Outcomes of the First 54 Pediatric Patients on Long-Term Home Parenteral Nutrition from a Single Brazilian Center

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ABSTRACT

Objectives: Data on multidisciplinary programs dedicated to home parenteral nutrition (HPN) in Latin America are limited. This study describes the results of the first multidisciplinary pediatric intestinal rehabilitation program for HPN at a public tertiary hospital in Brazil.

Methods: We retrospectively reviewed patients aged 0–18 years with intestinal failure (IF) who required parenteral nutrition (PN) for >60 days between January/2014 and December/2020.

Results: Fifty-four patients were discharged on HPN (15 achieved enteral autonomy, 34 continued on HPN at the end of the study, 1 underwent intestinal transplantation, and 4 died). The median (IQR) age at the study endpoint of patients who achieved enteral autonomy was 14.1 (9.7–19) versus 34.7 (20.4–53.9) months in those who did not achieve enteral autonomy. Overall prevalence of catheter-related thrombosis was 66.7% and catheter-related bloodstream infection rate was 0.39/1000 catheter-days. Intestinal failure-associated liver disease (IFALD) was present in 24% of all patients; none of the patients who achieved enteral autonomy had IFALD. All patients showed significant improvement in anthropometric parameters during the HPN period. The sociodemographic characteristics of the patients' family members were mothers less than 20 years old (7.5%), schooling time more than 10 years (55.5%), and household income between 1 and 3 times the minimum wage (64.8%). The 5-year survival rate for HPN is 90%, and 27.7% of patients achieve enteral autonomy.

Conclusion: The treatment of pediatric patients with IF followed by a multidisciplinary pediatric intestinal rehabilitation program with HPN is feasible and safe in the Brazilian public health system.

Key Words: intestinal rehabilitation, intestinal failure, short bowel syndrome, home parenteral nutrition, children

What Is Known

- Long-term home PN is well established in Europe and North America with high survival rate of patients.
- There are few data on patients on long-term home PN followed by multidisciplinary intestinal rehabilitation programs from middle-income countries, especially in Latin America.

What Is New

- With dedicated multidisciplinary teamwork and care protocols, a high survival rate with intestinal autonomy is achievable in middle-income countries.
- The use of SMOF lipids in PN solutions, taurolidine catheter lock, and interdisciplinary management are potentially associated with a low CRBSI rate and mild liver disease in Brazilian patients on home PN.

Intestinal failure (IF) is characterized by the reduction of functional intestinal mass below that which can sustain life, resulting in dependence on parenteral support for a minimum of 60 days within a 74 consecutive day interval (1). Short bowel syndrome (SBS) is the most frequent cause of IF and is defined as the need for parenteral nutrition (PN) for more than 60 days after intestinal resection or a bowel length <25% of the expected length (2).

Over the past decades, there has been a vast improvement in the survival of these patients (3,4), and the development of multidisciplinary intestinal rehabilitation programs (MIRP) is one of the leading factors for such improvement (5,6). In addition to MIRPs, several factors contribute to better outcomes in IF patients, such as the composition of omega-3 fish oil, soybean oil, medium-chain triglycerides, and olive oil in PN solutions (7), surgical interventions, such as serial transverse enteroplasty (8), and the advent of ethanol and taurolidine central venous catheter (CVC) locks (9,10).

The main goals of MIRP are to promote intestinal adaptation and enteral autonomy, while decreasing the morbidity and mortality of IF (2). MIRPs are well established in traditional centers in Europe and North America, and there has been an increasing number of new MIRPs worldwide. However, published data on patients with IF on long-term home PN (HPN) followed by MIRPs from middle-income countries, especially Latin America, are limited (11,12). This study aimed to evaluate the outcomes of the first pediatric MIRP with HPN in the public health system of a tertiary public hospital in Brazil.

METHODS

This study was approved by the Research Ethics Committee of Hospital de Clinicas de Porto Alegre (protocol no. 13-0383).

We conducted a retrospective study that included all children referred to our institution with chronic IF between January 1, 2014, and December 31, 2020. The Pediatric MIRP of the Hospital de Clinicas de Porto Alegre in Southern Brazil is the first referral center in the public health system in Brazil supported by the Brazilian Ministry of Health. The inclusion criteria were patients with primary digestive problems who required PN for >60 days and were discharged on HPN.

