Galactooligosaccharide (GOS) Fortified Formula Feeding in Premature Infants

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Galactooligosaccharide (GOS) Fortified Formula Feeding in Premature Infants

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Abstracts

Background: Nutritional problems are one of the serious problems in low birth weight or preterm infants. This causes medical and nutrition management of premature infants to be more individual.

Objective: To evaluate the outcome of the premature infants with Galactooligosaccharides (GOS) fortified formula feeding

Methods: This was prospective, open label cohort study that conducted during March- December 2019 in Neonatology Unit at the one of the main referral hospitals in East Java, Indonesia. The population of the study was very low birth weight infants (1,000 g - ≤1,500g) who needed formula feeding. Weight, body length, head circumference, fecal models and the incidence of diarrhea, colic, regurgitation, and vomiting was observed. Patients were observed for 28 days or adjusted according to length of stay.
Results: Totally, 20 infants were included. Mean birth weight was 1236.2±148.5 grams. Mean total volume Galactooligosaccharides fortified formula at the start of recruitment was 209.4±46.1 ml and at the end of observation was 267.9±41.2 ml. There were change in amount and consistency of feces before and after intervention. No patient experienced adverse events (diarrhea, colic, regurgitation or vomiting) while consuming Galactooligosaccharides fortified formula.

Conclusion: Galactooligosaccharides fortified formula in premature infant formula did not have a detrimental effect on premature infants and did not cause intolerance

Keywords: *Formula feeding; Oligosaccharides supplementation; low birth weight infant; premature*

Introduction

Nutritional problems are one of several problems in low birth weight (LBW) or preterm infants. This is closely related to various conditions or complications in organ systems of the body such as the airway, central nervous system, gastrointestinal tract, liver, kidneys, and others. In general, nutrition is an absolute necessity for optimal survival and growth or prevention of complications. In addition, conditions in premature infants can vary widely. This is influenced by many factors such as gestational age and birth weight. This condition causes the medical and nutrition management of premature infants to be more

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individual. Specific nutritional problems in premature infants are low nutrient reserves, immaturity of organ function, unpredictable potential for rapid growth, and a high risk of morbidity.[1] The main objective of nutritional support in premature infants is to achieve optimal growth and development. Oligosaccharides are one of the main components in human milk, which contain about 10 g / l neutral oligosaccharides and 1 g / l acidic oligosaccharides.[2] The concentration of these oligosaccharides changes with the lactation period, with the largest oligosaccharide concentrations found in colostrum. The oligosaccharide composition of breast milk is very complex and it has been reported that there are more than 100 oligosaccharide-like structures present in the human milk.

Breastfeeding and formula feeding may have different effects on the development of microorganisms in the digestive tract. Studies show that the gastrointestinal tract of exclusive breastfed infants is dominated by *Bifidobacteria* and *Lactobacilli* compared to formula-fed infants.[3] This predominance of bacteria is believed to reduce the risk of diseases related to the digestive tract. Oligosaccharides in human milk are believed to contribute to the development of *Bifidobacteria* and *Lactobacilli* in infants, thereby human milk is said to have a bifidogenic effect. Furthemore, the composition and structure of oligosaccharides in human milk is very complex. Prebiotic compounds that have been used in many studies for various infant formula products are GOS and FOS. Clinical studies that have been carried out prove that the addition of GOS or FOS to formula milk produces a bifidogenic effect, which stimulates the growth of *Bifidobacteria* and *Lactobacilli*.[4] Studies have shown that giving fortified formula with a mixture of GOS / FOS with a concentration of 0.4 g / 100 ml or 0.8 g / 100 ml for 28 days showed increased fecal *Bifidocateria* and *Lactobacilli*. The increase in *Bifidobacteria* depends on the dose of oligosaccharides. Long-chain (5-60 monomer) inulin mixtures with GOS (2-7 monomers) at a ratio of 10-90% have been added to European infant milk for more than 5 years.[5] Clinical studies show that this prebiotic fortified formula is significantly affect the composition of microorganisms in the feces similar to the composition of microorganisms in the stool of breastfed infants, improve stool consistency, reduce intestinal permeability, and reduce the risk of gastrointestinal infections, respiratory tract and skin diseases in infants. Fortification of formula milk with a mixture of GOS and FOS also increases calcium absorption. Giving weaning foods fortified with oligofructose at a dose of 4.5 g / day for 6 weeks showed an increase in the number of *Bifidobacteria* in the feces and decreased clostridia and softened the stool and reduced the risk of gastrointestinal diseases.

