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ABSTRACT

Background: Previous studies have shown that feeding high-energy formula to infants after cardiac surgery increased energy intake with fewer side effects on cardiopulmonary function. However, impacts on weight gain and gastrointestinal function remain unclear.

Aims: To determine the impact of high-energy formula compared to standard formula on weight gain and gastrointestinal tolerance in postoperative infants with congenital heart disease.

Design: Randomised Controlled Trial.

Method: The setting of the study was at a 20-bed Cardiac Intensive Care Unit at a tertiary children's hospital in China. Study population were infants <1 year of age who underwent cardiac surgery were allocated to the intervention group (n=32) and control group (n=32). The intervention group received high-energy formula (100kcal/100 mL) and the control group received standard formula (67kcal/100 mL) for 7 days during the stabilized postoperative period at the Cardiac Intensive Care Unit. Primary outcomes were weight gain and gastrointestinal intolerance. Secondary outcomes were energy intake and standard intensive care characteristics.

Results: Infants who received high-energy formula (n=30) showed greater mean weight gain than those who received standard formula (n=29); -16g (95% CI: -74 to 42) versus -181g (95%CI: -264 to -99), P =0.001. The evaluation of gastrointestinal intolerance showed that the intervention group had several side effects, such as abdominal distension (n=1), gastric retention (n=2), and diarrhea (n=1), while the control group had no problems. Enteral energy intake in the intervention group was higher than control group from day three.

Conclusion: Infants after cardiac surgery fed with high-energy formula gained more weight but had increased feeding intolerance. However, the feeding intolerance symptoms could be relieved by medication and did not affect feeding advancement.

Relevance to Clinical Practice: Paediatric intensive care clinicians should consider gradually increasing energy density of the formula during feeding and assess feeding intolerance signs in children with malnutrition after cardiac surgery.

INTRODUCTION

Congenital Heart Disease (CHD) is one of the most common prenatal defects comprising structural abnormalities of the heart and great vessels with a reported incidence of 6~10 per 1,000 live births (Van der Linde D et al., 2011). Infants with CHD are usually born at full term and have a normal birth weight. However, their growth might gradually become underdeveloped over time. Approximately 20-50% of children with CHD suffer from malnutrition (Costello et al., 2015; Toole et al., 2014; Monteiro et al., 2012), which is highest in infants (Dalili et al., 2011; Ratanachu-Ek et al., 2011).

With new advances in surgery and perioperative technologies, surgical treatment of CHD is becoming more common in infants, including neonates. Early surgical intervention can reduce the occurrence of heart failure and helps to promote growth such that weight and growth rates become more normal (Daymont et al., 2013). However, the intense stress response, reperfusion injury, hyper-metabolism, and mechanical ventilation in infants with CHD can lead to increased energy needs (Irving et al., 2013; De Wit et al., 2010; Trabulsi et al., 2015). Although current studies agree that the energy needs are highly variable between patients in the immediate post-operative period, there are several factors which can aggravate malnutrition in children and seriously affect their mortality, such as inadequate food intake, malabsorption (Hong et al., 2014), fluid restriction (Leong et al., 2014; Tume et al., 2013), various medications (Laura et al., 2012; Dong et al., 2012), and postoperative complications (Zuluaga, 2012; Iannucci et al., 2013). Nurses are concerned about the nutrition of children while evidence suggest that high-energy feed might be important for some postoperative infants with CHD (Wong et al., 2015). High-energy feeds can counteract the problem with fluid restriction and inadequate food intake.

Energy density refers to food that contain a high number of calories per serving or weight. These foods include those that are concentrated and those with a high fat content. Food concentrates reduce water intake without reducing the nutrient supply, whereas additional supplements that increase nutrient intake can increase energy density. Several clinical studies (Pillo-Blocka et al., 2004; Taniguchi-Fukatsu et al., 2010) were designed to explore the effects of feeding high-energy formula (HF) to

infants with CHD. The results from these studies showed that feeding HF increased calorie intake with fewer side effects on cardiopulmonary function. Yet, we do not have strong evidence on calorie intake (Tume et al., 2010) and the impact on weight gain and gastrointestinal function remains unclear.