Standard of Care

A multidisciplinary IF management protocol was implemented in January 2014. The program is composed of pediatric gastroenterologists, pediatric surgeons, nutrition specialists, nurses, pharmacists, dietitians, psychologists, social workers, physiotherapists, speech and language therapists, and administrative staff. The program is conducted in collaboration with the patients' municipality of origin, which provides local nurses with supervision of the HPN process (13). All patients discharged on HPN followed standard protocols with formal training of parents and local health professionals regarding CVC care, infusion pump handling, and PN care.

PN solutions: All-in-one individualized and tailor-made PN admixtures (14) were prescribed by our center, prepared by a local manufacturer (Life Pharma, Porto Alegre, Brazil), and delivered daily to children's homes. The amount of parenteral energy was calculated according to the Schofield or World Health Organization (WHO) equation (15), and it was increased up to 50% to 100% of the caloric requirement if catch-up growth was needed (16). SMOF (soy 30%, medium-chain triglyceride 30%, olive 25%, and fish 15%) lipids were the standard lipid solutions used in all patients.

Oral and enteral feeding: Oral feeding and eating skills are always stimulated unless severe gastrointestinal dysmotility is observed. Enteral feeds were routinely introduced by mouth or nasogastric tubes using an extensively hydrolyzed formula or an amino acid-based formula. Breast milk was offered when the mothers provided it. Percutaneous gastrostomy tubes were placed when nasogastric tubes were required for more than 2 months. Solid foods were introduced at the age of 4–6 months (corrected for gestational age in preterm babies) to stimulate oral motor activity and to avoid feeding aversion behavior.

Vascular access and handling: Long-term tunneled CVC (Broviac or Hickman) were used in all patients for HPN delivery. Either heparin or taurolidine CVC lock was randomly started in 2014 (as in another study, unpublished data); however, from January 2017 onwards, all patients had been using taurolidine+citrate lock (Taurolock®) as a local standardized protocol, regardless of the occurrence of CVC infection. CVC thrombosis was assessed every 6 months or once a year using vascular ultrasound and angioMRI/angioCT, when needed. Secondary prophylaxis for CVC thrombosis with subcutaneous low-molecular-weight heparin (LMWH) was administered during the 3-month period after the first CVC thrombosis was identified. Subsequently, a new assessment of thrombosis was performed, and prophylactic doses were administered until removal of the CVC in case the patients did not improve from thrombosis.

PN training and patient discharge: The minimum socioenvironmental criteria assessed for HPN were as follows: household location, presence of a sewage system, tap water, and electrical energy in the environment. All mothers and other close relatives were formally trained by specialist nurses during a period of not less than 2 weeks for PN care (13). Nurses from the respective cities were trained before hospital discharge. Family and caregivers were supervised daily at home by the local nurses for PN installation and CVC care for a period of 2–3 months. From that onwards, parents could manage PN by themselves at the discretion of the local health professionals under 24-hour phone support by nurses and physicians.

Patient follow-up and enteral autonomy (EA): All patients had follow-up visits every 2 weeks soon after discharge and every 2–4 months thereafter. Periodical clinical checkups included assessment of anthropometric data; ultrasonography of the liver and large vessels; and laboratory tests that included hematological assessment, plasma and urine electrolytes, iron balance, vitamin and trace element assays, lipid profiles, TSH, parathyroid hormone, and renal and liver function tests. Successful EA was considered when a child was able to sustain growth and fluid balance without parenteral support for more than three months (17,18).