Materials and Methods

This study is a prospective, open label cohort study conducted during March-December 2019. The study was conducted in the Neonatology Unit at the one of the main referral hospital in East Java, Indonesia. The aim of the study was to evaluate the outcome of the premature infants that give Galactooligosaccharides (GOS) fortified formula.

The population of the study was infants with very low birth weight (1,000 g - ≤1,500g) who needed formula feeding. Before performing intervention, parents were given information for consent and signed an informed consent to use formula milk for their infants according to standard operating procedures (SOP) hospital. Inclusion criteria were infants with hemodynamic stable conditions, infants with severe infections or infants with mothers who died during childbirth, so they could not get their own mothers' milk, infants with mothers with absolute contraindications to breastfeeding (mothers with HIV or mothers in chemotherapy medication), or infants with insufficient enteral nutrition of the human milk. The exclusion criteria were infants with congenital abnormalities and infants who their nutrition needs had fulfilled by the exclusive breastfeeding. The dropout criteria were arising of serious side effects, failure to follow up, and parents proposing the use

only exclusive breastfeeding. The sample size was 20 patients with an estimated number of screenings of 40 patients.

Infants that included in inclusion criteria would obtain the intervention of GOS fortified formula feeding. GOS fortified formula volume is adjusted to the doctor's recommendation. Outcomes that observed were weight, body length, head circumference, the incidence of diarrhea, colic, regurgitation, vomiting, and fecal models (with *Amsterdam Stool scale criteria Chart*). These outcomes would be observed at baseline (measurement before intervention, at the early of observation) and at end line (measurement after intervention, at the end of observation) Patients were observed for 28 days or adjusted according to length of stay. If after 28 days of observation, the patient is still hospitalized, then the intervention will be continued until the patient is discharged. Patients still receive medication regarding to the patient's condition. All of medication will be written in the *Case Report Form* (CRF).

Findings

Table 1. Infants characteristic data

Variable	Patient (n=20)	
	n	Percentage(%)
Gender		
Boy	11	55
Girl	9	45
Mode of Delivery		
Sectio caesarean	13	65
Vaginal	7	35
Feeding		
Formula feeding	0	0
Mixed feeding	20	100

Table 2. Infant anthropometric characteristic data at baseline and end line

Variable	Baseline		Endline		Δ Baseline and Endline
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD
Weight (gr)	1345,4 ± 121,7	1398,5 (1100-1466)	1585,0 ± 123,4	1579,5 (1372-1815)	240,3 ± 170,4
Length (cm)	39,9 ± 3,4	40,3 (34-45,4)	40,4 ± 3,3	41 (35-45,5)	0,5 ± 0,6
Head circumference (cm)	28,1 ± 1,5	28 (26-31,5)	28,5 ± 1,3	28,5 (26,8-31,5)	0,5 ± 0,5

A total of twenty infants were included in this study. Infants were dominated by the eleven male infants (55%). Sectio Caesarean was dominated the mode of delivery in 13 infants (65%). All infants consumed formula milk and human milk and none of them consumed formula milk only (table 1). Data at the early of recruitment (baseline) showed the mean of body weight was 1345.4 ± 121.7 grams, mean of body length was 39.9 ± 3.4 cm and the head circumference of 28.1 ± 1.5 cm. At the end of the observation, the mean body weight of the infants increased to 1585.0 ± 123.4 grams, the lenght of the body increased to 40.4 ± 3.3 cm and the head circumference to 28.5 ± 1.3 cm (Table 2).

