Early high-energy feeding in infants following cardiac surgery: a randomized controlled trial

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Background: Effective nutrition programs are beneficial for nutritional recovery in infants. Few studies have focused on the effect of early high-energy feeding after open heart surgery. This study sought to assess the effects of early high-energy feeding in infants after congenital heart surgery.

Methods: Patients at a tertiary pediatric cardiology center who underwent open heart surgery between July 2016 and July 2018 were recruited and randomly allocated to 1 of the following 2 groups: (I) the intervention group (postoperative early high-energy feeding; n=124); and (II) the control group (no intervention; n=120). The primary endpoints of average energy delivery and growth Z-scores [i.e., weight-for-height Z-score (WHZ), weight-for-age Z-score (WAZ), and height-for-age Z-score (HAZ)] were recorded preoperatively, during the intensive care unit (ICU) stay, at discharge, and at 1 and 3 months postoperatively. The secondary endpoints of malnutrition recovery, ventilator support time, infection rate, and cardiac ICU (CICU) stay were also recorded.

Results: A total of 244 infants were included in the study. There were no significant differences in the baseline features between the 2 groups. The intervention group received higher calories on average than the control group (44.5 *vs.* 34.7; P<0.001). At discharge from the ICU, the WHZ (−2.29 *vs.* −2.76; P<0.001) and WAZ (−3.08 *vs.* −3.43; P=0.005) of patients in the intervention group were higher than those of patients in the control group. Ventilator support time (P=0.004), CICU stay (P=0.045), and infection rate (P=0.001) were significantly lower in the intervention group than the control group. At 3 months post-surgery, the intervention group exhibited a higher malnutrition recovery rate than the control group (19.4% *vs.* 6.5%; P=0.002).

Conclusions: The administration of early high-energy feeding to infants after congenital heart surgery is associated with improved growth, reduced CICU stay, decreased ventilator support time, and reduced postoperative infection rates.

Trial Registration: ClinicalTrials NCT04609358.

Keywords: Congenital heart disease; malnutrition; high-energy nutrition; randomized controlled trial

Introduction

Congenital heart disease (CHD) is a malformation caused by the abnormal development of the fetal heart and blood vessels (1). CHD is the most common birth defect, and affects approximately 10–12 per 1,000 (1–1.2%) (1) live-born infants. Advances in surgical (2) techniques and perioperative care have markedly improved the survival of infants who undergo surgical repair for CHD. Most patients with CHD require surgical treatment, and their nutritional status directly affects their postoperative prognosis and rehabilitation.

Malnutrition and reduced growth have been increasingly recognized as crucial factors associated with patient outcomes (3,4). Irrespective of the nature of the cardiac defect or the presence or absence of cyanosis, malnutrition is common among children with CHD (5). Children with CHD are prone to malnutrition due to decreased energy intake and malabsorption, and increased energy requirements caused by enhanced metabolism, heart failure, and infections (5-9). Malnutrition increases mortality in children with CHD. Due to differences between developed and developing countries (6,7,10), studies have reported varied prevalence rates of malnutrition (ranging from 15–92%) in infants with CHD. In a previous study, we reported a predilection to malnutrition in patients aged <1 year, who had high proportions of weight-for-age Z-scores (WAZs) <–2 (73.4%), height-for-age Z-scores (HAZs) <–2 (45%), and weight-for-height Z-scores (WHZs) <–2 (41.2%). Undernutrition (22 cases, 3.2%), stunting (19 cases, 2.7%), and wasting (13 cases, 1.9%) continued to be detected in children at the end of a 3-year follow-up period (11). Thus, special attention should be paid to the nutrition of these infants.

Studies (12,13) have shown that malnutrition leads to increased hospital costs, prolonged hospital stays, increased postoperative complications, and poor surgical outcomes. Malnutrition not only delays growth and development but also increases the risk of secondary infection, leading to decreased immune function, aggravating disease, and increasing morbidity and mortality in children with CHD (10). The adverse effects of malnutrition in children include increased hospitalization, poor surgical outcomes, dysplasia of body length, and increased mortality (14). Thus, the nutritional status of children with CHD must be studied.

