Nutritional support with energy and nutrient-dense formula for children with congenital heart defects: A clinical trial

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Abstract

Background: A large proportion of infants with congenital heart defects (CHD) suffer from malnutrition. The aim of this study was to assess the impact of using energy- and nutrient-dense formula on weight gain in malnourished infants with CHD before surgery.

Methods: This was a one arm, open label intervention study, conducted in the pediatric cardiology department of children's medical center, Teheran, Iran. 49 infants with moderate/high risk cardiac defects who were undernourished (WFA z-score $\leq$ - 2) and were candidates for surgical repair were enrolled in this study. Infants on regular infant formula were switched completely to energy- and nutrient-dense formula. The infants were evaluated for growth parameters (weight and length) at enrolment and every 3 weeks thereafter at the center for a period of 12 weeks.

Results: The average head circumference was 37.1$\pm$2.8 cm at baseline and 39.0$\pm$3.46 cm at the final assessment (p=0.079). The mean MUAC increased from 11.25$\pm$1.39 cm at baseline to 14.75$\pm$2.06 cm at the final assessment (p=0.001). The average intake of energy- and nutrient-dense formula was 148.24$\pm$214.737 Kcal/day (36.23$\pm$ 52.49 Kcal/kg/day) at study start and 455.4$\pm$177.21 Kcal/day (98.61 $\pm$ 38.27 Kcal/kg/day) at the end of the study. The WFA z-score improved significantly on each visit during the follow-up interval (p<0.0001).

Conclusion: The results of the current study highlight the efficacy of preoperative feeding with energy- and nutrient dense formula in improving weight gain of malnourished infants with CHD.

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Background:

A large proportion of infants with congenital heart defects (CHD) suffer from malnutrition (1−4) and Faltering Growth (5). Although the cause of growth failure is multifactorial in these infants, it is fundamentally related to increased energy expenditure and inadequate caloric intake for growth (6−8). Because of this hyper metabolic state (9), their need for energy may be 20 to-50% higher compared to that of healthy children, to obtain normal growth and development (3, 10−12). Furthermore, associated chromosomal or other abnormalities and syndromes may also have an impact on feeding/nutrition (3, 6). Although the underlying cause of nutritional problems in infants with CHD is variable, an important contributing factor is inadequate energy intake for prolonged periods of time (7, 13, 14).

The severity of malnutrition in infants with CHD may range from mild to severe, depending on factors such as the criteria used to assess nutritional status and the type of cardiac defect (13, 15). The severity of growth failure in these infants is most commonly determined using the weight for age Z-score, length for age Z-score and head circumference (16, 17). Failure to thrive is an important factor in the decision-making algorithm for the treatment of patients with CHD (11, 18). Persistent malnutrition at the time of

surgery has been reported to affect the outcome of cardiac surgery and to increase ICU and hospital stay and morbidity (6, 19–22).

Various types of feeds (and feeding regimens) have been used to increase the energy intake of infants with CHD and to assess whether growth improves as a result or not (5). These feeds (and regimens) should be safe, simple and suitable for use at home. Furthermore, the feeds used should be suitable for young infants since the prevention or limitation of FG by early management is preferable to treatment once FG has developed (5).

The aim of this study was to assess the impact of using energy- and nutrient-dense formula on weight gain in malnourished CHD infants before surgery.

Methods

Study design and setting

This was a one arm, open label intervention study, conducted in the pediatric cardiology department of children's medical center, Teheran, Iran.

Study Population

We performed this clinical trial with 49 infants with moderate/high risk cardiac defects (Table 1) who were undernourished (WFA z-score ≤ − 2) and were candidates for surgical repair. Infants known to have non-cardiac medical problems that could independently affect nutrient intake, such as gastrointestinal malformations, renal failure, liver disease, neurological sequelae or genetic conditions associated with growth failure, were excluded. Infants with low risk cardiac defects (Table 1), cow's milk allergy, galactosaemia, history of operation within 4 weeks from the time of screening or receiving parenteral nutrition were also excluded. Parents of potentially eligible patients received a detailed explanation about the study. Verbal and written informed consent were obtained before the beginning of the study.

Table 1. Degrees of nutrition risks in cardiac defects.

