Eight infants, who received both HM and formula beyond day 7 of life, were not included in the review. Eighty six percent of infants (125 of 146) received HM and 14% (21 of 146) received formula. There were no statistical differences in the number of infants who

Table 4. Characteristics of infants with NEC

Case	Feeding group	GA (weeks)	BW (grams)	PPROM/ chorioamnionitis	Antenatal steroids	PDA/ indomethacin	CPAP	Umbilical catheter	Age success feeds (hour)	Age exclusive HM (hour)	Age NEC developed (day)	Milk volume when NEC developed (mL/kg/d)	Age full feed (day)
1	HMG	25	690	No/No	Yes	Yes/Yes	No	No	12	168	22	150	22
2	HMG	27	860	No/Yes	No	Yes/No	No	No	15	15	15	150	15
3	HMG	30	1,320	No/No	No	Yes/Yes	Yes	No	20	66.5	9	80	56
4	HMG	31	1,570	Yes/No	Yes	Yes/Yes	No	No	11	84	12	122	35
5	FG	29	870	No/No	Yes	Yes/No	No	Yes	27	-	19	160	16
6	FG	31	1,340	No/No	No	Yes/Yes	Yes	No	27	-	14	125	56
7	FG	33	1,720	Yes/Yes	No	No/No	No	No	3	-	6	70	26

received HM and formula between infants in the two periods (p = 0.85). The overall incidence of NEC was almost similar (6.16% vs. 5.98%) while that of LOS was higher (12.32% vs. 4.27%) in pre-study period when compared to the present study.

Discussion

The evidence-based guidelines and recommendations for parenterally fed preterm infants are to provide a caloric intake of 50-60 kcal/kg/d, which approximates resting energy expenditure. It is a value for the maintenance requirements of preterm infants to prevent further glycogen, muscle, and fat breakdown for gluconeogenesis in the first few days to seven postnatal days[5].

The provision of PN requires the availability of essential components of PN, administration equipment (infusion/syringe pumps), pharmacists/ trained personnel and lamina airflow devices for mixing parenteral nutrition solutions, and venous catheters. Furthermore, facilities for intensive medical and nursing care and biochemical monitoring using microtechniques must be available when administering PN to preterm infants[16]. However, resources for providing PN are not available at every hospital where preterm infants are cared. Some hospitals have full resources and facilities but avoidance of its high cost, complications related to PN administration and intravenous catheter indwelling[17] and substantial risk of morbidity and mortality from bacterial contamination in the parenteral solutions is chosen unless there are absolute indications for PN[7]. Moreover, the beneficial effect of PN to premature infants in terms of developmental outcome compared to enteral feedings is of concern. Morris et al demonstrated that, with a caloric intake of 90-95 kcal/kg/day from total PN in one week of life started on day 2-3 after birth, there was an association between the length of time to reach full enteral feedings (120 kcal/kg/day) and mental developmental outcome at 24 months corrected age. Infants who reached full enteral feedings at an earlier age had a better developmental outcome when severity of respiratory illness, gestational age, and socioeconomic status were controlled. The explanation for this finding was that infants achieving full enteral feedings earlier received presumably better nutrition to meet the high growth demands of prematurity. In addition, there were hormonal effects produced by enteral feedings that were not reproducible with PN and might enhance an infant's ability to adapt, mature and grow in the extrauterine environment. All of these factors then provide for better development of the brain[18]. This evidence indicates that PN cannot be considered as a substitute for enteral feeding unless it is contraindicated or inadequate. As a result, feeding strategies that are feasible and suitable for preterm infants taken care of at hospitals with limitations in using PN and do not increase the risk of NEC, nosocomial infection, or suboptimal nutritonal status to the infants, should be sought.

This present study used a strategy that promotes gastrointestinal growth and motor function while preventing NEC by initiating enteral feeding within 24 hours after birth and using expressed HM from the premature infant's own mother, if available, and avoiding withholding of enteral feeds unless there was evidence of NEC. Close monitoring for signs of NEC while advancing feeds is crucial in preventing the devastating illness of NEC.

The present study has its limitation in that randomization of infants into HMG and FG was not feasible and that infants in the HMG received formula if HM was not available or enough at the beginning of enteral feeding since the authors used only mother's own human milk. Formula might increase the incidence of NEC in the HMG since it has been documented to increase the risk of NEC when compared to HM[1]. However, it should not be in the present cases. All infants in the HMG who had NEC had received exclusive HM for six days or longer (6-14 days) before developing NEC.

