Original Article

The Comparative Effect Of Nutrition With Hydrolyzed Formula And Standard Formula On Necrotizing Enterocolitis In Preterm Infants

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DOI: 10.47750/pnr.2022.13.S09.392

Abstract

Background: Despite an increased prevalence of necrotizing enterocolitis (NEC) or acute inflammatory bowel disease among preterm infants, there is still a lack of literature in the comparative effects of nutrition with hydrolyzed formula and standard formula on the rate of NEC among neonates.

Methods: A randomized clinical trial study was conducted on 104 preterm neonates hospitalized in two NICUs of training hospitals affiliated by Iran University of Medical Sciences between 2020 and 2022. The participants were randomly divided into an experimental group and a control group, each with 52 neonates. In the intervention group, infants were given milk with hydrolyzed formula during the first 14 days after the newborn's onset of feeding. On the other hand, milk with standard formula was given to the control group. The study outcome was feeding tolerance and the prevalence of NEC in neonates comparing between groups.

Results: No statistical association was found between the average time to achieve full enteral nutrition; the rate of NEC; the prevalence of proven early neonatal sepsis; the frequency of receiving cell packs; average duration of mechanical ventilation; an average time to reach birth weight; the growth rate of height and head circumference per week; and the duration of

hospitalization in NICU; and mortality rate between two groups. The rate of feeding intolerance was reported in 32.7% and 69.2% of neonates in the intervention and control groups, respectively.
Conclusion: Feeding with hydrolyzed formula in neonates may reduce the incidence of feeding intolerance. To confirm study findings, we recommend further studies with optimal sample size allocation in designing multicenter setting clinical trials.

Keywords: Hydrolyzed formula, necrotizing enterocolitis, preterm infants.

Introduction

Prematurity in infants is defined as birth before 37 weeks of pregnancy. Rates of preterm birth have increased worldwide (1). According to national, regional, and worldwide estimates of preterm birth rates in the year 2010, the prevalence of preterm birth was estimated at 11.1% ranging between 11% in babies weighing less than 1500 grams and 22% in infants having a birth weight less than 1000 grams (1). Preterm infants are at increased risk of developing prematurity-related morbidities such as NEC. According to Neu and Walker, the prevalence of NEC among preterm infants was about 7% with a mortality rate reported to be 20–30% (2). NEC is a complex and devastating gastrointestinal disease associated with bowel immaturity and excessive inflammatory responses in preterm newborns (3, 4). NEC might also damage parts of the small intestine and cause short gut syndrome which makes it hard for the baby to absorb nutrients. Ineffective digestion in the lumen allows the microorganisms to use these nutrients for their own growth. The devastating condition combined with immunodeficiency of preterm babies can cause intestinal permeability and inflammation (5, 6). Furthermore, most of the preterm infants, particularly those under 1500 gram and/ or less than 34-week gestation, are not able to breastfeed or start enteral feeds shortly after birth. Breast milk is beneficial to meet both physiological and psychological needs of newborns. It also protects the infant from antiviral diarrhea, allergies, asthma, respiratory and gastrointestinal infections, diabetes, and NEC as well as facilitating a proper evolution of the nervous system (7-9).

Due to the fact that most of the premature infants are deprived of maternal breast feeding, and are also unable to establish the necessary coordination between sucking, swallowing and respiration due to the neuro-developmental impairment, two feeding alternatives including formula and donor breast milk have been proposed (7, 10). In terms of formula milk, standard term formula and nutrient-enriched formula were main types of nutritional interventions to meet the specific needs of infants (7, 11). Standard term formula which was designed on the basis of human breast milk composition is suitable for term infants. Its energy content is 20 kcal/Oz, and the concentration of protein, carbohydrate, calcium and phosphorus is approximately 1.5 g/100 mL, 50 g/100 mL, 30 mg/100 mL and 15 mg/100 mL, respectively (7, 11). As standard term formula is not sufficient to satisfy recommended nutrient needs for preterm infants, an energy-enriched (about 80 kcal/100 mL), protein-enriched (1.7-2.1 g/100 mL) and carbohydrate-enriched (8-9 g/100 mL) formula containing 75 mg/100 mL calcium and 42 mg/100mL phosphorus, in addition to variable vitamin levels was suggested as an effective strategy for nutritional intervention to support intrauterine rates of growth and nutrient accretion (12-14). Feeding of nutrient-enriched formula may be associated with gastric motility disorder and delays in the emptying of food contents from the stomach into the small bowel; which may consequently reduce nutrient delivery and aggravate slow growth and development (15-18). To resolve the issue, in case of limited gastrointestinal injury, an interest to use hydrolyzed formulas with adjustable content of medium-chain triglycerides increased recently (19, 20). Hydrolyzed formulas, compared to standard protein formula have been shown to reduce digestive transit time, regulate bowel movements, increase the number of times a person discharges stool from the large intestine, and promote an early full enteral feeding in preterm infants (19-21).Given the potential of hydrolyzed formulas to affect the development of preterm infants, we designed this randomized controlled trial to compare the effects of hydrolyzed formula versus standard formula on the rate of NEC and feeding tolerance in preterm infants.

