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Original Article

Risk Factors Affecting the Length of Improvement of Nutritional Status in Children with Congenital Heart Disease and Malnutrition

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Abstract:

Background: To date, limited data are available regarding the factors that contribute to the delay of improvement in nutritional status as well as data regarding the optimal duration to improve malnutrition among children with congenital heart disease (CHD). Such data are important for pediatricians to fully optimize the nutritional status for those children prior to surgical procedure This study aims to identify those aforementioned factors in hope for better surgical outcome and quality of life of children with CHD.

Methods: This is a descriptive analytic study using retrospective cohort design to identify the factors that contribute to the delay of improvement in nutritional status among children with CHD. Variables such as the type of CHD, classification of CHD complexity, pulmonary hypertension, heart failure, corrective surgery, the route of nutrition access, pneumonia, diarrhea, special diets and patients undergoing routine control at the nutrition outpatient clinic were evaluated in this study.

Results: A total of 216 children with a diagnosis of CHD and weight-for-length z-score under -1 SD were included in this study. Based on multivariate analysis, there were two significant risk factors, which were the occurrence of diarrhea and consulting at nutrition outpatient clinic. The improvement in nutritional status in children with CHD who did not have diarrhea was faster than those with diarrhea (HR 1.94; 95% CI 1.10 – 3.47) (p value <0.025). Improvement in nutritional status of those children that underwent control at the nutrition outpatient clinic was faster than those who did not (HR 1.87; 95% CI 1.20 – 2.92) (p value <0.006).

Conclusion: Risk factors that significantly lengthen the duration of improvement in the nutritional status of CHD patients were the incidence of diarrhea and those who did not undergo control at the nutrition outpatient clinic.

Keywords: CHD, duration of nutritional status improvement, malnutrition, risk factor

Introduction

Congenital heart disease (CHD) is commonly associated with malnutrition in children. The incidence of growth failure among children with CHD is 64% in developed countries while higher number is observed in developing countries with varying incidence of 27% to 90.4%.[1] One study by Amelia et al in Indonesia reported that the incidence of wasting and stunting among children with CHD were 56.8% and 46.6% respectively.[2]

Children with CHD are known to have a higher basal metabolic rate with poorer calories intake, which explain the greater prevalence of malnutrition among those population.[3,4] There are other factors that may also exacerbate this condition, such as chronic hypoxia due to cyanotic CHD, pulmonary hypertension, heart failure, delayed surgery, dietary pattern as well as infections (pneumonia and diarrhea).[3,5-7] Several conditions that are associated with CHD have been linked to impaired growth in children. Acyanotic CHD is reported to be associated with underweight, pulmonary hypertension is associated with wasting and lastly, cyanotic CHD as well as single ventricle disease are associated with stunting in children.[8] Malnutrition in children with CHD is known to negatively impact the surgical outcome as well as morbidity and mortality.[4] According to a study, CHD children with good nutritional status have lower complication rates during surgical intervention later on.[9]

Devaera et al. reported that in general, there 5 risk factors that cause children with CHD to be more susceptible to malnutrition.[10] First is the increased energy requirement among those children which is due to increased basal metabolic rate, total energy expenditure as well as nutritional requirement for cardiac and respiratory muscles. Moreover, conditions such as infection and prematurity may further increase the energy requirement. Second, children with CHD are most likely to have decreased food intake due to anorexia, early satiety as well as dysphagia and gastrointestinal reflux disease. Third, increased loss of nutrients is commonly found in those children due to gastrointestinal malabsorption, hyperosmolarity, protein-losing enteropathy and loss of electrolytes from the kidney. Fourth, children with CHD are inefficient in utilizing nutrients as a result of acidosis, cellular hypoxia and increased pulmonary pressure. Lastly, other factors such as chromosome disorder, nutritional impairment during pregnancy as well as low birth weight may contribute to susceptibility of children with CHD to malnutrition.[10]

To date, limited data are available regarding the factors that contribute to the delay of improvement in nutritional status as well as data regarding the optimal duration to improve malnutrition among children with CHD. Such data are important for pediatricians to fully optimize the nutritional status for those children prior to surgical

procedure. Therefore, this study aims to identify those aforementioned factors in hope for better surgical outcome and quality of life of children with CHD.