Data Collection, Definitions, and Outcomes

We collected patient data from our institutional database and medical records between January 1, 2014, and December 31, 2020. Patients were separated into two groups: those who achieved EA and those who did not achieve EA. Data included age at entry to MIRP, considered when patients were eligible to be discharged on HPN; age when HPN started and at the endpoint; hospitalization time to discharge on HPN; duration of HPN until EA; causes of IF for PN treatment; length of remnant small bowel considering a cutoff of 40 cm (3,19); presence of ileocecal valve; preserved colon was considered when transverse, descending, and rectum were present; complications related to CVC; growth parameters; PN dependency

ratio; and sociodemographic status of patients' caregivers. Patients with SBS were classified anatomically into 3 types: type I, end jejunostomy; type II, jejuno-colic anastomosis; and type III, jejuno-ileal anastomosis (20). Data were collected from discharge on HPN until four endpoints: full EA, ongoing HPN on December 31, 2020, referral for intestinal transplantation, or death.

The PN dependence ratio was defined as the ratio of non-protein energy intake (NPEI) to resting energy expenditure (REE). This ratio ranges from mild PN dependence (<80%) to high PN dependence (>120%) (21).

Catheter-related bloodstream infection (CRBSI) was defined as clinical evidence of a systemic infection and at least one positive blood culture from the CVC and/or peripheral vein in the absence of an obvious source of infection other than CVC (22). The CRBSI rate was calculated as the number of CRBSI episodes per 1000 catheter-days (23). CVC thrombosis was defined as the presence of at least one CVC site with thrombosis.

Intestinal failure-associated liver disease (IFALD) was sub-divided into mild, moderate, and severe according to classification proposed by Beath et al (24). Anthropometric measurements of weight, height, and body mass index (BMI) were used according to WHO references. The WHO Anthro software was applied to children under five years of age, and the WHO Anthro Plus (version 3.2.2.1) was applied for children above five years of age. Z-scores for weight-for-age, height-for-age, and BMI-for-age were calculated at baseline and when patients achieved EA or at the end of the study for those who did not achieve EA. Differences (delta) between the two periods were calculated.

Statistical Analysis

Fisher's exact test was used to compare frequencies. The Student's *t*-test and Mann–Whitney U test were used to compare continuous variables. Kaplan–Meier curves were used to describe survival. Odds ratio estimates for categorical variables with zero counts were obtained using Haldane's correction (adding 0.5 to each cell). Statistical analyses were performed using SPSS version 18.0. Statistical significance was set at $P < 0.05$.

RESULTS

The medical records of 77 patients with the likelihood of long-term PN dependence during hospitalization were reviewed. Of these, 54 patients were discharged on HPN and met the inclusion criteria. At the end of the study, out of 54 patients, 34 were on HPN, 15 achieved EA, 4 died (2 due to CRBSI septicemia, 1 venous access loss, and 1 IFALD) and one underwent intestinal/multivisceral transplant at another center. Patient outcomes are shown in Figure 1. Twenty-three patients were excluded from the analysis because they could not be discharged on HPN, mainly because of sociopsychological factors or lack of a stable clinical condition.

The causes of IF in the 54 patients who were discharged on HPN were intestinal atresia (n = 14, 25.9%), volvulus (n = 12, 22.2%), gastroschisis (n = 10, 18.5%), necrotizing enterocolitis (NEC) (n = 7, 13.0%), long-segment Hirschsprung's disease (n = 2, 3.7%), chronic intestinal pseudo-obstruction syndrome (n = 2, 3.7%), mesenteric ischemia (n = 2, 3.7%), Berdon's syndrome (n = 1, 1.9%), and other causes (n = 4, 7.4%).

Of the 54 patients, 15 (27.7%) achieved EA after HPN. The patient characteristics associated with EA achievement are presented in Table 1. The age at entry into MIRP and the age when HPN was started in patients who achieved EA were significantly lower than those who did not achieve EA. Median (IQR) age at the study endpoint of patients who achieved enteral autonomy was 14.1 (9.7–19) versus 34.7 (20.4–53.9) months in those who did not achieve enteral autonomy. The hospitalization
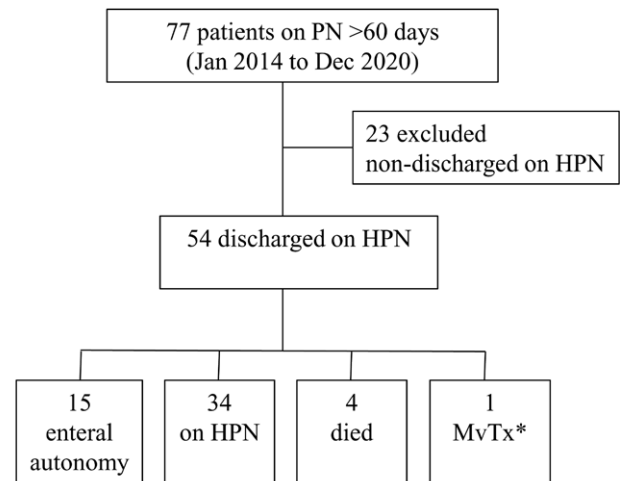
* 1 patient underwent multivisceral transplant at other center