1 LOW NUTRITION RISK	2 MEDIUM NUTRITION RISK	3 HIGH NUTRITION RISK
• COARCTATION OF AORTA • PATENT DUCTUS ARTERIOSUS – (IF EARLY SURGERY) • ATRIAL SEPTAL DEFECT (MINOR LESION) • COR TRIATRIATUM • TRANSPOSITION OF GREAT ARTERIES • TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE • VSD (SMALL LESION) • PULMONARY STENOSIS	• PULMONARY ATRESIA • TETRALOGY OF FALLOT • ATRIAL SEPTAL DEFECT – (SEVERE LESION)	• VENTRICULAR SEPTAL DEFECT – (MODERATE TO LARGE) • ARTERIOVENTRICULAR SEPTAL DEFECT • HYPOPLASTIC LEFT HEART SYNDROME • TRUNCUS ARTERIOSUS • AORTOPULMONARY WINDOW • PATENT DUCTUS ARTERIOSUS (IF LARGE OR DELAYED SURGERY) • TRICUSPID ATRESIA • EBSTEIN ANOMALY • PARTIAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Study Intervention

In this study, infants on regular infant formula were switched completely to energy- and nutrient-dense formula (100 kcal and 2.6 g protein per 100 ml; Infatrini®, Nutricia, Zoetermeer, the Netherlands). Infants who received a combination of breast milk and regular infant formula continued on breast milk and were given energy- and nutrient-dense formula to replace the regular formula. Infants who only received breast milk were included at the discretion of the clinician (for top up with energy- and nutrient-dense formula). The infants were evaluated for growth parameters (weight and length) at enrolment and every 3 weeks thereafter at the center for a period of 12 weeks. Head circumference and mid upper arm circumference (MUAC) were assessed at enrolment and 12 weeks thereafter. Infants were weighed naked on the same calibrated digital scale. Length measurements were made using a standardized length board. Z-scores for WFA, LFA, and BMI were calculated based on World Health Organization (WHO) standards. All the calculations were done using WHO Anthro (version 3.2.2, January 2011) software. Weight and length were plotted on appropriate growth charts. Parents recorded formula intake at least 3 days per week in a study diary. Necrotising enterocolitis, acute renal failure and chylothorax were considered as withdrawal criteria.

Data analysis

All data were analyzed using SPSS version 22. The quantitative variables were expressed by mean and standard deviation and the qualitative variables by number and percent. Repeated measurement ANOVA test was applied in order to investigate the effect of the nutrient-dense formula on growth indices (including WFA, LFA, and BMI z-scores). A p-value below 0.05 was considered statistically significant.

Results

A total of 49 patients were enrolled in the study. The mean age, weight and height of the patients at the time of enrolment were 4.0 ± 2.85 (0.26−20.28) months, 4.12 ± 1.28 (2.5−8.2) kg and 57.5 ± 6.64 (47.0-73.5) centimeters, respectively. One patient was excluded due to non-compliance, 2 due to the fact that their WFA z-score was >-1 and 3 due to spontaneous closure of the defects. Therefore, 43 subjects were evaluated during the total follow-up period of 12 weeks. The average gestational age at birth was 37.5 ± 1.69 weeks and 29 (59.2%) patients were female. The patients had the following cardiac problems: 26 (53.1%) VSD (moderate to large), 3 (6.1%) ASD, 4 (8.2%) TOF, 8 (16.3%) AVSD, 2 (4.1%) TGA, 1 (2.0%) severe PS, 3 (6.1%) double outlet right ventricle (DORV), 2 (4.1%) hypoplastic left heart syndrome (HLHS). The average head circumference was 37.1 ± 2.8 cm at baseline and 39.0 ± 3.46 cm at the final assessment (p = 0.079). The mean MUAC increased from 11.25 ± 1.39 cm at baseline to 14.75 ± 2.06 cm at the final assessment (p = 0.001). The average intake of energy- and nutrient-dense formula was 148.24 ± 214.737 Kcal/day (36.23 ± 52.49 Kcal/kg/day) at study start and 455.4 ± 177.21 Kcal/day (98.61 + 38.27 Kcal/kg/day) at the end of the study, respectively. The WFA z-score improved significantly on each visit during the follow-up interval (P < 0.0001) (Table 2, Fig. 1). The LFA and BMI z-score of the infants did not change significantly (p > 0.05).