The aim of this study was to assess the efficacy and safety of feeding HF to early postoperative infants with CHD. Our hypothesis was that infants with CHD fed with HF gain more weight with no gastrointestinal intolerance compared with those fed with standard-energy formula (SF).

DESIGN AND METHODS

Study design and setting

A randomised controlled clinical trial was conducted from March 18, 2015, to September 28, 2015 in the Cardiac Intensive Care Unit (CICU) of our hospital.

Participants

Inclusion criteria were: diagnosed with CHD based on symptoms, ultrasound, and imaging; <1 year of age; and parent agreement to open-heart surgery. The exclusion criteria were: other diseases that caused nutritional disorders (gastrointestinal malformation, preoperative gastroesophageal reflux, or genetic diseases related to growth restriction); preoperative gastrointestinal intolerance (e.g., gastric retention, abdominal distension, diarrhea, and vomiting); total parenteral nutrition after surgery; or length-of-stay in the Cardiac Intensive Care Unit (CICU) was predicted to be <5 days.

A randomized block design was created to ensure a balanced representation of the study participants in the two groups. There were four variables in each block, and the sequence was determined using computer-generated random numbers. The final sequences were respectively sealed in 64 encoded opaque envelopes. The statistician generated the random allocation sequence and envelopes. The CICU chief doctor and researcher enrolled participants by the envelope sequence.

Sample size

The patients were divided into two groups: an intervention group and a control group. Based on Jackson's study (Jackson et al., 1991), citing an average rate of weight gain of 1.3 g/d (SD=0.7) in the control group and 5.8 g/d in the intervention group (SD=1.2), and considering α error rate of 5%, 80% power, partition ratio=1, superior efficiency value = 4.0 g, and 20% loss rate, 32 children needed to be recruited for each group in the study (Jia et al., 2012).

Intervention

1. Intervention methods

Infants in the intervention group were fed with HF (100 kcal/100 mL; osmotic pressure: 340 mOsm/L; a standard milk powder with 2.6g protein, 5.4g fat, 9.9g carbohydrate and other vitamins and trace elements per 100ml) after surgery once they could begin enteral feeding. Infants in the control group were fed with SF (67 kcal/100 mL; osmotic pressure: 310 mOsm/L; a standard milk powder with 2.0g protein, 3.4g fat, 7.0g carbohydrate and other vitamins and trace elements per 100ml). The intervention continued for 7 days. The CICU chief doctor and researcher enrolled participants by the envelope sequence. 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. Then, the nutrition department prepared the milk according to medical prescription and pasted patients' hospitalization information (name and admission number) on the bottle. The nurses fed the infants according to medical advice. The bottles were not coded or blinded because non-study participants admitted to the CICU at time of the study were also receiving milk. Blinding of the CICU doctors and nurses was secured by not informing them which child was included in the study.

2. Enteral feeding methods

Both groups were fed according to our standard enteral feeding protocol that is used among all infants in the CICU (Electronic Supplement Material 1). Six hours after surgery, a comprehensive assessment every 12 hour was performed by doctors and nurses to determine whether infants could begin enteral feeding. Enteral feeding was initiated after the following items were adequate: hemodynamic status; heart rate, blood

pressure, central venous pressure, and SpO_2 were at desired levels; Gastric Residual Volumes (GRV) was decreased and the colour was normal; and there were no symptoms of abdominal distension and gastrointestinal infection.

Infants with mechanical ventilation were fed through a nasogastric tube. To choose the appropriate feeding method, doctors and nurses were responsible for assessing the infant's feeding capability based on the suck–swallow coordination, sucking ability, feeding completion time, and changes in life signs during feeding. Infants with poor oral intake capability were fed through a nasogastric tube only or nasogastric tube combined with oral feeding.

The initial volume of enteral feeding was 10 mL/kg/d with a target volume of 100~120 mL/kg/d. If the infant's gastrointestinal system tolerated the initial volume, feeding was gradually increased to the standard rate of 20~30 mL/kg/d. When the diet given was only mildly intolerant, gastrointestinal motility and microecological drugs (e.g., domperidone, medilac-vita, glycerin enema, and smecta) were preferred to decrease enteral feeding volume or stop feeding altogether. In addition, if gastrointestinal bleeding occurred, enteric feeding was stopped until the bleeding was under control.