Figure 1. Outcome of patients.

time to discharge on HPN was not significantly different between those who achieved EA and those who did not. The median (IQR) time to achieve EA for those who were weaned off PN was 4.3 (3.3–10.2) months.

Regarding the anatomical classification of SBS in 49 patients, 4 (8.2%) patients were classified as type I, 26 (53.1%) as type II, and 19 (38.8%) as type III. None of the type I patients achieved EA at the end of the study, whereas 19.2% of type II patients and 42.1% of type III patients achieved EA. We found that EA was achieved in 13 of 49 (26.5%) patients with SBS and in 2 of 5 (40%) patients without SBS, with no significant difference between them ($P = 0.610$).

The presence of a preserved colon was significantly more frequent in patients who achieved EA than in those who did not achieve EA ($P = 0.024$). The odds ratio of EA to preserved colon was estimated to be 14.1 (95% CI 0.9–233.0) with a wide confidence interval due to a cell with zero count (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C835*). The frequency of remnant intestine >40 cm and the presence of ICV were not significantly different between the two groups.

IFALD was present in 24% of all patients, of whom two had severe IFALD and all others had mild IFALD. Moreover, all patients who had IFALD were from the group that did not achieve EA, and none of the patients who achieved EA presented with IFALD (Table 1). Of the 2 patients with severe IFALD, 1 died of decompensated cirrhosis and the other was alive with compensated cirrhosis. The absence of IFALD was also associated with a higher chance of achieving EA ($P = 0.011$). Therefore, the odds ratio of presence of IFALD to achieve EA was 0.06 (95%CI <0.01–1.04), also with a wide confidence interval due to a cell with zero count (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C835*).

The prevalence of CRBSI/1000 catheter-days and CVC thrombosis were not significantly different between those who achieved EA and those who did not. All patients with CVC thrombosis had pre-existing thrombosis, and 6 patients developed new thrombosis during the HPN period.

Concerning PN dependency rate of HPN patients who did not achieve EA, the median (IQR) rate was 0.82 (0.62–0.98) at the end of the study. Of these patients, 17 (50%) presented mild PN dependency, 13 (29.3%) presented moderate dependency, and 4 (11.7%) presented high dependency.

TABLE 1. Patients' characteristics associated with achievement of enteral autonomy

Patients' characteristics	Enteral autonomy: no (n = 39)	Enteral autonomy: yes (n = 15)	P
Sex, boys:girls (no.)	24:15	10:5	>0.999‡
Age (months) at entry into MIRP median (IQR; range)	4.5 (2.6–13.3; 1–193)	2.6 (1.7–4,3; 0.6–10.3)	0.04†
Age (months) when HPN started, median (IQR; range)	10.9 (6.3–12.9; 3.7–197)	7.2 (5.8–10.2; 4.4–15)	0.043†
Age (months) at the endpoint*, median (IQR; range)	34.7 (20.4–53.9; 5.2–238)	14.1 (9.7–19; 7.1–28.3)	<0.001†
Hospitalization time (days) to discharge on HPN, median (IQR; range)	105 (65.5–153; 23–343)	120 (76.5–167; 28–249)	0.569†
Death, n (%)	4 (10%)	0 (0.0%)	0.567‡
Remnant intestine >40 cm, n (%)	25 (64.1%)	10 (66.7%)	>0.999‡
Presence of ICV, n (%)	16 (41%)	10 (66.7%)	0.131‡
Colon preserved, n (%)	27 (69.2%)	15 (100%)	0.024‡
Prevalence of IFALD, n (%)	13 (33.3%)	0.0	0.011‡
Episodes of CRBSI/1000 catheter days, mean ± SD	0.46 ± 0.91	0.19 ± 0.73	0.087†
CVC thrombosis, n (%)	28 (71.8%)	8 (53.3%)	0.21‡