Methods

This is a descriptive analytic study using retrospective cohort design to identify the risk factors that contribute to the delay of improvement in nutritional status among children with CHD. This study was conducted at an outpatient pediatric cardiology clinic in a national referral hospital with integrated cardiac unit. Inclusion criteria for this study were children with CHD age 0-5 years, weight-for-length z- score below -1 SD based on WHO 2005 growth chart when first admitted and were followed up until either they reached good nutritional status (z-score > - 1 SD) or at least 1 year, as well as patients who went for routine control for at least 3 times during that period at cardiology outpatient clinic. Exclusion criteria were incomplete data and patients who were lost to follow up (death or patients stopped coming for routine control). Subjects were sampled by total sampling method of those who were treated at our hospital throughout the period of 1 year (August 2016 to July 2017). The minimal number of subjects for each risk factors in this study were 38 subjects based on the formula to determine the differences between two proportion. Rule of thumb was utilized to determine the number of risk factors to be included for analysis. Dependent variable in this study was the length of time until improvement in nutritional status, while independent variables were the type of CHD, classification of CHD complexity, pulmonary hypertension, heart failure, corrective surgery, the route of nutrition access, pneumonia, diarrhea, special diets and patients undergoing routine control at the nutrition outpatient clinic.

Determination of the subject's nutritional status and stature was carried out using the WHO Anthro tool by entering the date of birth, date of monitoring, weight and height. Then the weight-for-length and height-for-age z-score data were transferred to the Statistical Package for the Social Science (SPSS) version 25 software for analysis. Factors that affect the length of time needed for nutritional improvement were assessed by using a survival analysis test for each of these factors, so that the mean or median value of the duration for nutritional improvement was obtained. Significance was evaluated using the log rank test or Breslow depending on the distribution of the data. Risk factors that had p values under 0.2 were included in the multivariate analysis. Multivariate analysis was carried out using the Cox regression test to produce a hazard ratio (HR), confidence interval, and significance. The p value <0.05 was considered significant in this multivariate test.

Results

A total of 336 children with a diagnosis of CHD and weight-for-length z-score under -1 SD were recruited in this study. However, after screening by applying inclusion and

exclusion criteria, only 216 remained eligible for this study. Baseline characteristics of all subjects are presented on **Table 1**. Children with CHD and malnutrition in this study had the same proportion of boys and girls (47% and 53% respectively). Most of our patients were under one year old with fewer number of patients were observed with increasing age groups. The median age of subjects was 9.1 months. Eighty percent of those patients presented with acyanotic CHD, while the other 20% were cyanotic. As many as 74% of CHD patients had normal birth weight (> 2500 grams), while the rest had low birth weight. The median of weight-for-length z-score during initial monitoring period was -2.73 SD. Meanwhile, by the end of follow up, the median z-score was -1.62 SD.

Table 1. Baseline characteristics of children with CHD and malnutrition.

Characteristics	Frequency
Gender, n (%)	
Boys	102 (47)
Girls	114 (53)
Age (months), median (range)	9,1 (0 – 48,7)
Age classification, n (%)	
under 1 year old	140 (65)
1-2 years old	44 (20)
2-3 years old	16 (7,4)
3-4 years old	12 (5,6)
4-5 years old	4 (1,9)
Classification of CHD, n (%)	
Acyanotic	172 (80)
Cyanotic	44 (20)
Classification of birth weight, n (%)	
<2500 gram	56 (26)
≥2500 gram	160 (74)
Weight-for-length z-score initial follow up, median (range)	-2,73 (-6,39 – -1,10)
Weight-for-length z-score end of follow up, median (range)	-1,62 (-6,56 – 1,21)
Changes in weight-for-length z-score, median (range)	1,18 (-2,85 – 6,25)

Nutritional status for each patient was collected at the first hospital admission and continued to be monitored until they had reached good nutritional status (weight-for-length z-score above 1 SD) or at least 1 year of follow up. Data regarding the nutritional status before and after follow up period are presented on **Table 2**.

