ORIGINAL ARTICLE

Complications and Outcomes of Nutritional Guidelines Implementation in Low Birth Weight Infants

Chayanit Punsawat, MD[1], Thananjit wongsinin, MD[1]

[1] Department of Pediatrics, Bhumibol Adulyadej Hospital, Royal Thai Air Force Bangkok, Thailand

Background: Necrotizing enterocolitis (NEC) is one of the most disastrous complications of premature infants. Using preterm feeding protocols can decrease NEC risk and improve feeding intolerance.

Objective: To compare the rate of NEC and other comorbidities between low-birth-weight (LBW) infants that received a Bhumibol Adulyadej Hospital (BAH) standardized feeding protocol and those that underwent previous nutritional practice.

Materials and Methods: A quasi-experimental study was conducted at neonatal intensive care unit (NICU) in BAH, Thailand. Participants were LBW newborns delivered at BAH between December 1, 2018 and March 31, 2020. The subjects were divided into the control group who underwent previous nutritional practice and the study group who were implemented with a new nutritional guideline. Primary outcome was NEC rate. Secondary outcomes were preterm complications such as neonatal sepsis, catheter-related bloodstream infection, parenteral nutrition-associated liver disease, osteopenia of prematurity, and intraventricular hemorrhage. Feeding achievement outcomes and growth outcome parameters were also evaluated.

Results: Data were analyzed on 71 infants in the control group and 68 infants in the study group. The rate of NEC was not different between the two groups with 7% in the control versus 5.9% in the study (p=1.000). In addition, other preterm complications were not different between groups. However, the time to reaching full enteral feeding was shorter in the study group at 14 in the control versus 10 in the study (p<0.001). Day of life when the fortification start was significantly earlier in the study group at 15.5 in the control versus 12 in the study (p=0.008). Other feeding achievement outcomes also improved, which was evidenced by fewer parenteral nutrition (PN) days at 11.55 in the control versus 7.0 in the study (p=0.004) and shorter duration of indwelling central line at 9.5 in the control versus 7 in the study (p=0.001).

Conclusion: Initiation of the new nutritional guideline produced a lower rate of NEC as compared to previous practice. Furthermore, the time to full enteral feeding, PN days, and central line days were decreased without increasing other preterm complications.

Keywords: Low birth weight; Nutrition; Complication; NEC

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Low birth weight (LBW) is defined as a birth weight of less than 2,500 g as per the World Health Organization (WHO)[1]. Globally, it is estimated that 15% to 20% of all deliveries, or more than 20 million newborns annually, are LBW infants. In Thailand, the incidence of preterm birth is about 5.6% of live birth, and LBW is 9.8% of live births[2].

LBW infants may experience comorbidity, namely necrotizing enterocolitis (NEC) neonatal sepsis, feeding intolerance, and always need neonatal intensive care unit (NICU) care. NEC is one of the most catastrophic complications of premature infants[3]. Incidence of NEC in NICU is inversely correlated to gestational age and birth weight. It can be found in 5% to 10% of all very low birth weight (VLBW) infants, which weight between 1,000 to 1,499 g, and 10% of all extremely low birth weight (ELBW), which weight below 1,000 g[2,4].

In all infants, the feeding pattern is composed of enteral and parenteral routes.

As a consequence of feeding difficulties, achieving recommended dietary intakes needs longer time. Therefore, extrauterine growth restriction (EUGR) remains a problem in VLBW infants due to periods of inadequate nutrition, especially for neonates who are critically ill[5].

The use of preterm feeding protocols in NICU can improve feeding intolerance and decrease NEC

Correspondence to:

Punsawat C.

Department of Pediatrics, Bhumibol Adulyadej Hospital, 171 Phahonyothin Road, Khlong Thanon Subdistrict, Sai Mai District, Bangkok 10220, Thailand.

Phone: +66-81-2535796, **Fax**: +66-2-5347000

Email: chayanitnp@gmail.com

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risk[6,7]. Those studies recommended standardized nutritional guidelines.

In BAH, the incidence of preterm infants was 12% in 2019. Preterm were usually subjected to comorbidity, especially NEC. No standard feeding protocol existed at NICU at BAH for LBW infants.

The main objective of the present study was to compare the rate of NEC, based on Bell's stage 2 or greater, and other comorbidities that comprised of cultured proven neonatal sepsis, catheter-related bloodstream infection (CRBSI), Cholestasis jaundice (PNALD), osteopenia of prematurity (OOP), intraventricular hemorrhage (IVH) defined as grade 4, and death between LBW infants who received a BAH proposed standardized feeding protocol compared to those cared for under previous nutritional practice.