Materials and Methods

Study Design

To compare the effects of hydrolyzed formula versus standard formula on the rate of NEC and feeding tolerance in preterm infants who were deprived of maternal breast feeding, a randomized, controlled, clinical trial of two formula-fed (hydrolyzed and standard) groups was designed in the NICUs of training hospitals affiliated by Iran University of Medical Sciences. The study has been conducted between November 2017 and November 2019.

Inclusion and Exclusion Criteria

Infants less than 34-week gestation without any particular birth defects who were nonbreastfed at the time of enrollment were participated in the study. On the other hand, those with congenital metabolic diseases, intrauterine growth restriction (IUGR) and the Apgar score less than 7 at 5 minutes were excluded. Other exclusion criteria included parents request to withdraw from the research and babies from addicted parents.

Sampling Method

Considering 95% reliability, 80% power, significance level less than 0.05 and 20% loss of study samples, a random sample of 104 infants divided in to two groups of 52 preterm babies was calculated.

$n = 2 (Z\alpha + Z\beta)^2 * \sigma 2 / (\mu 1- \mu 2)^2$

Written informed consent was obtained from the parents of participating infants. The study has been reviewed by the Ethics Committee of Clinical Research of Iran Medical University, and was registered in the Iranian clinical trial system (IRCT). Randomization was conducted by a researcher who was not involved in the recruitment and treatment procedures of the infants. Reference to similar study literature, randomized allocation through the use of Excel software was applied to ensure that all participants have an equal chance of taking part in the intervention group. Based on the patients' order of arrival to NICU, infants were randomly allocated to each of the nutritional strategy groups (22, 23).

Study Objectives and Endpoints

Then, preterm babies in intervention group were fed with hydrolyzed milk formula, while the control group was fed with standard formula from enrollment until 2 weeks. In hydrolyzed milk formula, most of the protein content contains molecular weight <b1500 kDa. Texture and appearance of case and control formula were the same and provided in powder form. During two-week diet, parents were asked to follow appropriate daily feeding volumes based on general feeding advice as provided by their health care professional. The outcome variable was the rate of food intolerance in preterm babies. Other endpoint variables included the incidences of NEC; time to achieve full enteral nutrition; time of NICU stay; growth and development conditions during the NICU stay including weekly body length growth rate, weekly head circumference growth rate, and daily weight growth rate.

Data analysis

In order to compare the incidence figures between preterm infants who were fed with hydrolyzed formula achieved similar feeding intolerance, and those receiving the standard formula, χ^2 test was used. Secondary objectives included the comparison of other growth parameters including anthropometric parameters; as well as time to achieve full enteral nutrition; the age of newborn's onset of feeding; the rate of NEC; the prevalence of proven early neonatal sepsis; the frequency of receiving cell packs; average duration of mechanical ventilation; the duration of hospitalization in NICU; and mortality rate were compared by paired t-test between groups. The data analysis was done using the Statistical Package for Social Sciences (SPSS) version 20.0. The accepted level of statistical significance was mentioned $p< 0.05$.

Results

Following exclusion criteria, 52 individuals from the intervention group and 52 from control group were included in the study. As shown in Table 1, there were no significant differences in gender, gestational age, birth weight, birth length, head circumference, birth height, comorbidities, the age of newborn's onset of feeding, and time to achieve full enteral nutrition between two groups ($p>0.05$).

