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Original Articles

Comparison of Very Low Birth Weight Preterm Infants with And Without Experienced Target Weight Gain on The Administration of Human Milk Fortifier

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Abstract

Background: Human milk fortifier (HMF) is defined as a supplement added to breastmilk to increase various nutrition of breastmilk. The purpose of HMF administration is to increase the concentration of breastmilk nutrients to improve the weight of very low birth weight preterm infants. The administration of HMF is insufficient to fulfill protein needs in 20-40% very low birth weight babies, thus the weight gain did not meet the expected target.

Objective: To compare between very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of HMF.

Methods: An observational study with cross sectional design was done to determine characteristic differences of very low birth weight preterm infants.

Results: Data were obtained from medical records consisted of 26 very low birth weight premature infants who experienced weight gain according to the target and 26 who experienced weight gain not according to the target. There was no characteristic difference of cyanosis (PR 1.43; 95% CI 0.51-10.4), chest retraction (PR 1.0; 95% CI 0.32-3.1), apnea of prematurity comorbid (PR 1.0; 95% CI 0.25-3.9), neonatal infections (PR 0.79; 95% CI 0.21-1.9), starting age of HMF administration (PR 0.78; 95% CI 0.21-1.89), bloating (PR 0.74; 95% CI 0.17-1.9), and vomiting (PR 1.09; 95% CI 0.38-3.7) in both groups.

Conclusion: There was no characteristic difference between very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of HMF.

Key words: Preterm Infants; VLBW; HMF

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INTRODUCTION

Very low birth weight preterm infant is defined as a baby born with a birth weight less than 1500 grams and a gestation period of fewer than 37 weeks. Very low birth weight preterm infant is one of the most important predictors of infant mortality, especially in the first couple of months.

Very low birth weight preterm infants also play a crucial role as significant predictors of infant and child morbidity, especially neurodevelopmental disorders such as mental retardation and learning disorders. Besides, very low birth weight preterm infants are reported to be 100 times more likely to die in the first year of life than infants with normal birth weight.¹

The prevalence of very low birth weight preterm infants is expected to increase globally. Several reports showed that very low birth weight preterm infants occurs in 4-8% of live births but cause one-third of deaths in the newborn group.² Other data showed that very low birth

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weight preterm infants are a group of infants with high morbidity and mortality rates and are the main cause of death in 60% of neonates. The prevalence of very low birth weight preterm infants varies in several regions in Indonesia. Several studies that took place in seven regions in Indonesia, namely Aceh, Palembang, Yogyakarta, Surabaya, Bali, Ujung Pandang, and Manado, showed that the prevalence of very low birth weight preterm infants ranges from 2.1-17.7%.³

Very low birth weight preterm infants are a special population with several distinctive characteristics. Cyanosis and chest retraction are known clinical symptoms of very low birth weight preterm infants. Several researches showed that the prevalence of cyanosis in very low birth weight preterm infants was around 7.5% while chest retractions estimated to occur in 2% to 13% of very low birth weight preterm infants.^{4,5} Neonatal infections and apnea of prematurity (AOP), which are defined as a cessation of breathing for > 20 seconds or a shorter pause accompanied by bradycardia <100 beats per minute, are also often found in very low birth weight preterm infants. Drinking intolerance symptoms such as bloating and vomiting are often found in very low birth weight preterm infants due to immature gastrointestinal tract function.^{6,7}

Research shows that breastfeeding, which is the best nutrition source for infants, cannot meet the nutritional needs of very low birth weight preterm infants if given without fortification. The nutritional composition contained in the breast milk of mothers who give birth to very low birth weight preterm infants is similar to mothers who give birth to full-term babies about three to four weeks after birth. Therefore, the increased nutritional needs of very low birth weight preterm infants cannot be met by unfortified breast milk alone.⁸ An example of this case is breast milk which contains 260 mg/L of calcium. Accordingly, if very low birth weight preterm infants breastfed at the normal volume (for example, around 200 mL/kg/day), unfortified breast milk can only provide about 50 mg/kg/day of calcium. It can only be met one-third of the total calcium needs of very low birth weight preterm infants, assuming a maximum absorption rate of 60% to 70%.⁹

Based on the problems above, breast milk must be fortified with various substances, especially protein, calcium, and phosphate, to meet very low birth weight preterm infants' nutritional needs. The other importance of breast milk fortification is supported by the fact that inadequate protein intake in very low birth weight preterm infants can cause growth retardation and lead to decreased fat-free mass (FFM). This ultimately leads to low neurocognitive development. Therefore, breastmilk fortification with a human milk fortifier (HMF) is now widely used to meet very low birth weight preterm infants' nutritional needs.¹⁰