MIRP = Multidisciplinary Intestinal Rehabilitation Program; IFALD = intestinal failure-associated liver disease; CRBSI = catheter-related blood stream infection. *At the end of study, at enteral autonomy, and at referral for intestinal transplantation or death. †Mann-Whitney U test. ‡Fisher's exact test.

Z-scores between -1 and +1 for weight-for-age, height-for-age, and BMI-for-age were observed in 72.3%, 47.1%, and 58.8% of the patients at the end of the study, respectively. A significant difference (delta) was observed between the endpoint and the baseline weight-for-age and height-for-age z-scores of all patients. A significantly higher difference (delta) was observed in the weight-for-age z-scores than in the height-for-age z-scores. The BMI-for-age z-scores were not significantly different between the 2 groups (Table 2).

The sociodemographic characteristics of the family members of patients who were discharged on HPN were as follows: mothers and other family members of all patients were trained for PN care, and mothers younger than 20 years of age represented 7.5% of the group (n = 4). In terms of family caregivers' schooling time, 30 (55.5%) had more than 10 years of schooling, 20 (37%) had 5–10 years, and 4 (7.5%) had less than 5 years of schooling. Regarding household income, 9 (16.7%) were less than the minimum wage, 35 (64.8%) were 1–3 times the minimum wage, and 10 (18.5%) were more than 3 times the minimum wage. (Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C835*.

The 5-year survival rate of all patients (who achieved or did not achieve EA) was 90% (Kaplan–Meier) (Figure 2).

DISCUSSION

This study demonstrated the successful implementation of the first pediatric MIRP in a public tertiary hospital in the public health system in Brazil. Data from Latin American countries are scarce, as the modality of HPN conducted by multidisciplinary programs has only recently been developed in most countries over the past decades.

Intestinal atresia, gastroschisis, volvulus, and NEC were the most frequent causes of SBS in our study. NEC was the fourth most common cause, while it was the first in Europe and the United States, probably due to better survival of extremely premature newborns in these countries (25).

The outcomes of patients with IF on long-term PN are influenced by many factors, including CVC-related complications such as CRBSI, CVC-related thrombosis, IFALD, and growth failure (26). In our cohort, the overall rate of CRBSI in HPN patients was 0.39/1000 catheter-days, similar to other centers that described 0.3 to 1.7 episodes of CRBSI/1000 catheter-days (17,27).

At least 1 venous access with thrombosis was observed in 66.7% of the patients, which is in accordance with the literature that reported a prevalence of up to 57-80% (26,28). Most patients had pre-existing thrombosis at the time of referral to our center, possibly reflecting previous recurrent CVC infections and inadequate CVC care.

IFALD was present in 24% of all patients, similar to other studies that reported rates of 7.7% to 26% (18,27). Two patients had severe IFALD and all others had mild IFALD, probably as a result potentially associated with the use of alternative lipid strategies, for example, SMOF lipids and a low CRBSI rate.

All patients were in the normal range for anthropometric parameters of less than two standard deviations at the end of the study. However, when z-score between -1 and +1 were assessed, the frequency ranged from 47% (height-for-age) to 72% (weight-for-age). Another study showed that approximately 30% of patients on long-term PN were underweight, with a significant difference between the final and target heights (3). We found a significantly higher delta (difference between the endpoint and the baseline) of the weight-for-age z-score than the height-for-age z-score, indicating that weight can be more easily recovered than height.

According to the PN dependence rate (NPEI/REE) (27), most HPN patients have mild-to-moderate dependence. Furthermore, we found that all patients with SBS who achieved EA had a preserved colon, indicating that this might be a factor in achieving EA (29). We were unable to confirm this finding using regression modeling because of sample size restrictions. The presence of ICV and remnant intestine >40 cm did not differ between patients who achieved and those who did not achieve EA. We employed a cutoff of 40 cm for the remnant small bowel, as it has been associated with EA achievement in some studies (3,19).