Materials and Methods

Study design, participants, and setting.

A quasi-experimental study was conducted at NICU of Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand. The study was approved by the Ethics Committees of BAH (IRB No.30/63). In addition, written informed consents were obtained from the parents of all the patients before study entry.

Participants were LBW newborns delivered at BAH between December 1, 2018 and March 31, 2020 admitted to NICU. Inclusion criteria were LBW newborn of 1,800 g or less. Exclusion criteria were newborn with contraindication for enteral feeding and congenital anomalies affecting the feeding ability, lethal congenital anomalies, and death before participation such as before starting enteral feeding.

Sample size estimation

The sample size was calculated based on a result from McCallie's study[8]. A power analysis was conducted with the primary outcome of interest being the rate of NEC in infants. Estimated proportions were derived from the results of a previous trial, revealing an estimated proportion of 0.18 in the group before initiation of a standardized feeding protocol group and 0.03 in after initiation. The significance level (α) was set a priori at $p<0.05$, and a power of 80% was chosen. The projected sample size was determined to be 65 infants in each group, ensuring adequate statistical power for the study. This calculation factored in a possible withdrawal rate of 10%. The actual sample size (per-protocol) was 72 subjects per group.

Subjects were divided into two groups, the study group and the control group. The control group consisted of subjects who underwent previous nutritional practices during the early phase of the present study. Among those with breast milk availability, breast milk was supplemented by 24 kcal/oz preterm formula as needed. Subjects with no available breast milk received 24 kcal/oz preterm formula according to the feeding guideline. The preterm formula was commercially purchased and related on a monthly basis with 24 kcal/oz requirement.

The study group comprised all the newborns who were born after implementation of the standardized feeding guidelines, which were changed in the later phase of the present study. The study group included newborns both with and without breast milk availability. Those with breast milk availability had their mother receive breastfeeding promotion program and support to increase milk production. The feeding followed the guideline. Those without mother breastmilk received 24 kcal/oz preterm formula with feeding quantity and schedule as presented.

Feeding guidelines in NICU

There were variations in nutritional practices when the previous feeding pattern was implemented. There was no specific day when to start enteral feeding or a defined duration for step feeding to achieve full total enteral feeding for LBW newborns. Additionally, there were no specific recommendations about choosing between breast milk or formula, nor about the appropriate components of nutrition in parenteral nutrition (PN) for LBW newborns. As a result, the authors developed standardized feeding guidelines designed to specify nutritional intakes, preferred feeding substances, advancement, and fortification of feeding, as well as the initiation and duration of trophic feeding.

These standardized LBW newborn feeding guidelines were developed in-house in 2018 through consensus of the NICU medical team, a multi-disciplinary working group that comprised neonatologists, NICU medical team, and nutritionist experts, and was based on recent literature.

Enteral feeding initiation in the study group was started as early as possible after birth, depending on the status of the respiratory and circulatory systems when there was no contraindication for enteral feeding. Colostrum care was promoted and enforced to be used as soon as possible in all participating infants. Enteral feeding was started with breast milk when available. However, when breast milk was

unavailable or inadequate, preterm formula was given as a substitute. Breast milk was fortified to 24 kcal/oz with human milk fortifier (Enfamil™, Mead Johnson and company, Indiana, United States of America) when feeding volume reached 80 mL/kg/day. The amount of trophic feeding and advancement was based on birth weight of the infants divided into three groups, less than 1,000, 1,001 to 1,400, and 1,401 to 1,800 g. Volume was fed in each day were defined. The advancement of volume each day was suggested based on pooled knowledge of these studies[6,8,9].

PN was started within 24 hours after birth with components described by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[10-16].

BAH current feeding guidelines recommended placing an umbilical venous catheter in infants to provide total parenteral nutrition (TPN) while increasing enteral feeding volume as tolerated. The central line would be removed when enteral feeding reached a total volume of 120 mL/kg/day. A peripherally inserted central catheter (PICC) line would be placed for infants when the central line was still needed after reaching a total volume of 120 mL/kg/day. Special considerations were considered in the present study.

Data collection

Baseline characteristics, complications, growth outcome parameters, and data about feeding achievement were obtained from the electronic medical record of each infant. The clinical data included information on gender, gestational age, birth weight, and others. Small for gestational age (SGA) is defined as birth weight of less than the tenth percentile based on the Fenton 2013 growth chart[17,18].

