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Original Research Paper

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THE EFFECTIVENESS OF POWDERED AND LIQUID FORMULA IN PREVENTING FEEDING INTOLERANCE IN PREMATURE INFANTS

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ABSTRACT Feeding intolerance is the most common digestive problems in feeding to premature infants. For nowadays, there is no guideline in giving formula milk, liquid or powder, for preventing intolerance in premature infants. A RCT was conducted in NICU, H. Adam Malik Hospital, Medan from March 2017 to March 2018. The inclusion criteria was infants with gestation age below 37 weeks with three-quarter full enteral feeding was formula milk. Data analysis was done by bivariate test. P value < 0.05 was considered significant. Of participants 80, 41 and 39 samples had powder and liquid formula, respectively. Prevalence of formula milk tolerance was 95.1% in powder and 92.30% liquid. Risk factors didn't affect to feeding intolerance in both group. The NNT value was 35 and NNH value was 36. Both powder and liquid formulas do not effective in preventing feeding intolerance based on this study.

KEYWORDS : feeding intolerance, preterm, effectiveness, powder formula

INTRODUCTION

The main of caring preterm infants is neurodevelopmental care so that optimal quality of life will be obtained. One effort that can be done is to provide adequate nutrient intake for the process of growing chase in preterm infants.1

Feeding intolerance is the most common digestive problem that occurs during infant feeding. Feeding intolerance will cause the baby not to get adequate nutrition that affects the growth process.2 Breast milk is the main choice for infants. Breast milk is the gold standard for nutrition in infants because of the complete combination of nutrients, enzymes, hormones and immunological components. If breastmilk is not available, there are two alternatives to full enteral feeding of breastfed donors and preterm infants formula.3

For decades, there have been reported in Western Europe and the United States there was an outbreak of Enterobacter sakazakii in infants fed powdered formulas due to contamination during the process of powdered milk formula serving in hospital, so WHO in 2006 developed guideline to reduce the risk of intrinsic bacterial contamination on powdered milk formula. This serious problem causes dairies to produce ready-made liquid milk formula as sterile feeding. The US Food and Drug Administration, the American Dietetic Association and the Centers for Disease Control and Prevention recommend that powdered milk formula should not be used in the Neonatal Intensive Care Unit (NICU) unless there are no alternative available, the NICU has switched to ready- using a bottle.4

Studies conducted in Turkey in 2010 reported that liquid milk formula can lead to an increase in the incidence of feeding intolerance and delay growth in the first week of life in premature infants due to changing of gastric acidity or disruption of protein bioavailability due to different production and sterilization processes.2 This study aims to assess the effectiveness of powder and liquid milk formula in preventing feeding intolerance in preterm infants.

METHODE

Study Design

A randomized control trial, single blind was conducted in NICU, H. Adam Malik Hospital, Medan from March 2017 to March 2018. The inclusion criteria was infants with gestation age below 37 weeks with three-quarter full enteral feeding was formula milk. The exclusion was infants with NEC, IUGR, on respiratory distress and sepsis, congenital anomaly, and infants who began feeding exclusively or dominantly (>75 % of daily enteral feeding volume) with breast milk. Samples randomized into 2 groups, powder and liquid formula milk. This study was approved by the Health Research Ethical Committee, Medical School, University of Sumatera Utara.

Sample Recruitment and Procedure

Preterm infants who have been stable given trophic feeding, then performed a simple random randomization, then informed consent from parents. The baseline data were obtained from medical record status supporting inclusion and exclusion criteria. The division of the group is divided into groups I, premature infants receiving powdered formula and group II, premature infants who are fed with liquid formula. Treatment is done when premature infants are planned for trophic feeding diets. Provision of milk is given by using 5cc syringes for premature infants using orogastric tubes and bottles of milk for premature infants who can suck. All premature infants receive enteral nutrition every 2 hours. Premature infants who have attained full enteral diet and fulfill inclusion criteria are weight measured using a pre-weighed apparatus and recording done in decimal (sensitive to 0.1 kg), using a charder brand scale. Evaluation of feeding intolerance is a gastric residual volume of more than 50% of previous volume enteral, vomiting or abdominal distension or both, from day one to day 7 of full enteral feeding.

Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package for Social Science Windows SPSS (version 22, 2013) with 95% of confidence interval, p value < 0,05 was consider as significant. Randomisation was used Microsoft Excel Randomisation 2010. Calculation of the number needed to treat (NNT) of powdered milk formula against the occurrence of feeding intolerance and the number needed to harm (NNH) of powdered formula feeding to the incidence of feeding intolerance. Bivariate tests were used to analyze risk factors that affect the incidence of feeding intolerance in premature infants. Statistical calculation was done at 95% confidence interval and P-value <0.05 was considered significant.

RESULTS

During the study, 129 preterm infants were sick, but 21 preterm infants were included in the exclusion criteria, and there were 108

premature infants who met the inclusion criteria. Premature infants are alive and have had a full enteral diet of 80 neonates and are included as research samples. Sampling was done randomly by using Microsoft Excel table on 108 sick premature babies to be divided into powder and liquid formula. The study sample that achieved full enteral diet was 80 preterm infants, divided into two groups: 41 premature infants received powdered formula (group 1) and 39 premature infants received the liquid formula (group 2), then monitored from the beginning of full enteral diet for seven days to assess the effectiveness of powder and liquid milk formula in preventing the incidence of feeding intolerance in premature infants. Consort research diagram can be seen in Figure 1.

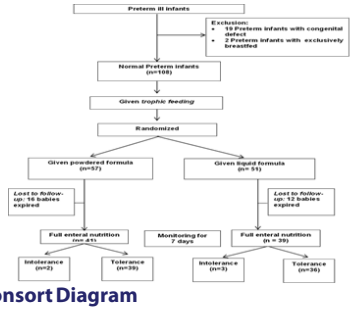

Figure 1. Consort Diagram

Characteristics of this study include sex, gestational age, prenatal risk factors and previous disease history. Based on the sex of premature babies, it was found that female sex (61% and 56.4%) got more formula milk either milk powder or liquid milk. Based on gestational age, the most widely used powder and liquid formula were 32-37 weeks gestation (53.7% and 69.2%). Premature infants who received powdered and liquid milk formula had the highest prenatal risk were severe preklampsia (65.9 and 48.7%) and premature rupture (19.5% and 28.2%). Premature infants who received powdered and liquid milk formulas had a history of the most common diseases were sepsis (68.3% and 66.7%) and Respiratory distress syndrome (51.2 and 61.5%). Data is shown in table 1.

Table 1. Comparison of demographic and clinical characteristics of preterm infants who were fed with powdered or liquid (ready-to feed) preterm formula

	Infants fed with powdered formula (n=41)	**Infants fed with liquid formula(n=39)**
Gender, n (%)		
Male	16 (39)	17 (43.6)
Female	25 (61)	22 (56.4)
Gestational age, n(%)		
<28 weeks	1 (2.4)	1 (2.6)
28-31 weeks	18 (43.9)	11 (28.2)
32-37 weeks	22 (53.7)	27 (69.2)
Prenatal risk factors, n (%)		
Premature rupture of membranes	8 (19.5)	11 (28.2)
Severe preeclampsia	27 (65.9)	19 (48.7)
Eclampsia	2 (4.9)	3 (7.7)
Human Immunodeficiency Virus (HIV)	2 (4.9)	4 (10.3)
Congestive heart failure (CHF)	1 (2.4)	1 (2.6)
Hepatitis B	0 (0)	1 (2.6)
Placenta previa	0 (0)	1 (2.6)
Gemelli	3 (7.3)	0 (0)
Hellp syndrome	1 (2.4)	0 (0)
Hyperthyroid	1 (2.4)	0 (0)
Multicystic kidney	1 (2.4)	0 (0)
History of previous illness, n (%)		
Respiratory distress syndrome	21 (51.2)	24 (61.5)
Sepsis	28 (68.3)	26 (66.7)
Neonatal pneumonia	3 (7.3)	2 (5.1)
Apnoe of prematurity	0 (0)	2 (5.1)
Patent ductus arteriosus	1 (2.4)	0 (0)
Hyperbilirubinemia	1 (2.4)	1 (2.6)
Mother with HIV	2 (4.9)	4 (10.3)
Mother with hepatitis B	0 (0)	1 (2.6)
None	11 (26.8)	8 (20.5)

Table 2 shows the NNT value of powdered milk formula to drinking tolerance is 35, which means to avoid 1 incidence of feeding intolerance in premature infants it takes 35 premature infants receiving powdered formula and for NNH value of powdered milk formula feeding intolerance is 36, which meaning that of 36 premature infants who get formula milk powder, there will be 1 premature infants who experienced feeding intolerance.