Table 2
the average WFA z-score during each follow-up

	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
					25th	50th (Median)	75th
WAZ1	-3.981429	.8481043	-5.2100	-3.0100	-4.700000	-3.650000	-3.220000
WAZ2	-3.3514	.37006	-4.00	-3.01	-3.5800	-3.1800	-3.0200
WAZ3	-2.8186	.40350	-3.68	-2.44	-2.9000	-2.6600	-2.6500
WAZ4	-2.6414	.57296	-3.72	-2.10	-3.0600	-2.4900	-2.1200
WAZ5	-1.4286	.23010	-1.69	-1.00	-1.6400	-1.3900	-1.3600

Discussion

About 8−9 neonates out of every 1000 live births suffer from congenital heart defects (CHD), causing high morbidity and mortality (33%) in this population (23, 24). The reported prevalence of CHD in the United States of America is 40 thousand each year (25). The prevalence of CHD among Iranian children is reported to be 12.30 per 1000 live births(26). About 15−60% of these patients are affected by malnutrition, indicating it as a frequent problem (13, 27−30). Malnutrition is a common phenomenon in infants and children with CHD in low and middle-income countries, probably partly due to late presentation, delayed intervention and frequent hospitalization caused by respiratory infections (2, 31, 32). The prevalence of malnutrition by Mehrizi and Drash was reported to be 27% in 1962 (33); however, 85% was reported in a study in Turkish infants with CHD in 2010 (34). Aghaei-Moghadam et al. reported

that the prevalence of malnutrition among Iranian patients with acyanotic cardiac lesions were 68.7% and 66.4%, based on WFA and WFL (4). Cyanosis, pulmonary hypertension and congestive heart failure influence the severity and type of the malnutrition. Furthermore, the severity of growth impairment is dependent on the type of the cardiac defect (33). The growth is impaired severely in moderate to large VSD and TGA, and moderately in TOF patients (13, 33, 35).

In the current study, the prevalence of moderate to large VSD, TGA and TOF was 53.1%, 4.1% and 8.2%, respectively; hence most of our patients suffered from the aforementioned defects; which highlights the importance of the performed intervention in our study. The congestive heart failure and recurrent respiratory infection occur as a result of delayed corrective surgery in developing countries. This vicious cycle results in the high preoperative malnutrition (36).

Different mechanisms have been considered to be involved in the etiology of malnutrition in infants and children with CHD, including inadequate energy intake, increased energy expenditure, and malabsorption, due to low cardiac output and impaired gastrointestinal function (37), as well as fluid restriction, disturbed hemodynamic situation (38, 39), fatigue during feeding and recurrent respiratory infections (38–40). Diminished blood flow of the splanchnic circulation, despite adequate caloric intake, may contribute to the impaired growth by malabsorption; however, there is a considerable controversy about the impact of malabsorption on malnutrition (13, 41). The total energy expenditure of critically ill children is estimated to be increased up to 30% in mild to moderate stress, up to 50% in severe stress and 100% in major burns (42). Decreased energy intake is known as the most import factor involved in the malnutrition of patients with CHD (13), as it is 76% of that in normal population (43). Putting altogether, increased energy requirement and decreased energy intake necessitate further intervention for improvement of the feeding in children with CHD.

Our current study shows that WFA z-score improved significantly when energy- and protein-dense formula was given to malnourished CHD infants instead of standard infant formula. Other growth indices (LFA and BMI z-score) also improved, but non-significantly, probably because it takes more time to catch up in length than to catch up in body weight.

According to a study evaluating the daily energy intake in 100 infants with CHD, the median intake was less than 100 kcal/Kg/ day, which is the minimum requirement for normal infants (44). Our patients were given 36.23 ± 52.49 kcal/kg/day at first which was increased up to 98.61 ± 38.27 kcal/kg/day at the end of the study.

Growth and development, wound healing and immune system function are influenced by nutritional status. Malnutrition affects both short term and long-term postoperative outcomes. Recurrent infection due to impaired immune system function and delayed surgical wound healing are considered as the short term outcomes, while disturbed growth, physical and cognitive development are seen as the long term ones (41, 45, 46). The Society of Thoracic Surgeons Congenital Heart Surgery Database has confirmed the correlation between lower WFA z-scores and poorer surgical results (47). High postoperative mortality (48) and morbidity, such as increased frequent hospitalization, persistent delayed growth, prolonged

recovery time, and increased hospital stay (15) are associated with the preoperative malnutrition. Many studies have indicated that adequate nutritional status preoperatively highly influences the ability of the patient to recover following the surgery (19–22, 30, 46, 49).