HMF is defined as a dietary supplement added to breast milk to increase the content of calories, minerals, protein, vitamins, and various nutrients in breast milk.¹¹ The goal of HMF supplementation is to increase the nutrient concentration of breast milk to meet very low birth weight preterm infants' nutritional needs. The nutritional needs of very low birth weight preterm infants are defined as the nutritional intake that can cause the growth rate of very low birth weight preterm infants

equal to normal infants' growth rate. The composition of HMF may vary between countries, but some substances that can always be found in HMF include long-chain fatty acids, minerals, vitamins, and amino acids.¹²

The onset of HMF administration can affect the weight gain outcome of very low birth weight preterm infants. Research conducted by Tillman et al. showed that early onset of HMF administration before ten days gave better anthropometric measurement results than late onset administration.¹³ This result is supported by a study conducted by Alizadeh et al. who reported that early onset administration resulted in faster weight gain than late onset. Research conducted by Alizadeh et al. recommends early fortification in infants less than ten days old.¹⁴

Several reports, however, suggest that HMF administration to very low birth weight preterm infants, both early and late onset administration, still failed to achieve weight gain as expected target. Previous research stated that giving HMF was still unable to meet the protein needs of 20-40% of very low birth weight preterm infants, so that the increase of weight could not reach the expected target.¹⁵ Research conducted by Picaud et al. in 2017 indicates that in addition to HMF supplementation, some very low birth weight preterm infants still need additional protein supplements to achieve weight gain as an expected target.¹⁶

This study was conducted to examine the characteristic differences between very low birth weight preterm infants who experience weight gain according to the target and not according to the target on the administration of HMF. The characteristic differences consist of cyanosis, chest retraction, AOP, neonatal infections, HMF starting age, and drinking intolerance symptoms. The purpose of this study is to analyze characteristic differences between very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of HMF.

MATERIALS AND METHODS

This study includes an analytical study using a cross sectional approach to determine characteristic differences found in very low birth weight preterm infants who experience weight gain according to the target and not according to the target on the administration of human milk fortifier (HMF). This research was conducted at Dr. Kariadi Hospital, Semarang. Data collection and analysis were carried out from June to July 2020. Sampling was carried out by a consecutive sampling method from medical records of very low birth weight preterm infants at Dr. Kariadi Hospital, Semarang. Using this method, every neonate who met the research criteria was included in the study until the minimum sample size was reached. The minimum sample size was determined using the unpaired case control sample size formula. Based on this formula, the minimum sample size was 52.

The inclusion criteria used in this study were very low birth weight preterm infants who experienced weight gain according to and not according to the target on the administration of HMF treated in Dr. Kariadi Hospital Semarang from January 2019 to January 2020. Weight gain target for preterm infants set in this study was 15

grams/kg/day as recommended by the American Academy of Pediatrics Committee on Nutrition and the Nutrition Committee of the Canadian Pediatrics Society. The exclusion criteria were infants with major congenital abnormalities, infants with necrotizing enterocolitis, and infants who died at the end of hospitalization. The independent variables in this study were cyanosis, chest retraction, apnea of prematurity, neonatal infections, HMF supplementation starting age, bloating, and vomiting. The dependent variables in this study were the weight gain of very low birth weight preterm infants on the administration of HMF. Data analysis includes descriptive analysis and hypothesis testing. Proportion and percentage were used in descriptive analysis while Chi-square test was used for hypothesis testing. Research protocol declared to be ethically appropriate by the Health Research Ethics Committee of Faculty of Medicine, Diponegoro University, Semarang, Indonesia registered by No. 77/EC/KEPK/FK-UNDIP/V/2020.

RESULTS

This research was conducted at Dr. Kariadi Hospital Semarang from the period of June 2020 to July 2020. The samples were obtained from medical records and were selected by consecutive sampling. There are 52 samples, with 26 very low birth weight preterm infants who experienced weight gain according to the target and 26 babies who experienced weight gain not according to the target on the administration of HMF. Based on the respondents' characteristics, it was found that the mean gestational age of very low birth preterm infants' weight was 30.7 weeks with a standard deviation of 2.5 weeks. The median value of the respondent's birth weight was 1280 grams (700-1450 grams), with the lowest birth weight being 700 grams and the highest birth weight being 1450 grams. The median value of infants' birth body length was 39 cm (32–43 cm), with the lowest birth length was 32 cm and the highest body length at birth was 43 cm. It also shows that 76.9% of very low birth weight preterm infants were babies born from a singleton pregnancy. Most of the very low birth weight preterm infants were born to mothers aged between 20 and 35 years (82.7%) and were multigravida mothers (69.2%). **Table 1** also shows that the majority of very low birth weight preterm infants were born to mothers who had comorbidities (63.5%).