Outcome measures

The primary outcome measures were: weight gain (g) by the seventh day from the beginning of the enteral feeding; and feeding intolerance from the first day to the seventh day after starting enteral feeding. Infants were considered to have feeding intolerance if any of the following symptoms appeared vomiting no less than three times/day, abdominal distension (abdominal circumference increased by more than 10%), milk volume decrease or no increase for 3 days, GRV > 1/3 of the previous feed, unscheduled feeding stops more than twice, or diarrhoea.

The secondary outcomes were measured as follows: prealbumin (mg/L) was assessed within 24 hours after surgery (baseline) and at 3 and 7 days during intervention period; enteral energy intake every day during intervention period; duration of mechanical ventilation, CICU length-of-stay, hospital length-of-stay, and number of participants with necrotizing enterocolitis.

Data Analysis

All data were initially tested for normality of distribution. An independent Student's t-test was used when appropriate. Data that were non-transformable to normal distributions were compared using the Mann-Whitney U test for ranked scores. Fisher's exact test was used to assess frequency distribution. The results are presented by mean and SD (for normally distributed variables) or median and quartile for non-normally-distributed variables or frequency/percentage for categorical variables. $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS 22 (IBM Corp., Armonk, NY, USA).

Ethical and research approvals

The randomised controlled trial was approved by the Pediatric Research Ethics Board of the Clinical Pharmacology Base in our hospital, on October 18, 2014 (Approval number: [2014]146), and registered at the National Institutes of Health (ClinicalTrials.gov; NCT02389491). Parents or legal guardians of all study participants provided a signed informed consent form.

RESULTS

In total, 64 infants were recruited, and 59 infants completed the trial (intervention group n=30; control group n=29). Five infants dropped out because of death, formula change and relocation to another hospital (Electronic Supplement Material 2). The median age of infants was 60 days (range: 35-120 days), and the mean preoperative body weight was 4880g (SD=1431.8). The two groups did not significantly differ in any of the baseline characteristics before intervention (Table 1).

Table 1. Patient Demographics

Characteristics	**Intervention group (n = 30)**	**Control group (n = 29)**	**P-value**
Gender; Male, (n; %)	19 (63.3)	20 (69.0)	0.648
Premature; Yes, (n; %)	2 (6.9)	2 (7.1)	1.000
Age in days; Median, (P_{25}-P_{75})	60.0 (35.2 - 127.5)	63.0 (34.5 - 120.0)	0.964
Birth weight in grams; Median, (P_{25}–P_{75})	3300.0 (3100.0 - 3600.0)	3425.0 (3125.0 - 3600.0)	0.719
Preoperative body weight in grams; mean, (SD)	4629.9 (1086.4)	5138.0 (1699.5)	0.179
Preoperative serum prealbumin, mg/L; mean, (SD)	174.30 (58.21)	167.00 (50.42)	0.609
Diagnosis; (n; %)			
VSD +ASD	11 (36.7)	10 (34.5)	0.173
TGA	4 (13.3)	7 (24.1)	
TOF	2 (6.7)	5 (17.2)	
TAPVC	6 (20.0)	1 (3.4)	
DORV	1 (3.3)	3 (10.3)	
Other	6 (20.0)	3 (10.3)	
Delayed sternal closure; Yes, (n; %)	4 (13.3)	7 (24.1)	0.287
CPB blocking time, minutes; mean, (SD)	95.37 (47.11)	97.41 (31.82)	0.846
Aortic clamping time, minutes; mean, (SD)	53.37 (26.45)	54.18 (23.65)	0.903
Minimum rectal temperature, ℃; mean, (SD)	30.85 (3.19)	31.01 (3.47)	0.857
Time to start enteral feeding, hours; mean, (P_{25}-P_{75})	52.67 (48.00-71.77)	71.00 (48.42- 91.92)	0.234
Continuous use of diuretics; Yes, (n; %)	3 (10.0)	7 (24.1)	0.148
Use of blood products; Yes, (n; %)	4 (13.3)	2 (6.9)	0.413

SD, Standard Deviation; VSD, ventricular septal defects; ASD, atrial septal defect; TGA, transposition of the great arteries; TOF, tetralogy of fallot; TAPVC, total anomalous pulmonary venous connection; DORV, double outlet right ventricle