The feeding strategy used in the present study seemed not to increase NEC risk when compared to the present pre-study incidence (5.98% vs. 6.16%). The incidence of NEC in HMG, which was 3.92%, was lower than a previous report (4% to 13%)[1]. The incidence of NEC for infants weighing 1001 to 1500 g (4.08%) was also lower than a previous report (8%)[19]. For infants weighing 751 to 1000 g, the number of infants (4 infants) was too small for comparison.

All infants in the present study who developed NEC had multiple risk factors in addition to prematurity for NEC (Table 4). The major risk factors for NEC were PDA (86%; 6 in 7 infants) and receipt of indomethacin (57%; 4 in 7 infants), which have been linked to the development of NEC[20].

Factors that may affect LOS include prior antimicrobial use; prematurity; a high infant-to-nurse ratio in the NICU; and the presence of foreign materials such as indwelling venous catheters. Contaminated parenteral fluids also have been associated with systemic infections[21]. The practices used in the present

study can be considered as preventive measures for LOS. They were avoidance or discontinuation of intravenous fluid and PN as much or as soon as possible and parent empowerment by having mother participate in the infant care 24 hours a day. Mother participation could compensate for the high infant-to-nurse ratio by reducing the number of times that nurses had to contact the infants. Since mother participation in the infant care has been implemented in the studying unit since 1983, the contributing factor to a change in the incidence of LOS should be the early initiation of enteral feeding that reduced the use of parenteral fluid and PN.

The overall incidence of LOS was lower than the pre-study incidence (4.27% vs. 12.32%). In infants less than 1500 g (very low birth weight; VLBW), the incidence of both early-onset sepsis and LOS in this study was 13% (7 in 54), which was lower than previous reports from retrospective chart review performed in VLBW infants receiving either human milk or preterm formula of 42% (163 in 385) for nosocomial infection (sepsis appearing after 72 hours of age)[22]. Furthermore, the incidences of LOS, 2.12% (1 in 47) in the HMG, and 28.57% (2 in 7) in the FG, are lower than previous reports from retrospective study of 19.5% (24 in 123) in the HM-fed VLBW infants compared with 32.6% (29 in 89) in the exclusively formula-fed VLBW infants[23].

The present results are in agreement with previous systematic review and meta analysis[24] and studies[22,23,25,26] indicating a protective effect of HM against NEC[24,25] and LOS[22,23,26]. Moreover, it supports the practice of starting feeding within 24 hours of life without adding to the risk of NEC[27,28]. The protective effect of HM against NEC and sepsis is widely accepted[1,29]. Fresh HM contains many immunoprotective factors and PAF acetylhydrolase which inhibits platelet-activating factor (PAF), the phospholipid inflammatory mediator in the pathogenesis of NEC[1]. Furthermore, human milk is believed to promote intestinal colonization with Lactobacillus[1]. Studies comparing HM from preterm mothers with that from term mothers suggest that these immunologic benefits may be even greater for preterm infants because secretory immunoglobulin A (IgA), lysozyme, lactoferrin, and interferon are found in greater concentrations in preterm HM as compared with term milk[31-33]. In addition, the lower incidence of LOS can probably be the beneficial effect of early enteral feeding and shortening the period of and/or an avoidance of administering intraveonus nutrition that have been found associated with a decreased rate of infection/nosocomial sepsis[1,33,34].

The practices used in the present study are in agreement with those considered by the Vermont Oxford Study Group as care practices that can reduce the risk of nosocomial sepsis. They are initiation of enteral feedings as early as possible, promotion of the use of HM, reduced exposure to intravenous lipids and hyperalimentation, and reduced frequency of skin punctures for placement of an intravenous catheter[17]. Moreover, the advantage of gavage bolus feed by gravity in 15 to 30 minutes used in the present study was supported by a previous study conducted by Schanler et al[35]. They found that bolus feeding over 20 minutes resulted in better feeding tolerance and growth than the continuous tube-feeding method, and obviated the need for costly infusion pumps and support care. They concluded that early GI priming with HM, using the bolus tube-feeding method, might provide the best advantage for the preterm infant.

The practice of positioning infants in right lateral decubitus and prone positions during and after bolus feeding is supported by a study of the effect of body position during and after bolus feeding upon gastric emptying or gastric residual by Cohen et al[36]. They found that the amount of gastric residuals measured at 1 hour after a meal appeared to be in the following decreasing order: left, supine, prone, right.