Early nutrition support is crucial, particularly for those following congenital heart surgery in the neonatal and infant period. This is because there is little reserve during the critical time for body development and at high risk of rapid nutrition depletion. Insufficient nutrition supply can lead to muscle wasting, impairment of vital organ function, compromised wound healing, and decreased immune function. Optimal nutrition in the CICU is important to sustain organ function and prevent dysfunction of the cardiovascular, respiratory, and immune systems until the acute phase inflammatory response resolves. Longitudinal studies have shown significant recovery in growth during the first year post surgery in children (8,15,16). Further, research has shown that the energy needs of infants with CHD may be 20–50% higher than that of healthy children. In 2009, the American Society of Parenteral and Enteral Nutrition recommended feeding protocols as standard for pediatric patients in the intensive care unit (ICU), including a feeding protocol for infants with CHD (17,18). Standardized feeding protocols have been shown to decrease the incidence of necrotizing enterocolitis and death, decrease episodes of sepsis, and reduce the overall duration of hospital stays (18). Recent studies suggest that protein- and energy-enriched infant formulas may assist in achieving nutrition targets early and promoting anabolism in critically ill infants (19-22). In addition, Zhang *et al.* (23) proposed that infants after cardiac surgery fed with high-energy formula gained more weight. Thus, we promote earlier feeding times, and the present randomized study sought to assess the effects of early high-energy feeding in infants after congenital heart surgery. We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/tp-21-360).

Methods

Study design and patients

The present single-center randomized controlled trial was conducted between July 2016 and July 2018 at the cardiac ICU (CICU) of the Shanghai Children's Medical Center. A randomized, parallel-controlled experiment was used, which allocation ratio is closed to 1:1. Children aged less than 6 months, undergoing surgery for CHD, with moderate or severe malnutrition according to World Health Organization (WHO) standards (mild and moderate or severe malnutrition are defined as $-2 < Z < -1$ and $Z \le -2$, respectively) were included in the study. Patients with genetic diseases, no or mild malnutrition, and those whose guardians did not provide consent for the study were

excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and prior informed consent was obtained from surrogate decision makers. The participants who recovered adequately after surgery were included after consent was obtained from their guardians for their continued participation. The study protocol was approved by the Shanghai Children's Medical Center's Ethics Committee (SCMCIRB-K2015024) and registered with the ClinicalTrials.gov PRS (NCT 04609358).

Randomization

The guardians of patients who met the inclusion criteria were informed of the study, treatment, risk of complications, and the anticipated period of recovery for both treatment groups. The patients were randomly allocated to either the intervention or control group. Simple randomization method was used. An investigator performed the randomization using a random number table and sealed opaque envelopes.

Interventions

The patients in the intervention group received early high-energy feeding (100 kcal/100 mL) in the form of milk powder. Feeding in infants was initiated at 1–2 mL/kg/h within 6–24 h of surgery and was increased by 1–2 mL/kg/h per day, if tolerated, to reach the target energy supply until discharge. In the control group, patient nutrition was initiated and supported according to the prescription of physicians and dieticians at our hospital (67–82 kcal/100 mL) until discharge. During the study period, when the patient could start enteral nutrition, the chief doctor would prescribe a diet (type of milk, amount and frequency) in the medical order system.

Measurements

Age, sex, weight, and height at surgery, risk adjustment for congenital heart surgery score version 1 (RACHS-1), actual calorie intake, the duration of mechanical ventilation, the length of CICU stay, the incidence of infection, and nutritional recovery were assessed. Follow-up data were collected at 1 and 3 months after surgery in the absence of death. The collected follow-up data included weight, height or length, and rehospitalization. Trained staff contacted the parents or guardians of the patients via telephone calls or text messages.