Table 2. Feeding intolerance in preterm infants between powdered and liquid formula.

Types of formula milk	**Tolerance, n (%)**	**Intolerance, n (%)**
Powdered	39 (95.1)	2 (4.9)
Liquid	36 (92.3)	3 (7.7)

Differences in feeding problems in premature infants are seen from four factors: the duration of parenteral nutrition, return to birth weight, enteral nutrition until reaching full feeed. To determine the difference of feeding problems in premature infants, the Mann-Whitney test was used (abnormally distributed data). The difference in mean difference of weight gain between premature infants receiving powdered and liquid formula was used unpaired t-test.

Table 3 shows no significant difference between feeding problems in premature infants in both groups of formula milk and there was no significant difference from the mean difference in weight gain between preterm infants receiving powdered or liquid formula formula.

Table 3. Feeding problem and difference weight increase between powdered liquid formula in preterm infants

	Infants fed with powdered formula (n=41)	**Infants fed with powdered formula (n=41)**	P
Duration of parenteral nutrition (day), median (min–max)	9.6 (0-24)	7 (0-27)	0.238*
Regain birth weight (day), median (min–max)	10.5 (0-30)	11 (0-33)	0.915*
Age reaches full enteral nutrition (day), median (min–max)	10.1 (0-30)	8 (0-52)	0.842*
Duration of enteral nutrition (until full feed) (day), median (min–max)	10.1 (0-18)	5 (0-22)	0.357*
Difference weight increase (gram), mean (SD)	131.1 (63.10)	124.3 (48.47)	0.594**

Mann-Whitney Test
Independent Samples T-Test

Table 4 shows that the types of milk, gestational age, sex, sepsis, birth weight were not a risk factor for the occurrence of feeding intolerance.

Table 4 Risk factors of feeding intolerance

Risk factors	**RR [95 % CI]**
Liquid formula	1.25 (0.59-2.7)
Gestational age <32 weeks	2.37 (0.42-13.39)

Male gender	2.14 (0.38-12.1)
Sepsis	0.72 (0.13-4.1)
Birth weight <1500 g	0.66 (0.08-5.8)

DISCUSSION

This study is the first study to discuss the effectiveness of powder and liquid milk formula in preventing the incidence of feeding intolerance in premature infants in Indonesia. Early feeding is known to be an important part of premature infant care to promote growth and maturation of the gastrointestinal tract, increased lactase and motor intestinal activity, reduced incidence of ulcer stress, reduced complication of sepsis, and increased immune function.5,6 Feeding intolerance becomes one of the causes of delayed enteral nutrition in full and requires longer parenteral nutrition. In premature infants, one of the causes of drinking intolerance is the imperfect motility of the gastrointestinal tract causing gastric emptying and transit in the bowel that is slower and increases the residuals in the stomach.7

When breast milk is limited, formula for premature infants can be used. The nutrient composition of the premature formula is enhanced to meet the nutritional needs of premature infants. Low birth weight babies had been given premature formulas showed improvement of fat absorption, weight gain and bone mineralization compared to very low birth weight infants given standard formula milk.8 A premature formula is given when HMF-fortified milk is insufficient to achieve a growing pace (ideal body weight) or an anthropometric indicator (weight, length, and head circumference) below the 25th percentile in the Infant Health and Development Program (IHDP) graphs.9 Until now there has been no consensus that determines the optimal formula for premature infants. However, the common macronutrient profile that should be present in premature infant formula has been determined. The energy content ranges from 80 to 82 kcal / 100 ml, protein 2.0-2.4 g / 100 ml and enriched minerals, vitamins, and trace elements to support the nutritional adequacy of premature infants in order to achieve intrauterine growth rates.8

