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Utilization of Parenteral Nutrition in Pediatric Cystic Fibrosis Patients

Zena Ghazala, Christina Baldwin, Lauren Lazar, Preeti Sharma, Karyn Shaw*, Song Zhang, Meghana Sathe

Department of Children's Health, University of Texas Southwestern Medical Center, United States

***Corresponding author:** Karyn S, Cystic Fibrosis Clinic, Division of Pulmonary Medicine, Department of Pediatrics, Children's Health, University of Texas Southwestern Medical Center, United States, Tel: 214-456-7254, E-mail: Karyn.Shaw@childrens.com

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Abstract

Background: Malnutrition in patients with cystic fibrosis (CF) is common, multi-factorial and can be aggravated during illness. During an episode of illness, inflammation can trigger increased metabolic demands and insensible losses; additionally, illness can be associated with decreased appetite and feeding intolerance. These factors can lead to malnutrition which can result in a weakened immune system, poor appetite, and further malnutrition. Utilizing parenteral nutrition (PN) may be instrumental in breaking this vicious cycle. However, there is limited literature on its use in pediatric patients with CF.

Methods: The medical charts of 12 pediatric patients with CF who received PN within a 16-month period were retrospectively reviewed. Data was compared one year prior to one year after PN was initiated. Results were analyzed for weight percentiles, weight-for-length/Body-Mass-Index (BMI) percentiles, lung function measured as forced expiratory volume in one second (FEV1), hospitalizations, and adverse events.

Results: During the study period, there was overall significant and sustained improvement in both weight and weight-for-length/BMI percentiles. Most importantly, there was a dramatic decrease in hospital admission durations 3-6 months post-implementation of PN compared to the prior 12 months.

Conclusion: In selected cases, aggressive use of PN has overall short- and long-term benefits in minimizing the consequences of anabolic stress in pediatric patients with CF.

Keywords: Cystic Fibrosis; Malnutrition; Parenteral Nutrition

Background

The effect of malnutrition on health outcomes in patients with Cystic Fibrosis (CF) is well known. In 2008, the CF Foundation (CFF) published recommendations based on evident associations between adequate weight-for-stature and improved lung function [1]. Despite increased efforts to improve nutritional status, malnutrition persists in the CF population [2]. Nutritional interventions routinely include diet education, oral supplementation, tube feedings (gastric and jejunal), adjustment to pancreatic enzyme regimens, and the use of appetite stimulants. However, each of these interventions has limitations and may not produce adequate weight gain due to nausea, vomiting, antibiotic-induced diarrhea, chronic illness, and intolerance to enteral feeding. The sheer volume of calories required to achieve and maintain health can be overwhelming, equaling 110-200% of energy needs for people without CF [1]. Malnutrition in patients with CF can be attributed to increased energy losses, increased energy needs due to illness, and inadequate calorie intake [2]. Commonly, this results in a cycle of malnutrition leading to weakness of the immune system to fight off infection; with subsequent infection causing poor appetite and further malnutrition. When nutritional goals cannot be met with traditional interventions, parental nutrition (PN) may be utilized. PN is an intravenous solution of macronutrients, micronutrients, fluid, electrolytes, and additives [3]. It is preferentially given through a central intravenous line and is considered an aggressive form of nutrition support [3]. Currently, there is limited data on the use of PN in pediatric patients with CF and malnutrition. Although not a traditional form of nutrition support in CF care, utilizing PN in particular cases of malnutrition, in conjunction with traditional nutritional interventions, may be instrumental in breaking this cycle. The effect of PN use on long-term outcomes in pediatric patients with CF is not known.