Nutritional recovery was defined as Z>–1. Participants were divided into early and delayed rehabilitation groups according to the length of CICU stay. Based on the overall CICU stay, delayed rehabilitation was defined as a CICU stay of more than 5 days. Finally, the intervention effect was examined in the delayed rehabilitation group. Accumulated liquid volume (mL/kg/d) referred to the cumulative value of the net intake divided by weight in the first 5 days of the CICU stay. Average calories (calories/kg/d) were derived as total calories per kilogram divided by the number of days spent in CICU. The Z-scores were obtained according to WHO standards for each anthropometric indicator by using the Anthro v.3.2.2 program 12 (14). Stunted growth was defined as a HAZ of ≤–2. Being underweight was defined as a WAZ of ≤–2. Wasting was defined as a WHZ of ≤–2 (19).

Endpoints

The primary endpoints were average energy delivery and Z-score, which included the WHZ, WAZ and HAZ. The secondary outcomes were malnutrition recovery, ventilator support time, infection rate, and CICU stay length.

Sample size

The estimated mean WHZ of the control group 3 months after surgery was –2.13. The application of the high calorie nutrition regimen increased the experimental group by 0.38 compared to the control group [standard deviation (SD): 0.85, alpha: 5%, power: 90%], which resulted in a sample size of 107 patients per group. Assuming a dropout rate of 10%, 119 patients were required for each group.

Statistical analysis

The data were analyzed using SPSS version 20. Descriptive statistics and a Shapiro-Wilk test of normality were calculated for the continuous variables, while a Chi-square test was used for the categorical variables. The Kruskal-Wallis test was performed to compare continuous variables (independent samples). A Student's t-test or Wilcoxon signed-rank test was performed to compare the continuous variables (related samples), and the covariance analysis was performed to assess the treatment effects between the 2 groups. Time-to-event data were evaluated using Kaplan-Meier estimates and Cox proportional hazards models. We assessed the consistency of the treatment effect
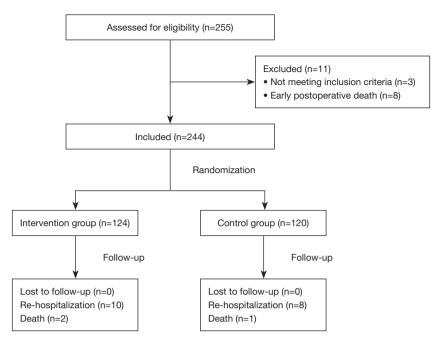
Figure 1 Flowchart for patient screening, randomization, and follow-up.

1 prespecified subgroup. A P value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the intervention and control groups

The present single-center randomized controlled trial was conducted between July 2016 and July 2018. A total of 255 infants were recruited, of whom 244 infants (124 in the intervention group and 120 in the control group) completed the trial. Of the 244 patients, 2 died within 3 months of surgery in the intervention group, and 10 were re-hospitalized (2 for re-operation and 8 with pneumonia). In the control group, 1 patient died within a month of surgery and 8 patients were re-hospitalized (1 patient for re-operation and 7 with pneumonia; see *Figure 1*). The difference in the preoperative baseline characteristics between the 2 groups was not statistically significant (see *Table 1*). The mean age of the intervention and control groups was 109.1 days (SD =46.1) and 103.3 days (SD =46.1), respectively. The mean preoperative body weight of the intervention and control groups was 4.7 kg (SD =0.9) and 4.4 kg (SD =0.9), respectively. The most common cardiac diagnosis in both groups was ventricular septal defect. Additionally, the median

RACHS-1 score was 2 (interquartile range, 2–3) in both groups.

Primary endpoints

The initial feeding time of the intervention group was earlier than that of the control group (12 *vs.* 22 h; P<0.001). Additionally, the actual daily energy delivery of the intervention group was higher than that of the control group (44.5±10.7 *vs.* 34.7±9.5 kcal/kg; P<0.001). However, the difference in the accumulated liquid volume between the 2 groups was not statistically significant (P=0.285). Infants in the intervention group had a higher WHZ (−2.29 *vs.* −2.76; P<0.001) and WAZ (−3.08 *vs.* −3.43; P=0.005) than those of the control group. However, the difference in the HAZs (−1.92 *vs.* −1.96; P=0.446) between the 2 groups was not statistically significant (see *Table 2*).