Infants who received HF showed greater mean weight gain than those who received SF: -16g (95% CI: -74 to 42) versus -181g (95%CI: -264 to -99), P=0.001. Mean weight gain is negative. This means the average body weight of both group infants were lower than before. The evaluation of gastrointestinal intolerance revealed that the intervention group had several problems (abdominal distension (n=1), GRV > 1/3 of the previous feed (n=2), and diarrhoea (n=1)), while infants in the control group showed no gastrointestinal problems. There were 9 infants using drugs for improving gastrointestinal function in the intervention group (domperidon (n=5), medilac-vita (n=5), and enema (n=2)), while 6 infants in the control group (domperidon (n=2), medilac-vita (n=4), enema (n=2), and smecta (n=1)).

The serum prealbumin levels gradually increased in the intervention group and declined in the control group (Day 3: 188mg/L versus 175 mg/L, P=0.128; Day 7: 196mg/L versus 175 mg/L, P=0.002). The enteral nutrition energy intake of both groups gradually increased, with that of the intervention group increasing faster than the control group from day 3 (Figure 1). There was no statistical difference in the duration of mechanical ventilation (86hrs versus 89hrs, P=0.749), CICU length-of-stay (238hrs versus 191hrs, P=0.430), and hospital length-of-stay (29days versus 30days, P=0.769).

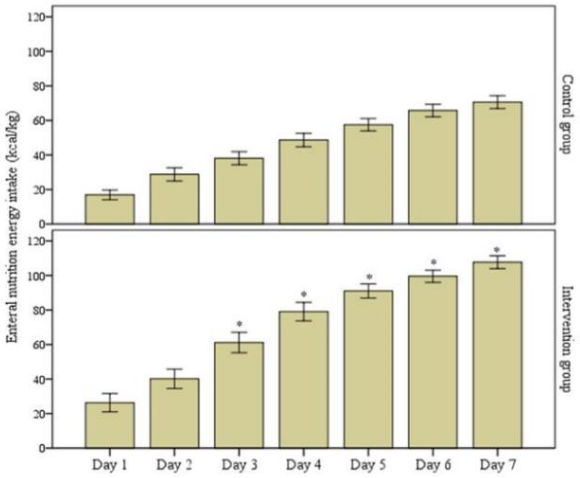

Figure 1. Enteral nutrition energy intake of both groups. Each error bar represents one SE. t tests were used for group comparisons from day 3. *p < 0.05 versus control group.

Enteral nutrition energy intake of both groups

DISCUSSION

The purpose of this study was to assess the efficacy and safety of feeding high-energy formula to early postoperative infants with CHD. Our hypothesis was that infants with CHD fed with HF could gain more weight with no gastrointestinal intolerance compared with those fed a standard-energy formula. The gastrointestinal function of the study participants was negatively affected by several factors, including gastrointestinal tract ischemia and reperfusion injury after cardiopulmonary bypass, postoperative mechanical ventilation, and vasoactive drugs. However, clinical staff were sensible in providing early enteral nutrition and infants were given formula milk (approximately 15-30 mL/kg/d) in the first 1-2 days after surgery. Fluid restriction was gradually decreased with improvement of heart function. Although there was no difference between the two groups in the amount of nutritional intake, HF given to the intervention group provided the infants with more energy intake and increased weight gain.

Providing early nutrition to postoperative infants can improve clinical outcomes. Feeding protocols and adherence of clinical staff to these protocols can promote these practices (Mehta et al., 2017). The strength of our study was having an enteral feeding protocol in place which seems to be unique compared to a recent survey among 59 European Pediatric Intensive Care Units (Tume et al., 2018). Only 39% of these units reported to have specific written guidelines in place for feeding postoperatively and only 30% of these units stated that all infants are routinely fed within 12–24 hours after surgery (Tume et al., 2018).