Table 2. Nutritional status before and after follow up period.

Nutritional status	Initial follow up			End of follow up		
	acyanotic (n=172)	cyanotic (n=44)	p	acyanotic (n=172)	cyanotic (n=44)	p
Nutritional status						
Good nutritional status	0	0		74 (43)	10 (23)	
Mild malnutrition	38 (22)	12 (27)	0.767	38 (22)	20 (45)	0.005
Moderate malnutrition	58 (34)	14 (32)		30 (17)	10 (23)	
Severe malnutrition	76 (44)	18 (41)		30 (17)	4 (9)	
Stature						
Normal stature	102 (59)	24 (54)		110 (64)	16 (36)	
Short stature	24 (14)	10 (23)	0.490	24 (14)	16 (36)	0.002
Very short stature	46 (27)	10 (23)		38 (22)	12 (27)	

The change of nutritional status was evaluated at the end of follow up period by calculating the difference of weight-for-length z-score during that period (**Table 3**).

Table 3. Changes in nutritional status after follow up period.

Changes in nutritional status	Total 216; n (%)
Worsen	16 (7)
No changes	52 (24)
Improvement	148 (69)

The significance test was assessed by using the log rank test or Breslow test depending on the distribution of the data (**Table 4**).

Table 4. Analysis of possible risk factors that may affect the length of time needed for nutritional improvement

Risk Factors	Median of duration to improve nutritional status (months)	p-value
Classification of CHD		
Cyanotic	7.81	0.046*
Acyanotic	4.97	
Heart failure		
Yes	5.96	0.635
No	7.14	

Route of nutrition administration		
Oral	6.80	0.083*
Enteral	4.99	
Diet		
Normal/polymeric formula	7.24	0.059*
Special formula	4.99	
Pneumonia		
Yes	9.28	0.072*
No	7.23	
Diarrhea		
Yes	8.44	0.018*
No	6.54	
Routine control at nutrition clinic		
Yes	4.99	0.002*
No	8.14	

*Statistically significant (p<0.05)

There were six factors that had a p value <0.2 based on log rank test or Breslow test. Those factors were then included in multivariate analysis by using Cox regression to obtain significant risk factors with p value <0.05. There were two significant risk factors, which were the occurrence of diarrhea and consulting at nutrition outpatient clinic. The results of this multivariate analysis can be seen in **Table 5**.

Table 5. Multivariate analysis possible risk factors that may affect the length of time needed for nutritional improvement

Risk factors	Hazard ratio (95% CI)	p-value
Cyanotic CHD	1.37 (0.88 – 2.13)	0.160
Oral nutrition route	0.97 (0.64 – 1.48)	0.893
Normal diet	1.02 (0.67 – 1.55)	0.934
Pneumonia	1.64 (0.96 – 2.80)	0.069
Diarrhea	1.94 (1.10 – 3.47)	0.025*
No routine control at nutrition clinic	1.87 (1.20 – 2.92)	0.006*

*Statistically significant (p<0.05)

The improvement in nutritional status in children with CHD who did not have diarrhea was faster than those with diarrhea. Those children without diarrhea experienced an improvement in their nutritional status in 6.54 months, while those

with diarrhea experienced an improvement in 8.44 months. Multivariate analysis showed that children with CHD without diarrhea would have their nutrition improved 1.94 times faster to increase the weight-for-length z-score by 0.67 SD based on the WHO growth chart compared to the those who had experienced diarrhea.

Improvement in nutritional status of children with CHD that underwent control at the nutrition outpatient clinic was faster than those who did not. CHD patients who went for control experienced an improvement in nutritional status in a median of 4.99 months, while those who did not go for control experienced an improvement in a median of 8.14 months. Multivariate analysis showed that the CHD group that controlled the nutrition outpatient clinic experienced improved nutrition 1.87 times faster to increase the z-score by 0.67 SD based on the WHO curve compared to the CHD group that had never been in control.