Complications in the present study included NEC based on Bell's stage 2 or greater, cultured proven neonatal sepsis, CRBSI, cholestasis jaundice (PNALD), OOP, IVH as defined as grade 4, and death. Body weight was recorded daily while length and head circumference were recorded once a week, specifically in the morning before the feeding, using an electronic digital scale (accuracy ±1 g). Each weight was measured with no clothes. The present study converted growth parameter to Z score was based on the Fenton 2013 growth chart and calculated by PediTools electronic growth chart calculator[17,18].

Feeding achievements during a stay in NICU were collected. These included the information about the day of life when feeding started, time to full feeding, time to regain weight, day of life when start fortification, number of day that infant did not receive enteral feeding as NPO days/number of days that infant received PN days/indwelling central line days, and rate of exclusive breast feeding at discharge.

Data analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe patient characteristics. Continuous data using the Man-Whitney U test in non-parametric data or independent t-test in parametric data. Chi-square or Fisher's exact test for categorical data. All p-values were two-sided, and p-values less than 0.05 were considered statistically significant.

Results

Electronic medical records from 152 infants with birth weight of 1,800 or less were reviewed. Five infants were excluded due to congenital anomaly and referred cases. One hundred forty-seven infants were analyzed. The control group started with 75 infants, but four infants were excluded due to early death before being fed. The study group started with 72 infants, but four infants were excluded due to early death, 68 infants left in the nutritional guidelines group (Figure 1).

The Demographic character of the control and the study groups are shown in Table 1. No significant differences were detected between the groups in baseline demographic data with male at 38 in the control versus 40 in the study (p=0.529), gestational age at 29.9±3.36 in the control versus 30.5±2.7 in the study (p=0.252), head circumference at 28 in the control versus 28 in the study, p=0.937), length at 41 in the control versus 40 in the study (p=0.310), birth weight at 1,408 in the control versus 1,422 in the study (p=0.646), SGA infants in 11 in the control versus 12 in the study (p=0.733), and route of delivery by normal labor by 39 in the control versus 33 in the study (p=0.45). A higher proportion of infants in the nutritional guideline group had been given antenatal steroids (p=0.044). The difference in the rate of use of antenatal maternal steroids used between the study group and the control group was possibly due to a change of trend in steroid-using from recent obstetrical guidelines. In addition, there were no significant differences in groups regarding the problem at birth, respiratory problem, respiratory support, inotrope use, gastrointestinal problems, and CVS disease (Table 2).

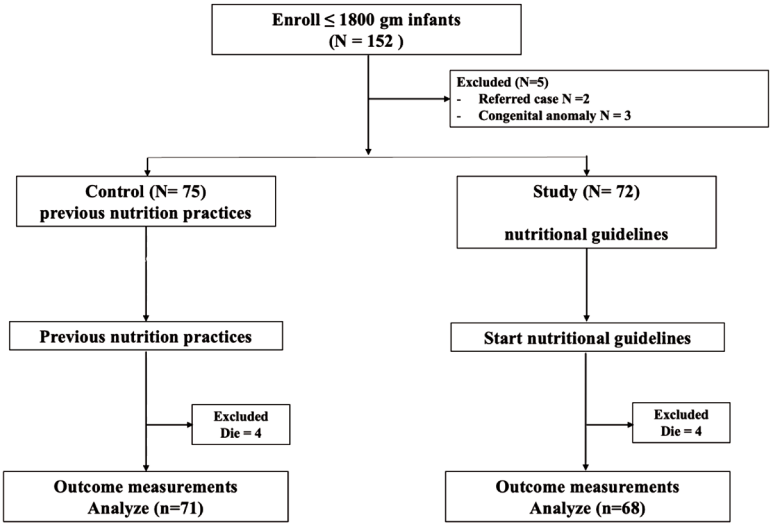

Figure 1. Study flow.