Table 2 shows clinical symptoms characteristic differences of very low birth weight preterm infants who experienced weight gains according to the target and not according to the target on the administration of HMF. In **table 2**, it can be seen that clinical symptoms of cyanosis are more common in the very low birth weight preterm infants who experienced weight gain not according to the target group. Cyanosis occurs as much as 23.1% in very low birth weight preterm infants who experienced weight gain not according to the target group compared to the group of very low birth weight preterm infants who experienced an increase in body weight according to the target group which is 11.5%. However, based on the chi-square test, the clinical symptoms of cyanosis in the two groups are not statistically significant [$p = 0.271$; $PR = 1.43$ (0.51-10.4)]. There was also no statistically

difference in chest retraction between two groups [$p = 1,000$; $PR = 1$ (0.32-3.1)].

The results of very low birth weight preterm infants' comorbid that underwent increased weight gain according to the target and not according to the target are shown in **table 3**. Looking at this table, it can be concluded that there is no significant difference between the two groups.

Chi-square and Mann Whitney test analysis for the starting age of HMF administration revealed in **table 4**. Mann Whitney test analysis showed a p-value of > 0.05 so it can be concluded that there is no significant difference in the starting age of HMF administration in the two groups. Similar to the Mann Whitney test analysis, the Chi-square test also showed no statistically significant difference in the starting age of HMF in both groups.

Drinking intolerance characteristics of very low birth weight preterm infants in both groups which consist of bloating and vomiting can be seen in **table 5**. According to this table, it can be concluded that there is no significant difference in both groups.

Table 1. Differences in clinical symptoms

Variable	Weight Gain		P
	Not According to The Target (n=26)	According to The Target (n=26)	
Gestational Age	31.0 ± 26 weeks [∇]	30.4 ± 2.3 weeks [∇]	0.323 [‡]
Birth Weight	1320 (1000-1450) grams ^Φ	1207 (700-1450) grams ^Φ	0.019 ^{#*}
Birth Length	52.3 cm	48.9 cm	0.019 ^{#*}
Singleton or Multiple Pregnancy			
Singleton	17 (65.4%)	23 (88.5%)	0.048 ^{¥*}
Multiple	9 (34.6%)	3 (11.5%)	
Mother's age			
< 20 or > 35 years	3 (11.5%)	6 (23.1%)	0.465 [¥]
20 - 35 years	23 (88.5%)	20 (76.9%)	
Gravida			
Primigravida	10 (38.5%)	6 (23.1%)	0.229 [¥]
Multigravida	16 (61.5%)	20 (76.9%)	
Comorbidities			
Exist	17 (65.4%)	16 (61.5%)	0.773 [¥]
Absence	9 (34.6%)	10 (38.5%)	

[∇]Mean ± SD; ^ΦMedian (min-maks); * Significant ($p < 0,05$); [‡]

Independent t-test; [#] Mann whitney; [¥]Chi Square

Table 2. Differences in clinical symptoms

Variable	Weight Gain		P	PR (95% Confidence Interval)
	Not According to The Target (n=26)	According to The Target (n=26)		
Cyanosis				
Exist	6 (23.1%)	3 (11.5%)	0.271 [‡]	1.43 (0.51-10.4)
Absence	20 (76.9%)	23 (88.5%)		
Chest Retractions				
Exist	17 (65.4%)	17 (65.4%)	1.000 [‡]	1.0 (0.32-3.1)
Absence	9 (34.6%)	9 (34.6%)		

[‡]Chi Square test

Table 3. Comorbid differences

Variable	Weight Gain		P	PR (95% Confidence Interval)
	Not According to The Target (n=26)	According to The Target (n=26)		
Apnea of Prematurity				
Exist	5 (19.2%)	5 (19.2%)	1.000 [‡]	1.0 (0.25-3.9)
Absence	21 (80.8%)	21 (80.8%)		
Neonatal Infection				
Exist	10 (38.5%)	13 (50%)	0.402 [‡]	0.79 (0.21-1.9)
Absence	16 (61.5%)	13 (50%)		