Table 1. Characteristics of premature infants between the two groups

Demographic characteristics	Intervention group (n=52)	Control group (n=52)	χ^2/ t	p-value
Gestational age (weeks)	28.153±1.93	28.28±2.09	t=-0.143	0.73
Birth weight (gr)	1074.71±183.2	1080.48±185.79	t=-0.143	0.87
Head circumference (cm)	26.84±1.59	26.89±1.78	t=-0.143	0.88
Birth height (cm)	38.03±3.78	38.11±3.29	t=-0.143	0.91
Age of newborn's onset of feeding	6.42±2.6	6.11±2.4	t=-0.586	0.53
Time to achieve full enteral nutrition	26.1±8.5	28.7±10.6	t=-0.143	0.22

Comorbidities	(premature with RDS*)	50(96.2)	48(92.3)	χ^2=0.273	0.080
	premature	2(3.8)	4(7.7)		
Gender	Male	22(42.3)	23(44.2)	χ^2=0.265	0.84
	Female	30(57.7)	29(55.8)		
RDS=Respiratory distress syndrome					

In this study, the total incidence of food intolerance in 104 premature infants was 49.05%. The incidence of food intolerance in the intervention group (30.8%) was significantly lower than that in the control group (67.3%), as $p < 0.01$. As it is shown in Table 2, the incidence of NEC in the intervention group (3.84%) was similar to that in the control group; thus no significant difference was observed between groups ($p>0.05$). Furthermore, the incidence of early neonatal sepsis in the intervention group was the same as control group ($p>0.05$), revealing no significant difference between two study groups. Similarly, in terms of the frequency of receiving cell packs no significant difference was found between intervention and control groups ($p>0.05$). Finally, this study found that the mortality rate was lower in the intervention group, but p was also more than 0.05 with no statistical significance (Table 2).

Table 2. Comparison of incidence of feeding intolerance, NEC, early neonatal sepsis, receiving cell packs and mortality rate between two groups

Study groups		Feeding indolence		χ^2	p-value
		Occurred	Non-occurred		
Group	Intervention (n%)	16(30.8)	36(69.2)	12.01	0.001
	Control (n%)	35(67.3)	17(32.7)		
Total		51(49.05)	53(50.95)		
Study groups		NEC		χ^2	p-value
		Occurred	Non-occurred		
Group	Intervention (n%)	2(3.84)	50(96.15)	14.17	p>0.05
	Control (n%)	2(3.84)	50(96.15)		
Total		4(3.84)	100(96.15)		
Study group		Early neonatal sepsis		χ^2	p-value
		Occurred	Non-occurred		
Group	Intervention (n%)	1(1.92)	51(98.07)	9.86	p>0.05
	Control (n%)	1(1.92)	51(98.07)		
Study group		Receiving cell packs		χ^2	p-value
		Yes	No		
Group	Intervention (n%)	23(44.2)	29(55.8)	11.82	p>0.05
	Control (n%)	23(44.2)	29(55.8)		
Study group		Health outcome		χ^2	p-value
		discharged	dead		
Group	Intervention (n%)	49(88.5)	6(11.5)	8.67	p>0.05
	Control (n%)	43(82.7)	9(17.3)		

Findings depicted that in intervention group, the duration of stay in NICU was longer than the control group, but p –value was more than 0.05 affirming no statistical significance. The average daily weight growth of preterm infants in the intervention group was higher than that in the control group, but p-value was also more than 0.05 with no statistical significance. Although the average duration of mechanical ventilation and an average time to reach birth weight in the intervention group was slightly longer than that in the control group, the values of p were

both above 0.05. Finally, no differences of the body length, and head circumference between patients of the two groups were observed (Table 3).

Table 3. Comparison of duration of NICU stay, daily weight, length, and head circumference growth, duration of mechanical ventilation and an average time to reach birth weight between study groups

Group (n)	duration of NICU stay	Weight growth	Length growth	head circumference growth	duration of mechanical ventilation	average time to reach birth weight
Intervention (52)	38.7±14.08	12.3±2.51	1±0.36	1±0.66	6.2±3.94	15±3.53
Control (52)	37.69±15.32	11.73±2.4	1±0.48	1±0.23	5.69±3.01	14.82±2.12
Z	-1.52	-1.87	-0.365	-0.432	-0.0313	-0.998
P	0.162	0.256	0.621	0.413	0.145	0.136

Discussion

To the best of our knowledge, this is the first study which attempts to compare the effects of hydrolyzed formula versus standard formula on the rate of NEC and feeding intolerance in preterm infants. In this research, a random sample of 104 infants divided in to two groups of 52 preterm babies received two formula milk including hydrolyzed and standard formula. Most of the literature emphasizes on the importance of nutritional strategies to prevent NEC instead of treatment procedures. Despite the necessity, there are no clear recommendations on the benefits of hydrolyzed milk for preterm infants (24, 25).