Preterm infants will be relatively protein and calorie restricted with an initiation and advancement rate of 10 mL/kg/d. The length of time needed to reach an energy intake of 50 kcal/kg/d is 8 days and 4 days if with 60 mL/kg/d of dextrose 10% in water. It has been documented that infants receiving glucose alone without amino acids obligatory lose at least 1% of their endogenous nitrogen stores daily[37]. Nonetheless, HM from mothers delivering preterm, which contains higher protein content and caloric density than milk from mothers who deliver at term, may render both less negative nitrogen balance and inadequacy of provision of nutrition/caloric intake[38-40]. The disadvantages of receiving a caloric intake less than the resting energy expenditure and having a negative nitrogen balance while advancing feeding volume should be weighed against various complications associated with PN and lipid if started at day 1 of life and indwelling catheter. Moreover, the increased risk of poor growth and neurodevelopmental delay associated with NEC and LOS should be enough for balancing the risks of inadequate nutrition in the first few days of life with those of PN[1,41-43]. Whether these risks clinically

outweigh the benefits of higher energy intake for small preterm infants has not been studied. The benefit of PN that improves the survival of infants through better growth evidenced in institutes with full facility for PN may not be found in those with limitation in administering PN. At this time, when the optimal feeding strategies have not been defined, appropriate and specific markers by which to monitor the safety of various approaches to enteral feeding in preterm infants are lacking and as randomization to HM and formula is unethical, the present study has provided another feeding strategy for future clinical trials of adequate size to address this fundamental issue.

Conclusion

The feeding regimen applied in the present study population is based on experience, which has proved to be safe and well tolerated by premature infants. It demonstrates that early feeding in premature infants is possible at early hours of life. The feeding volume adjustment is based on the amount of milk passing out of the stomach. The observation favors human milk as it is shown to reduce risk of NEC by 5 times, compared with infants fed formula.

References

1. Jesse N, Neu J. Necrotizing enterocolitis: relationship to innate immunity, clinical features, and strategies for prevention. NeoReviews 2006; 7: e143-9.
2. Patole S. Strategies for prevention of feed intolerance in preterm neonates: a systematic review. J Matern Fetal Neonatal Med 2005; 18: 67-76.
3. Desai NS. Nutritional management. In: Gomella TL, Cunningham MD, Eyal FG, editors. Neonatology. 6th ed. New York: McGraw-Hill; 2009: 77-108.
4. Jirapaet K. Use of breast milk in preterm and sick infants. In: Jirapaet K, Jirapaet V, editors. Principles of basic newborn care. Bangkok: The War Veterans Organization of Thailand Press; 2002: 55-64.
5. Poindexter BB, Leitch CA, Denne SC. Parenteral nutrition. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 679-93.
6. Spear AL, Coleman MM. Intravenous alimentation. In: Spitzer AR, editor. Intensive care of the fetus and neonate. 2nd ed. Philadelphia: Elsevier Mosby; 2005: 1001-5.
7. Georgieff MK. Nutrition. In: Donald MG, Mullett MD, Seshia MMK, editors. Avery's neonatology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 380-412.
8. Cronin WA, Germanson TP, Donowitz LG. Intravascular catheter colonization and related bloodstream infection in critically ill neonates. Infect Control Hosp Epidemiol 1990; 11: 301-8.
9. Beganovic N, Verloove-Vanhorick SP, Brand R, Ruys JH. Total parenteral nutrition and sepsis. Arch Dis Child 1988; 63: 66-7.
10. Nicholls JM, Yuen KY, Saing H. Malassezia furfur infection in a neonate. Br J Hosp Med 1993; 49: 425-7.
11. Sherertz RJ, Gledhill KS, Hampton KD, Pfaller MA, Givner LB, Abramson JS, et al. Outbreak of Candida bloodstream infections associated with retrograde medication administration in a neonatal intensive care unit. J Pediatr 1992; 120: 455-61.
12. Williams AF. Role of feeding in the pathogenesis of necrotizing enterocolitis. Semin Neonatol 1997; 2: 263-71.
13. Pereira GR, Chan SW. Feeding the critically ill neonate. In: Spitzer AR, editor. Intensive care of the fetus and neonate. 2nd ed. Philadelphia: Elsevier Mosby; 2005: 987-9.
14. Ryckman FC, Balistreri WF. Upper gastrointestinal disorders. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 1263-8.
15. Edwards MS. Postnatal bacterial infections. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's Neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 791-829.
16. Yu VY. Extrauterine growth restriction in preterm infants: importance of optimizing nutrition in neonatal intensive care units. Croat Med J 2005; 46: 737-43.
17. Polin RA, Saiman L. Nosocomial infections in the neonatal intensive care unit. NeoReviews 2003; 4: e81-8.
18. Morris BH, Miller-Loncar CL, Landry SH, Smith KE, Swank PR, Denson SE. Feeding, medical factors, and developmental outcome in premature infants. Clin Pediatr (Phila) 1999; 38: 451-7.
19. Stoll BJ. Epidemiology of necrotizing enterocolitis. Clin Perinatol 1994; 21: 205-18.
20. Rodriguez RJ, Martin RJ, Fanaroff AA. Respiratory distress syndrome and its management. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 1097-107.
21. Edwards MS. Postnatal bacterial infections. In:

Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 791-804.
22. Flidel-Rimon O, Friedman S, Lev E, Juster-Reicher A, Amitay M, Shinwell ES. Early enteral feeding and nosocomial sepsis in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004; 89: F289-F292.
23. Hylander MA, Strobino DM, Dhanireddy R. Human milk feedings and infection among very low birth weight infants. Pediatrics 1998; 102: E38.
24. McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed 2003; 88: F11-4.
25. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol 2007; 27: 428-33.
26. el Mohandes AE, Picard MB, Simmens SJ, Keiser JF. Use of human milk in the intensive care nursery decreases the incidence of nosocomial sepsis. J Perinatol 1997; 17: 130-4.
27. Troche B, Harvey-Wilkes K, Engle WD, Nielsen HC, Frantz ID III, Mitchell ML, et al. Early minimal feedings promote growth in critically ill premature infants. Biol Neonate 1995; 67: 172-81.
28. Ostertag SG, LaGamma EF, Reisen CE, Ferrentino FL. Early enteral feeding does not affect the incidence of necrotizing enterocolitis. Pediatrics 1986; 77: 275-80.
29. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005; 115: 496-506.
30. Gross SJ, Buckley RH, Wakil SS, McAllister DC, David RJ, Faix RG. Elevated IgA concentration in milk produced by mothers delivered of preterm infants. J Pediatr 1981; 99: 389-93.
31. Murphy JF, Neale ML, Matthews N. Antimicrobial properties of preterm breast milk cells. Arch Dis Child 1983; 58: 198-200.
32. Goldman AS, Chheda S, Keeney SE, Schmalstieg FC, Schanler RJ. Immunologic protection of the premature newborn by human milk. Semin Perinatol 1994; 18: 495-501.
33. Okada Y, Klein N, van Saene HK, Pierro A. Small volumes of enteral feedings normalise immune function in infants receiving parenteral nutrition. J Pediatr Surg 1998; 33: 16-9.
34. Kilbride HW, Powers R, Wirtschafter DD, Sheehan MB, Charsha DS, LaCorte M, et al. Evaluation and development of potentially better practices to prevent neonatal nosocomial bacteremia. Pediatrics 2003; 111: e504-18.
35. Schanler RJ, Shulman RJ, Lau C, Smith EO, Heitkemper MM. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. Pediatrics 1999; 103: 434-9.
36. Cohen S, Mandel D, Mimouni FB, Solovkin L, Dollberg S. Gastric residual in growing preterm infants: effect of body position. Am J Perinatol 2004; 21: 163-6.
37. Anderson TL, Muttart CR, Bieber MA, Nicholson JF, Heird WC. A controlled trial of glucose versus glucose and amino acids in premature infants. J Pediatr 1979; 94: 947-51.
38. Denne SC, Poindexter BB, Leitch CA, Ernst JA, Lemons PK, Lemons JA. Enteral nutrition. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 8th ed. Philadelphia: Mosby Elsevier; 2006: 661-79.
39. Kovacs A, Funke S, Marosvolgyi T, Burus I, Decsi T. Fatty acids in early human milk after preterm and full-term delivery. J Pediatr Gastroenterol Nutr 2005; 41: 454-9.
40. Gross SJ, David RJ, Bauman L, Tomarelli RM. Nutritional composition of milk produced by mothers delivering preterm. J Pediatr 1980; 96: 641-4.
41. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004; 292: 2357-65.
42. Sonntag J, Grimmer I, Scholz T, Metze B, Wit J, Obladen M. Growth and neurodevelopmental outcome of very low birthweight infants with necrotizing enterocolitis. Acta Paediatr 2000; 89: 528-32.
43. Walsh MC, Kliegman RM, Hack M. Severity of necrotizing enterocolitis: influence on outcome at 2 years of age. Pediatrics 1989; 84: 808-14.