Early and effective nutritional intervention is crucial for children with CHD, in order to ameliorate growth and reduce the aforementioned complications. Nutritional support should preferably start as soon as possible after diagnosis and continue during the post-operative period (50). Several studies support the use of a high energy formula for increasing energy intake and promoting weight gain in infants with CHD (50, 51). In the early study by Jackson and Poskitt, an 31.7% increment in energy intake by the use of a high energy formula lead to increased weight gain from 1.3 g/kg/day to 5.8 g/kg/day (5). Recently, nutritional guidelines were developed for infants with CHD awaiting surgery, using a modified Delphi process (10). For infants with moderate nutrition risk, an energy intake of 100–110 kcal/kg/day was recommended, with protein contributing 9–12% of energy. For those with high nutrition risk, the recommended energy intake was 120–150 kcal/kg/day, with 10-15en% of protein (up to 4 g/kg/day). These high-risk infants should preferably receive 50–100% of their nutrition requirements as energy and nutrient dense formula (1).

Preoperative use of high energy formula has been associated with weight gain and decreased hospital stay and postoperative complications (50). Postoperative use of energy- and nutrient-dense formula has been found to improve weight gain in infants with CHD (1) and to decrease hospital stay and reduce antibiotic use in these patients (52). In line with these findings, we observed a clinically and statistically significant weight gain (indicated by an increase in WFA z-score) when energy- and nutrient-dense formula was given preoperatively to malnourished infants with CHD. Furthermore, head circumference and mid-upper arm circumference were increased at the end of the study, compared to the first assessments. A better preoperative nutritional status, as observed in our study, may reduce post-operative mortality and complications and improve recovery.

One of the strengths of this study was its prospective nature; moreover, it was conducted in a tertiary center. Most patients with the diagnosis of CHD needing surgical repair, are referred to this center; It could be concluded that the patients enrolled in this study are an acceptable representation of the whole patients with moderate to high risk CHD.

There are some limitations to this study as well. The relatively short intervention period is a limiting factor for interpreting the results. We expect that the effect of giving energy and nutrient-dense formula on weight and length gain would have been more pronounced with a longer intervention period. Furthermore, we did not evaluate the postoperative outcome of the infants in this study.

In conclusion, the results of this study highlight the efficacy of preoperative feeding with energy- and nutrient dense formula in improving weight gain of malnourished infants with CHD.

Conclusion:

The weight gain was increased when energy- and nutrient-dense formula was given preoperatively to malnourished infants with CHD. Furthermore, head circumference and mid-upper arm circumference were increased at the end of the study, compared to the first assessments. A better preoperative nutritional status, as observed in our study, may reduce post-operative mortality and complications and improve recovery.

Abbreviations

CHD
Congenital Heart Defects
FG
Faltering Growth
WFA
Weight For Age
LFA
Length For Age
WFL
Weight For Length
IMF
Infant Milk Formula
MUAC
Mid-Upper Arm Circumference
HC
Head Circumference
VSD
Ventricular Septal Defect
ASD
Atrial Septal Defect
TGA
Transposition of the Great Arteries
PS
Pulmonary valve Stenosis
TOF
Tetralogy of Fallot
AVSD
Atriventricular Septal Defect
SD
Standard Deviation

Declarations

Ethics approval and consent to participate:

This study was approved by the Research Deputy and the Ethics Committee of Tehran University of Medical Sciences on April 29, 2017 (reference number: IR.TUMS.VCR.REC.1396.3543). The clinical trial was approved by our governmental clinical trial center. This trial was retrospectively registered at the Iranian Registry of Clinical Trials (www.irct.ir), which is a Primary Registry in the WHO Registry Network (Registration Number = IRCT20191224045880N1). Written and verbal informed consent were obtained from all participants.

Consent to publish:

All participants consented to publish the final collected data.

Availability of data and materials:

N/A

Competing interests:

JH and ACG are employed by Danone Nutricia. Other authors declare no conflicts of interest.