Introduction

The objectives of this study were 1) to determine if the use of PN improves weight, weight-for-length/Body-Mass-Index (BMI),

and forced expiratory volume in one second (FEV1), or decrease hospitalization; and 2) if so, are the effects maintained over time. Enteral nutrition (EN) is always preferred, both long-term and short-term, but there exist situations where PN can be beneficial. The patients recruited for this study were placed on PN primarily during time frames when they had interval placement of a central venous line for pulmonary exacerbation. Three patients had central venous lines specifically placed for PN secondary to bowel surgery and anticipated prolonged period of bowel rest. Patients were noted to be nutritionally at-risk based on weight, weight-for-length/BMI, deceleration of weight gain, z-scores, or other parameters as delineated by the inpatient dietitian or other clinician. EN was typically attempted for a period of time or even maintained in some capacity throughout the study. PN was added to EN or used exclusively in situations where EN was not being tolerated.

Feeding intolerance is common in the CF population and may include: diarrhea (specifically antibiotic-associated diarrhea during pulmonary exacerbation), vomiting/reflux (often worsened in setting of increased respiratory treatments during exacerbation), poor absorption (related to innate pancreatic insufficiency, inadequate pancreatic enzyme supplementation, and exacerbated by antibiotic-associated diarrhea), small intestinal bacterial overgrowth (SIBO), poor appetite, high caloric needs (due to increased metabolic demand), and dysmotilty (particularly in setting of malnutrition). Due to these issues, patient's diet may need to be adjusted in order to limit feeding intolerance. These dietary adjustments may lead to a restrictive diet, patients may still not tolerate EN despite changes, or patients may not be able to achieve adequate nutrition due to high metabolic demand. The advantage of PN is that the nutrients are directly absorbed into the bloodstream. Patients may even require fewer calories while on PN as there is less energy expenditure to process the calories when administered intravenously. With these advantages, PN can be an important tool in optimizing the nutrition of pediatric patients with CF particularly when they are undergoing hospitalization for acute pulmonary exacerbation. However, there are complications of PN reported including: central venous catheter related complications (e.g. infection, occlusion, or accidental damage), metabolic disturbances (e.g. hyperglycemia, electrolyte disturbances), and hepatobiliary disease [4].

Methods

In this retrospective chart review, we identified all pediatric CF patients at Children's Health (Claude B. Prestidge Cystic Fibrosis Care and Teaching Center, Dallas) identified by the CF registry who were hospitalized between January 2014 and April 2015 and received PN infusion for any period of time.

A waiver of consent was obtained from University of Texas Southwestern (UTSW) Institutional Review Board (IRB) committee due to the nature of retrospective chart review and therefore no risk to patient care. Once patients were identified; de-identified data was collected in a password protected spreadsheet that was only accessible to the clinical research staff directly involved in the study and on IRB.

Patient charts were examined for indication of initiation of PN, duration of PN, weight percentile, length percentile, weight-for-length/BMI percentile, and FEV1 at initiation. Short-term PN was defined as < 30 days and long-term PN was defined as > 31 days in duration. Data for weight percentile, weight-for-length/BMI percentile, FEV1 and hospitalizations were collected starting one year prior to PN initiation and every 3 months thereafter, until one year after discontinuation of PN. The patient's own data in the one year prior to PN initiation, was used for comparison. Additionally, patient charts were analyzed for complications including line infections, hyperglycemia, cholestasis, transaminitis, blood clots, and line dysfunction requiring removal or replacement.

Linear mixed-effect models were constructed to assess whether there was significant difference in intercept or slope parameters. The outcome was one of weight percentile, weight-for-length/BMI percentile, and FEV1. The covariates include intercept, time, indicator of treatment, and the interaction of the treatment indicator and time. Mixed-effect models also included patient random effect to account for within-subject correlation among the multiple measurements from the same patient. Paired T-test was performed to assess whether the numbers of hospitalizations were significantly different before and after the treatment. P-value of significance was defined as $p < 0.05$.