Secondary endpoints

With median recovery times of 93 and 91 days, respectively, the intervention group exhibited a higher incidence of recovery from malnutrition than the control group (P=0.015). The difference in the postoperative nutrient recovery rates at 1 month (7.3% *vs.* 0.2%; P=0.003) and 3 months (19.4% *vs.* 6.5%; P=0.002) was statistically

Table 1 Baseline characteristics of the 244 patients

Characteristic	Total (N=244)	Intervention group (N=124)	Control group (N=120)	P
Age (days)	106.2±46.1	109.1±46.1	103.3±46.1	0.332
Female sex, n (%)	102 (41.8)	48 (38.7)	54 (45.0)	0.319
Weight (kg)	4.5±0.9	4.7±0.9	4.4±0.9	0.065
Height (cm)	57.6±5.1	58.2±5.1	57.0±5.0	0.061
WAZ	−2.68±1.04	−2.61±0.99	−2.75±1.09	0.277
HAZ	−2.68±1.71	−1.66±1.76	−1.98±1.66	0.143
WHZ	−1.74±1.67	−1.81±1.59	−1.68±1.76	0.549
Cardiac diagnosis, n (%)				
VSD	128 (52.5)	66 (53.2)	62 (51.7)	
CoA	24 (9.8)	13 (10.5)	11 (9.2)	
DORV	17 (7.0)	4 (3.2)	13 (10.8)	
CAVSD	14 (5.7)	9 (7.3)	5 (4.2)	
TAPVC	11 (4.5)	8 (6.5)	3 (2.5)	
ASD	10 (4.1)	3 (2.4)	7 (5.7)	
TOF	8 (3.3)	5 (4.0)	3 (2.5)	
TGA	7 (2.9)	2 (1.6)	5 (4.2)	
Valvular disease	6 (2.5)	3 (2.4)	3 (2.5)	
PA	5 (2.0)	3 (2.4)	2 (1.7)	
PDA	3 (1.2)	1 (0.8)	2 (1.7)	
ALCAPA	2 (0.8)	2 (1.6)	0 (0)	
Other	9 (3.7)	4 (3.3)	5 (3.5)	
RACHs-1 score (IQR)	2 (2,3)	2 (2,3)	2 (2,3)	0.721

VSD, ventricular septal defect; CoA, aortic coarctation; DORV, double outlet right ventricle; CAVSD, complete atrial ventricular septal defect; TGA, transposition of great arteries; ASD, atrial septal defect; TAPVC, total anomalous pulmonary venous connection; PA, pulmonary atresia; TOF, tetralogy of Fallot; PDA, patent ductus arteriosus; ALCAPA, the left coronary artery originates from the pulmonary artery; WAZ, weight-for-age z-score; HAZ, height-for-age z-score; WHZ, weight-for-height z-score; SD, standard deviation; RACHS-1, Risk Adjusted classification for congenital heart surgery 1; IQR, interquartile range.

Table 2 WHZ, WAZ, HAZ, and other primary outcomes at discharge

Outcomes	Intervention group (N=124)	Control group (N=120)	P
WHZ	−2.29±0.06	−2.76±0.06	<0.001*
WAZ	−3.08±0.05	−3.43±0.05	0.005*
HAZ	−1.92±0.05	−1.96±0.05	0.446*
Accumulated liquid volume (mL/kg/d)	−13.4±14.1	−15.4±13.3	0.285
Average calories (calories/kg/d)	44.5±10.7	34.7±9.5	<0.001
Peak of calories (calories/kg/d)	75.7±19.6	55.6±13.5	<0.001
Initial feeding time (h)	12 (8, 15.75)	22 (15, 33.75)	<0.001

*, the P value was adjusted by covariance analysis. WAZ, weight-for-age z-score; HAZ, height-for-age z-score; WHZ, weight-for-height z-score.

Table 3 Ventilator support time, length of hospital stay, length of CICU stay, fluid management, and dietary status

Outcomes	Intervention group (N=124)	Control group (N=120)	P
Ventilator support time (IQR), h	25.7 (11.7, 53.4)	31.6 (11.7, 81.3)	0.116
CICU length of stay (IQR), days	5.5 [3, 7]	5.5 [3, 8]	0.503
Hospital length of stay (IQR), days	14 (10, 19)	14.5 (11, 22.8)	0.233
Infection (%)	4 (3.2)	15 (12.5)	0.007

Table 4 Subgroup analysis of the delayed rehabilitation population.