Table 3. Total of GOS fortified formula consumption at baseline and end line

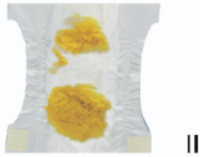
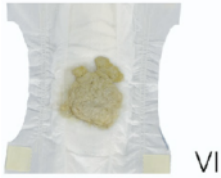
Variable	Baseline		Endline		Δ Baseline and Endline
	Mean±SD (ml)	Median (Min-Max) (ml)	Mean±SD (ml)	Median (Min-Max) (ml)	Mean±SD (ml)
GOS fortified formula volume					
Infant with partial feeding (human milk and formula feeding)	209,4 ± 46,1	228 (60-264)	267,9 ± 41,2	264 (216-360)	58,5 ± 66,6

The longest time of intervention was 28 days with the mean of total volume consumption was 229.1 ± 23.1 ml. Infants with the shortest intervention time was 2 days with the mean volume consumption was 246 ± 25.5 ml. The highest and the lowest of GOS fortified formula volume consuming were 276 ± 48.7 ml and 194.8 ± 83.6 ml, respectively. Table 3 shows the data on the total of all infant volume consumed of GOS fortified milk, both at the beginning and at the end of recruitment. The mean total volume at the beginning of recruitment was 209.4 ± 46.1 ml and at the end of observation was 267.9 ± 41.2 ml. During the study and observation period, no patient experienced any adverse events (diarrhea, colic, regurgitation or vomiting) while consuming GOS fortified formula.

Table 4. The infant feces model at baseline and end line

Variable	Baseline (n=20)		Endline (n=20)	
	n	Percentage (%)	n	Percentage (%)
Amount				
1: smear	0	0	0	0
2: up to 25%	13	65	6	30
3. 25-50%	7	35	14	70
4. >50%	0	0	0	0
Consistency				
A. Watery	1	5	0	0
B. Soft	10	50	8	40

Cont... **Table 4. The infant feces model at baseline and end line**

C. Formed	8	40	12	60
D. Hard	1	5	0	0
Color				
 I	1	5	0	0
 II	16	80	16	80
 III	3	15	4	20
 IV	0	0	0	0
 V	0	0	0	0
 VI	0	0	0	0

Observation of feces was using the patient's stool model refers to the *Amsterdam Stool Chart* (Figure 1). Observation of the feces included volume, consistency and color of the feces. At the beginning of recruitment (baseline) the amount of feces was dominated by number 2 in the Amsterdam Stool Chart model (up to 25%), but at the end of fecal observations there was an increment of the feces volume (dominated by number

3 of the feces amount in the Amsterdam Stool Chart model). Observation on feces contingency, at the baseline, consistency was dominated soft consistency and at the end of observation was dominated by the formed consistency. Regarding color at both the start and end of recruitment, the majority of infants dominated by number 2 of the feces color on the Amsterdam Stool Chart model (Table 4).

Discussion

Nutritional problems are one of several serious problems in preterm neonates. This is closely related to various conditions or complications in various systems or organs of the body such as the airway, central nervous system, gastrointestinal tract, liver, kidneys, and others. On the other hand, nutrition is an absolute necessity for optimal survival and development or prevention of complications. Meanwhile, nutrition also can lead to complications. Every premature infant has a different condition that influenced by many factors. Two of them are gestational age and birth weight. Medical management and nutrition of premature infants are crucial. Premature infants have some specific nutritional problems such as low nutrient reserves, immaturity of organ function, low potential for rapid growth, and a high risk of morbidity.[1] The main objective of nutritional support for preterm infants is the achievement of optimal growth and development.

Oligosaccharides are the third largest component in human milk. It is known that the main function of oligosaccharides is as a prebiotic.[1] Prebiotic is a term used for foodstuffs that can be a source of energy and nutrients for certain species in the human intestine, especially the Bifidobacterium and Lactobacillus. [2,3] The composition of the intestinal microbiota which is rich in both types of bacteria can increase the acidity of the feces and the short-chain fatty acids. As a result, the consistency of the stool becomes soft and the frequency of bowel movements becomes more frequent. [3,4] Oligosaccharides also have a function in intestinal protection because of anti-adhesion function that can resemble ligands where certain pathogens attach. It also has the effect of modifying the glycosylated activity of intestinal epithelial cells.[5] The protective function of these oligosaccharides is associated with a reduced risk of intestinal infection in infants who are exclusively breastfed.[1,5] Because of its advantages, researchers propose an idea to produce synthetic oligosaccharides and added to infant formula so that infants who are not breastfed can obtain the benefits.[6]

The composition of the intestinal microbiota is necessary as a defense against pathogenic bacteria.[1] The Bifidobacterium and Lactobacillus groups are the dominant microbiota in the intestines of breastfed infants, whereas in formula-fed infants there are more variations, consisting of Bacteroides or Clostridium group, Staphylococcus, and Enterobacteriaceae. [1,2] Factors that affect the diversity of the microbiota composition in the infant's gut, including gestation, mode of delivery, environment, drug consumption, and type of infant nutrition.[3] Many studies show that oligosaccharides can provide benefits as prebiotics and have bifidogenic effects such as those found in human milk.