Results

Twelve patients from our cohort of 270 pediatric CF patients (Table 1) met criteria for the study. Patient age ranged from neonates to late teens (1 month - 17 years). About 50% (n=6) of the patients received short-term TPN and 50% received long-term TPN. Three of the patients (3, 7, and 8) received PN peri-operatively. All other patients were started on PN during admission for a pulmonary exacerbation due to low weight-for-length/BMI and either weight loss or no weight gain over significant period of time. The rest of the calories were obtained from oral or enteral feeds. Patient #1's course was complicated with recurrent pancreatitis which added to PN needs. Patient #2 had difficulty obtaining adequate calories so received partial PN starting with 44% of goal calorie needs. Patient #3 had a small bowel tapering procedure complicated by small bowel obstruction requiring multiple surgeries leading to prolonged need for PN. Patient #4 was receiving PN due to severe failure to thrive prior to lung transplantation. Two of the patients had >100 days of PN (Table 1).

Linear mixed-effect models were constructed to assess statistical significance for weight percentile, weight-for-length/BMI percentile, and FEV1 outcomes at 3-month intervals, as seen in Table 2. While receiving PN, weight gain and increased weight-for-length/BMI were observed, as demonstrated by a mean shift in weight percentile of 0.142 ($p = 0.036$) and mean shift in weight-for-length/BMI percentile of 0.327 ($p = <0.001$).

Patient	Age	Sex	TPN Start	TPN end	TPN days	% calorie needs	Reason for TPN initiation
1	17 Yr	F	1/3/2015	3/3/2015	42	100	BMI< 10%,weight loss, recurrent pancraetitis
2	14 Yr	F	4/23/2014	10/30/2014	190	44	BMI< 5%, no weight gain
3	13 Yr	M	3/10/2015	ongoing	128+	100	BMI< 5%, s/p small bowel taper
4	11 Yr	F	7/3/2014	9/10/2014	69	100	BMI< 0%
5	13 Yr	M	4/4/2014	4/13/2014	9	28	BMI< 5%
6	7 Yr	M	3/9/2015	3/29/2015	10	100	BMI< 5%
7	1 mo	F	8/7/2014	9/17/2014	41	100	Meconium ileus s/p resection
8	1 mo	F	2/11/2015	3/4/2015	21	100	Meconium ileus s/p resection
9	10 Yr	M	1/6/2014	1/23/2014	17	30	BMI< 0%, no weight gain
10	10 Yr	M	11/9/2014	11/23/2014	14	100	BMI< 10-25%, no weight gain
11	7 Yr	M	7/18/2014	9/17/2014	61	100	BMI < 10%, weight loss
12	7 Yr	F	12/4/2014	12/15/2014	11	53	BMI < 5%, weight loss

Percent calorie needs: % of calories from PN; TPN: Total Parenteral Nutrition; BMI: Body-Mass-Index percentile; Yr: year

Table 1: Study Patient Characteristics

Outcome	N	Variable	Mean ± Standard Error	P-Value	95% CI
Weight	90	Intercept	0.070 ± 0.035	0.0454	(0.0015 -0.1391)
	-	I Time	0.142 ± 0.067	0.0363	(0.0093 -0.2741)
	-	time	-0.001 ± 0.005	0.836	(-0.0098 -0.0080)
BMI	89	Intercept	0.019 ± 0.041	0.6553	(-0.0636 - 0.1006)
	-	I Time	0.327 ± 0.079	<.0001	(0.1700 - 0.4842)
	-	time	-0.009 ± 0.005	0.098	(-0.0193 - 0.0017)
FEV1	75	Intercept	65.123 ± 4.727	<.0001	(55.6985 -74.5483)
	-	I Time	5.774 ± 7.020	0.4135	(-8.2227 - 19.7712)

PN: Parenteral Nutrition; CI: Confidence Interval; I Time: Intercept time; BMI: Body-Mass-Index; FEV1: Forced expiratory volume in 1 second

Table 2: Comparison of Outcomes (Weight, BMI and FEV1) with Respect to Use of PN

The rate of change, or slope, was not significant in our data. However, there was significant shift of the slope with $p < 0.05$ in weight and weight-for-length/BMI percentiles, of 0.145 and 0.313 respectively. These results suggest that PN increased patients' weight and weight-for-length/BMI, placing them on a higher growth curve, and improving their growth trajectory. There was no significant change in FEV1 over the study period with the use of PN. However, there was no worsening of FEV1 observed. The stability of FEV1 is significant considering the natural progression of the disease. Long-term studies may be needed to explore the effect of PN and long-term FEV1 patterns more specifically.