Our study hypothesized that in the absence of human breast milk, using hydrolyzed formula might be useful for preventing the rate of NEC and food intolerance among preterm infants. Literature has proven that nutrition with hydrolyzed formula could be helpful in improving absorption during refeeding due to its lactose and significant amount of medium-chain triglycerides (26). In case of human milk unavailability, hydrolyzed formulas can be also used to improve feeding tolerance or reduce gastro esophageal reflux through accelerating the process of gastric emptying, facilitating more efficient enteric peptide digestion, and stimulating small intestinal enzymatic and motilin activity (9, 19).

In our study, after adjusting the intervention and control groups based on demographic and anthropometric characteristics of preterm infants, findings revealed no significant differences between two study groups in terms of the age of newborn's onset of feeding, average time to achieve full enteral nutrition, the rate of NEC, the prevalence of early neonatal sepsis, the frequency of receiving cell packs, the duration of mechanical ventilation, an average time to reach birth weight, the growth rate of height and head circumference, the duration of NICU stay, and the rate of mortality. However, regarding the feeding intolerance, a significant statistical difference was approved between two study groups. In fact compared with standard formula, nutrition with hydrolyzed formula in preterm infants within two weeks after enrolment could significantly reduce the incidence of food intolerance. In a study conducted by Di Mauro et al. nearly 75% of low birth weight infants were reported to suffer from food intolerance (27). Similarly, Yin et al. expanded their research findings and affirmed that the incidence rate of food intolerance in premature infants who have been fed by hydrolyzed formula was 14.1% compared to those fed by standard formula at 30.3% (28). Mihatsch et al. explained that hydrolyzed milk accelerates early enteral feeding advancement particularly in low birth weight infants (20). They also confirmed that hydrolyzed formula improves gastrointestinal motility and feeding tolerance through different mechanisms (9, 19).

Regarding the rate of weigh, height and head circumference growth in infants, our study did not affirm any significant differences between intervention and control groups. However, Koletzko et al. suggested that higher levels of protein in milk formulas can accelerate weight gain during infancy (29). Similarly Zuppa et al. assessed the impact of hydrolyzed milk on preterm infants' growth and found that hydrolyzed formulas were associated with normal growth and development of babies (9). Another research reported that a hydrolyzed milk formula could improve the clinical symptoms of gastro esophageal reflux and decrease the gastric emptying time in infants (30). A randomized trial study conducted by Vandenplas et al. found that infants receiving hydrolyzed formula experienced a lower rate in respiratory tract infections, otitis media, gastrointestinal infections, acute diarrhea, and urinary tract infections compared to that of infants in the control group (31). On the other hand, in line with our research findings, some of the studies did not show a significance difference between infants who were fed by

hydrolyzed formula and those fed by standard formula regarding the growth rate, side effects and food intolerance. They added that the use of hydrolyzed formula is similar to standard formula in terms of weight gain and thus it can be considered as a suitable nutritional strategy for term infants (8). Furthermore, Hu et al. found no significant differences in terms of the age of newborn's onset of feeding, average time to achieve full enteral nutrition, timing of the passage of first meconium and stooling, time of the appearance of jaundice symptoms, albumin level in the first and second weeks after hospital admission, and an average time to reach birth weight (32). Similarly, Lucas (1990) and Carver (2001) detected no statistically significant differences in weight, length or head circumference of infants in the intervention group following nutrition with hydrolyzed formula (33, 34). Cooke (2001), Picaud (2005) and Peng (2004) also found no significant differences in the rate of weight gain during the study period (35-37).

This study has a number of limitations. First, it suffers from a small number of infants who have been participated in our research; thus it lacks the power to evaluate the clinical efficacy of hydrolyzed formula on several clinical parameters. However, the results of this study suggest that in some preterm infants with symptoms of feeding intolerance, a hydrolyzed formula can reduce the difficulty of digesting certain foods causing abdominal pain, diarrhea, gas and bloating, heartburn, and nausea. It is suggested that future research with adequate sample size and robust methodology focuses on the evaluation of hydrolyzed formula for preterm infants in improving clinical symptoms of NEC.

Conclusion

In conclusion, feeding hydrolyzed formula to preterm infants reduces the incidence of food intolerance. Increased food tolerance can consequently reduce the time taken to attain full enteral feedings in preterm infants and therefore eliminate the risk of infectious complications due to prolonged exposure to parenteral nutrition. However, limited data did not indicate any important effects on preventing NEC; reducing the duration of NICU stay; decreasing the age of newborn's onset of feeding; reducing the average time to achieve full enteral nutrition; eliminating the prevalence of early neonatal sepsis, the duration of mechanical ventilation, and the frequency of receiving cell packs. Thus, adequate evidence should be available to assess the effects of hydrolyzed formula on preterm infants' growth and developmental outcomes beyond the initial hospital admission.

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