TABLE 2. Anthropometry of patients with IF at hospital discharge and endpoints

|	At discharge on HPN	At enteral autonomy	Continuing on HPN	Delta z-score (95% CI)	P^*
No enteral autonomy (n = 37)					
z-score for height-for-age, mean ± SD	−1.71 ± 1.50	–	−1.29 ± 1.39	0.42 (0.12; 0.73)	0.007
z-score for weight-for-age, mean ± SD	−1.27 ± 1.68	–	−0.47 ± 1.27	0.80 (0.31; 1.29)	0.002
z-score for BMI-for-age, mean ± SD	−0.16 ± 1.59	–	0.32 ± 1.32	0.48 (0.02; 0.99)	0.59
With enteral autonomy (n = 14)					
z-score for height-for-age, mean ± SD	−2.07 ± 2.35	−1.29 ± 1.61	–	0.78 (0.11; 1.47)	0.026
z-score for weight-for-age, mean ± SD	−1.47 ± 1.64	0.07 ± 1.37	–	1.54 (0.61; 2.46)	0.003
z-score for BMI-for-age, mean ± SD	−0.25 ± 1.16	0.04 ± 1.29	–	0.29 (0.60; 1.18)	0.497

*Student's t test for paired samples.
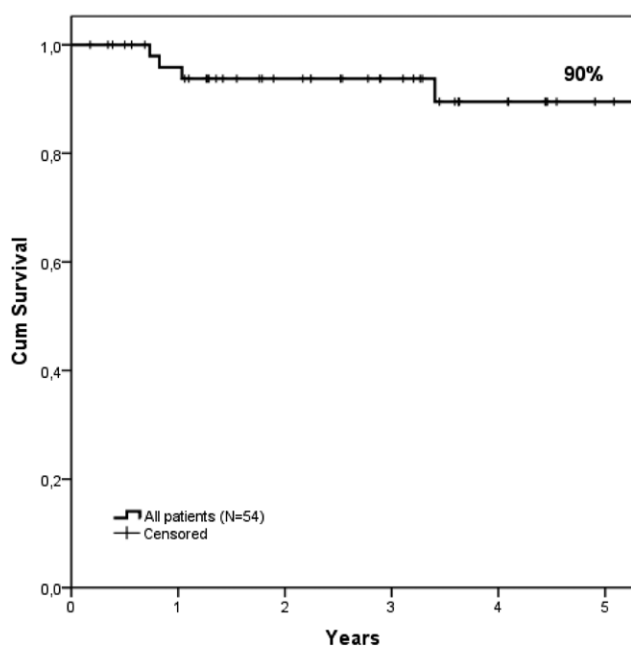
Figure 2. Kaplan-Meier curve of 5-year survival rate of all patients discharged on HPN.

The total EA rate was 27.7%, which was lower than that in other centers in Europe and North America, ranging from 42% to 84% (17,30). This might be explained by our shorter period of assessment compared with periods longer than 10 years in other traditional centers. Moreover, several patients who were still on HPN at the end of the study period may achieve EA in the future.

We found a 5-year survival rate of 90% for patients with HPN, which is in line with the literature reporting a survival rate of 84%–95% (17,27). Our study brings to light a group of socially vulnerable patients in a middle-income country. In Brazil, HPN care has been available mainly in private health insurance settings. Nevertheless, this study showed that it is possible to provide safe and effective HPN by MIRP, even in unfavorable scenarios.

The limitations of this study include the small number of patients and the retrospective design. However, the long-term study period following a standardized protocol allowed us to report accurate data on the survival, growth, and complications associated with HPN use. Considering that most patients were referred from different centers, the heterogeneity of care before enrollment could have influenced the patient's ability to achieve EA; however, the standardized approach applied to all patients enrolled in the MIRP may have attenuated this effect.

We conclude that the treatment of patients with IF by a MIRP with HPN is feasible and safe in the public health system in Brazil. The high survival rate supports the use of HPN as the primary treatment for IF in the middle-income scenario.

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