Discussion

We found 2 factors that significantly contribute to delayed nutritional improvement in children with CHD; those are any episode of diarrhea and low adherence to control to pediatric nutrition clinic. Diarrhea is one of the main causes of increasing morbidity and mortality in developing countries with an estimated death in children reaching 1.5 million per year due to this disease. Complication due to frequent diarrhea, such as malnutrition, may occur through anorexia, decreased ability of food absorption, damage to the gut mucosa and loss of nutrients. Eventually, this condition may hinder the normal growth of those children. Severe diarrhea is more common in malnourished patients compared to those without. Meanwhile, malnourished children are more likely to contract infections, particularly gastrointestinal infection. Hence, both diarrhea and malnutrition may have influenced one another.[11] Our study demonstrated that diarrhea was a significant risk factor in determining the duration of improvement of malnutrition in children with CHD. Those patients with diarrhea took 8.44 months to improve their nutritional status while those without diarrhea only took 6.54 months (HR 1.97; 95% CI 1.10-3.55). Children with CHD without diarrhea were 2 times faster to see an increase of the Z-score by 0.67 SD ($p<0.023$) in comparison to those with diarrhea. However, the operational definition of the incidence of diarrhea in this study was based on medical records and history taking from parents or caregivers, not from the objective assessment during hospital admission. Therefore, it is important to note that information bias may occur.

The gut microbiota plays an important role in nutritional status as those beneficial bacteria provides both protective and metabolic function for the gastrointestinal tract. The role of microbiota on nutritional status occurs in several ways: (1) providing nutrients for colonic epithelium by producing short chain fatty acids (SCFA) which is a byproduct of polysaccharides fermentation by those bacteria, (2) induction of genes

activation which is crucial for nutrient absorption and development intestinal immune system, and (3) triggering neurotransmitter and hormone responses that affect the speed of glucose and fat metabolism, appetite, and intestinal transit time.[12] In children with CHD, especially those with cyanotic, the presence of mesenteric hypoperfusion and chronic hypoxia can disrupt the development of the gut microbiota resulting in dysbiosis.[13] On the other hand, research in Bangladesh showed that the microbiota maturation index in children with diarrhea was lower than those in normal children. This indicated that some degree of dysbiosis was occurring on children with diarrhea.[14] The presence of diarrhea on children with CHD may further disturb the already abnormal gut microbiota and hence may prolong the duration for improvement in nutritional status among those children.[12] Infections such as acute diarrhea can also trigger an inflammatory cascade resulting in decreased appetite and reduced fat mass. Research by Kosek et al., found that children who suffered from diarrhea 3-5 times a year was at risk of short stature.[15] Research in Malawi found that most patients with severe malnutrition had some coexisting infections, even if they were mild, including diarrhea.[16] Giving antibiotics in this study had been shown to accelerate healing and reduced mortality, but unfortunately it was not proven whether antibiotics can improve dysbiosis. In this study, dysbiosis was not examined because the incidence of diarrhea was only obtained based on the history taking.

Another risk factor that was also significant in determining the duration of improvement in nutritional status among children with CHD was whether or not those patients went for routine control at the nutrition outpatient clinic. There was a difference in the duration of improvement in nutritional status between CHD patients who underwent control at the nutrition outpatient clinic and those who did not. Those patients who were under control at the nutrition outpatient clinic experienced an improvement in nutritional status in a median of 4.99 months, while those who were not, experienced an improvement in nutritional status in a median of 8.14 months (HR 1.87; 95% CI 1 .20-2.92). The proportion of CHD patients with improved nutritional status was greater in those who underwent routine control compared to those who did not, indicating that regular monitoring of growth parameters is important in the nutritional management of those patients. Accurate and periodic measurements accompanied by special attention to nutritional intake and tolerance have a major impact in the management of malnutrition in children with CHD.[17] Those children who consult at the nutrition outpatient clinic will receive nutritional care in the form of an initial assessment, determination of caloric requirements, selection of diet, determination of nutritional pathways, and monitoring in the form of acceptability, tolerance and efficacy.