[‡]Chi Square test

DISCUSSION

Data analysis between very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of human milk fortifier (HMF) did not show much of a difference. Data from the respondents' characteristics showed a statistically significant difference between singleton and multiple pregnancies in the two groups. Most very low birth weight preterm infants who experienced weight gain not according to the target are babies born from multiple pregnancies. The hypothesis behind this is babies born from multiple pregnancies are less likely to receive adequate nutrition due to the placenta's limited ability, especially during late gestation.¹⁷ Another hypothesis stated that mothers who carry multiple babies are more likely to experience pregnancy complications such as anemia and preeclampsia.¹⁸

Other statistically significant characteristics are birth weight and birth length. The group with weight gain according to the target tends to have smaller birth weight and smaller birth length. These characteristics are different from the group experiencing weight gain that is

not according to the target. This study's results are consistent with the research conducted by Kupers et al., whose finding reveals that babies with a lower birth weight have a more significant increase rate of body weight than babies with higher birth weight. Kupers et al. proposed a concept called "the lower the birth weight, the more rapid the growth." According to this concept, infants with low birth weight tend to experience rapid weight gain, mainly due to low muscle mass, which changes muscle sensitivity to insulin.¹⁹ This study's results, however, are not in accordance with the study conducted by Ehsanpour S et al., which found that a slower growth rate is observed in babies with lower birth weight.²⁰

Cyanosis is a bluish discoloration of the skin and mucous membranes due to a decrease in hemoglobin levels ≥ 5 g/dL which indicates a decrease in blood oxygen supply to the tissue.²¹ This study found that the incidence of cyanosis was more common in the group of very low birth weight preterm infants who experience weight gain not according to the target, although it was not statistically significant. This finding is in accordance with the study conducted by Irving S. et al. according to which there was no growth rate and weight gain difference between infants who have cyanosis and infants who do not have cyanosis.²²

Another possibility that resulted in the absence of significant differences between the two groups in terms of cyanosis is edema that often coexist with cyanosis. Cyanosis is caused primarily by a congenital heart disease, which results in low systemic blood saturation and a bluish discoloration around the mouth or fingers. Babies who have end-stage congenital heart disease may also develop heart failure often manifesting as edema. Edema ultimately affects the measurement of very low birth weight preterm infants' weight who have cyanosis.²³

Chest retraction means that the child is having to use chest muscles to get air into the lungs and this condition indicates an increased effort to breathe. Analysis of chest retraction clinical symptom showed that there was no statistically significant difference in very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of HMF. Therefore, the results of this study are not in accordance with the research conducted by Ivana K. et al. which states that there is a negative correlation between the incidence of chest retraction and infants' growth rate.²⁴

This insignificant difference is probably due to the high incidence of chest retraction in very low birth weight preterm infants. The condition that often causes chest retraction in very low birth weight preterm infants includes respiratory distress syndrome (RDS). Respiratory distress syndrome (RDS) is defined as respiratory distress due to the lack of surfactant resulting in alveoli collapses.²⁵ High incidence of pneumonia in very low birth weight preterm infants also significantly increases chest retraction incidence in both groups.²⁶

Apnea of prematurity (AOP) is described as a cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia <100 beats per minute, cyanosis, or pallor.²⁷ Oxygen and nutrient insufficiency should result in weight gain disorders thus affecting the weight of the baby.

Table 4. HMF supplementation starting age

Variable	Weight Gain		P	PR (95% Confidence Interval)
	Not According to The Target (n=26)	According to The Target (n=26)		
Average HMF Starting Age (days)	13.23 ± 5.3 [∇]	13.92 ± 6.7 [∇]	0.406 [‡]	-
HMF Starting Age				
≤ 10 days	9 (34.6%)	12 (46.2%)	0.397 [¥]	0.78 (0.21-1.89)
>10 days	17 (65.4%)	14 (53.8%)		

[∇]Mean ± SD [‡]; Independent t-test; [¥] Chi-Square test

This present study cannot demonstrate the above theory because of the high incidence of central nervous system immaturity in premature babies, which often causes AOP in both groups.²⁸