Outcomes	Intervention group (N=62)	Control group (N=60)	P
Ventilator support time (IQR), h	36.8 (29.7, 83.78)	80.3 (34.8, 136.28)	0.004
CICU length of stay (IQR), days	7 [6, 9]	8 (7, 10.8)	0.045
Hospital length of stay (IQR), days	17 (13, 24.5)	20 [14, 27]	0.158
Infection (%)	3 (4.8%)	15 (25%)	0.002
Accumulated liquid volume (mL/kg/d)	−21.0±10.7	−23.1±11.2	<0.001
Average calories (calories/kg/d)	45.1±11.0	35.0±10.0	<0.001
Peak of calories (calories/kg/d)	77.2±20.0	55.9±15.9	<0.001

Table 5 Tolerance parameters

Adverse effect	Intervention group (N=124)	Control group (N=120)	P
Ventosity (%)	11 (8.9)	13 (10.8)	0.607
Constipation (%)	3 (2.4)	2 (1.7)	0.678
Diarrhea (%)	4 (3.2)	4 (3.3)	0.962
Emesis (%)	0	0	–
Allergy (%)	2 (1.6)	0	0.162
Change of formula (%)	2 (1.6)	13 (10.8)	0.003

significant. Additionally, the intervention group had a faster recovery time than the control group during the 3-month follow-up period (see Figure S1).

Differences in the ventilator support times (25.7 *vs.* 31.6 h; P=0.116), length of hospital stay (17 *vs.* 20 days; P=0.233) and length of CICU stay (7 *vs.* 8 days; P=0.503) between the 2 groups was not statistically significant (see *Table 3*).

In the subgroup with delayed recovery, ventilator support time (36.8 *vs.* 80.3 h; P=0.004), length of CICU stay (7 *vs.* 8 days; P=0.045), and infection rate (4.8% *vs.* 25%; P=0.002) were significantly lower in the intervention group than in the control group (see *Table 4*).

An evaluation of the gastrointestinal intolerance revealed

that with the exception of a change of formula, no significant differences were observed between the 2 groups (see *Table 5*). In the intervention group, 2 patients required a change of formula because of a protein allergy to cow's milk. In the control group, formula was replaced for 13 patients based on postoperative demand.

Follow-up

Patients' WHZ, WAZ, and HAZ decreased to the baseline values by the time of patients' discharge from the CICU. The WAZ and WHZ were significantly reduced in the control group compared to the intervention group. This

finding was consistent with other results. Additionally, WAZ and WHZ increased after the patients were transferred from the CICU. However, HAZ only increased after the patients were discharged. Figure S2 shows the overall curves for WAZ, WHZ, and HAZ from the preoperative period to the end of the 3-month follow-up period.

Discussion

High-energy infant formulas can assist in achieving nutrition targets among infants with CHD at an early stage and promote anabolism. The present study evaluated the efficacy of high-energy feeding in infants after they underwent surgery for CHD. Among the primary outcomes, our study examined the effects of a significantly earlier initial feeding time, higher daily energy delivery, and higher WHZ and WAZ between an intervention and control group. We found that patients in the intervention group had a higher incidence of recovery and faster recovery than those in the control group. Further, the postoperative nutrient recovery rates at 1 and 3 months were significantly better in the intervention group than the control group. This study also showed that early high-energy feeding in infants undergoing cardiac surgery was well tolerated and effectively achieved high nutrition intake. Additionally, early high-energy feeding was associated with shorter CICU stay, reduced ventilator support time, and a lower infection rate.

Generally, when patients are discharged (11), there is a decline in growth due to limited fluid intake in the early stage after open heart surgery (20). Infants possess a limited reserve for body development during this critical time and are at high risk of rapid nutrition depletion. Thus, early nutrition support is crucial. Arnon *et al.* reported that preterm infants on an early feeding protocol achieved full enteral feeding (with no excess morbidity) and were discharged significantly earlier than those on a delayed regimen. However, postoperative nutritional recovery was not assessed in this study.