Table 1. Demographic character of LBW infant who were treated under previous feeding pattern group and nutritional guidelines

	Control (n=71)	Study (n=68)	p-value
Male; n (%)	38 (53.5)	40 (58.8)	0.529
GA (weeks); mean±SD	29.9±3.3	30.5±2.7	0.252
HC (cm); median [IQR]	28.0 [3]	28.0 [3]	0.937
LT (cm); median [IQR]	41.0 [8]	40.0 [6]	0.310
BW (g); n (%)			0.995
<1,000	15 (21.1)	14 (20.6)	
1,001 to 1,400	20 (28.2)	19 (27.9)	
1,401 to 1,800	36 (50.7)	35 (51.5)	
Median [IQR]	1,408.0 [522]	1,422.0 [593]	0.646
SGA; n (%)	11 (15.5)	12 (17.6)	0.733
Maternal antenatal steroid; n (%)	43 (60.6)	52 (76.5)	0.044
NL; n (%)	39 (54.9)	33 (48.5)	0.450
APGAR score; median [IQR]			
1 minute	8.0 [3]	8.0 [4]	0.947
5 minutes	9.0 [2]	9.0 [2]	0.785
10 minutes	10.0 [0]	10.0 [0]	0.838
LOS; median [IQR]	42.0 [36]	40.0 [47]	0.911

LBW=low birth weight infants; SD=standard deviation; IQR=interquartile range; GA=gestational age; HC=head circumference; LT=length of newborn; BW=birth weight; SGA=small for gestational age; NL=normal labor; LOS=length of stay

Control: previous feeding pattern, Study: nutritional guidelines

Table 2. Problem at birth of LBW infant who were treated under previous feeding pattern group and nutritional guidelines

	Control (n=71) n (%)	Study (n=68) n (%)	p-value
RS problem			0.393
TT	9 (12.7)	10 (14.7)	
TTNB	12 (16.9)	11 (16.2)	
RDS	42 (59.2)	34 (50.0)	
Others	0 (0.0)	3 (4.4)	
IRS	19 (26.8)	15 (22.1)	0.589
Inotrope	12 (16.9)	5 (7.4)	0.086
GI problem	5 (7.0)	2 (2.9)	0.442
Blood transfusion	31 (43.7)	19 (27.9)	0.054
CVS			
PDA	34 (47.9)	23 (33.8)	0.092
CHD	13 (18.3)	6 (8.8)	0.104
Others	1 (1.4)	5 (7.4)	0.111

LBW=low birth weight infants; RS=respiratory; TT=transitional period (period of adaptation from fetal to neonatal circulation); RDS=respiratory distress syndrome; IRS=invasive respiratory support (on endotracheal tube with ventilator); GI=gastrointestinal; CVS=cardiovascular problem; PDA=patent ductus arteriosus; CHD=congenital heart disease

Control: previous feeding pattern, Study: nutritional guidelines, Inotrope: inotropic drug used, Others: such as atrial septal defect, hypotension, arrhythmia

Complications are shown in Table 3. The present study found no statistically significant differences in the rate of NEC between the two groups with 7% in the control versus 5.9% in the study (p=1.000). Other complications included cultured proven neonatal sepsis at 15.5% in the control versus 10.3% in the study (p=0.361), CRBSI with 1.4% in the control versus 0% in the study (p=1.000), PNALD with 5.6% in the control versus 2.9% in the study (p=0.681), OOP with 2.8% in the control versus 0% in the study (p=0.497), IVH with 4.2% in the control versus 2.9% in the study (p=1.000), and death at 5.6% in the control versus 2.9% in the study (p=0.681) were not different between the two groups.

Table 3. Neonatal complications of LBW infant who were treated under previous feeding pattern group and nutritional guidelines

	Control (n=71) n (%)	Study (n=68) n (%)	p-value
NEC	5 (7.0)	4 (5.9)	1.000
Neonatal sepsis	11 (15.5)	7 (10.3)	0.361
CRBSI	1 (1.4)	-	1.000
PNALD	4 (5.6)	2 (2.9)	0.681
OOP	2 (2.8)	-	0.497
IVH	3 (4.2)	2 (2.9)	1.000
Death	4 (5.6)	2 (2.9)	0.681

LBW=low birth weight infants; NEC=necrotizing enterocolitis; CRBSI=catheter-related bloodstream infection; PNALD=parenteral nutrition-associated liver disease; OOP=osteopenia of prematurity; IVH=intraventricular hemorrhage

Control: previous feeding pattern, Study: nutritional guidelines

The results of feeding achievement outcomes, including time to full enteral feeding were significantly earlier in the nutritional guideline group with 14 in the control versus 10 in the study ($p<0.001$). Fortification started significantly earlier in the nutritional guideline group with 15.5 in the control versus 12 in the study ($p=0.008$) (Table 3). Feeding achievement also improved, as evidenced by fewer PN days at 11.55 in the control versus 7.0 in the study ($p=0.004$), a decreased number of indwelling central line days at 9.5 in the control versus 7 in the study ($p=0.001$), and a decreased number of NPO days with 1 in the control versus 0 in the study ($p=0.019$).