In this study the powdered milk formula used contains whey protein while the liquid milk formula contains whey protein and casein. Statistically, the difference of feeding intolerance between powdered and liquid feeding of preterm infants was not significant, however from the data obtained, premature infants fed a larger liquid formula resulted in feeding intolerance (7.7%) than infants receiving powdered formula (4.9%). This was possible because of whey proteins are more easily digested than casein and their use greatly reduces the development of unusual lactobazoars in overcapitalized babies with high casein products.10 Caseins are more easily coagulated when acidified in the stomach, leading to slower digestion and more gastric emptying slow, both of which cause a slower increase in plasma amino acid concentrations.11 However, infant formula with a ratio of 60% whey protein and 40% proteinase leads to faster gastric emptying, digestion, absorption of amino acids, and reduced incidence of metabolic acidosis. In premature infant formulas, whey proteins are more dominant and produce plasma free amino acid concentrations more similar to those produced by breast milk than with casein protein.10

Study in 2010 that conducted in Turkey reported that the feeding of liquid formula caused 26.5% to have an increased incidence of feeding intolerance.2 However, this study showed that there was no significant difference in drinking intolerance between premature infants who were fed with powdered formula. This is due largely to gestational age in samples over 32 weeks, where functional and biochemical maturation occurs gradually during the last trimester of pregnancy so as to allow the digestive tract in the sample to have functional and biochemical maturation.1 Monitoring drinking intolerance in preterm infants is associated with dysmotility or impaired absorption due to gastrointestinal immaturity.12

This study showed no significant differences between 2 groups of samples received powdered and liquid formulas, between length of parenteral nutrition (9.6 / 7 days), long returning to birth weight (10.5 / 11 days), age reached full enteral nutrition (10.1 / 8 days) and duration of enteral enteral feeding to full enteral (10.1 / 5 days). This was consistent with study in Turkey in 2010. The mean duration of enteral nutrition achieving full enteral nutrition was 7-10 days at gestational age ≥28 weeks or >1500 grams and a maximum of 14 days at gestational age <28 weeks or <1000 grams.39 Duration of returning to birthweight in preterm infants longer than with mature infants, whereby weight gain generally begins in the second week.13

This study reported that there was no difference in weight gain in premature infants given either powdered or liquid milk formula. This may be influenced by the maturity of the gastrointestinal tract in terms of food absorption, the number of calories and evaporation (body surface area). But until now there has been no further research on comparing weight gain in premature infants with the provision of either liquid or powdered milk formula.

There are many risk factors that affect the incidence of feeding intolerance in premature infants. In this study it was reported that giving of liquid formula, age <32 weeks gestation and male gender did not become risk factor of feeding intolerance. A 2010 Turkish study showed that liquid milk formula was a risk factor for drinking intolerance in premature infants.2 Research in Turkey, 2010 reported that liquid milk formula can lead to an increase in the incidence of feeding intolerance and delayed growth in the first week of life in premature infants due to acidity stomach that changes or disrupts the protein bioavailability due to the production process and sterilization is different. Some limitations of this study are the small number of subjects.

In this research, NNT value of powdered milk formula to drinking tolerance was 35, it means to avoid one incidence of drinking intolerance in premature babies requires 35 premature infants who got powdered formula. With these values indicate that powdered milk formula is not effective in preventing the incidence of feeding intolerance.

The limitation of this study is that sample do not perform fasting and postprandial gastric pH, where increased intolerance of feeding and inhibition of growth may result from changes in the pH of stomach fluid or heat sterilization resulting in protein digestion or bioavailability.2 Research in Australia, 2005 after breast-feeding or formula, the median pH of the stomach increased rapidly to 6.0-7.0 in 30 minute, then decreased to 4.5-5.0 at 60 minute, and reached basal level of 1.5-3.0 at 120 minute at the midpoint of the abdomen in premature infants.14 Other susceptibility in this study did not specify the milk temperature before it was administered, as the milk temperature affects the absorption of the given diet, where by WHO recommends that the milk temperature when serving should not be less than 70oC.15

In conclusion, powdered milk formula is not effective in preventing the incidence of feeding intolerance. Based on this study, there was no statistically difference between drinking problems in premature infants in both groups of formula milk and there was no difference in weight gain between premature infants receiving powdered formula or milk formula, then milk, gestational age , sex, sepsis, birth weight not a risk factor for feeding intolerance. Selection of formula milk is recommended if breast milk is inadequate to meet the nutritional needs of premature babies. Referring to this study, the selection of formula based on the cost. Currently, the price of liquid milk for preterm infants is more expensive than powdered milk formula.

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