The effects of PN on rate of hospitalizations were also assessed using a paired T-test. The most significant difference noted was frequency of hospitalizations in the year prior compared to the year after the use of PN. There was a mean reduction, approaching 50%, in the number of hospitalizations.

Generally, patients tolerated short-term PN well. Laboratory studies including basic metabolic panel, glucose, creatinine and BUN, liver function tests, albumin, triglycerides and complete blood counts were followed closely (daily while advancing PN and spaced to weekly once they were on a stable PN regimen). Long-term PN seemed to be associated with more complications. Patient #7, who was a neonate, was identified to have cholestasis and was subsequently started on ursodeoxycholic acid until PN was discontinued and cholestasis resolved. Patient #2 developed hyperglycemia requiring insulin which was ultimately stopped as PN was tapered. Patient #11 was admitted to the hospital for fever in the setting of a central line. However, blood cultures remained negative for 48 hours, and the patient was able to be discharged. No serious infectious complications, line dysfunction, or blood clots were noted during the duration of the study.

Discussion

PN has been used in infants and children since the 1960s. Formulations initially were fat-free until intravenous lipid emulsions became available in 1970s [5]. The present study demonstrates that PN is feasible and safe for providing further nutritional support to patients with CF during periods of acute illness, which is particularly relevant due to increased needs. This retrospective study suggests that providing PN and intralipids has short-term and long-term benefits in pediatric patients with CF as shown by increased weight and weight-for-length/BMI during the study. Our most significant finding was the reduction in hospitalization

rate over the 12 months following initiation of PN. There was a mean reduction of nearly 50%. Our results are consistent with those previously reported [6,7].

Our patients had no significant change in pulmonary function as measured by FEV1 during the study duration, but yet, there was no reduction in FEV1. In a disease defined by declining lung function, this stability could be considered as a positive result. However, it is difficult to assess if one-year post PN is long enough to determine significance of this parameter, hence, no conclusions can be made based on this study due to the relatively short period of study and small sample size. Larger studies are needed to explore this potential correlation further. Lester et al. concluded that providing short-term PN during pulmonary exacerbations contribute to significant weight gain and fewer courses of antibiotics. Additionally, their results showed decrease in hospitalization rates but with no sustained improvement in pulmonary function [6]. Importantly, PN was generally well-tolerated, with only two patients requiring further interventions (insulin for hyperglycemia and ursodeoxycholic acid for cholestasis). These interventions were no longer necessary after discontinuation of PN.

Further work is needed to better assess if PN is more beneficial during brief times of anabolic stress like pulmonary exacerbations. The results from our study are limited due to the small number of patients, the heterogeneity of the causes for PN initiation, and the severity of pulmonary status of the patients in the study group. Therefore, the majority of our results are descriptive. This study shows safety and emphasizes the need for further studies regarding the use of PN in cystic fibrosis patients including: the optimal time to provide PN and which characteristics are significant risk factors for poorer outcomes without PN. PN is not an appropriate intervention for all pediatric patients with CF admitted for pulmonary exacerbation. This intervention should be used with caution and careful consideration. In our institution, the decision to place a patient on PN is a multidisciplinary decision involving the pediatric CF pulmonologist, pediatric CF gastroenterologist, CF dietitian, and discussion with the patient and their family. The need for ongoing PN or re-initiation of PN is continuously reevaluated to maximize benefit to our patients and minimize risk.

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