The effects of administering high-energy formula to infants during the postoperative period has attracted considerable attention. High-energy nutrition has been observed to reduce postoperative weight loss and shorten ICU stay (20,22-27). These findings support Cui *et al.*, and show the tolerance and effectiveness of early high-energy feeding at achieving higher nutrition intake and shorter CICU stays in infants following cardiac surgery (20). Additionally, such feeding promotes early catch-up growth, significantly shortens ventilator support time, and reduces

infection in patients with delayed rehabilitation. Notably, a negative fluid balance was observed in the first 5 days of the CICU stay; however, the intervention group exhibited better results than the control group. Thus, more water must be removed to maintain cardiac functions. Additionally, with similar fluid management, short-term prognosis and recovery from malnutrition are also associated with a digestive system that does not exhibit significant complications (28-30). The difference in the short-term prognoses of the patients was not significant. However, when patients with delayed rehabilitation were analyzed separately, an obvious effect emerged. These findings suggest that such a nutritional regimen requires prolonged application for efficacy.

Additionally, early high-energy feeding not only improved early postoperative prognosis but also promoted recovery from malnutrition. This effect has not been observed in other studies. The intervention in this study was limited to the hospitalization period; however, a high postoperative nutritional status improved the nutritional base of the infants. The nutritional status of the infants appeared to recover faster when combined with improved postoperative cardiac function. Unfortunately, the nutritional recovery rate only reached 19.4% at the end of the 3-month follow-up period. Thus, the effect of continuing nutritional support at home on nutritional recovery needs to be studied.

The first part of the growth curves spanned the preoperative period to discharge from the CICU; the remaining parts generally exhibited an upward trend. These findings are consistent with those of Medoff-Cooper *et al.*, who suggested that infants with single-ventricle physiology experience a 1 Z decrease in Z-scores between neonatal surgery and discharge from the hospital (31). Several factors may explain the decrease in Z-score values observed from the preoperative period to discharge from the CICU, including excessive weight loss, altered resting energy expenditure, and fluid restriction (28,29). In particular, fluid restriction and the volume required for supportive drug therapy limit the volume available for feeding, further exacerbating malnutrition (32), which is common in the CICU. This highlights the advantage of high-energy feeding. Specifically, the administration of the high-energy formula led to an increased intake of calories, reduced ventilator support time, and decreased the incidence of ventilator-associated pneumonia without complications of the digestive system or feeding intolerance.

Finally, the WAZ and WHZ of patients in the intervention group improved significantly in the present study; however, the HAZ did improve significantly. This

is consistent with the general law of malnutrition. WAZ and WHZ reflect acute malnutrition mainly caused by weight change, and increase soon after an improvement in nutrition. Conversely, HAZ reflects long-term malnutrition and represents chronic malnutrition over a long period. Thus, a change will not be obvious in the short term. However, patients' HAZ gradually increased with a gradual improvement in nutrition.

Compared with the ordinary feeding, early enteral administration of the high-energy feeding is well tolerated in infants following congenital heart surgery and effective in achieving higher nutrition intakes as early as the first day after the operation. In addition, the high-energy feeding does appear to reduce infectious complications or other early clinical outcomes compared with the ordinary feeding for critical patients. Therefore, for severe patients, we recommend high-energy formula feeding as early as possible under tolerable circumstances.

Limitations

The present study had certain limitations. The intervention was only implemented during hospitalization. Thus, growth in the follow-up period was affected by a number of factors. Further investigation is required to assess feeding after discharge. Additionally, further studies need to be conducted to examine the effects of malnutrition on long-term outcomes.

Conclusions

Early high-energy feeding is associated with improved growth, shorter CICU stay, decreased ventilator support time, and reduced infection during the early postoperative period in infants who have undergone congenital heart surgery.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-360

Trial Protocol: Available at https://dx.doi.org/10.21037/tp-21-360

Data Sharing Statement: Available at https://dx.doi.org/10.21037/tp-21-360

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and prior informed consent was obtained from surrogate decision makers. The participants who recovered adequately after surgery were included after consent was obtained from their guardians for their continued participation. The study protocol was approved by the Shanghai Children's Medical Center's Ethics Committee (SCMCIRB-K2015024).