In terms of growth outcomes, the nutritional guideline group had much better weight, length, and head circumference parameters at 2 weeks compared to at admission. They also had better average birth weight, length, head circumference gain per day. Z score of weight, length, and head circumference, which were also improved from admission to discharge. However, no statistically significant differences were noted between the two groups. The head circumference difference from 2 weeks to admission is one of growth parameter that was increased at 0.99±1.19 in the control versus 1.39±0.94 in the study ($p=0.040$) in the nutritional guideline group.

Discussion

Since 2018, a new nutritional protocol was introduced in BAH NICU, according to the commitment between neonatologists, nutritionists, and NICU medical team. A new in-house nutritional protocol replaced the previous individual nutritional treatment pattern. The six baseline characters of preterm infants during the previous nutritional and the recent patterns were similar. Only the percentage of maternal antenatal steroid usage among of study group was higher than the control group with statistical significance. It was possibly due to a trend toward early steroid usage according to the American College of Obstetricians and Gynecology (ACOG) Guideline 2017, which recommends steroid usage in neonates whose gestational age was lower than 37 weeks instead of 34 weeks. Other baseline characteristics about the problems at birth were also similar between the two groups.

The goal of implementing recent nutritional protocol was to reduce the rate of NEC, Neonatal sepsis, PNALD, OOP, CRBSI, and neonatal death.

However, the parameters for monitoring of nutritional protocol among pre- and post-recent protocol were comparable in all parameters as mentioned.

In the present study, the NEC rate among infants in the study group decreased from 7% to 5% in the control group ($p=1.000$). However, even though the rate declined, it was not statistically significant. In previous studies, there was protective benefit in the implementation of standardized nutritional guidelines to decrease the incidence of NEC. McCallie et al.[8] found a difference in NEC rate from 18% before to 3% ($p=0.005$) after implementation among VLBW infants. It was probably due to the promotion of using breast milk, including donor milk, when mother's milk was unavailable. Therefore, the rate of using formula was decreased, due to increasing rate of banked donor breast milk.

Concerning neonatal sepsis due to prolongation of central line use, trophic feeding in the present study was applied only on the first day of life, and increased feeding per day in the group that had a difference in birth weight. From Barr et al.[6], the duration of trophic feeding was about three to four days, and McCallie et al.[8] was six to eight days, longer than the present study by about one to three days. Not only was the longer time in trophic feeding in these two studies, but the rate of using breast milk was higher in McCallie's study[8]. In Barr et al.[6], infants post protocol had also reduced rate of NEC at 7.8% versus 0% ($p=0.038$), but there was no decreased rate of late-onset neonatal sepsis at 19% versus 17% ($p=0.8$). The authors decreased the duration of trophic feeding in the study group concerning that the days of using of central line could be associated with an increased rate of CRBSI. However, the result

Table 4. Feeding initiation and achievement

	Control (n=71)	Study (n=68)	p-value
Day of life when start enteral feeding; median [IQR]	1.0 [1]	1.0 [0]	<0.001
Time to full enteral feeding; median [IQR]	14.0 [9]	10.0 [5]	<0.001
Time to regain birth weight; median [IQR]	10.0 [6]	9.0 [4]	0.230
NPO days; median [IQR]	1.0 [5]	0.0 [1]	0.019
PN days; median [IQR]	11.5 [9]	7.0 [6]	0.004
Central line days; median [IQR]	9.5 [6]	7.0 [9]	0.001
Fortification initiation; median [IQR]	15.5 [15]	12.0 [10]	0.008
Exclusive breastfeeding (yes); n (%)	20 (28.2)	25(36.8)	0.279

LBW=low birth weight infants; IQR=interquartile range; NPO days=number of day that infant was not received enteral feeding; PN days=number of days that infant was received parenteral nutrition

Control: previous feeding pattern, Study: nutritional guideline; Day of life when start feeding: day of life that enteral feeding was started, Time to full enteral feeding: day of life that infant received full enteral feeding 150 to 160 mL/kg, Central line days: number of days that infant was on central line, Fortification initiation: day of life when start fortification, Exclusive breast feeding: exclusive breast feeding at discharge

showed no significant rates of CRBSI between the two groups. The authors' working hypothesis is that a shorter duration in trophic feeding and reduced total days of using central line can be achieved without increasing the rate of neonatal sepsis.