One study suggested that monitoring of growth should be carried out periodically through consultation with a nutritionist. Nutritional interventions such as the type of

diet, route of administration, and eating rules should be tailored individually to each patient.[18] Furthermore, regular visits to nutritionist may provide information and solve food intake problems for patients. This is also said to help parents reduce stress due to confusion in dealing with eating problems in their children.[19]

Children with CHD often suffered from hypermetabolic state in which they have an increase of 30% of resting energy expenditure and consequently exposing them to catabolic stress.[20] Furthermore, in developing countries such as Indonesia, the prevalence of malnutrition, growth failure as well as pulmonary hypertensin in children with CHD are higher due to limited access to timely surgical intervention for those children. As such, those children are left in those hypermetabolic and catabolic conditions for such a prolonged time and eventually develop malnutrition and growth failure.[21] Moreover, malnutrition that occur during preoperative in children with CHD has been associated with negative outcomes after surgery such as death, cardiac arrest, infection, increased ICU and hospital length of stay as well as longer duration of ventilation support.[22] Based on a systematic review, human breast milk is believed to be the first choice of nutrition as it is better tolerated, promotes intake and growth, and is associated with less postoperative complications for newborns who suffer from CHD.[21,23] However, in certain condition, infant formulas with a higher calorie (above 0.67 kcal/mL) can be given as an option when required. Early initiation of enteral nutrition during perioperative phase has been reported to produce better outcomes such as improve wound healing, less gastrointestinal dysfunction and reduce muscle loss. Perioperative enteral nutrition is recommended to be high in calorie and should be adjusted to individual needs or water restriction, if required. In the immediate postoperative period (0–3 days), nutrition required is approximately 35–65 kcals/kg/d since resting energy expenditure in this condition is considerably reduced.[24]

This research has several limitations. First, the interval period of control schedule at the clinic for each subject differs, hence, there was a possibility of inaccurate data regarding the exact timing of nutritional improvement in patients. Second, this was a retrospective study, so there was a possibility of both information bias and observation bias during data collection. Furthermore, medical records were not written by one person, thereby, the assessment by each physician may not the same in assessing risk factors. Retrospective study design also resulted in some subjects not being able to be assessed due to incomplete data and consequently had to be excluded. Third, in this study, monitoring time was only limited to one year, so long-term effects could not be evaluated. Lastly, in this study, we utilized weight-for-length z score to determine the nutritional status of children with CHD. However, such parameters that only depend on weight and height should be used with caution for determining the nutritional status among those children because it could mask undernutrition and may not reflect the real weight of the child. Children with CHD may present with edema and fluid

retention which may be reflected on their weight. Even though there is no gold standard to assess the nutrition status in disease-related malnutrition, Devaera et al. recommended the use of arm anthropometric assessment (triceps skinfold thickness and mid-upper arm circumference) to better evaluate the nutritional status of those children in order for appropriate monitoring and management as well as to establish correct diagnosis of the child's nutritional status, particularly in developing countries such as Indonesia.[10] Furthermore, this study also suggested that the frequency and interval of nutritional status monitoring in children with chronic illnesses, such as CHD, should be tailored according to the conditions of the each child as nutritional status is greatly influenced by the course of their illness which may change during the course of their illness and treatment.[10]

Conclusion

Based on the results of this study, most of our patients with CHD had an improvement in nutritional status (69%), while 24% had not changed and 7% had worse nutritional status after follow up period. Risk factors that significantly lengthen the duration of improvement in the nutritional status of CHD patients were the incidence of diarrhea and those who did not undergo control at the nutrition outpatient clinic. CHD patients who experienced diarrhea took almost twice as long to improve in nutritional status than those who did not experience diarrhea. On the other hand, CHD patients who underwent control at the nutrition outpatient clinic were twice as fast to improve in nutritional status than those who did not.

Conflict of Interest

None declared.

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