The body weight of study participants decreased, most likely from mechanical ventilation, early postoperative fluid restriction, or the use of diuretics. It is noteworthy that body weight began to rebound after 4-5 days of intervention mainly from adequate caloric intake. Other reports suggested that the resting energy expenditure of children with CHD was approximately 40-60 kcal/kg/d in the first 3-5 days after surgery (Mehta et al., 2012; Li et al., 2008). In our study, the intervention group was given 51-89 kcal/kg/d during the intervention period compared with 44-56 kcal/kg/d given to the control group. The intervention group was overfeeding in certain degree, but there was

no difference in length of ventilation between the two groups, which may indicates that such feeding does not harm children. The residual energy intake of infants was in the form of synthetic metabolism; a small quantity was transformed into liver and muscle glycogen, which regulates the body's blood sugar changes and supplies the needs for muscle contraction. The other intake was converted into fat or muscle for energy storage, which resulted in a weight increase in those participants who were fed the HF diet. This relationship between energy intake and weight gain was also observed in other studies, but there is still controversy over the dose–response relationship. One study suggested that the children continue to gain weight when the energy intake is >170 kcal/kg/d (Sables-Baus et al., 2012), while another study showed that at 78 kcal/kg/d there was no weight gain and that infants can achieve 1.0 g/d weight gain with each additional intake of 7.4 kcal/kg/d (Jackson et al., 1991). The level of serum albumin, which can rapidly increase in response to protein consumption and fluctuations in nutritional status, has a short half-life of 1-2 days and is less affected by liver disease. In our study, the serum albumin levels increased in the intervention group but decreased in the control group, which may indicates that HF feeding improved the nutritional status of the infants.

The HF had a higher osmotic pressure (340 mOsm/L), which increased the risk of imbalance in the intestinal humoral system in these infants; consequently, three infants suffered from abdominal distension, diarrhoea, and gastric retention in the intervention group within nearly 1-3 days after the onset of HF feeding. Fortunately, this type of gastrointestinal intolerance was relieved with medication and did not affect the feeding process. By gradually increasing the formula density within the first 3 days of treatment, we believe that an infant's gastrointestinal intolerance to HF can be improved.

Limitations

One of the limitations of our study is the blinding and assessments. Although the doctors and nurses were blinded in this study by not knowing which infant was included in the study, the outcome indicators such as abdominal distension might have been subjective and could be prone to reporting bias. Another limitation is the intervention time, which was limited to 7 days, and the follow-up data collection was limited to the CICU

admission time. In a follow-up study we will consider a prolonged intervention time to explore patient's long-term clinical outcomes, such as weight gain during hospitalization, the incidence rate of postoperative complications, and length of hospital stay. Future studies should also consider expanding the sample size and other variables. Our sample size calculation included a 20% loss rate, resulting in 32 children in each group. Our final sample size was 30 in the intervention group and 29 in the control group. If we excluded the 20% loss rate, the total sample size in each group would be 26 children justifying the results of primary outcome measure, weight gain. Although all children were fluid restricted and diuresed, weight gain in cardiac children might not be reliable in the acute phase as it may indicate generalised edema. Finally, the majority of the children assess for study eligibility had a predicted length-of-stay of less than 5 days reducing significantly the study sample.

CONCLUSION

High-energy formula enteral feeding might increase infant's energy intake, reduce weight loss, and improve the nutritional status after CHD surgery. However, it can increase gastrointestinal intolerance within nearly 1-3 days after the onset of HF feeding. In addition, this kind of gastrointestinal intolerance could be relieved by medication and did not affect the support of the feeding process. We were able to reduce the incidence of feeding intolerance by increasing the formula density gradually within 3 days post cardiac surgery. More studies are needed to confirm the efficacy and safety of HF in infants with CHD. The clinical implication of our study is that clinicians should consider to gradually increase the energy density of the formula during feeding and assess feeding intolerance signs and symptoms in children after cardiac surgery.

WHAT IS KNOWN ABOUT THE SUBJECT

- High-energy formula feeding in infants with congenital heart disease after surgery can increased energy intake with limited side-effects on cardiopulmonary function.
- Limited evidence is available on the impact of high-energy formula feeding on weight gain and feeding intolerance.

WHAT THIS PAPER CONTRIBUTES

- High-energy formula feeding might increase weight gain in infants after cardiac surgery.
- Feeding practice with high-energy formula in critically ill infants might lead to more gastrointestinal intolerance within 1-3 days after feeding.
- Intensive care nurses should be cautious when providing high-energy formula to infants and assess the gastrointestinal function frequently.

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