There may be other factors related to the rate of NEC in BAH compared to the previous study. It is possible that the rates of NEC are influenced not only by the implementation of the nutritional guidelines, but also by other related factors.

Sullivan et al. demonstrated that feeding exclusively with a human-milk-based diet is associated significantly a lower rate of NEC than a diet of human-milk fortified with bovine milk-based products. However, in the present study, the rate of applying exclusive breastfeeding in both groups did not show any significant difference, which may influence the rate of NEC, despite the initiation of standardized feeding guidelines[19].

The present study most significant outcome noted was improved feeding achievement. Time to full feed of the study group was significantly shorter than previous nutritional practice at 14 days in the control versus 10 in the study (p<0.001). As a consequence of early removal of PN at 11.55 days in the control versus 7.0 in the study (p=0.004) and central lines at 9.5 days in the control versus 7 in the study (p=0.001), both of the duration was earlier than the control. Fortification of breast milk was also quicker implemented to the newborn in the study group at 15.5 days in the control versus 12 in the study (p=0.008). That was due to the implementation of nutritional guidelines that prescribed a definite time by the total volume of feeding in each day. The new protocol had an advantage over the previous protocol in decreasing the parameter of time to reaching full enteral feeding, PN days, central line days, and the day starting fortification with the similar complication to the previous protocol (Table 4).

McCallie et al.[8] noted that implementation of feeding guidelines for infants made time to reach enteral volume of 160 mL/kg/day faster than before feeding protocol group at 34.9 days in the control versus 28.4 in the study (p=0.05) and received fewer days of PN. In addition, the protocol decreased the rate of NEC and late-onset neonatal sepsis.

There was an overall average reduction of approximately 11 days in time to full enteral feeding. It reduced days receiving PN, reduced central line days, and reduced NPO days. This follows and supports the safety and benefits of feeding protocol in premature infants from these previous studies[6-8,20].

Street et al.[20] found that instituting standard nutritional guidelines for infants weighing less than 2,000 g reduced variability in feeding outcomes, including the number of NPO days and number of days to reach full enteral feeding. Therefore, these results are consistent with the present study showing the benefits of nutritional guidelines that implementation of nutritional guidelines for LBW infants in earlier successful enteral feeding. Furthermore, in the present study, the authors can reduce PN days and decrease central line days without increasing the rate of complications.

Reducing the time to full enteral feeding at a total volume of 150 to 160 mL/kg/day could help the growth outcome. This is likely due to improvement of increasing in parameters about differences in weight, head circumference, and length from birth to 2 weeks after birth. Not only the increasing of different of parameter and rate of gaining per day, but the difference in Z score also improved in increasing of

Z score of weight, and head circumference. Although there were no statistically significant improvements in growth parameters, but trending most of the growth parameters were improved when compared to the control group.

Limitation and suggestion

Previous studies were RCTs, thus, they were not included in the present study. Most of the authors recommended that further research is needed using prospective designs to establish a causative link between standardized feeding protocol and reduction of NEC.

Due to the short period of the present study, the numbers of patients in each group were different. More than half of patients in the present study were in the 1,401 to 1,800 g group, and the authors suggest more time assessment to evaluate and follow outcomes in the lower weight group.

Another limitation of the present study is that the authors cannot control if all infants used the same formula or human milk due to lack of lactational collection storage of the expressed breast milk. Moreover, during the novel coronavirus (COVID-19) outbreak, exclusive breastfeeding was limited due to the social distancing policy.

The present study shows no statistically significant rate of NEC between the control and the study groups, which is different from the previous study. The authors presume that a longer time in trophic feeding in other nutritional guidelines may decrease NEC event.

For an upcoming study, the authors are considering the possibility that prolonging of trophic feeding might lead to reduction of NEC. Further studies could also focus on late outcomes and complications, especially growth outcomes in the first year after discharge and neurodevelopmental outcomes.

Conclusion

The advantages of the new protocol were shorter time to full enteral feeding, earlier removal of catheter, shorter time of PN days, and central line days with prior starting fortification with an acceptable low rate of complications compare to the previous protocol.

What is already known on this topic?

Previous studies showed that using preterm feeding protocols in NICU can improve feeding intolerance and decrease NEC risk[6,7].

What does this study add?

This study shows that applying the new nutritional guideline in the authors' center cannot reduce NEC risk. However, this guideline can reduce time to reach full enteral feeding, PN days, central line days, and the day starting fortification without increasing the rate of NEC.

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Conflicts of interest

The authors declare no conflict of interest.

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