To be classified as a prebiotic, a food ingredient must be acid-resistant and cannot be hydrolyzed or absorbed in the upper tract, can be fermented by the intestinal microflora, and selectively increases the growth and activity of one or more commensal bacteria in the colon.[5,6] The expected functional effects of prebiotics are to affect the production and determination of stool, increase the bioavailability of several minerals such as calcium and magnesium. These substances an immunomodulatory that can reduce the risk of diseases such as infectious diarrhea, metabolic syndrome, obesity, and inflammatory bowel disease, and colon cancer. [7–9] Several types of prebiotics that have been accurate are inulin, fructooligosaccharide (FOS), galactooligosaccharide (GOS), polydextrose (PDX), and lactulose. [6,8]

Ziegler et al found intolerant effects in the form of gas, vomiting and diarrhea, especially in the group who received the prebiotic mixture. Compared to the control group, all categories of the intervention group experienced more frequent adverse effects.[17] In this study we did not find any subjects who experienced intolerant effects in the form of diarrhea, colic, regurgitation and vomiting. The two clinical trials above also assessed the effect of GOS fortification in formula milk on stool characteristics (feces amount, consistency and color). At the end of the study, it was found that there was no statistically significant difference between all the intervention groups and the control group, but the consistency of the feces in the subjects who received the prebiotic combination was found to be softer than the control group. However, in this study, there was no breastfeeding only group as a comparison.[10] In another study, it was found that the highest number of defecations occurred in subjects who received GOS and other prebiotic combinations at the start of administration (30 days), but in subsequent observations (> 30 days) the number of defecations was not different meaningful with other groups.[11]

In this study, we also monitored the effect of GOS fortified formula feeding on the feces characteristics of premature infants, included amount, consistency and color of the feces, and intolerance. Parameters of feces characteristics were observed before and after the intervention. The consistency of the subject was changed from hard consistency to be softer consistency after the intervention. The effect on feces color did not have a significant change after intervention.

Through the results of this and another study about GOS fortified formula feeding in preterm infants, GOS as supplementation for a premature infant does not interfere with the growth process and does not cause significant differences in stool characteristics, both consistency and color of stool. Also includes the absence of any intolerant effects during the consumption of premature infant milk with partial GOS supplementation. Although in the comparison process, we found only a few studies related to GOS as a single supplementation, because most studies used a mixture of two or three other prebiotics.[12] However, despite different methods, this study and other research propose the widely used of prebiotics. The effect of adding GOS fortification on growth rate and feces characteristics was not different. In this study, the feces characteristics of the patients who got GOS fortified formula also showed the same results as the systematic review and other meta-analyzes of several prebiotics either alone or in combination.[8, 13,14, 15] In these studies, the composition of the gut microbiota also showed a predominance of Bifidobacterium (bifidogenic effect) and a reduction in the number of pathogenic bacteria. The study of Watson et al, FOS, GOS, inulin, maltodextrin, PDX and lactulose, showed that GOS had the best ability to increase the amount of Lactobacillus and Bifidobacterium compared to other types of prebiotics[16]

Conclusion

Nutritional support is the important problems in preterm infant for optimal survival, growth and prevention of complications. Galactooligosaccharides (GOS)is one of human milk component that affect the composition of microorganisms in the feces and can reduce the risk of gastrointestinal infections. In our study, we conclude that GOS fortified formula did not have a detrimental effect which is shown by no one of participant experience an adverse event. GOS fortified formula might be safe for the nutritional support choices in premature infant. Research with a larger number of infants could be conducted to carry out continuing research in GOS fortified formula feeding for preterm infants

Conflict of Interest: Author declares that there is no conflict of interest

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Ethical Clearance : Approved by researched ethical committee Dr. Soetomo General Hospital Surabaya

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