References

1. Pierpont ME, Brueckner M, Chung WK, et al. Genetic Basis for Congenital Heart Disease: Revisited: A Scientific Statement From the American Heart Association. Circulation 2018;138:e653-711.
2. Albers EL, Bichell DP, McLaughlin B. New approaches to neuroprotection in infant heart surgery. Pediatr Res

2010;68:1-9.

3. Sachdeva R, Valente AM, Armstrong AK, et al. ACC/
AHA/ASE/HRS/ISACHD/SCAI/SCCT/SCMR/SOPE
2020 Appropriate Use Criteria for Multimodality Imaging
During the Follow-Up Care of Patients With Congenital
Heart Disease: A Report of the American College of
Cardiology Solution Set Oversight Committee and
Appropriate Use Criteria Task Force, American Heart
Association, American Society of Echocardiography,
Heart Rhythm Society, International Society for Adult
Congenital Heart Disease, Society for Cardiovascular
Angiography and Interventions, Society of Cardiovascular
Computed Tomography, Society for Cardiovascular
Magnetic Resonance, and Society of Pediatric
Echocardiography. J Am Coll Cardiol 2020;75:657-703.

4. Burch PT, Spigarelli MG, Lambert LM, et al. Use of
Oxandrolone to Promote Growth in Neonates following
Surgery for Complex Congenital Heart Disease: An Open-
Label Pilot Trial. Congenit Heart Dis 2016;11:693-9.

5. Monteiro FP, de Araujo TL, Lopes MV, et al. Nutritional
status of children with congenital heart disease. Rev Lat
Am Enfermagem 2012;20:1024-32.

6. Blasquez A, Clouzeau H, Fayon M, et al. Evaluation of
nutritional status and support in children with congenital
heart disease. Eur J Clin Nutr 2016;70:528-31.

7. Arodiwe I, Chinawa J, Ujunwa F, et al. Nutritional status
of congenital heart disease (CHD) patients: Burden and
determinant of malnutrition at university of Nigeria
teaching hospital Ituku - Ozalla, Enugu. Pak J Med Sci.
2015;31:1140-5.

8. Vaidyanathan B, Radhakrishnan R, Sarala DA, et al. What
determines nutritional recovery in malnourished children
after correction of congenital heart defects? Pediatrics
2009;124:e294-9.

9. Mitting R, Marino L, Macrae D, et al. Nutritional status
and clinical outcome in postterm neonates undergoing
surgery for congenital heart disease. Pediatr Crit Care
Med 2015;16:448-52.

10. Okoromah CA, Ekure EN, Lesi FE, et al. Prevalence,
profile and predictors of malnutrition in children with
congenital heart defects: a case-control observational
study. Arch Dis Child 2011;96:354-60.

11. Zhang M, Wang L, Huang R, et al. Risk factors of
malnutrition in Chinese children with congenital heart
defect. BMC Pediatr 2020;20:213.

12. Wallace MC, Jaggers J, Li JS, et al. Center variation in
patient age and weight at Fontan operation and impact
on postoperative outcomes. Ann Thorac Surg. 2011

May;91(5):1445-52.

13. Suchdev PS. What Pediatricians Can Do to Address
Malnutrition Globally and at Home. Pediatrics
2017;139:e20161666.

14. Ross F, Latham G, Joffe D, et al. Preoperative malnutrition
is associated with increased mortality and adverse
outcomes after paediatric cardiac surgery. Cardiol Young
2017;27:1716-25.

15. Tamayo C, Manlhiot C, Patterson K, et al. Longitudinal
evaluation of the prevalence of overweight/obesity in
children with congenital heart disease. Can J Cardiol
2015;31:117-23.

16. Nydegger A, Bines JE. Energy metabolism in infants with
congenital heart disease. Nutrition 2006;22:697-704.

17. Karpen HE. Nutrition in the Cardiac Newborns:
Evidence-based Nutrition Guidelines for Cardiac
Newborns. Clin Perinatol 2016;43:131-45.