The absence of statistically significant differences of AOP in both groups can also be based on the research conducted by Mathew et al. The research suggests that AOP, notably obstructive and mixed type AOP, is found more frequently during sleep.²⁹ As an infant sleeps, upper airway muscle activity is reduced, causing the upper airway to collapse, mainly during inspiration. The existence of poor-quality sleep causes an increased ghrelin hormone and decreased leptin hormone. Ghrelin plays a significant role in increasing appetite, food intake, and reducing energy expenditure by lowering fat catabolism, while leptin plays a significant role in decreasing appetite. This hormonal balance disorder may ultimately cause babies who experience AOP to still gain weight according to the target despite having AOP.³⁰

Neonatal infection is defined as the presence of microorganisms in body tissues followed by host immune response and is closely associated with infants' decreased growth rate.³¹ This study showed that there is no statistically significant difference between both groups. This study's results, which did not find any statistically significant differences, may be caused by several factors. The first possibility was based on research conducted by Eleonora P. et al. and Amos T. et al., which found a significant relationship between

infection and accelerated weight gain.^{32,33} Amos T. et al. states that infection causes an adipocyte stress response, adipocyte dysfunction, and dysregulation of adipokine secretion, which ultimately increase the weight of infants who have the infection.³³ The second possibility is based on research conducted by Dawson-Hahn et al., who stated that the use of antibiotics in the first year of life significantly increased the rate of infants' weight gain compared to the infants who did not take antibiotics.³⁴

This study also found that there is no statistically significant difference in terms of the starting age of HMF administration in both groups. This study's results are consistent with a study conducted by Peymaneh A et al. according to which there was no significant difference in weight gain between very low birth weight preterm infants who received early and later HMF supplementation.¹⁴ The results of this study were also supported by research conducted by Wesam A et al. whose conclusion states that there was no significant difference in weight gain between groups of infants who received early and later HMF.¹³

This study found that there is no significant difference in drinking intolerance, consisting of bloating and vomiting between both groups. However, Fanaro S et al. have a different view. They stated that very low birth weight preterm infants who experience weight gain not according to the target tend to have drinking intolerance symptoms.³⁵ Morton et al., who aimed to evaluate growth in infants with drinking intolerance also found that drinking intolerance resulted in lesser weight gain.

Table 5. Drinking intolerance differences

Variable	Weight Gain		P	PR (95% Confidence Interval)
	Not According to The Target (n=26)	According to The Target (n=26)		
Bloating				
Exist	6 (23.1%)	9 (34.6%)	0.358 [¥]	0.74 (0.17-1.9)
Absence	20 (76.9%)	17 (65.4%)		
Vomiting				
Exist	10 (38.5%)	9 (34.6%)	0.773 [¥]	1.09 (0.38-3.7)
Absence	16 (61.5%)	17 (65.4%)		

[¥] Chi-Square test

It is interesting to note that Morton et al. found that the weight gain rate in the group of very low birth weight infants with drinking intolerance was 19.97 g/kg/day, with an increase in body length of 0.81 cm/week during three months of hospitalization. The growth rate, then, also increased up to 20.56 g/kg/day after three months of age.³⁶

Growth rates of infants with drinking intolerance symptoms in Morton's research are still much greater than the weight gain target set in this study, which is 15 g/kg/day. This finding indicates, despite having symptoms of drinking intolerance, infants with the registered symptoms are still able to gain weight according to the target set by the American Academy of Pediatrics Committee on Nutrition and the Nutrition Committee of the Canadian Pediatrics Society.³⁶ Other factors could also cause insignificant difference between both groups in terms of drinking intolerance. Excessive drinking, crying for too long, improper breastfeeding and drinking process, incorrect position while breastfeeding, and excessive lactose can eventually cause bloating. Similar to bloating, vomiting can also be caused by other conditions such as a small stomach size, incorrect position when breastfeeding, or infections.³⁷

This study has several limitations. The first limitation is that other common comorbid in very low birth weight preterm infants, such as hyperbilirubinemia and congenital heart disease, were not studied. These factors can affect the weight gain of very low birth weight preterm infants and thus influence the results of the study. Samples taken from medical records also have limitations. Data taken from medical records are less representative and cannot fully describe patient's current condition since it is written only when the patient was in the hospital

CONCLUSION

In conclusion, our study demonstrated that there was no characteristic differences in terms of cyanosis and chest retraction clinical symptoms, apnea of prematurity and neonatal infections comorbid, starting age of HMF administration, and drinking intolerance symptoms which consists of bloating and vomiting between very low birth weight preterm infants who experienced weight gain according to the target and not according to the target on the administration of HMF. Further research which includes other variables that can affect the growth rate of very low birth weight preterm infants such as hyperbilirubinemia and congenital heart disease may be needed to obtain more accurate results.

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