Authors' Contributions:

EA and MM equally contributed to the conception and design of the research; ACG, JH and AZ contributed to the design of the research; AA, SS, AM, SA and AA contributed to the acquisition and analysis of the data; MA, AR, NE and KS contributed to the interpretation of the data; and EM and AG drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Figures
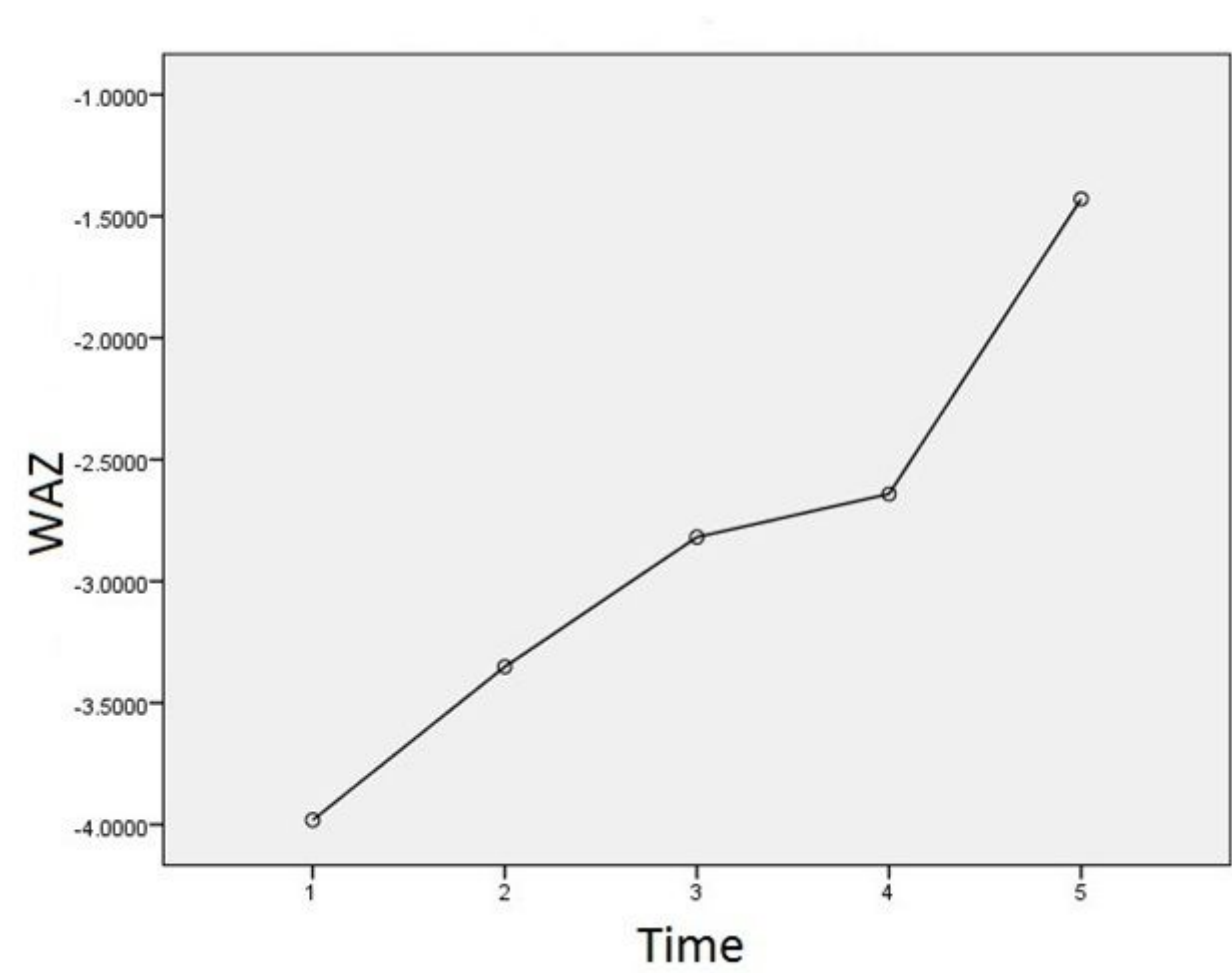
Figure 1

The alterations of the weight for age z scores (WAZ) during the study (p <0.0001).

Supplementary Files

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