ความปลอดภัยในการเริ่มป้อนนมเร็วร่วมกับการเพิ่มนมอย่างช้า ในทารกเกิดก่อนกำหนด

เกรียงศักดิ์ จีระแพทย์, วีณา จีระแพทย์, สุทธิดา ศรีทิพย์สุโข

วัตถุประสงค์: *เพื่อศึกษาความปลอดภัยในการเริ่มป้อนนมภายใน 24 ชั่วโมง หลังเกิดร่วมกับการเพิ่มนมอย่างช้าต่ออุบัติการณ์ของการเกิดภาวะลำไส้เปื่อยเน่าเฉพาะที่ (necrotizing enterocolitis; NEC) และการติดเชื้อในเลือดหลังเกิด 7 วัน (late-onset sepsis; LOS)*

รูปแบบการศึกษา: *การศึกษาไปข้างหน้า*

วัสดุและวิธีการ: *ทำการศึกษาทารกเกิดก่อนกำหนดที่เกิดระหว่างเดือนมกราคม พ.ศ. 2541 และเดือนธันวาคม พ.ศ. 2544 จำนวน 117 ราย ที่มีน้ำหนักแรกเกิดเท่ากับหรือต่ำกว่า 1,750 กรัม ทารก 102 ราย ได้รับน้ำนมแม่ (กลุ่มนมแม่) และ 15 ราย ได้รับนมผสม (กลุ่มนมผสม) การแบ่งกลุ่มขึ้นกับความสมัครใจของแม่ กลยุทธ์ใหม่ของการให้นมมีดังนี้ ให้ป้อนนมภายใน 24 ชั่วโมง หลังเกิด และเพิ่มนม 10 มิลลิลิตร/กิโลกรัม/วัน เพื่อให้ได้ปริมาณ 150 มิลลิลิตร/กิโลกรัม/วัน ใน 15 วัน หลีกเลี่ยงการงดนม ยกเว้นเมื่อทารกได้รับการวินิจฉัยว่าเป็น NEC เท่านั้น เน้นการจัดให้ทารกนอนคว่ำ หรือ นอนตะแคงขวาหากมีน้ำนมค้างในกระเพาะอาหาร ถ้าต้องลดปริมาณนมเพราะมีน้ำนมค้าง ให้เท่าปริมาณน้ำนมที่สามารถผ่านกระเพาะอาหาร โดยดูจากผลต่างของน้ำนมที่ป้อนกับของเหลือค้างในกระเพาะอาหาร รายงานของทารกเกิดก่อนกำหนดจำนวน 146 ราย ที่เกิดในปี พ.ศ. 2539 และ พ.ศ. 2540 ที่ได้รับการป้อนนมเมื่ออายุ 3 วัน และส่งเสริมการงดนม และที่เข้าเกณฑ์การศึกษา นำมาทบทวนเพื่อเปรียบเทียบอุบัติการณ์ โดยรวมของ NEC และ LOS*

ผลการศึกษา: *NEC พบในทารกกลุ่มนมแม่ร้อยละ 3.92 และทารกในกลุ่มนมผสมร้อยละ 20 ความแตกต่างนี้มีนัยสำคัญทางสถิติที่ ($p = 0.044$) LOS พบในทารกกลุ่มนมแม่ร้อยละ 2.94 และทารกในกลุ่มนมผสมร้อยละ 13.33 ความแตกต่างนี้ไม่มีนัยสำคัญทางสถิติ ($p = 0.122$) ทารกเกิดก่อนกำหนดที่ได้รับการป้อนนมเร็วมีอุบัติการณ์โดยรวมของ LOS ต่ำกว่าทารกเกิดก่อนกำหนดก่อนที่ใช้กลยุทธ์การป้อนนมช้า (4.27% vs. 12.32%) ขณะที่มีอุบัติการณ์โดยรวมของ NEC เกือบเท่ากัน (5.98% vs. 6.16%)*

สรุป: *การศึกษานี้ได้เสนอกลยุทธ์ใหม่ของการป้อนนมทารกเกิดก่อนกำหนดที่ลดการเสี่ยงต่อการเกิด LOS โดยไม่เพิ่มความเสี่ยงต่อ NEC และยืนยันฤทธิ์ปกป้องการเกิด NEC ของน้ำนมแม่*