18. Mirtallo JM, Ayers P, Boullata J, et al. ASPEN Lipid
Injectable Emulsion Safety Recommendations, Part 1:
Background and Adult Considerations. Nutr Clin Pract
2020;35:769-82.

19. Oyarzún I, Claveria C, Larios G, et al. Nutritional
recovery after cardiac surgery in children with congenital
heart disease. Rev Chil Pediatr 2018;89:24-31.

20. Cui Y, Li L, Hu C, et al. Effects and Tolerance of Protein
and Energy-Enriched Formula in Infants Following
Congenital Heart Surgery: A Randomized Controlled
Trial. JPEN J Parenter Enteral Nutr 2018;42:196-204.

21. Arnon S, Sulam D, Konikoff F, et al. Very early feeding
in stable small for gestational age preterm infants: a
randomized clinical trial. J Pediatr (Rio J) 2013;89:388-93.

22. Fitria L, Caesa P, Joe J, et al. Did Malnutrition Affect
Post-Operative Somatic Growth in Pediatric Patients
Undergoing Surgical Procedures for Congenital Heart
Disease? Pediatr Cardiol 2019;40:431-6.

23. Zhang H, Gu Y, Mi Y, et al. High-energy nutrition in
paediatric cardiac critical care patients: a randomized
controlled trial. Nurs Crit Care 2019;24:97-102.

24. El-Koofy N, Mahmoud AM, Fattouh AM. Nutritional
rehabilitation for children with congenital heart disease
with left to right shunt. Turk J Pediatr 2017;59:442-51.

25. Wong JJ, Cheifetz IM, Ong C, et al. Nutrition Support
for Children Undergoing Congenital Heart Surgeries: A
Narrative Review. World J Pediatr Congenit Heart Surg
2015;6:443-54.

26. da Silva VM, de Oliveira Lopes MV, de Araujo TL.
Growth and nutritional status of children with congenital
heart disease. J Cardiovasc Nurs 2007;22:390-6.

27. Toole BJ, Toole LE, Kyle UG, et al. Perioperative nutritional support and malnutrition in infants and children with congenital heart disease. Congenit Heart Dis 2014;9:15-25.

28. Ross FJ, Radman M, Jacobs ML, Sassano-Miguel C, Joffe DC, Hill KD, Chiswell K, Feng L, Jacobs JP, Vener DF, Latham GJ. Associations between anthropometric indices and outcomes of congenital heart operations in infants and young children: An analysis of data from the Society of Thoracic Surgeons Database. Am Heart J 2020;224:85-97.

29. Bhatt M, Roth SJ, Kumar RK, et al. Management of infants with large, unrepaired ventricular septal defects

and respiratory infection requiring mechanical ventilation. J Thorac Cardiovasc Surg 2004;127:1466-73.

30. Saunders J, Smith T. Malnutrition: causes and consequences. Clin Med (Lond) 2010;10:624-7.

31. Medoff-Cooper B, Irving SY, Marino BS, et al. Weight change in infants with a functionally univentricular heart: from surgical intervention to hospital discharge. Cardiol Young 2011;21:136-44.

32. Cabrera AG, Prodhan P, Bhutta AT. Nutritional challenges and outcomes after surgery for congenital heart disease. Curr Opin Cardiol 2010;25:88-94.
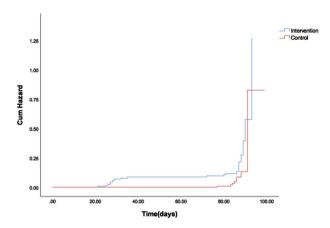
Figure S1 Cumulative incidence rates of malnutrition recovery.
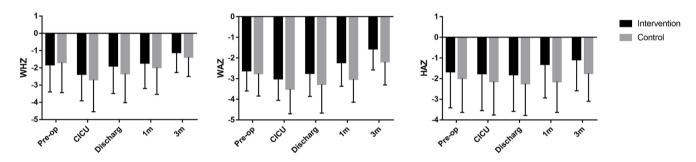

Figure S2 WAZ, WHZ, and HAZ curves from the preoperative period to the end of the 3-month follow-up period.